A11. CV131-019: A report on the effect of concomitant administration of irbesartan on the steady-state pharmacodynamics of warfarin.

A11.1. Source documents

Study report: NDA 20-757, vol 1.62-1.63.

A11.2. Investigators

Peter U. Witte, M.D., Ph.D., IMFORM GmbH, Augustrastraße 13, D-02826 Goerlitz, Germany.

A11.3. Study design

The objective of the study was to assess the effect of irbesartan on the steady-state pharmacodynamics of warfarin and to evaluate possible pharmacokinetic interactions of irbesartan and warfarin.

This was a double-blind, two-period, randomized, placebo-controlled, multiple-dose study in healthy male volunteers (aged 18-45). The dose on Day 1 was 10 mg and on Days 2-21 2.5 to 10 mg). Concomitant administration of 300 mg irbesartan/placebo was done on Days 15-21. Prothrombin time (PT) and prothrombin time ratio (PTR) were evaluated for each subject daily prior to dosing of warfarin with or without irbesartan. After concomitant administration of irbesartan, an absolute difference of PTR of 0.4 between the group mean PTR values at Day 22 (end point) and Day 15 (baseline), was considered to be clinically significant. Plasma and urine samples for the pharmacokinetic analysis of warfarin and its metabolites were collected before and up to 24 hours after drug administration on Days 14, 15 and 21.

Drug supplies are shown in Table 140 below.

Table 140. Drug supplies (CV131-019).

	Lot number		Lot number
Irbesartan placebo	L94F014C	Irbesartan 75 mg capsule	L95008
Warfarin 5 mg tablet	5208		

Prothrombin time (PT) prothrombin time ratio (PTR) were evaluated throughout the study. After concomitant warfarin and irbesartan, an absolute difference of PTR of 0.4 between the group mean PTR values at Day 22 (end point) and Day 15 (baseline) was considered clinically significant.

Plasma and urine C_{max}, T_{max}, AUC_{0-T}, AUC_{∞} of warfarin and its metabolites were collected before and up to 24 hours after administration on Days 14, 15 and 21.

A11.4. Results

One subject was discontinued for personal reasons. Warfarin was administered for 21 study days.

All subjects achieved the target PTR of 1.3 to 1.6 after a 2-week warfarin titration period and were randomized to irbesartan or placebo on Day 15. After administration of 20 mg vitamin K on Day 23, PTR-values returned to normal in all subjects. The measure of warfarin-irbesartan interaction (Table 141 below) was not statistically significant.

Table 141. Prothrombin time ratios (CV131-019).

	Placebo	Irbesartan
Baseline (day 15)	1.49±0.19	1.50±0.12
End point (day 22)	1.45±0.34	1.41±0.12

A11.4.1. Safety

Not reviewed.

A11.5. Summary.

Irbesartan dose not alter the warfarin PTR-values in healthy subjects. Pharmacokinetic results were not submitted in this report.

A12. CV131-024: Effect of concomitant administration of irbesartan on the steady-state pharmacokinetics of digoxin in healthy male subjects

A12.1. Source documents

Study report: NDA 20-757, vol 1.164.

A12.2. Investigators

Howard Uderman, M.D., Clinical Pharmacology Unit at Princeton House, 905 Herrontown Road, Princeton, NJ 08540.

A12.3. Study dates

A12.4. Study design

This study description was based upon the final study report of 31 January 1996.

The objective of the study was to assess the effect of concomitant irbesartan on the steady-state pharmacokinetics of digoxin. A 50% change in AUC and C_{max} at steady-state of digoxin was considered clinically significant.

This was an open-label, multiple-dose study in 10 healthy male subjects. Digoxin was administered 0.25 mg qid on Day 1, and 0.25 mg qd Days 2-14; irbesartan was administered 150 mg qd Days 8-14. Blood samples were collected on Days 7, 8 and 14 at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 hours after drug administration. Urine samples were collected at pre-dose, 0-6, 6-12 and 12-24 hour intervals post-dose.

Drug supplies are shown in Table 142 below.

Table 142. Drug supplies (CV131-024).

	Lot number
Irbesartan 75 mg tablet	N94J126C
Digoxin (Lanoxin®) 0.25 mg	4U1231

Assays are described in Table 143 below. Both assays were satisfactory.

Table 143. Assays (CV131-024).

Assay	Sample	Technique	Linearity	Specificity	Sensitivity LOQ	Accuracy %RSD inter-day	Precision %RSD intra-day
Digoxin	Plasma Urine			—*	0.2 ng/ml 3.0 ng/ml		

*No cross-reactivity with irbesartan.

ANOVA was used to evaluate $\log AUC_t$, $\log C_{max}$ and $\log C_{min}$ of digoxin. The T_{max} analyses were based on rank data. %UR, CLT/F and Clr were not transformed.

A12.5. Results

Table 144 below summarizes the pharmacokinetic parameters for this drug interaction study of digoxin and irbesartan.

Table 144. Pharmacokinetic parameters (±SD; CV131-024).

	Digoxin (steady-state) Day 7	Digoxin + irbesartan Day 8	Digoxin + irbesartan Day 14
C_{max} (ng/mL)	1.43 (0.23)	1.55 (0.36)	1.65 (0.44)
AUC_τ (ng.mL/h)	15.7 (3.0)	15.7 (2.9)	15.5 (3.3)
T_{max}* (h)	1.0 (0.5-1.5)	1.0 (0.5, 3.0)	1.0 (0.5-3.0)
%UR	64 (16)	61 (11)	58 (9)

*For T_{max}, the values are the median and the minimum and maximum values are shown parenthetically.

A12.5.1. Safety Not reviewed.

A12.6. Summary. Irbesartan (150 mg qd) shows no significant effect on the steady-state pharmacokinetics of digoxin.

A13. CV131-025: Dose ranging study II: a multicenter trial of the antihypertensive activity and safety of 100 mg, 200 mg and 300mg irbesartan in mild-to-moderate hypertension.

A13.1. Source documents

Study report: NDA 20-757, vol 1.263 to 1.267; electronic document: MAST025.PDF.

A13.2. Investigators

Multi-center trial; 38 investigators, 35 in the U.S.

A13.3. Study dates

28 February 1994 to 04 July 1994

A13.4. Study design

This study description was based upon the protocol dated 15 December1993. There was one amendment written after the start of enrollment and pertained to the open label trial with HCTZ.

This was a randomized, double-blind, placebo-controlled, parallel-group study of irbesartan 100, 200, and 300 mg. The study had 2 primary hypotheses: (1) administration of irbesartan once daily for 8 weeks at doses between 100 and 300 mg reduces blood pressure in patients with mild-to-moderate hypertension (SeDBP 95 to 110 mmHg), and (2) administration of irbesartan once daily for 8 weeks at doses between 100 and 300 mg is well-tolerated. The study had 2 secondary hypotheses: (1) administration of irbesartan will be associated with trough-to-peak ratios in SeDPB >50%, and (2) addition of hydrochlorothiazide once daily for 2 weeks to patients with SeDPB >90 mmHg after 8 weeks of treatment with irbesartan will be well-tolerated and produce a further reduction in blood pressure.

After screening (history, physical examination, ECG, chest x-ray, standard clinical laboratory tests), provision of consent, and discontinuing/tapering of prior antihypertensive medications, subjects entered a single-blind placebo lead-in period lasting 4 to 5 weeks. All study visits were to be within ±3 days of scheduled visits. To continue into the double-blind phase of the study, the SeDBP at weeks 3 and 4 (or 4 and 5) were to average 95 to 110 mmHg, with a difference between the 2 readings <8 mmHg. Subjects meeting these criteria were entered into the double-blind phase of the study and were randomized to receive placebo or irbesartan 100, 200, or 300 mg once daily for 8 weeks. There was no stratification, but there was randomization in blocks of 4 by center to minimize imbalance at a site.

Subjects were seen on the first day of dosing in (day 1) and thereafter at 2-week intervals. Daily doses were to be taken between 6 and 10 am, with study visits to occur 24±2 hours after ingestion of the prior daily dose. At this time, seated and standing blood pressure were measured, and adverse events were recorded. On the first and final visits (days 1 and 57), 'peak' effect was measured 3 hours after dosing. Subjects meeting criteria to receive hydrochlorothiazide entered a third phase of the study with a final visit 2 weeks later. ECG, laboratory tests, interview for adverse events, weight, drug levels, and medication dispensing and counts occurred at reasonable intervals during the study. Breakfast was permitted before a day's blood pressure measurements. Blood pressure was taken prior to the next daily dose, using the same arm throughout study, and was determined as the mean of 3 readings taken 2 minutes apart after 10 minutes seated and 2 minutes standing, with 2 further readings if the first DBP readings were not within 8 mmHg.

Open-label HCTZ, atenolol, or nifedipine could be added after the 8-week double-blind period was completed.

Drug supplies are shown in Table 145 below.

Subjects in the study were males or surgically sterile or post-menopausal females >18 years of age with diagnosed essential hypertension or newly-discovered DBP >95 mmHg. Study sites were requested to enroll a study population with >30% SeDBP >104 mmHg and not to enroll a study population with >30% blacks. Study exclusions

Table 145. Drug supplies (CV131-025).

	Lot		Lot
Placebo	N93M11C N94A007C	IRB 100 mg	N93M16C N94C036C

were: (1) women of child-bearing potential, (2) known or suspected secondary hypertension, (3) SeDBP >110 mmHg or SeSBP >200 mmHg, (4) angina pectoris, (5) certain cardiac procedures within 12 months, (6) history of TIA or CVA, (7) evidence of CHF, (8) certain valvular heart diseases, (9) significant arrhythmias, (10) anti-arrhythmic medication, including digitalis, (11) pre-excitation syndrome, (12) second- or third-degree atrio-ventricular block, (13) sick sinus syndrome, (14) certain renovascular occlusive disease, (15) renal allograft, (16) certain other clinical conditions, (17) insulin-dependent or uncontrolled diabetes mellitus, (18) certain autoimmune, allergic diseases, or asthma requiring medication, (19) certain malignancies, (20) seizure disorders, (21) psychiatric disorders, (22) alcohol or drug abuse, (23) certain degrees of obesity, malabsorption, or inability to tolerate oral medication, and (24) prior participation in studies of irbesartan. Excluded medications were: (1) anti-hypertensive drugs, (2) nitrates, (3) β-adrenergic drugs, including ophthalmic drugs, (4) drugs to treat potassium loss, (5) psychotropic drugs, (6) oral contraceptives, (7) certain steroids, (8) omeprazole or cimetidine, (9) bile acid-binding resins, (10) cytotoxic drugs, (11) NSAIDs or high-dose ASA, and (12) investigational drugs within 30 days of enrollment. Concomitant medications allowed during the study included acetaminophen, antacids or H2 receptor antagonists except cimetidine, low-dose ASA therapy, allopurinol, HMG CoA reductase inhibitors, and antibiotics.

The efficacy and safety end points in this study were (1) reduction of blood pressure after 8 weeks, (2) safety and tolerability, and (3) trough:peak ratio.

Peak and trough plasma irbesartan levels were to be measured on days 1 and 57.

The primary efficacy variable was analyzed using analysis of covariance by treatment, center, and baseline. Analyses were done with an intent-to-treat dataset and an evaluable dataset after significant protocol deviations were removed. Cochran-Mantel Haenszel χ^2 test, stratified by site, was used to assess response rates.

Summary statistics were prepared before the study ended in order to choose a dose for subsequent studies. No hypothesis testing was conducted at that time and the results were not distributed to study site personnel.

Safety assessments were done both in the single- and double-blinded periods. Tests included (1) ECGs at enrollment and day 57, (2) laboratory tests (CBC, SMA20, urinalysis), and (3) physical examination. Clinical adverse events and their relationship to the study drug were recorded.

A13.5. Results

There were 499 subjects enrolled. Disposition of enrolled subjects is shown in Table 146 below.

Table 146. Subject disposition (CV131-025).

	N
Enrolled	499
Not Randomized	180
Randomized	319
Discontinued	20
Completed	299

Table 147 below shows reasons for exclusion prior to randomization.

Table 147. Reasons for exclusion (CV131-025).

Reason	N	Reason	N
Did not qualify	132	Adverse event	13
Subject request	15	Lost to Follow-Up	6
Other	5	Comcominant Meds	2
BP High (per Invest.)	2	Laboratory Abnorm.	1
Investigator Request	1	Poor Compliance	1
Protocol Violation	1	Drug Unavailable	1
Total	180		

Reasons for discontinuation are shown inTable 148 below.

Table 148. Reasons for discontinuation (CV131-025).

	Placebo N=79	Irbesartan 100 mg N=82	Irbesartan 200 mg N=79	Irbesartan 300 mg N=79		Placebo N=79	Irbesartan 100 mg N=82	Irbesartan 200 mg N=79	Irbesartan 300 mg N=79
Adverse event	2	0	2	0	BP above limit	1	0	0	1
Lost to follow-up	1	1	0	1	Comcom med.	0	0	1	0
Subject request	1	0	1	1	BP high per inv.	2	2	0	0
Admin reason	1	1	0	0	Protocol dev.	1	0	0	0
Completed	70	78	75	76					

Demographics of the 4 treatment groups are shown in Table 149 below. There were no statistically significant differences among groups in terms of gender, race, or age. The majority of subjects were male. In all 4 treatment groups, the percent of subjects with SeDBP >104 mmHg was approximately 24%, which did not achieve the protocol goal of >30%. One-quarter of entering subjects had not received prior antihypertensive therapy.

Table 149. Demographics (CV131-025).

	Placebo N=79	Irbesartan 100 mg N=82	Irbesartan 200 mg N=79	Irbesartan 300 mg N=79
Male (%)	68	74	65	70
Female (%)	32	26	35	30
White (%)	76	91	85	80
Black (%)	18	7	11	14
Other (%)	6	1	4	6
Age (mean±SD)	52±10	53±10	53±10	53±11
>65 years (%)	10	12	16	10
>75 years (%)	0	2	1	2

A13.5.1. Pharmacodynamics

Table 150 below shows seated baseline blood pressures and heart rate on day 4. There were no significant statistical differences among the 4 groups.

Table 151 below shows the mean change from baseline in seated trough systolic and diastolic blood pressure. Dose-response relationships for all subjects and by subgroups

Table 150. Baseline blood pressure and heart rate (CV131-025).

	Seated (mean±SD)				Standing (mean±SD)			
	Placebo N=79	Irbesartan			Placebo N=79	Irbesartan		
		100 mg N=82	200 mg N=79	300 mg N=79		100 mg N=82	200 mg N=79	300 mg N=79
DBP (mmHg)	101±5	100±4	101±4	101±4	102±7	101±5	102±6	101±6
SBP (mmHg)	152±13	148±13	151±14	149±13	151±14	149±14	151±14	148±14
HR (bpm)	73±9	73±9	72±9	75±10	77±9	75±9	76±10	78±9

by sex, race, and age are shown in Figures 42 and 43 below. Irbesartan 100, 200, and 300 mg doses were statistically significantly different from placebo for all measured blood pressures.

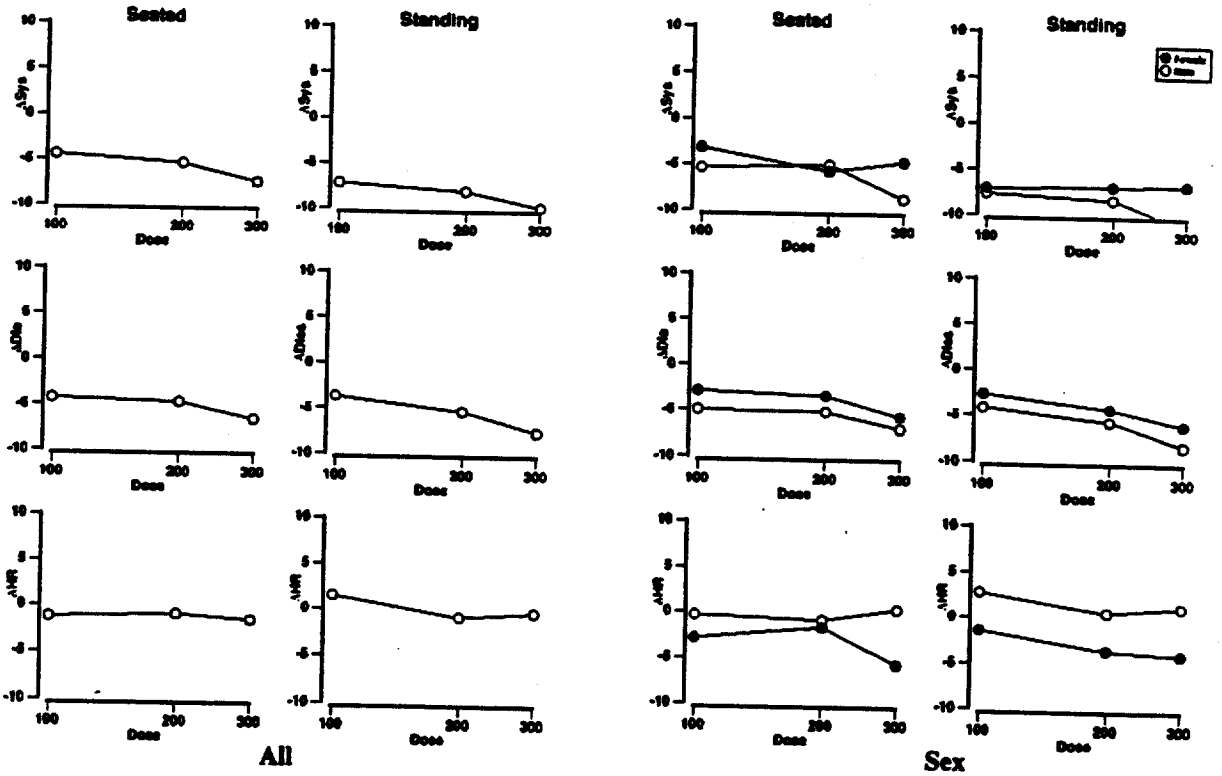

Figure 42. Dose-response (LOCF): all subjects and by sex (CV131-025).

Table 151. Mean change in seated and standing blood pressure (CV131-025).

	Seated (mean±SE)				Standing (mean±SD)			
	Placebo N=21	Irbesartan			Placebo N=21	Irbesartan		
		100 mg N=23	200 mg N=22	300 mg N=21		100 mg N=23	200 mg N=22	300 mg N=21
DBP (mmHg)	-5±1	-9±1	-10±1	-12±1	-3±1	-7±1	-9±1	-11±1
SBP (mmHg)	-4±1	-10±1	-10±1	-13±1	-2±1	-11±1	-10±1	-13±1

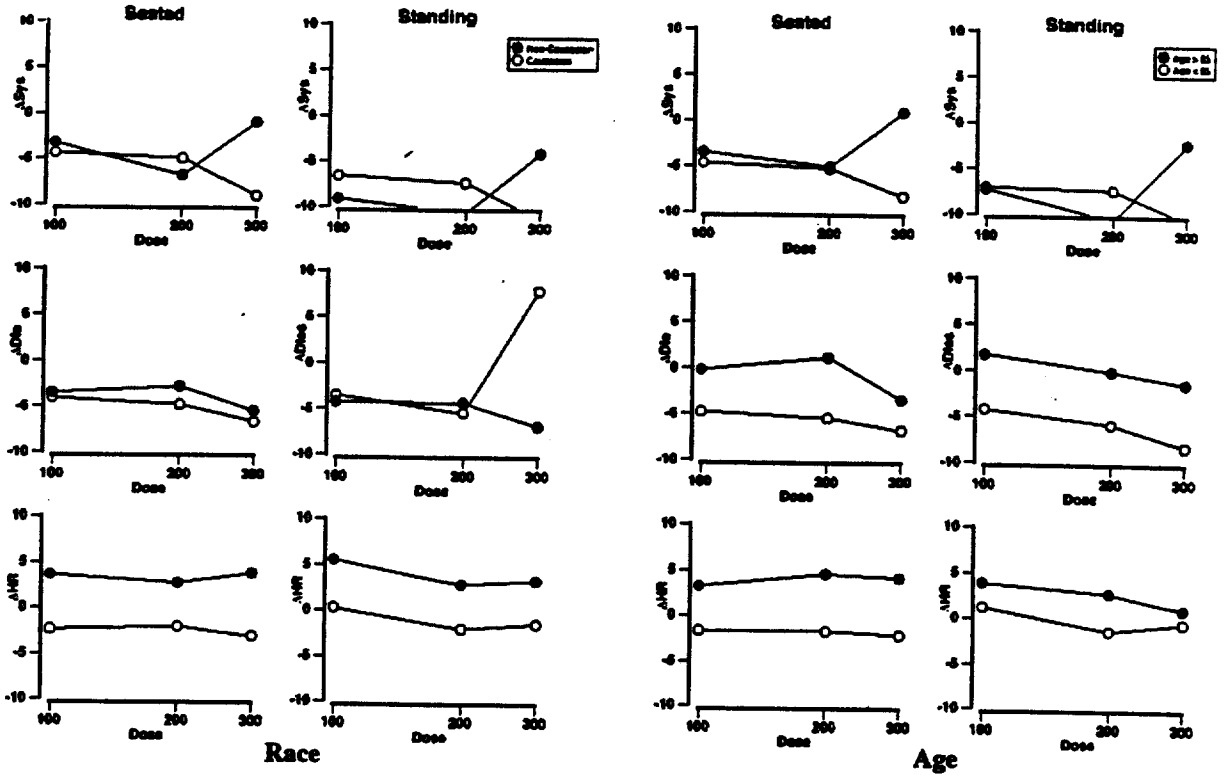

Figure 43. Dose-response (LOCF): by race and age (CV131-025).

The time course of seated and standing blood pressure changes are shown in Figure 44 below. Statistically significant blood pressures compared with placebo were observed for all irbesartan doses for weeks 2, 4, and 6. There were no significant changes in heart rate (data not shown).

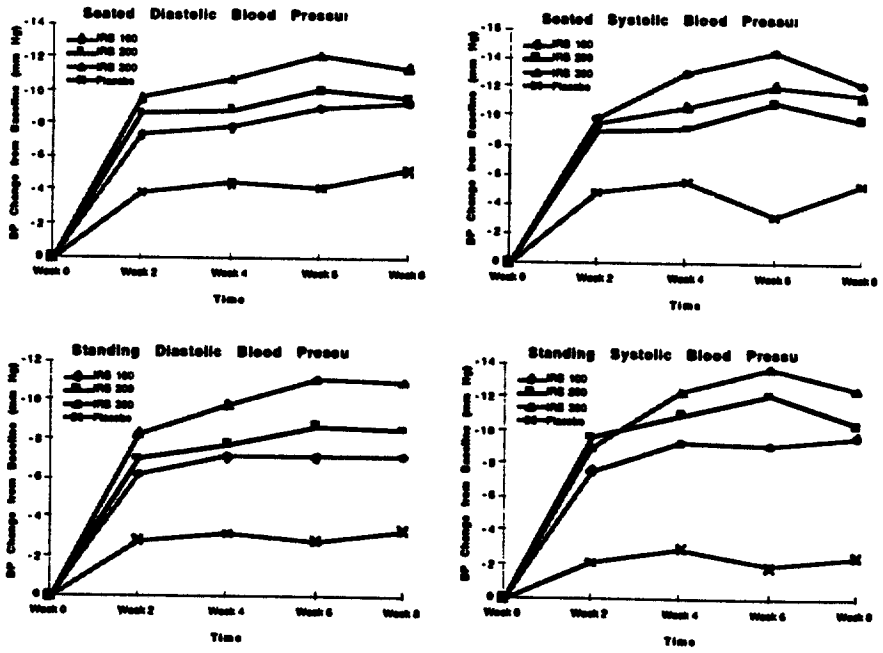

Figure 44. Time course of seated and standing blood pressure (CV131-025).

The response rate of irbesartan against placebo is given in Table 152 below.

Table 152. Response rate (CV131-025).

	Placebo N=73	Irbesartan 100 mg N=100	Irbesartan 200 mg N=75	Irbesartan 300 mg N=78
Normalized (%)*	23	44	41	60
Relative benefit (95%CI)**		2.0 (1.3, 3.3)	1.8 (1.1, 3.0)	2.7 (1.7, 4.2)
Total responders (%)***	30	56	55	67

*Normalized defined Trough SeDBP < 90 mmHg
**Proportion responders on drug / proportion responders placebo
***Total responders = normalized plus subjects with SeDBP decreased at least 10 mmHg from baseline.

Changes in peak seated diastolic and systolic blood pressures are given in Table 153 below.

Table 153. Changes in peak SeDBP and SeSBP (CV131-025).

	Peak seated diatolic				Peak seated systolic			
	Placebo N=73	Irbesartan 100 mg N=100	Irbesartan 200 mg N=75	Irbesartan 300 mg N=78	Placebo N=73	Irbesartan 100 mg N=100	Irbesartan 200 mg N=75	Irbesartan 300 mg N=78
Baseline (mean±SD)	100±4	100±4	101±4	100±4	151±13	147±14	150±13	148±12
Change from baseline	-6±1	-13±1	-13±1	-14±1	-5±2	-15±2	-15±2	-17±1
Difference from placebo		-7*	-7*	-8*		-10*	-10*	-12*

*p<0.01

The trough:peak ratios at week 8 for irbesartan 100, 200, and 300 mg in evaluable subjects with valid peak and trough measures were 0.58, 0.62, and 0.69 respectively.

Subjects entering the further two weeks study of hydrochlorothiazide numbered 143. Of these, 126 had data at the end of two weeks. The results, for SeDBP and SeSBP, are shown as changes from baseline or week 8 in Table 154 below.

Table 154. Antihypertensive effects with HCTZ at week 10 (CV131-025).

	Change from baseline (mean±SD)				Change from week 8 (mean±SD)			
	Placebo	Irbesartan 100 mg	Irbesartan 200 mg	Irbesartan 300 mg	Placebo	Irbesartan 100 mg	Irbesartan 200 mg	Irbesartan 300 mg
ΔSeDBP	-4.6±6.0	-8.4±6.8	-8.2±7.9	-13.1±6.4	-1.6±6.2	-2.9±7.3	-4.2±6.2	-7.7±7.9
ΔSeSBP	-4.7±11.6	-11.9±13.5	-12.3±12.5	-20.5±12.7	-0.3±10.0	-5.9±12.4	-7.5±9.6	-12.0±12.5

A13.5.2. Pharmacokinetics

Plasma irbesartan levels were not provided in the CANDA or in the hard copy submission. According to sponsor, there were mislabelling problems which prevented any meaningful analysis of the data.

A13.5.3. Safety

All 319 subjects randomized to therapy were included in the analysis. For these subjects, the sponsor's safety report focused on (1) extent of exposure, (2) deaths and discontinuations, (3) relative frequencies of clinical adverse events, (4) sponsor-defined markedly abnormal laboratory values, (5) investigator-defined abnormal laboratory values, and (6) changes in physical examination.

Most subjects (95% of 240 on irbesartan and 89% of 79 on placebo) completed the 10-week study. At the end of week 8, SeDBP was >90 mmHg in 143 subjects (47 on placebo, 34 on 100 mg, 39 on 200 mg, and 23 on 300 mg), and these subjects received hydrochlorothiazide 12.5 mg daily for an additional 2 weeks. All but 5 (3 on placebo, 1 on 100 mg, and 1 on 200 mg) of these received study drug plus HCTZ for at least 8 days of the final 2 weeks of the study.

A total of 4 subjects discontinued because of adverse events. Two subjects were randomized to irbesartan. One subject discontinued irbesartan 200 mg therapy after one day for worsening peripheral edema. The other subject discontinued irbesartan 200 mg after 8 days for a headache. Neither of these events was considered drug-related.

Two subjects randomized to irbesartan experienced serious adverse events. One subject was hospitalized for a renal calculus after 36 days of irbesartan 200 mg. The other subject was diagnosed with breast cancer after 6 weeks of irbesartan 100 mg therapy. Neither of these events was considered drug-related, and these subjects continued the trial to completion.

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most frequently reported adverse events were headache, musculoskeletal pain, fatigue, diarrhea and dizziness.

There were no clinically significant changes in physical exam findings.

Serum chemistry marked abnormalities were few.

Urinalysis showed an increase in urine WBCs with irbesartan therapy.

A13.6. Summary

In a conventional, 8-week, double-blind, parallel, placebo-controlled, fixed-dose trial design, irbesartan 100, 200, and 300 mg demonstrated a dose-related antihypertensive effect, irrespective of whether data from all randomized subjects were considered (intent-to-treat with last observation carried forward) or data from 'per protocol' subjects were assessed. Absence of a crossover design precluded information about individual dose-response relationships. Visual estimates of population dose-response based on graphs of mean response versus dose, irrespective of week of treatment, suggest that maximum effect occurs just above 300 mg, with a half-maximum effect at approximately 100 mg. Overall, between 40% and 70% of subjects with mild-to-moderate hypertension achieved control of their blood pressure (SeDPB <90 mmHg or reduction by 10 mmHg) with fixed doses of 100, 200, or 300 mg, with the highest percentage at the highest dose. Addition hydrochlorothiazide 12.5 mg resulted in additional antihypertensive effect. These observations suggest that 100 mg is a reasonable starting dose for most patients, followed at 2- to 4-week intervals, as necessary to achieve optimal blood pressure control, by an increment to 300 mg and then addition of hydrochlorothiazide 12.5 mg. Control of blood pressure during a 24-hour period appears to be reasonable: comparing peak to trough responses, irbesartan at any dose resulted in trough SeDPB values that averaged between approximately 60 to 70% of peak.

There were no deaths or serious adverse events to comment upon.

A14. CV131-027: Multicenter, randomized, double-blind comparison of irbesartan and atenolol for treatment of hypertension.

A14.1. Source documents

Study report: NDA 20-757, vol 1.306 to 1.312.

A14.2. Investigators

Multi-center study in Europe.

A14.3. Study dates

19 November1994 to 11 October 1995.

A14.4. Study design

This study description was based upon the protocol dated 22 November 1994. There were 4 protocol amendments prior to enrollment of the first subject. There were a total of five administrative changes. One administrative change, after the start of enrollment, excluded subjects with insulin-dependent diabetes mellitus subjects with HgA_{1C} >7.5%.

This is a randomized, double-blind, parallel group study in subjects with mild to moderate hypertension (95<SeDBP<110 mmHg and SeSBP≤200 mmHg) Figure 45 below shows a schematic of this trial. After a single-blind 4-week lead-in period, eligible subjects were to be randomized to irbesartan 75 mg or atenolol 50 mg. If the subject's SeDBP was >90 mmHg at 6 weeks, the dose was to be doubled. The subjects were followed for another 6-week period. After the initial 12 weeks, the subjects continued in a double-blind fashion for an additional 12 weeks. If the subject's SeDBP was >90 mmHg, the subject was to be titrated in the following sequence: (1) irbesartan 150 mg or atenolol 100 mg if the subject was not titrated at 6 weeks, (2) HCTZ up to 25 mg, and (3) sustained release nifedipine. The intent was to randomize approximately 90 subjects equally among the treatment groups for a total of 180 subjects.

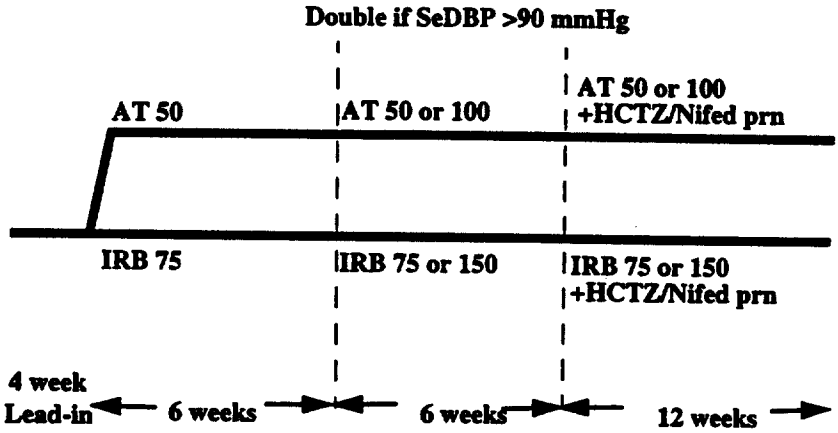

Figure 45. Study design (CV131-027).

Drug supplies are shown in Table 155 below.

Table 155. Drug supplies (CV131-027).

Dose	Lot	Dose	Lot	Dose	Lot	Dose	Lot	Dose	Lot
Placebo	L94F013C	Atenolol 50 mg	M94F034C M94M056C M95002	HCTZ 12.5 mg	M94G041C M95013	HCTZ 25 mg	M94G042C M94G044C M95014	Irbesartan 75 mg	L94J022C L94L031C

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage

except for mild funduscopic changes). Subject with significant renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values (with exception of mild increases in serum creatinine and urine protein) prior to randomization were excluded. Subjects who were taking the following agents were excluded (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilator, and (8) NSAIDs greater than 7 day duration (low dose ASA excepted). Subjects must have been able to wean antihypertensives and other vasoactive agents.

The primary efficacy variable in this study was the change in trough SeDBP from baseline (last single-blind placebo visit) to week 12 of double-blind treatment. Secondary end points are as follows: (1) trough SeDBP at 6 weeks, (2) safety and tolerability of irbesartan for 24 weeks, (3) the incidence and proportion of subjects reporting fatigue and/or weakness following 12 weeks of therapy, (4) changes in seated and standing heart rate at weeks 6, 12, and 24. The subjects' blood pressure during the double-blind period was measured at weeks 2, 6, 8, 12, 16, 20, and 24. Subjects were eligible for a long-term open label extension after completion of the double-blind period.

Intent-to-treat and per-protocol analyses were performed. Statistical significance was determined by analysis of covariance using baseline and center as covariates.

Safety assessments were done both in the single and double blinded period. Tests included ECG and laboratory tests (CBC, SMA20, urinalysis). Clinical adverse events and its relationship to the study drug were recorded.

A14.5. Results

There were 297 subjects enrolled. Disposition of enrolled subjects is shown in Table 156 below.

Table 156. Subject disposition (CV131-027).

Subject disposition	N
Enrolled	297
Not randomized	66
Randomized	231
Discontinued	31
Completed week 24	200
Completed week 12	209

Table 157 below shows reasons for exclusion prior to randomization.

Table 157. Reasons for exclusion (CV131-027).

Reason	N	Reason	N
Did not qualify	25	Lost to follow-up	1
Subject request	9	Concomitant medication	3
Adverse event	20	Poor compliance	1
Blood pressure elevated	6	Other	1
Total	66		

Table 158 below gives the reasons for discontinuations from study medication in the double-blind period.

Table 158. Reasons for discontinuation (CV131-027).

	Irbesartan N=110	Atenolol N=121		Irbesartan N=110	Atenolol N=121
Adverse Event	5	11	Lost to Follow-up	1	0
Poor Compliance	1	1	Subject Request	1	3
Other	5	3			
Discontinued	13	18			
Completed	97	103			

There were a total of 123 protocol deviations (7 subjects all visits, 116 visits). These were excluded from the secondary dataset but were included in the primary (ITT) dataset.

Demographics of the two treatment groups are shown in Table 159 below.

Table 159. Demographics (CV131-027).

		Atenolol N=121	Irbesartan N=110			Atenolol N=121	Irbesartan N=110
Gender	Male (%)	55	62	Age	Mean±SD	56±9	55±12
	Female (%)	45	38		Min, max	29, 80	29, 82
Race	White (%)	100	100		≥65 years (%)	18	23
					≥75 years (%)	1	6*

*P<0.05

A14.5.1. Pharmacodynamics

There was no statistical relationship between baseline seated blood pressure (at last visit before randomization) or heart rate for any of the treatment groups (see Table 160 below). There were site interactions among some of the baseline variables.

Table 160. Baseline vital signs (CV131-027).

	Irbesartan N=110	Atenolol N=121		Irbesartan N=110	Atenolol N=121
SeDBP (mean±SD)	102±4	101±4	StDBP (mean±SD)	104±6	104±6
≥104 mm Hg (%)	31	21			
SeSBP (mean±SD)	158±16	158±13	StSBP (mean±SD)	157±16	157±15
SeHR (mean±SD)	76±9	72±9	StHR (mean±SD)	80±10	77±10

Analysis of seated and standing blood pressure using the intent-to-treat dataset is given in Table 161 below. There was no significant difference between treatment groups in seated or standing heart rate. Trough SeDBP and SeSBP mean change showed no significant difference between male and female subjects. Trough SeDBP mean change showed similar response of seated diastolic blood pressures between subjects aged <65 and >65.

Table 161. Mean change in baseline blood pressure at week 12 (CV131-027).

	SeDBP		SeSBP		StDBP		StSBP	
	Atenolol N=121	Irbesartan N=110	Atenolol N=121	Irbesartan N=110	Atenolol N=121	Irbesartan N=110	Atenolol N=121	Irbesartan N=110
All (mean±SE)	-12±1	-12±1	-13±2	-15±1	-11±1	-11±1	-11±1	-13±1
Male (mean±SD)	-10±8	-12±6	-11±16	-16±11				
Female (mean±SD)	-13±7	-13±7	-15±13	-13±15				
<65 years (mean±SD)	-11±8	-12±6	-14±15	-14±11				
≥65 years (mean±SD)	-11±6	-12±8	-9±16	-19±19				

Seated and standing blood pressures as a function of time is given in Figure 46 below.

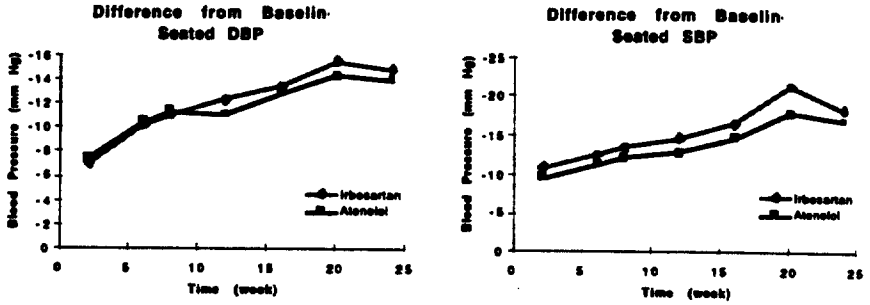

Figure 46. Placebo-subtracted blood pressure changes (CV131-027).

A summary table of therapeutic response provided by the sponsor is shown in Table 162 below.

Table 162. Therapeutic response rate (CV131-027).

	Irbesartan N=110	Atenolol N=121
Normalized (%)*	61	55
Relative benefit (95%CI)**		1.0 (0.83, 1.41)
Total responders (%)***	72	63

*Normalized defined as trough SeDBP <90 mmHg
**Proportion of responders on drug / proportion of responders on placebo
***Total responders = subjects normalized plus subjects not normalized but with SeDBP decreased at least 10 mmHg from baseline.

There was no significant difference between irbesartan and atenolol with respect to the percentage (50%) of subjects that required up-titration at week 6.

A14.5.2. Safety

There was a mean exposure of the study drug of approximately 173 days.

No deaths occurred during the double-blind period of the study.

There were 13 dropouts on irbesartan therapy. Of those, five were a result of adverse events. Table 163 below describes adverse events during the double-blind period.

Two subjects on irbesartan experienced a serious adverse event. Both were hospitalized for postmenopausal bleeding which required dilation and curettage.

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events were headache, dizziness, fatigue, musculoskeletal pain and upper respiratory infection.

Table 163. Discontinuations for adverse events (CV131-027).

Group	Days	Adverse Event	Group	Days	Adverse Event
Irbesartan	117	Headache/dyspnea/fatigue	Irbesartan	56	Headache
Irbesartan	21	Sexual dysfunction	Irbesartan	32	Abdominal pain
Irbesartan	3	Weakness/fatigue/headache			

A secondary objective of the protocol was to compare malaise, fatigue and weakness at week 12 between atenolol and irbesartan. The data were obtained through open-ended questioning, and a symptom checklist. The results were placed on the case-report form. Three percent (3/110) of subjects experienced these symptoms on irbesartan, as compared to 8.3% (10/121) on atenolol. The difference was significant at the level of 0.08.

Marked hematologic abnormalities observed on irbesartan were thrombocytopenia, leukophilia and eosinophilia. Marked serum abnormalities included increases in BUN, creatinine, sodium and potassium. All abnormalities happened to <2% of subjects on irbesartan.

No significant changes in physical exam or ECG were noted.

A14.6. Summary

The current study demonstrates that the antihypertensive effect of irbesartan 75 or 150 mg is roughly comparable to that of atenolol 50 or 100 mg. There was no placebo control arm in this study. This makes the interpretation of subgroup differences difficult, since the magnitude and variance of the placebo effect differs greatly among certain subgroups, especially among the elderly. The sponsor compared irbesartan and atenolol and found that subjects on irbesartan experienced less fatigue, weakness, and malaise at Week 12. If all treatment-emergent events throughout the trial were included, there was no significant difference between irbesartan (10%; 11/110) and atenolol (10.7%; 13/121).

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A15. CV131-028: Multicenter, randomized, double-blind comparison of irbesartan and enalapril for treatment of hypertension.

A15.1. Source documents

Study report: NDA 20-757, vol 1.313 to 1.317.

A15.2. Investigators

Multi-center study (49 centers in France and 2 in Spain).

A15.3. Study dates

01 December 1994 to 20 July 1995.

A15.4. Study design

This study description was based upon the protocol dated 30 August 1994. There were 3 protocol amendments prior to enrollment of the first subject. There were a total of 11 administrative changes.

This is a randomized, double-blind, parallel group study in subjects with mild to moderate hypertension (95 < SeDBP <110 mmHg and SeSBP ≤200 mmHg) Figure 47 below shows a schematic of this trial. After a single blind 4-week lead-in period, eligible subjects were randomized to either irbesartan 75 mg or enalapril 10 mg. If the subject's SeDBP was >90 at the end of 4 or 8 weeks, the dose was doubled. The intent was to randomize approximately 90 subjects equally between the treatment groups for a total of 180 subjects.

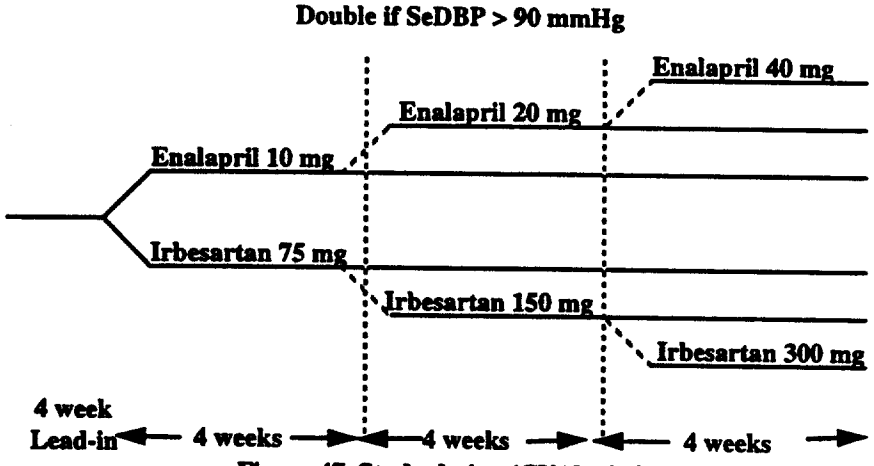

Figure 47. Study design (CV131-028).

Drug supplies are shown in Table 164 below.

Table 164. Drug supplies (CV131-028).

	Lot				
Placebo	L94F013C	Enalapril 10 mg	M94F035C M95001	Irbesartan 75 mg	L94J022C

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Subjects with significant renovascular disease, cardiovascular disease, diabetes, CHF, or collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values (with exception of mild increases in serum creatinine and urine protein) prior to randomization were excluded. Subjects who were taking the following agents were excluded (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis; (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilators, or (8) NSAIDs greater than 7 day

duration (low dose ASA excepted). Subjects must have been able to wean antihypertensives and other vasoactive agents.

The primary efficacy variable in this study was the change from baseline in trough SeDBP at week 12 of double-blind treatment. Secondary end points are as follows: (1) trough SeDBP at 4 and 8 weeks, (2) safety and tolerability of irbesartan for 12 weeks. Blood pressure was measured at weeks 2, 4, 8, and 12. Subjects were eligible for a long-term open-label extension after completion of the double-blind period.

The datasets used for the primary and secondary analyses were intent-to-treat (primary data set) and one which excludes protocol violations (secondary dataset). Statistical significance was determined by analysis of covariance using baseline and center as covariates.

Safety assessments were done both in the single and double blinded period. Tests included ECG and laboratory tests (CBC, SMA20, urinalysis). Clinical adverse events and their relationship to the study drug were recorded.

A15.5. Results

There were 232 subjects enrolled. Disposition of enrolled subjects is shown in Table 165 below.

Table 165. Subject disposition (CV131-028).

	N
Enrolled	232
Not randomized	30
Randomized	202
Discontinued	9
Completed Week 12	191
Available Week 12	193
Included Week 12	191*

*Subjects from Center 55 were excluded secondary to irregularities in CRF data.

Table 166 below shows reasons for exclusion prior to randomization.

Table 166. Reasons for exclusion (CV131-028).

Reason	N		
Did not qualify	4	Need for concomitant medication	4
Subject request	6	Other	10
Adverse event	5		
Total	29		

Table 167 below gives the reasons for discontinuations from study medication in the double-blind period.

There were 18 randomized subjects who had protocol violations which would effect all efficacy measurements and 6 subjects with violations that would affect efficacy measurements at week 12. These were excluded from the secondary dataset but were included in the primary (ITT) dataset.

Demographics of the two treatment groups are shown in Table 168 below.

Table 167. Reasons for discontinuation (CV131-028).

	Enalapril N=102	Irbesartan N=98
Adverse event	3	1
Lost to follow-up	2	0
Subject request	1	2
Completed	96	95

Table 168. Demographics (CV131-028).

		Enalapril N=102	Irbesartan N=98			Enalapril N=102	Irbesartan N=98
Gender	Male (%)	49	54	Age	(mean±SD)	58±11	58±12
	Female (%)	51	46		Min, max	26, 83	34, 88
Race	White (%)	100	99		≥65 (%)	30	28
					≥75 (%)	6	9

A15.5.1. Pharmacodynamics

There was no statistical relationship between baseline seated blood pressure (at last visit before randomization) or heart rate for any of the treatment groups (see Table 169 below).

Table 169. Baseline blood pressure and heart rate (CV131-028).

	Seated		Standing	
	Enalapril N=102	Irbesartan N=98	Enalapril N=102	Irbesartan N=98
DBP (mean±SD)	102±4	101±4	101±5	101±5
SBP (mean±SD)	165±13	164±13	162±13	161±12
HR (mean±SD)	74±9	74±10	76±10	76±10

Analysis of seated and standing blood pressure using the intent-to-treat dataset is given in Table 170 below. There was a significant treatment-by-site interaction for SeDBP, SeSBP and StSBP at week 12. According to the sponsor, this was due to a large treatment difference at center 15 and a large increase in SeSBP for one subject at site 20. If that data is excluded, the interactions are no longer significant. There was no significant difference in seated or standing heart rate between the two groups. Trough SeDBP and SeSBP mean change showed no significant difference between male and female subjects. Trough SeDBP mean change showed similar response of seated diastolic blood pressures between subjects aged <65 and >65.

Table 170. Change in blood pressure at week 12 (CV131-028).

	Enalapril N=102	Irbesartan N=98		Enalapril N=102	Irbesartan N=98
SeDBP (mean±SE)	-14±1	-13±1	SeSBP (mean±SE)	-18±2	-19±2
Male (mean±SD)	-14±7	-13±8	Male (mean±SD)	-20±11	-19±11
Female (mean±SD)	-14±8	-12±8	Female (mean±SD)	-19±16	-21±13
Age <65 years (mean±SD)	-14±7	-13±8	Age <65 years (mean±SD)	-20±12	-19±12
Age ≥65 years (mean±SD)	-14±8	-12±6	Age ≥65 years (mean±SD)	-18±16	-21±13
StDBP (mean±SD)	-12±8	-12±8	StSBP (mean±SD)	-17±13	-18±11

Seated and standing blood pressures as a function of time is given in Figure 48 below.

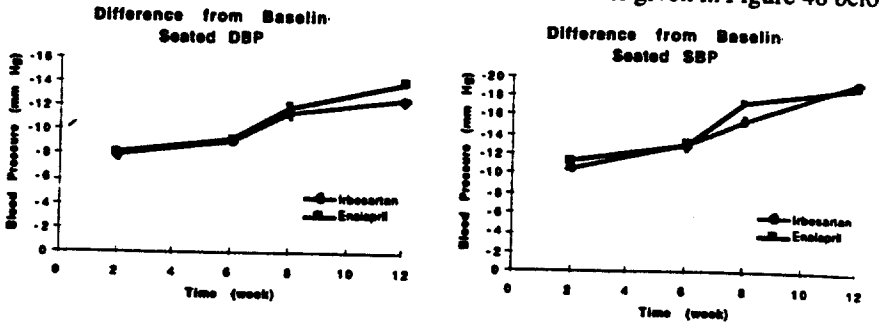

Figure 48. Placebo-subtracted blood pressure (CV131-028).

A summary table of therapeutic response provided by the sponsor is shown in Table 171 below.

Table 171. Response rate (CV131-028).

	Enalapril N=102	Irbesartan N=98
Normalized (%)*	63	66
Relative benefit (95%CI)**	1.0 (0.82, 1.33)	
Total responders (%)***	85	74
Relative Benefit (95%CI)		0.84 (0.7, 1.0)

*Normalized defined Trough SeDBP < 90 mmHg
**Proportion responders on drug / proportion responders placebo
***Total responders = normalized plus subjects with SeDBP decreased at least 10 mmHg from baseline.

There was no significant difference between irbesartan and enalapril with respect to the percentage of subjects that were up-titrated at week 8 and at week 12.

A15.5.2. Safety

There was a mean exposure of the study drug of approximately 84 days.

No deaths occurred during the double-blind period of the study.

There were 3 dropouts on irbesartan therapy. Of those, one was a result of an adverse event. The subject had a hypertensive crisis after 69 days of irbesartan treatment despite titration to 300 mg. The subject's mean seated blood pressure was 252/153 mmHg and he was symptomatic. The event resolved after treatment with vasodilator and diuretic therapy.

Four subjects on irbesartan experienced a serious adverse event. Three subjects had procedures (one knee arthroscopy and two urologic procedures). The fourth had chest pain after 59 days on irbesartan. Cardiac work-up, including a stress test, was normal.

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events associated with irbesartan were headache, cough, and upper respiratory infection.

There were no significant marked hematologic abnormalities in irbesartan subjects. Marked serum abnormalities included increases in BUN, creatinine and potassium. All abnormalities happened in <3% of subjects on irbesartan.

No significant changes in physical exam or ECG were noted.

A15.6. Summary

The current study demonstrates that the antihypertensive effect of irbesartan 75/150/300 mg is roughly comparable to enalapril 10/20/40 mg. Titrating enalapril and irbesartan have similar effects in reducing seated diastolic blood pressure in those subjects who normalize (<90 mm Hg). However, total responders are reduced with irbesartan therapy compared to enalapril. Thus, in the difficult-to-control hypertensive patient, irbesartan may have limited benefit as single therapy.

A16. CV131-029: Multicenter, randomized, double-blind, placebo-controlled trial of irbesartan for treatment of hypertension.

A16.1. Source documents

Study report: NDA 20-757, vol 1.277 to 1.282, Electronic document MAST029.PDF, CRF

A16.2. Investigators

This study was conducted at 27 sites in the US and Canada.

A16.3. Study dates

03 November 1994 to 19 May 1995.

A16.4. Study design

This study description was based upon the protocol dated 26 August 1994. Except for administrative changes, there were no amendments written after the start of enrollment. The administrative changes did not effect the reliability of the study.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (95 < SeDBP <110 mmHg). Figure 49 below shows a schematic of this trial. After a 4 to 5 week lead-in period, eligible subjects were randomized to either irbesartan 75 or 150 mg or placebo for 6 weeks. If the subject's SeDBP >90 at the end of 6 weeks, the dose was doubled. The subjects were followed for an additional 6-week period. The intent was to randomize approximately 100 subjects equally among the treatment groups for a total of 300 subjects. The total double-blind period was 12 weeks. Completing subjects were eligible for open enrollment.

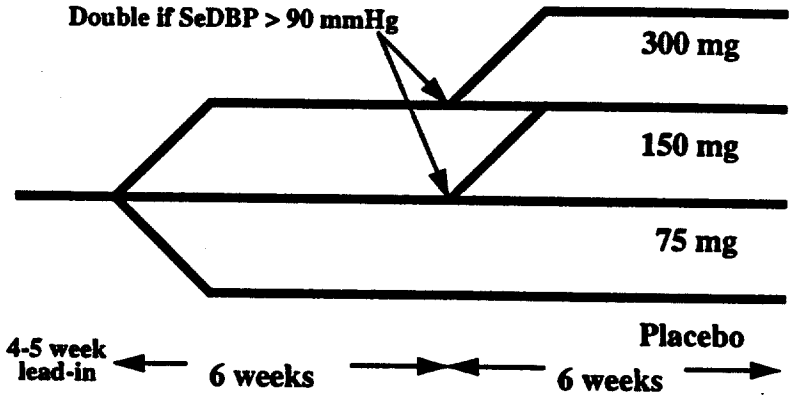

Figure 49. Study design (CV131-029).

Drug supplies are shown in Table 172 below.

Table 172. Drug supplies (CV131-029).

	Product code	Lot		Product code	Lot
Placebo	186295-R000-030	N94F090C	50 mg	186295-R050-032	N94G096C
25 mg	186295-R025-031	N94F095C	100 mg	186295-R100-033	N94G099C

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Untreated SeDBP was to have been between 95 and 110 mmHg in order to be randomized. Subject with renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were to be excluded. Subjects who were taking the following agents were excluded (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with

exception of low dose estrogen replacement therapy, (7) bronchodilators, and (8) NSAIDs for greater than 7 day duration (low dose ASA excepted). Subjects were to have been able to wean antihypertensives and other vasoactive agents.

The primary efficacy variable in this study was the change from baseline to week 12 in trough SeDBP. Secondary end points were as follows: (1) trough SeDBP at 6 weeks, (2) trough StDBP at 6 and 12 weeks, (3) trough SeSBP and StSBP at 6 and 12 weeks, (4) trough-peak ratio of seated and standing DBP and SBP at 6 and 12 weeks (peak measured 3 hours after ingestion), and (5) degree of therapeutic response at 6 and 12 weeks. The subjects' blood pressure was measured at week 2, 6, 8, and 12 after randomization.

Statistical analysis on the primary efficacy variable was by analysis of covariance (ANCOVA) model in which treatment, site, and baseline were covariates. Since the randomization algorithm did not maintain a 1:1:1 randomization at each site throughout the trial, additional ANCOVA was carried out in which treatment was the main factor and baseline blood pressure and other covariates were related to hypertension.

Safety assessments were done both in the single- and double-blinded period. Tests included ECG and laboratory tests (CBC, SMA20, urinalysis). Clinical adverse events and their relationship to the study drug were recorded.

A16.5. Results

There were 478 subjects enrolled. Disposition of enrolled subjects is shown in Table 173 below.

Table 173. Subject disposition (CV131-029).

	N
Enrolled	478
Not Randomized	159
Randomized	319
Discontinued	37
Completed	282
Evaluable Subjects Week 12	284

Table 174 below shows reasons for exclusion prior to randomization.

Table 174. Reasons for exclusion (CV131-029).

	N		N
Did not qualify	94	Unknown	3
Subject request	27	Concomitant medication	2
Adverse event	11	Investigator request	1
Blood pressure above limit	12	Other	5
Lost to follow-up	4		
Total	159		

Table 175 below gives the reasons for discontinuations from study medication in the double-blind period.

There were a total of 27 significant protocol deviations. Of those, there were 11 protocol violations which could affect the trough SeDBP. The reasons for the protocol deviations are given in Table 176 below.

Table 175. Reasons for discontinuation (CV131-029).

	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98		Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
Adverse event	5	1	5	Lost to follow-up	0	1	0
BP above limit	4	2	0	Poor compliance	1	1	0
BP high in investigator's opinion	0	0	1	Protocol violation	0	0	1
Death	0	0	1	Sponsor request	0	0	1
Did not qualify	1	0	1	Subject request	4	1	3
Lack of efficacy	2	0	0	Physician request	1	0	0
Subjects completed	99	98	85				

Table 176. Protocol deviations (CV131-029).

	Significant protocol deviations by week			
	2	4	6	8
Titration error before visit	0	1	1	0
High dose aspirin within 4 days of visit	0	0	0	1
Time since last dose <21 or >24 hours or missing	0	0	0	2
Poor compliance	1	0	0	0
Prohibitive meds within 4 days of visit	1	1	1	0
No titration at week 6 despite SeDBP>90 mmHg	0	0	1	1
Total	2	2	3	4

Demographics of the two treatment groups are shown in Table 177 below.

Table 177. Demographics (CV131-029).

		Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98			Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
Gender	Male (%)	68	68	63	Age	Mean±SD	53±11	53±11	53±11
	Female (%)	32	32	37		Min, Max	23, 78	30, 77	22, 74
Race	White (%)	85	91	88		≥65 years (%)	16	16	19
	Black (%)	10	4	9		≥75 years (%)	4	2	0
	Other N(%)	5	5	3					

There were no significant differences among treatment groups with respect to baseline values of seated blood pressure or heart rate (see Table 178 below).

Table 178. Seated baseline blood pressure and heart rate (CV131-029).

	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98		Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
DBP (mean±SD)	100±4	101±4	100±4	SBP (mean±SD)	148±14	149±14	148±13
>104 mmHg (%)	20	26	18	HR (mean±SD)	72±9	73±10	72±8

A16.5.1. Pharmacodynamics

The sponsors primary efficacy analyses included mean changes in trough SeDBP at weeks 2, 6, and 12 and for last observation carried forward (LOCF). There was a statistical change made from the original protocol on the primary efficacy variable. The analysis of the primary efficacy variable would be done using analysis of covariance with baseline as the only covariate. Because the randomization algorithm did not maintain a 1:1:1 randomization at each site was added to the model. Though this is a change from the original protocol, the correction is prudent to do. These results are tabulated in Table 179 below. The LOCF analysis included 32/37 dropouts after randomization. There were no statistically significant differences among groups with respect to changes in seated or standing heart rate at trough.

Table 179. Changes (mean±SE) in trough blood pressure (CV131-029).

	Seated diastolic			Seated systolic		
	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
Week 2	-3.4±0.6	-7.0±0.7*	-7.6 ±0.7*	-2.2±1.0	-7.5±1.1*	-9.4 ±1.2*
Week 6	-2.4 ±0.6	-7.4 ±0.6*	-8.3±0.7*	-1.3 ±1.1	-10.2 ±1.2*	-9.0±1.2*
Week 12	-4.2±0.8	-8.3±0.8*	-10.5±0.8*	-1.9±1.3	-9.4±1.3*	-12.6±1.4*
LOCF	-4.0±0.7	-8.3±0.1*	-10.1±0.8*	2.0±1.2	-9.6±1.3*	-12.9±1.3*

*P<0.01

As shown in Table 180 below, there was a similar significant treatment effect on peak vital signs compared to placebo (evaluable subjects with valid data).

Table 180. Changes (mean±SD) in peak blood pressure (CV131-029).

	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98		Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
Peak SeDBP, mmHg				Peak SeSBP, mmHg			
Baseline	100±4	100±4	99±4	Baseline	146±13	150±14	147±12
Change from baseline	-7±1	-14±1	-15±1	Change from baseline	-3±1	-15±1	-18±1
Difference from placebo		-7*	-8*	Difference from placebo		-12*	-15*

*P<0.01

The T:P ratio was calculated for subjects with valid data at 6 and 12 weeks post randomization. At week 6, the ratio was about 70% for both the 75- and 150-mg groups. By actual dose at week 12, the T:P ratios were 53% at 75 mg, 55% at 150 mg, and 75% at 300 mg.

Changes in trough SeDBP and SeSBP at week 12 showed no significant difference between male and female subjects.

Changes in trough SeDBP and SeSBP at week 12 showed smaller reductions in the black population. However, since there were only 14 black subjects who completed the study, any conclusion from the data is problematic.

Changes in trough SeDBP and SeSBP at week 12 showed no significant differences between subjects aged <65 than >65. However, since there were relatively few older subjects in each treatment group, the power is not adequate enough to draw any conclusions based on the data provided.

A summary of the sponsor's analysis of response rate is shown in Table 181 below.

Table 181. Response rate (CV131-029).

	Placebo N=117	Irbesartan 75 mg N=104	Irbesartan 150 mg N=98
Normalized (%)*	24	38	53
Relative benefit (95%CI)**		1.6 (1.0, 2.4)	2.4 (1.6, 3.4)
P-value		0.042	<0.01
Total responders (%)***	26	47	59

*Normalized defined as trough SeDBP <90 mmHg
**Proportion responders on drug / proportion responders on placebo
***Subjects normalized or with SeDBP decreased by10 mmHg.

Trough SeDBP was analyzed for subgroups of subjects who were titrated to a higher dose or not. Table 182 below gives these values for weeks 8 and 12. About 11% of placebo subjects did not require titration, suggesting they were probably not truly hypertensive.

Table 182. Trough SeBP for subjects titrated versus not titrated (CV131-029).

	Placebo		Irbesartan 75 mg		Irbesartan 150 mg	
	Not Titrated	Titrated	Not Titrated	Titrated to 150	Not Titrated	Titrated to 300
Week 8						
DBP	-15.1	-3.5	-12.8	-7.7	-11.1	-9.2
SBP	-14.5	0.1	-14.6	-10.0	-14.3	-9.2
Week 12						
DBP	-14.7	-3.3	-12.0	-7.0	-10.8	-9.6
SBP	-13.4	-0.2	-10.6	-8.5	-13.0	-10.9

The effect of titration on changes from baseline are given in Table 183 below.

Table 183. Effect of titration on changes from baseline trough SeBP (CV131-029).

	Trough SeDBP (mmHg)			Trough SeSBP (mmHg)		
	Placebo	75 to 150 mg	150 to 300 mg	Placebo	75 to 150 mg	150 to 300 mg
% Titrated*	89%	65%	53%	89%	65%	53%
Baseline (mean±SD)	100±4	102±4	101±4	146±13	151±14	150±12
Week 6 (mean±SD)	-2±8	-3±7	-6±11	-1±12	0±11	-6±11
Week 12 (mean±SD)	-3±7	-7±7	-11±12	0±12	-9±15	-11±11

*% based on all subjects with Week 12 data.

A16.5.2. Safety

There was a mean exposure of the study drug of approximately 80 days. Of the 202 subjects randomized to irbesartan, 1 (0.5%) died during the double-blind phase. Subject 026/014, a 74 year old white male who received irbesartan 150 mg for 40 days, suffered a cardiac arrest at home. Resuscitation attempts by neighbors and by emergency room personnel were unsuccessful and the cause of death was reported as cardiorespiratory arrest and myocardial infarction. The Investigator judged the events, resulting in death, as unlikely/unrelated to study medication.

There were 11 dropouts in the 12-week blind period. Five were on placebo medication. Table 184 below shows treatment duration and adverse events of the irbesartan subjects.

Table 184. Discontinuations due to adverse events during double-blind period (CV131-029).

Days	Dose (mg)	Adverse event	Days	Dose (mg)	Adverse event
1	150	Abdominal pain/ weight loss	17	150	Allergic reaction
8	150	Headache	8	150	Myocardial infarction
49	150	Anxiety/nervousness	1	75	Abnormality urinating

Ten (3.1%) of the 319 randomized subjects experienced a total of 17 serious adverse events. Of these 10 randomized subjects, 5 (2.5%) irbesartan-treated subjects experienced 7 serious adverse events and 5 (4.3%) placebo-treated subjects experienced 10 serious adverse events. Table 185 below shows serious adverse events on irbesartan.

Table 185. Serious adverse events during double-blind period (CV131-029).

Days	Dose (mg)	Adverse event	Days	Dose (mg)	Adverse event
45	150	Intervertebral disk Orthopedic surgery	40	150	Myocardial infarction Death
73	150	Abnormal brain MRI	8	150	Myocardial infarction
17	150	Allergic reaction			

Treatment-emergent adverse events will be discussed in the integrated review of safety. The most common treatment-emergent adverse events were musculoskeletal pain, headache, upper respiratory infection, and fatigue.

Marked hematologic abnormalities included transient lymphopenia in 3 subjects. Thrombocytopenia was found in one subject on irbesartan compared to none on placebo.

There was an increased incidence of increased triglyceridemia (7:0 drug:placebo) and creatine kinase (3:0 drug:placebo) with irbesartan. The abnormality in triglycerides was quite large (about 250 to 600% of baseline values). The values were taken in subjects who were "supposedly fasting."

No significant changes in physical exam or ECG were noted.

A16.6. Summary

The current study demonstrates that irbesartan 75 or 150 mg and 150 or 300 mg is efficacious in reducing trough SeDBP and SeSBP. There was no change in seated heart rate. The data support 75 mg as an effective starting dose. Trough:peak data are difficult to interpret where there was an opportunity to titrate for effect.

There were two myocardial infarctions, one resulting in death. Other safety concerns included an increase in triglycerides (which may have been due to subjects not fasting prior to the measurements) and transient lymphopenia.

A17. CV131-030: The antihypertensive activity of irbesartan as determined by 24-hour ambulatory blood pressure monitoring.

A17.1. Source documents

Study report: NDA 20-757, vol 1.283 to 1.287; electronic document MAST030.PDF.

A17.2. Investigators

This study was conducted at 16 sites in Italy.

A17.3. Study dates

21 March 1995 to 22 December 1995.

A17.4. Study design

This study description was based upon the protocol dated 7 November 1994. There were no amendments written after the start of enrollment. However, there were statistical changes made after the protocol was completed. The majority of changes were made prior to unblinding of the data.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (95 < SeDBP <110 mmHg). Figure 50 below shows a schematic of this trial. After a 4- to 5-week lead-in period, an ambulatory blood pressure monitor (APBM) was to be placed if the subject's seated diastolic blood pressure (SeDBP) was between 95 and 110 mmHg on the last 2 successive visits. A 24-hour baseline ambulatory blood pressure record was to be obtained. Readings were to be taken every 15 minutes during waking hours and every 20 minutes during sleep. If the average hourly diastolic blood pressure over the 24 hour period was greater than 85 mmHg (after checking for the adequacy of the data obtained) the patient was to be randomized either to placebo or irbesartan 75mg qd, 150 mg qd, or 75 mg bid. There were routine visits at 2 weeks and 4 weeks. At week 8, a final 24-hour APBM record was to be obtained after ingestion of study drug.

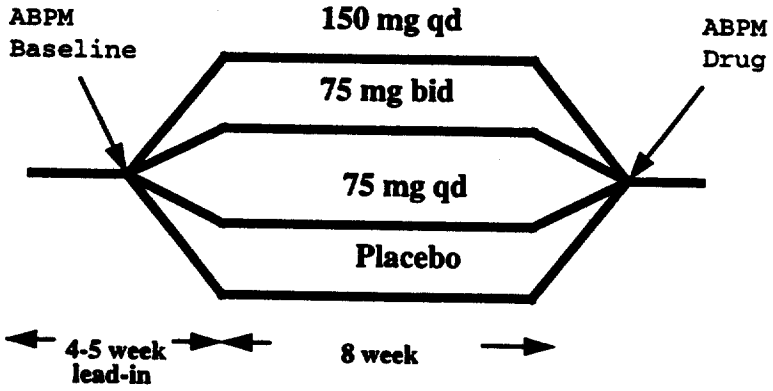

Figure 50. Study design (CV131-030).

Drug supplies are shown in Table 186 below.

Table 186. Drug supplies (CV131-030).

	Product Code	Lot		Product Code	Lot
Placebo	186295-R000-030	N94F090C	75 mg	186295-R075-054	L94F014C

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Subjects with renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded. If seated systolic blood pressure (SeSBP) was greater than 200 mmHg, the subject was to be excluded. Subjects who were taking the following agents were to be

excluded: (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilators, and (8) NSAIDs greater than 7-day duration (low dose ASA excepted). Subjects must have been able to wean other antihypertensives and vasoactive agents.

The primary efficacy variable in this study was the change from baseline in hourly-averaged APBM data over a 24-hour period after the ingestion of study drug. Secondary end points were as follows: (1) the reduction in trough (i.e., 24 ± 3 hours after the previous day's morning dose) office seated diastolic blood pressure, (2) the reduction in the mean daytime blood pressure (i.e. the first 12 hours after the morning dose), (3) the reduction in the mean 24-hour and daytime ambulatory systolic BP, (4) the trough:peak ratios of ambulatory blood pressure (ABP) reduction and the ABP reduction during the 24th hour after the morning dose, (5) the reduction at week 8 in trough office seated systolic blood pressure and standing systolic and diastolic BP, (6) the proportions of subjects whose office SeDBP was normalized (decreased to <90 mmHg) or responds (decreased by 10 mmHg), and (7) safety and tolerability compared with placebo.

According to the original protocol, sample size calculation of 50 per group was based on 90% power to detect a difference with standard deviation of 4.6 and 7.0 mmHg respectively (α=0.05). Changes in blood pressure from baseline would be compared between treatments using analysis of covariance (ANCOVA) with the baseline value as a covariate. Statistical significance was assessed using Dunnett's procedure to compare the 3 active treatment groups with placebo. In contrast, the final study report states that the study was powered to detect a difference of 5.1 mmHg, after corrections for multiplicity. Changes from baseline within each treatment group for each variable were tested with paired t-tests. Study sites were pooled if the site did not have subjects in all the treatment groups.

In the original protocol, any hours with missing values were to be interpolated from the preceding and following hours. The final study report states that missing hourly averages were ignored.

Subjects who discontinued early were to go through the schedule of events at week 8 including ABPM.

Irbesartan trough blood levels were obtained at Week 8 at selected sites. Correlation coefficients between trough blood levels and efficacy end points at Week 8 were calculated by Spearman's method.

Safety assessments were done both in the single and double blinded period. Tests included were ECG, laboratory tests (CBC, SMA20, urinalysis), and physical examination. Clinical adverse events and their relationship to the study drug were to be recorded.

A17.5. Results

There were 294 subjects enrolled. Disposition of enrolled subjects is shown in Table 187 below. One subject did not have a final ABPM or office assessment at week 8.

Table 187. Subject disposition (CV131-030).

	N
Enrolled	294
Not randomized	79
Randomized	215
Discontinued	13
Completed	202
Evaluable subjects week 12*	201

Table 188 below shows reasons for exclusion prior to randomization.

Table 188. Reasons for exclusion (CV131-030).

	N		N
Did not qualify	42	Lost to follow-up	3
Subject request	23	Concomitant medication	1
Adverse event	1	Other	4
Blood pressure above limit	5		
Total	79		

Table 189 below gives the reasons for discontinuations from study medication in the double-blind period. Also noted are the number of final ABPM records available for analysis.

Table 189. Reasons for discontinuation (CV131-030).

	Placebo N=50	Irbesartan		
		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57
Adverse Event # with final ABPM	2 1	1 1	2 1	0 0
BP↑ above limit # with final ABPM	3 2	1 1	2 1	0 0
Subject request # with final ABPM	0 0	0 0	2 1	0 0
Subjects completed	45	53	47	57

There were a total of 23 significant protocol deviations. Of those, there were 19 protocol violations in 10 subjects which could affect the primary efficacy variable. Of the 10 subjects, 6 were discontinued. The number of protocol violations per subject are given in Table 190 below.

Table 190. Protocol violations (CV131-030).

Site - Subject	Treatment	Violations	Discont'd	Reason for discontinuations	Site - Subject	Treatment	Violations	Discont'd	Reason for discontinuations
3-15	IRB 150	2	Y	Subject Req.	10-7	Placebo	1	Y	Adverse Event
3-16	IRB 75 qd	1	N	N/A	10-24	Placebo	1	Y	BP above limit
5-2	IRB 75 bid	1	N	N/A	12-6	IRB 75 bid	2	N	N/A
5-5	IRB150	5	Y	Adverse Event	12-9	IRB 75 bid	1	N	N/A
6-36	Placebo	2	Y	BP above limit	13-6	IRB 150	3	Y	Adverse Event

Demographics of the 4 treatment groups are shown in Table 191 below. There were no significant differences among the groups in terms of gender, race, or age. The majority of subjects were male.

There were no significant differences among groups with respect to baseline ABPM (Table 192 below) or office vital signs (Table 193 below).

Table 191. Demographics (CV131-030).

		Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57
Gender	Male (%)	72	67	60	63
	Female (%)	28	33	40	37
Race	White (%)	100	100	100	100
Age	Mean±SD	53±11	57±11	55±11	54±11
	Min, max	30, 75	30, 78	35, 79	29, 73
	≥65 (%)	18	18	21	18
	≥75 (%)	2	2	4	0

Table 192. Baseline ABPM (CV131-030).

	DBP (mean±SD)				SBP (mean±SD)			
	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57
(mean±SD)	91±7	91±7	91±6	91±7	145±13	144±11	143±10	144±13
Male	92±8	93±8	92±7	92±8	146±13	143±11	140±9	144±14
Female	89±4	89±5	89±3	89±4	143±12	144±12	145±9	145±11
Daytime	97±8	96±7	95±6	95±7	151±13	149±11	148±11	149±13
Trough	97±9	98±9	97±9	97±10	151±15	150±15	149±14	150±17

Table 193. Baseline cuff blood pressure and heart r (CV131-030).

	Seated				Standing			
	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57
DBP (mean±SD)	102±5	101±5	101±5	101±5	103±5	104±6	103±6	103±3
>104 mmHg (%)	30	28	28	27				
SBP (mean±SD)	158±13	157±14	159±14	156±13	157±12	157±14	159±16	156±14
HR (mean±SD)	73±9	74±8	74±7	74±7	78±9	79±8	80±8	80±8

A17.5.1. Pharmacodynamics

Hourly-averaged diastolic pressures from ABPM at week 8 are shown in Figure 51 below. Baseline- and placebo-subtracted changes in ABPM systolic and diastolic pressure are shown in Figure 52 below. The mean changes from baseline in 24-hour ambulatory diastolic and systolic pressures is given in Table 194 below. This was a last observation carried forward (LOCF) analysis. Included were available final ABPM measurements at week 8 and data from 6/13 dropouts. There was no attempt to exclude data secondary to protocol deviations. The LOCF analysis gave similar results to the sponsor's analysis of evaluable completing subjects.

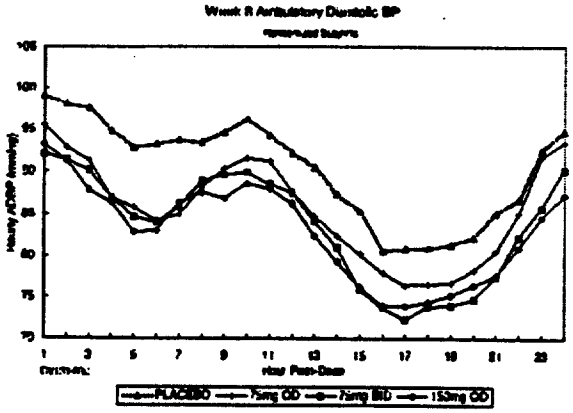

Figure 51. Week 8 hourly-averaged ABPM diastolic pressure (CV131-030).

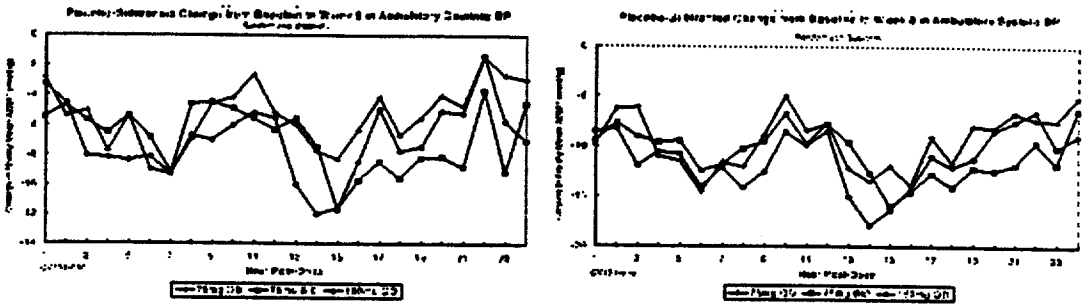

Figure 52. Baseline- and placebo-subtracted ABPM data (CV131-030).

Table 194. Changes in daytime and 24-hour averages and trough ABPM data (CV131-030).

	Diastolic (mean±SE)				Systolic (mean±SE)			
	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57	Placebo N=50	Irbesartan 75 mg qd N=55	Irbesartan 150 mg qd N=53	Irbesartan 75 mg bid N=57
24-hour	-1±1	-5±1	-7±1	-7±1	0±2	-8±2	-10±2	-10±2
Male	-1±1	-6±1	-6±1	-8±1	1±2	-8±2	-9±2	-10±2
Female	-2±1	-4±1	-8±1	-6±1	0±2	-8±2	-11±2	-8±2
12-hour daytime	-1±1	-6±1	-7±1	-7±1	0±2	-9±2	-11±2	-9±1
Trough	-2±2	-3±1	-8±2*	-6±1*	-1±2	-5±2	-10±2*	-7±2*

*P<0.05

The covariate analysis of this data showed a significant baseline and site effect on nearly all ABPM variables listed in Table 9. The baseline and site effect was also seen using the sponsor's valid Week 8 data. Preliminary assessments by the sponsor state that there were baseline interactions for trough ADBP and ASBP. This was caused by a subject with a high baseline value. The sponsor also mentions a treatment by site effect on 24 hour ADBP. This was secondary to a subject with a very large placebo response.

Mean change in trough seated diastolic and systolic blood pressure is given in Table 195 below. There were no significant statistical differences between the treatment groups in either trough seated or standing heart rate.

A summary of response rates at week 8 is given in Table 196 below.

Table 195. Changes in trough ABP (CV131-030).

	Diastolic (mean±SE)				Systolic (mean±SE)			
	Placebo N=50	Irbesartan			Placebo N=50	Irbesartan		
		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57
Week 2								
Mean change in baseline	-2±1	-7±1	-9±1	-11±1	-3±2	-7±2	-12±2	-12±2
Δ from placebo (98%CI)		-5 (-8, -2)*	-6 (-9, -3)*	-8 (-11, -6)*		- 4 (-9, -1)*	-8 (-13, -3)*	-9 (-14, -4)*
Week 8								
Mean change in baseline	-2±1	-6±1	-8±1	-10±1	4±2	-7±2	-11±2	-12±2
Δ from placebo (98%CI)		-4 (-7, -1)*	-6 (-10, -3)*	-8 (-11, -4)*		-3 (-8, -3)*	-8 (-13, -2)*	-8 (-13, -2)*

*p<0.01

Table 196. Response rate at week 8 (CV131-030).

	Placebo N=50	Irbesartan		
		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57
Normalized (%)	14	19	45*	47*
Total responders	20	28	55	60

*p<0.01

The trough:peak ratio was calculated for subjects with valid data at 6 and 12 weeks post randomization, as shown in Table 197 below.

Table 197. Trough to peak ratio in evaluable subjects (CV131-030).

	Ambulatory diastolic pressure				Ambulatory systolic pressure			
	Placebo N=50	Irbesartan			Placebo N=50	Irbesartan		
		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57
Not adjusted								
Trough: peak	41%	48%	76%	80%	24%	49%	68%	65%
Peak hour	2	6	3	4	2	4	3	4
Placebo-adjusted	—				—			
Trough: peak		36%	74%	66%		36%	66%	56%
Peak hour		6	5	4		6	3	6

A17.5.2. Pharmacokinetics

Trough plasma samples were obtained in 35 placebo and 118 irbesartan subjects. There were 4 subjects in the placebo group who had detectable levels. Three subjects on irbesartan had no detectable levels. Table 198 below gives summary statistics of the plasma levels. The maximal correlation between plasma levels and efficacy variables was 24-hour ADBP (0.38) and ASBP (0.40).

Elderly patients (>65 y) were not analyzed separately since they were few.

Table 198. Trough irbesartan levels (ng/ml; CV131-030).

	Placebo N=50	Irbesartan		
		75 mg qd N=55	150 mg qd N=53	75 mg bid N=57
Mean±SE	0.6±0.4	133±31	410±141	283±54
Min, max	0, 11	10, 908	0, 4265	0, 1938
Median	0	75	173	173

A17.5.3. Safety

There was a mean exposure of the study drug of approximately 60 days. No deaths or serious adverse events were reported.

There were 5 dropouts in the 8-week double-blind period. Table 199 below shows treatment duration and adverse event of the irbesartan subjects.

Table 199. Discontinuations due to adverse events during double-blind period (CV131-030).

Days	Dose (mg)	Adverse event	Days	Dose (mg)	Adverse event
18	75 qd	Headache	34	Placebo	Vertigo
5	150	Edema	30	Placebo	Vertigo
4	150	Anxiety/nervousness			

Treatment-emergent adverse events will be discussed in the integrated review of safety. The most common treatment-emergent adverse events occurred in the nervous, gastrointestinal, cardiovascular, and general body systems. The subjects randomized to 150 mg qd reported the highest rate of adverse events, of which the largest fraction were gastrointestinal in nature. Gastrointestinal symptoms included pain, diarrhea, dyspepsia/heartburn, and nausea/vomiting. None of the symptoms resulted in discontinuation of the study drug.

The most common treatment-emergent adverse events were weakness, headache, somnolence, hypertension, and anxiety/nervousness.

Seven subjects randomized to irbesartan reported 11 adverse events within the first 24 hours of treatment, while no events on placebo were reported. Symptoms reported were weakness, anxiety/nervousness, somnolence, nausea/vomiting, epigastric pain, headache, and vertigo.

Hypotension and orthostatic hypotension were reported in one subject each. They were randomized to irbesartan 75 mg qd and 150 mg, respectively.

Marked hematologic abnormalities include 2 subjects with thrombocytopenia during study treatment. One subject was discontinued due to headache on the same day as the marked abnormalities. Repeat values were normal. The other subject had a low platelet count (78K) at week 4. The subsequent value at week 8 was within normal limits (184K). Two subjects on irbesartan had leukopenia versus one subject in the placebo group.

Serum chemistry marked abnormalities were few. Hypercalcemia, hypoglycemia, and hyperuricemia were each detected in one irbesartan subject.

Urinalysis showed larger percentages of urine RBCs and WBCs on irbesartan than on placebo.

No significant changes in physical exam were noted. There were two clinically insignificant changes in the ECG noted (bradycardia and tachycardia; based on SAS data file ALLEVENT).

A17.6. Summary

The study was a randomized, placebo-controlled ABPM study of subjects on three doses of irbesartan versus placebo. After unblinding, the sponsor eliminated ABPM readings post-intake of the next morning's drug. After adjustment for multiplicity, the study was underpowered to detect a difference between groups of 4.6 mmHg. There was a significant baseline and site effect which will need to be evaluated by the statistics division.

APBM analysis conducted was done with all subjects randomized with available data either at week 8 or after discontinuation (LOCF). Even with inclusion of protocol violators and the sponsor's conservative analysis plan, irbesartan 75 mg bid and 150 mg qd were effective in reducing ambulatory blood pressure.

Seating and standing office blood pressures were statistically significant in all active treatment groups compared to placebo.

The highest trough:peak value was with the 150 mg qd dose. The median trough plasma concentration for irbesartan for once-daily dosing was similar to that for bid dosing; trough blood pressure effects were similar as well.

There were no deaths or serious adverse events to comment upon.

A18. CV131-031: Multicenter, randomized, double-blind comparison of irbesartan and amlodipine for treatment of hypertension in the elderly.

A18.1. Source documents

Study report: NDA 20-757, vols 1.318-1.325.

A18.2. Investigators

This study was conducted at 32 sites in the US, UK, Australia, New Zealand, and Canada.

A18.3. Study dates

2 December 1994 to 15 February 1996.

A18.4. Study design

This study description was based upon the original approved protocol dated 28 June 1994, modified and amended 5 times. A significant amendment was in the change of dose of irbesartan from 50 mg to 75 mg because recent studies showed that the effective dose range was between 75 and 150 mg. Other amendments did not impact the study.

The study design is shown in Figure 53 below. Following a 4-week single-blind, placebo lead-in period, qualified subjects were to be randomized in a ratio of 1:1 to regimens of irbesartan or amlodipine. Blinded treatment was to be administered once daily in the morning between 6 and 10 am for 24 weeks, starting at irbesartan 75 mg or amlodipine 5 mg. For subjects with SeDBP >90 mmHg, the dose was to be doubled at 6 weeks, HCTZ 12.5 mg was to be added at 12 weeks, HCTZ 25 mg at 16 weeks, and atenolol 50 mg at 20 weeks. Subjects discontinuing study drug for any reason were to be followed for the full 24 weeks.

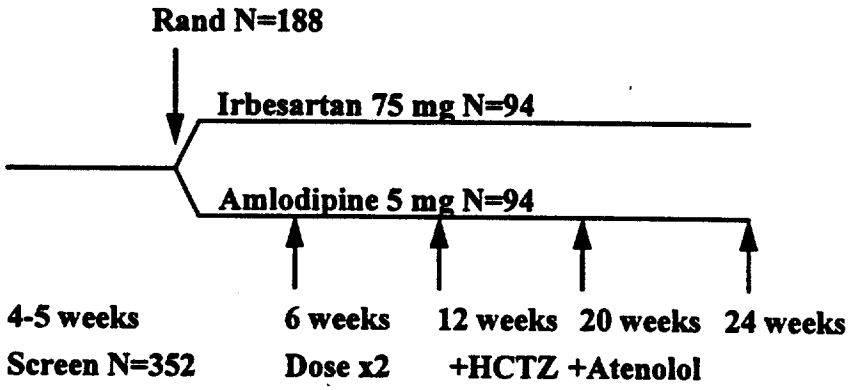

Figure 53. Study design (CV131-031).

Drug supplies are shown in Table 200 below.

Table 200. Drug supplies (CV131-031).

	Product number		Product number
Placebo	L94F013C	Amlodipine 5 or 10 mg	M94F036C M94M054C M95004
Irbesartan 75 mg	L94J022C L94L031C		
Atenolol 50 mg	LP953A	HTCZ 12.5 or 25 mg	M94G042C

Clinicopathological criteria for exclusions included (1) suspected or known causes of secondary hypertension, (2) SeDBP >110 mmHg or SeSBP >200 mmHg, (3) significant cardiovascular, neurologic, endocrinologic, renal, pulmonary, or gastrointestinal diseases or malignancy, (4) known hypersensitivity or intolerance to ACEI, dihydropyridine calcium channel blockers, β-blockers, or HCTZ, (5) abnormal

hematologic profiles, and (6) abnormal chemistry profiles, including serum potassium, ALAT, ASAT, creatinine and blood urea nitrogen.

The primary efficacy end point was to be change from baseline in trough SeDBP (the last single-blind placebo visit) at week 12 of double-blind treatment. Measurement of blood pressure was to be performed 24±3 hours after the previous morning dose of medication. Additional outcomes to be assessed included change from baseline in SeDBP at 6 and 24 weeks, StDBP at 6, 12, and 24 weeks, trough SeSBP and StSBP, SeHR and StHR at 6,12, and 24 weeks, response rates at 6, 12, and 24 weeks, and evaluations of the numbers of subjects requiring titration at week 6 or adjunctive therapy at 12, 16, and 20 weeks.

Safety assessments included medical history, physical examinations, identification of adverse serious and non-serious clinical events particularly the incidence of flushing, edema, and headache at 12 weeks, discontinuation of study drug, and evaluation of routine laboratory indices and parameters. ECGs for all randomized subjects were to be recorded in CRFs, and assessed for changes from baseline with reference to width of QRS complex, PR and QTc intervals, and heart rate. Holter monitor data from subjects with at least 18 hours of usable tape from a 24-hour recording were also recorded.

A18.5. Results

The study enrolled 352 subjects into the placebo lead-in period. Individual sites enrolled 0 to 74 subjects. Of the 352 subjects enrolled, 188 were randomized. Demographic and baseline characteristics are summarized in Table 201 below. Of the 188 randomized subjects, 149 (79%) had been on anti-hypertensive therapy within 1 month of enrollment. The distribution of the antihypertensive medications was similar in both treatment groups.

Table 201. Demographics (CV131-031).

	Amlodipine N=94	Irbesartan N=94		Amlodipine N=94	Irbesartan N=94
Age (mean)	70.6	70.9	Male (%)	46	44
Range			Female (%)	54	56
>65 years (%)	100	100	White	100	85
>75 years (%)	21	19	Black	0	13
			Other	0	2
SeSBP (mean±SD)	170.4±16.0	169.1±17.2	SeDBP (mean±SD)	100.9±4.0	99.9±4.0
			>104 mmHg (%)	21	14

Compliance was estimated at about 97%.

Completion rates were 74% on amlodipine and 72% on irbesartan. Twenty-one subjects in each group discontinued for adverse events. The proportion of subjects on each treatment level as a function of time, shown in Table 202 below, is similar between treatment groups.

Table 202. Distribution of subjects by treatment level (CV131-031).

	Irbesartan N=94		Amlodipine N=94			Irbesartan N=94		Amlodipine N=94	
	Level	n	Level	n		Level	n	Level	n
Week 8	Discontinued	14	Discontinued	6	Week 20	Discontinued	21	Discontinued	23
	75 mg	43	5 mg	49		75 mg	29	5 mg	35
	150 mg	37	10 mg	39		150 mg[a]	15	10 mg	18
	+HCTZ 12.5 mg	0	+HCTZ 12.5 mg	0		+HCTZ 12.5 mg	20	+HCTZ 12.5 mg	11
	+HCTZ 25 mg	0	+HCTZ 25 mg	0		+HCTZ 25 mg	7	+HCTZ 25 mg	7
	+Atenolol 50 mg	0	+Atenolol 50 mg	0		+Atenolol 50 mg	2	+Atenolol 50 mg	0
Week 12	Discontinued	15	Discontinued	13	Week 24	Discontinued	27	Discontinued	28
	75 mg	41	5 mg	44		75 mg	24	5 mg	32
	150 mg	38	10 mg	37		150 mg	17	10 mg	16
	+HCTZ 12.5 mg	0	+HCTZ 12.5 mg	0		+HCTZ 12.5 mg	15	+HCTZ 12.5 mg	10
	+HCTZ 25 mg	0	+HCTZ 25 mg	0		+HCTZ 25 mg	8	+HCTZ 25 mg	6
	+Atenolol 50 mg	0	+Atenolol 50 mg	0		+Atenolol 50 mg	3	+Atenolol 50 mg	2
Week 16	Discontinued	22	Discontinued	19					
	75 mg	31	5 mg	36					
	150 mg	23	10 mg	25					
	+HCTZ 12.5 mg	17	+HCTZ 12.5 mg	14					
	+HCTZ 25 mg	1	+HCTZ 25 mg	0					
	+Atenolol 50 mg	0	+Atenolol 50 mg	0					

a. One subject received 300 mg from week 20.

A18.5.1. Pharmacodynamics

The antihypertensive effects at trough at the end of week 12 are shown in Table 203 below. An intent-to-treat, LOCF analysis showed somewhat smaller changes from baseline in seated systolic and diastolic pressures and somewhat larger differences between treatment groups. Mean changes in blood pressure were greatest at 24 weeks, in both the amlodipine and irbesartan treatment groups; these observations cannot be used to support specific instructions regarding the appropriate rapidity of titration, given the multiple opportunities to adjust treatment to achieve desired antihypertensive effects.

Table 203. Antihypertensive effects at trough at week 12 (CV131-031).

	Amlodipine N=86	Irbesartan N=83		Amlodipine N=86	Irbesartan N=83
SeDBP, mmHg (mean±SE)	-14.9±0.8	-10.5±0.8*	Response rate		
SeSBP, mmHg (mean±SE)	-22.2±1.5	-17.8±1.6*	Normalized (%)	73	58*
			Total responders (%)	85	64

*P<0.05 by sponsor's analysis

In both treatment groups, males had smaller antihypertensive effects than females and subjects under age 75 had smaller effects than those >75, but neither gender nor age effects were statistically significant.

A18.5.2. Safety

There were no deaths. Serious adverse events were reported by 9 subjects on irbesartan and 7 subjects on amlodipine.

Treatment-emergent adverse events were reported by 75 subjects on irbesartan and 79 subjects on amlodipine.

Laboratory abnormalities were similar in the two treatment groups.

A18.6. Summary

This was a well controlled, double-blind, parallel group study in which the efficacy of irbesartan 75 or 150 mg and amlodipine 10 or 20 mg in an elderly (>64 years) population with mild-to moderate hypertensive subjects was compared. Addition of HCTZ and atenolol was allowed to achieve antihypertensive goals. Amlodipine induced a statistically significantly greater lowering of SeDBP compared to irbesartan at 6 and 12 weeks. The response rates, however, were similar at 24 weeks. There were no significant safety concerns.

A19. CV131-032: The efficacy and safety of the angiotensin II receptor antagonist irbesartan in the treatment of patients with severe hypertension.

A19.1. Source documents

Study report: NDA 20-757, vol 1.326-1.330.

A19.2. Investigators

This study was conducted at 24 sites in the US, Canada, Argentina, Brazil, and South Africa.

A19.3. Study dates

17 January 1994 to 6 December 1995

A19.4. Study design

This description was based on the original protocol dated 11 November 1994. Two amendments (dated 25 April 1995 and 17 January 1996) related to the long-term open-label extension.

This was a randomized, multi-center, double-blind, active-controlled, parallel study in subjects with severe hypertension (SeDBP 115 to 130 mmHg) designed to compare the antihypertensive efficacy and safety of irbesartan and enalapril.

Drug supplies are shown in Table 204 below.

Table 204. Drug supplies (CV131-032).

	Product number	Lot		Product number	Lot
Placebo	186295-R000-030	N94F090C	HCTZ 25 mg	186295-AXXX-013	N93K089C N94D066C
Enalapril 20 mg	186295-RXXX-039	N94H110C N94K131C	Nifedipine 30 mg	NDC0069-2650-66 186295-VXXX-010	4WT022A 2730A 2749A
Irbesartan 75 mg	186295-Ro75-054	N94J126C	Atenolol 50 mg	NDC0003-5040-50	4E074 4G100

Subjects were to be males and consenting post-menopausal or surgically sterile and non-lactating females >18 years old with severe essential hypertension (SeDBP 115 to 130 mmHg). Exclusions included (1) known or suspected causes of secondary hypertension, (2) SeSBP ≥220 mmHg, (3) significant neurologic, endocrinologic, renal, pulmonary, or gastrointestinal disease, a malignancy, or any other diseases considered by the investigator not to be in the interest of the subject, and (4) contraindication to ACE inhibitors or any of the allowed adjunctive study medications.

At the end of a one-week placebo lead-in period, qualifying subjects were randomized in a 2:1 ratio to receive 12 weeks of irbesartan 150 mg or enalapril 20 mg. Subjects with SeDBP ≥106 mmHg or SeDBP ≥90 mmHg at the end of 1 or 2 weeks, respectively, had the dose doubled. Subjects with SeDBP ≥90 mmHg at weeks 4, 6, 8, or 10 were given once daily open-label adjunctive antihypertensive therapy (HCTZ 25 mg followed by long-acting nifedipine 30 to 60 mg, and atenolol 50 to 100 mg), as needed to normalize blood pressure.

The primary end point was to be a change from baseline in trough SeDBP at week 12 of double-blind treatment.

Secondary objectives were (1) to compare reduction from baseline in trough SeSBP, StSBP, and StDBP, and peak SeDBP, StDBP, SeSBP, and StSBP at 4 and 12 weeks, (2) to compare the proportion of subjects normalized on monotherapy or in combination with HCTZ, nifedipine, or atenolol, and (3) to evaluate safety and tolerability of irbesartan and enalapril.

Drug safety was to assessed by frequencies of clinical adverse events, changes in physical examination, ECG, sponsor-defined marked laboratory abnormalities, and 24-hour Holter monitoring.

A19.5. Results

Individual sites enrolled 1 to 27 subjects. The study enrolled 250 subjects into the placebo lead-in period, 22 subjects were discontinued and 68 subjects were not randomized. Of the 182 randomized subjects, 160 (88%) completed the double-blind period. Demographic and baseline data of randomized subjects are shown in Table 205 below. There were no important differences between groups.

Table 205. Demographics (CV131-032).

	Enalapril N=61	Irbesartan N=121		Enalapril N=61	Irbesartan N=121
Age (mean)	54	52	Males (%)	56	63
Range			Females (%)	44	37
≥65 years (%)	11	10	White (%)	49	56
≥75 years (%)	2	0	Black (%)	33	31
			Other (%)	18	12
SeDBP (mean±SD)	119.2±3.9	119.0±3.3	SeSBP (mean±SD)	176.7±17.8	175.0±15.2
≥120 mmHg (%)	31	31			

Compliance was estimated to be about 96%.

Notable protocol violations included massive proteinuria, serum potassium <3.3 mM, and aspirin intake.

A19.5.1. Pharmacodynamics

The distribution of subjects among various titration steps was similar in the two groups, as shown in Table 206 below. After the first dose of the study drugs, the mean reduction from baseline to peak SeDBP was similar: 10.2 mmHg on irbesartan vs 10.6 mmHg enalapril.There was no statistically significant difference between groups for mean change from baseline in trough or peak SeDBP, and in the proportion of subjects normalized at 12 weeks, as shown in Table 207 below. Both seated and standing trough heart rates showed statistically significantly greater reductions at week 12 with the enalapril regimen than with the irbesartan regimen. However, 43% (24/56) of the enalapril-treated subjects were receiving atenolol at week 12, suggesting a β-blocker effect. The heart rates for the irbesartan-treated subjects remained constant throughout the study.

Table 206. Final titration steps for completers at week 12 (CV131-032).

	Enalapril N=56	Irbesartan N=103
Study drug—low dose (%)	0	4
Study drug—high dose (%)	7	5
Study drug + HCTZ (%)	18	24
Study drug + nifedipine or atenolol (%)	7	9
Study drug + HCTZ + nifedipine or atenolol (%)	68	58

The sponsor claims that there was a baseline-by-treatment interaction that precluded statistical comparison in subjects with the highest baseline SBP values. Generally, there were too few subjects in subgroups to permit any meaningful efficacy analysis. However, for both treatment groups, decreases from baseline in trough SeDBP and SeSBP appeared comparable for age, sex, and race.

Table 207. Antihypertensive effects for completers at week 12 (CV131-032).

	Trough		Peak	
	Enalapril N=56	Irbesartan N=103	Enalapril N=56	Irbesartan N=103
ΔSeDBP (mean±SE)	-30.5	-29.6±0.8	-34.2±1.1	-34.4±1.1
ΔSeSBP (mean±SE)	-39.3±1.9	-40.1±1.4	-44.5±2.1	-47.2±1.6
Response rate (% normalized)	57	59	—	—

A19.5.2. Safety

There were no deaths. Five irbesartan-treated subjects (vs none on enalapril) experienced serious adverse events during double-blind treatment. These events were removal of a benign lipoma, atrial rhythm disturbance plus angina pectoris, atrial rhythm disturbance, transient ischemic attack, and renal failure[1]. None of these events were considered drug-related.

A similar proportion of subjects discontinued because of adverse events: 6% on irbesartan vs 5% on enalapril. No hypotension was observed in either treatment group after the first dose.

Cough occurred more frequently in enalapril-treated subjects than in irbesartan-treated subjects (13% on enalapril vs 3% on irbesartan; p = 0.0074). The most common clinical adverse events in both treatment groups were headache, musculoskeletal pain and dizziness. Cough was more common on enalapril (13%) than on irbesartan (3%), with the majority of the difference being in the incidence of dry cough. Funduscopic improvement (grade 2 to grade 1) was seen in 4 subjects on irbesartan and 5 subjects on enalapril. Markedly elevated BUN was reported for 10% of subjects on enalapril vs 5% on irbesartan, elevated creatinine by 5% on enalapril vs 3% on irbesartan, and elevated glucose by 0% on enalapril vs 5% on irbesartan[2].

No clinically significant changes were seen in laboratory parameters or ECG.

A19.6. Summary

This was an actively-controlled, double-blind, randomized study of irbesartan and enalapril in subjects with severe essential hypertension (SeDBP 115 to 130 mmHg) and relatively normal renal function. Nifedipine, atenolol, and HCTZ were added to control severe hypertension during the study. Fewer than 10% of subjects remained on study drug alone, and use of adjunctive treatment was similar in the two groups. There was no difference between groups with regard to blood pressure control. The beneficial effect on hypertensive retinopathy at 12 weeks, by both regimens, is noteworthy. There were no deaths but there were two atrial rhythm disturbances with irbesartan 150 and 300mg dose level. No other serious safety problems were observed.

1. The case of renal failure was attributed to an herbal remedy.
2. Of the 5 irbesartan subjects with elevated glucose, 4 had elevations at baseline or before. The fifth case represented newly diagnosed diabetes mellitus, in a subject on irbesartan, HCTZ, nifedipine, and atenolol.

A20. CV131-033: The safety and efficacy of irbesartan in patients with hypertension and renal insufficiency.

A20.1. Study documents

Study report: NDA 20-757, vols 1.331 - 1.333.

A20.2. Investigators

This study was conducted at 26 sites by investigators in Belgium (6), Israel (9), Italy (3), Netherlands (5), and Russia (3).

A20.3. Study dates

01 April 1995 to 15 March 1996.

A20.4. Study design

The study description was based on approved protocol dated 12 November 1994. There were protocol amendments to include Russia as a participating country, to change the dosing of dialysis subjects on dialysis days, to provide guidelines for entry for systolic blood pressure, and to modify a number of exclusion criteria.

The primary objective of this study was to evaluate the safety and tolerability of irbesartan starting at 75 mg and titrating to 150 mg at 4 or 8 weeks (for SeDBP ≥90 mmHg), or to 300 mg at 8 weeks (for SeDBP ≥90 mmHg if previously titrated to 150 mg at 4 weeks), in subjects with mild to moderate hypertension (SeDBP ≥90 mmHg) and varying levels of renal insufficiency.

Secondary objectives were (1) to determine the effects of 12 weeks of irbesartan on 24-hour creatinine clearance, (2) to determine the reduction from baseline in trough SeDBP at 12 weeks, and (3) to determine the reduction from baseline in trough SeDBP at 4 and 8 weeks, SeSBP, StSBP, StDBP at 4, 8, and 12 weeks, and peak blood pressures in hypertensive subjects with varying levels of renal insufficiency.

This was a multi-center, uncontrolled trial in subjects mild to moderate hypertension (SeDBP 90 to 110 mmHg) and impaired renal function. Following a 2 to 3-week stabilization and evaluation of renal insufficiency, 3 groups of approximately 30 subjects each were to receive 12 weeks of treatment with once daily oral irbesartan 75 mg. At 4 or 8 weeks, subjects with SeDBP≥90 mmHg were to have irbesartan increased to 150 mg once daily, and then to 300 mg once daily if necessary.

Subjects were to be males and post menopausal or surgically sterile, non-lactating females >18 years old, with SeDBP 90 to 110 mmHg, and renal insufficiency (creatinine clearance ≤60 mL/min or requiring hemodialysis).

Drug supplies are shown in Table 208 below.

Table 208. Drug supplies (CV131-033).

	Product number	Lot
Irbesartan 75mg	186295-R075-054	L94J022C L94L031C

Safety was to be monitored by clinical treatment-emergent adverse drug experiences, changes in 24-hour urine creatinine clearance from baseline to weeks 4 and 8, change in blood urea nitrogen (BUN) and serum creatinine from baseline to day 5 and weeks 2,4,8, and 12, and changes from baseline for all routinely collected laboratory tests at weeks 2 (electrolytes only), 4, 8, and 12.

A20.5. Results

Individual sites enrolled 0 to 15 subjects. One hundred subjects were enrolled and assigned to 3 groups: mild-to-moderate renal insufficiency (creatinine clearance 30 to 60 mL/min), severe renal insufficiency (creatinine clearance <30 mL/min and not requiring dialysis), and severe renal insufficiency requiring hemodialysis. Of the 100 subjects, 79 (79%) completed the trial. Demographic characteristics of the subjects are presented in Table 209 below.

Table 209. Demographics (CV131-033).

	Renal impairment				Renal impairment		
	Moderate 30<CrCl<60 N=44	Severe CrCl<60 N=33	Hemodialysis N=23		Moderate 30<CrCl<60 N=44	Severe CrCl<60 N=33	Hemodialysis N=23
Male (%)	64	42	87	Weight, kg (mean±SD)	77±13	70±13	68±13
Female (%)	36	58	13	Range			
White	100	100	100	SeDBP (mean±SD)	97.8±6.3	98.8±7.2	100.3±5.0
Age (mean±SD)	58±11	57±11	57±17	Range			
Range				SeSBP (mean±SD)	160.9±17.6	168.7±13.5	169.8±17.0
>65 (%)	30	27	39	Range			
>75 (%)	5	6	13				

A20.5.1. Pharmacodynamics

Analysis of efficacy was based on 79 completing subjects. At week 12, about 40% of the completers remained on 75 mg irbesartan, 32% on 150 mg, and 25% on 300 mg. None of the subjects on hemodialysis were titrated to 300 mg. About 7% of subjects with mild-to-moderate renal insufficiency used concomitant antihypertensive medication. while 6% of severe insufficiency and 13% of hemodialysis subjects used antihypertensive medication. The effects on blood pressure are shown in Table 210 below. Mean changes in SeDBP and SeSBP from baseline to week 12 for completing subjects were statistically significantly different from zero. The greatest effects of irbesartan treatment on SeDBP, StDBP, and StSBP were seen among subjects requiring hemodialysis. SeHR and StHR were not affected by treatment. The percentages of normalized subjects and total responders, at the primary efficacy time point of 12 weeks, were highest in the subjects requiring hemodialysis.

Table 210. Blood pressure effects at week 12 (CV131-033).

	Renal impairment				Renal impairment		
	Moderate N=36	Severe N=27	Dialysis N=16		Moderate N=36	Severe N=27	Dialysis N=16
ΔSeDBP (mean±SD)	-9.4±1.7	-9.5±2.2	-17.1±2.0	Normalized (%)	64	56	89
ΔSeSBP (mean±SD	15.6±2.3	-14.9±2.7	-30.4±4.7	Total responders (%)	67	56	100

A20.5.2. Safety

There were no deaths during or within 30 days of double-blind treatment.

The sponsor discontinued 17 subjects from the study, namely; 5 (11%) with moderate renal impairment, 5 (15%) with severe impairment, and 7 (30%) on dialysis. These events are summarized in Table 3.

Table 211. Discontinuations for adverse events (CV131-033).

Subject	Group	Age	Sex	Dose	Day of		Event
					Onset	DC	
003/003	Moderate	65	F	75	1	1	Hypotension
024/002		51	F	75	1	1	Hypertension
024/005		51	F	150	35	35	Hypertension
024/006		64	F	75	45	57	Pulmonary infection
025/006		50	M	75	15	16	Angina pectoris

Table 211. Discontinuations for adverse events (CV131-033).

Subject	Group	Age	Sex	Dose	Day of		Event
					Onset	DC	
001/007	Severe	63	F	75	8	8	Hypertension
001/008		58	F	75	40	43	Asthma
004/004		67	M	75	30	35	Renal dialysis
006/008		60	M	75	4	8	Dyspnea, dysrhythmia
007/005		55	M	300	57	60	Hypertension
002/004	Dialysis	52	F	75	16	25	Headache
003/002		33	M	75	8	10	Dysrhythmia
004/002		54	M	75	80	80	Dizziness, hypotension
010/001		46	M	75	8	8	Headache
010/002		72	M	75	4	8	Headache
013/002		63	M	300	57	60	Orthostatic hypotension
023/012		72	M	75	8	8	Hepatitis

The most common safety issues were hypotension and hypertension. Both conditions predisposed to hospitalization and in some subjects they were considered life-threatening. Adverse events were more common in subjects requiring dialysis than in subjects not requiring dialysis.

Hyperkalemia was frequently seen in subjects with decreased renal function, the highest value being 6.5 mEq/L. These changes were not associated with serious adverse events. No significant mean changes were seen for creatinine clearance, serum creatinine, BUN, potassium, and hemoglobin.

A20.6. Summary

This was a 12-week study of the safety and efficacy of irbesartan 75 to 300 mg in subjects with mild to moderate hypertension and varying degrees of renal impairment. Irbesartan produced a significant reduction from baseline in trough SeDBP, SeSBP, StDBP, and StSBP, but the lack of a placebo control group makes these findings difficult to interpret. There was no significant alteration of SeHR and StHR with treatment. Although the sponsor argues from this study that irbesartan does not adversely affect serum potassium levels, subjects with severe renal impairment showed frequent, transient elevations of serum potassium. The disturbances of cardiac conduction observed in some subjects may be an indication of serum potassium abnormalities. The lack of a control group makes it difficult to identify effects of irbesartan, but safety concerns may necessitate lower doses or slower titration in patients with significant renal impairment.

A21. CV131-037: Factorial trial of the efficacy and safety of multiple dosages of irbesartan and hydrochlorothiazide in mild-to-moderate hypertension.

A21.1. Source documents

Study report: NDA 20-757, vol 1.296 to 1.305; electronic documents MAST037.PDF and SUPP037.PDF.

A21.2. Investigators

This study was conducted at 46 sites in the US.

A21.3. Study dates

17 November 1994 to 21 November 1995.

A21.4. Study design

This study description was based upon the protocol dated 2 September 1994. There were two amendments written after the start of enrollment. Neither amendment affected the integrity of the trial. However, there were statistical changes made after the protocol was completed.

This was a randomized, double-blind, placebo-controlled, 4 x 4 factorial study in subjects with mild to moderate hypertension (95 < SeDBP <110 mmHg). After a 4- to 5-week lead-in period, a subject was to be randomized into the double-blind period if the diastolic blood pressure was between 95 and 110 mmHg on the last 2 successive visits. The subject received a once-daily combination of irbesartan (0, 37.5, 100, or 300 mg) and hydrochlorothiazide (0, 6.25, 12.5, or 25 mg) for 8 weeks. There were routine office visits at 2, 4, 6, and 8 weeks. Trough seated and standing blood pressure were measured at all visits. In addition, on week 8, blood pressure was measured over 6 hours in order to calculate a trough:peak ratio. Drug supplies are shown in Table 212 below.

Table 212. Drug supplies (CV131-037).

	Product Code	Lot		Product Code	Lot
Placebo-IRB	186295-R000-030	N94F090C	Placebo- HCTZ	186295-A000-026	N94G098C
12.5 mg IRB	186295-R12X-043	N94F094C	6.25 mg HCTZ	186295-AXXX-012	N94F080C
100 mg IRB	186295-R100-033	N94G099C	12.5 mg HCTZ	186295-AXXX-012	N94F086C
			25 mg HCTZ	186295-AXXX-013	N93K089C

The subjects were to be taken from a healthy non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Subjects with renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded. If seated systolic blood pressure (SeSBP) was >200 mmHg, the subject was excluded. Subjects who were taking the following agents were excluded: (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilators, and (8) NSAIDs greater than 7-day duration (low dose ASA excepted). Subjects must have been able to wean other antihypertensives and vasoactive agents.

The primary objectives of this study were to assess (1) the dose-response relationship in blood pressure reduction with increasing doses of irbesartan and HCTZ, and (2) the safety and tolerability of the irbesartan and HCTZ combination.

The primary efficacy variable in this study was the reduction of seated trough diastolic blood pressure (SeDBP) at week 8 following once-daily administration of irbesartan and HCTZ.

Secondary objectives included (1) evaluation of SeDBP at weeks 2, 4, and 6, (2) evaluation of seated systolic blood pressure (SeSBP), standing diastolic (StDBP), and

systolic (StSBP) blood pressure at trough for weeks 2, 4, 6, and 8, (3) calculation of the trough:peak ratio for week 8, and (4) effect of combination on serum potassium and lipid levels.

After the 8-week double-blind period was completed, subjects were able to continue into an open-label, long-term protocol.

According to the original protocol, the primary efficacy variable was to be analyzed using a response surface model and by analysis of covariance (ANCOVA) based on baseline, site and treatment. Secondary efficacy parameters, SeSBP, StDBP, StSBP and SeDBP (weeks 2, 4, and 6) were to be analyzed similarly by a response surface model and ANCOVA. In contrast, the final study report states that only trough SeDBP and trough SeSBP were analyzed.

Safety assessments were done both in the single- and double-blinded periods. Tests included ECG, laboratory tests (CBC, SMA20, urinalysis), and physical examination. Clinical adverse events and their relationship to the study drug were to be recorded.

A21.5. Results

There were 1126 subjects enrolled. Disposition of enrolled subjects is shown in Table 213 below. Six subjects completed but were not included in efficacy analyses because of incomplete documentation.

Table 213. Subject disposition (CV131-037).

	N
Enrolled	1126
Not randomized	443
Randomized	683
Discontinued	52
Completed	631
Evaluable Subjects Week 8	625

Table 214 below shows reasons for exclusion prior to randomization.

Table 214. Reasons for exclusion (CV131-037).

	N		
Did not qualify	254	Concomitant Medication	13
Subject request	51	BP high in investigator opinion	6
Adverse event	41	Poor compliance	3
Blood pressure above limit	26	Not reported	2
Lost to follow-up	24	Other	23
Total	443		

Table 215 below gives the number discontinuations for the factorial trial in the double-blind period. The reasons for discontinuations are given in Table 216 below.

There were a total of 26 significant protocol deviations. There were 24/26 protocol violations which could affect the primary efficacy variable. Out of the 24 subjects, there were 6 subjects at Site 22 who were excluded in the ITT analysis because of inadequate source documentation. There were 5 discontinuations associated with protocol violations (Table 217 below).

Demographics are compared in Table 218 below. None of the differences among groups were statistically significant.

Table 215. Number of subjects randomized and discontinued (CV131-037).

Dose	Placebo	Irbesartan 37.5	Irbesartan 100	Irbesartan 300
HCTZ 0	44/6/38	42/3/39	41/4/37	43/0/43
HCTZ 6.25	44/5/39	44/6/38	44/2/42	40/2/38
HCTZ 12.5	40/1/39	45/5/40	43/4/39	44/2/42
HCTZ 25	39/3/36	41/1/40	44/3/41	45/5/40

Table 216. Reasons for discontinuation (CV131-037).

	Irbesartan 0 mg				Irbesartan 37.5 mg				Irbesartan 100 mg				Irbesartan 300 mg				Tot
HCTZ	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25	
N	44	44	40	39	42	44	45	41	41	44	43	44	43	40	44	45	
AE	2	2	0	3	0	3	2	1	0	2	1	2	0	1	1	2	22
Subject request	2	0	0	0	1	2	0	0	1	0	2	0	0	0	0	1	9
BP >limit	1	1	1	0	1	0	1	0	1	0	0	0	0	0	0	0	6
Lost to follow-up	0	0	0	0	0	1	1	0	1	0	0	1	0	0	0	0	4
BP high (investigator)	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	4
Concomitant meds	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	3
Compliance	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
Administrative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Unqualified	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Total	6	5	1	3	3	6	5	1	4	2	4	3	0	2	2	5	52

Table 217. Protocol violations leading to discontinuation (CV131-037).

Site-Subject	IRB, HCTZ	Reason for discontinuations	Site-Subject	IRB, HCTZ	Reason for discontinuations
12-002	0, 0	BP above limit	17-005	37.5, 6.25	Poor compliance
13-014	300, 25	Patient request	18-006	300, 12.5	Poor compliance
14-017	37.5, 12.5	Adverse event			

Table 218. Demographics (CV131-037).

	Irbesartan 0 mg				Irbesartan 37.5 mg				Irbesartan 100 mg				Irbesartan 300 mg			
HCTZ	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25
N	44	44	40	39	42	44	45	41	41	44	43	44	43	40	44	45
Male (%)	73	68	70	64	71	55	80	56	68	66	70	66	56	63	59	60
White (%)	91	77	83	95	76	86	84	85	88	84	84	82	88	78	84	91
Black (%)	9	18	8	5	14	9	9	10	10	9	9	9	5	15	14	7
Age (mean)	54	56	57	54	51	55	53	53	54	53	53	57	55	56	55	55
>65 (%)	14	16	18	15	10	18	11	17	15	16	19	25	23	13	23	27

There were no statistically significant differences among treatment groups with respect to baseline seated or stand blood pressure or heart rate. Table 219 below shows baseline seated vital signs.

Table 219. Baseline vital signs (CV131-037).

	Irbesartan 0 mg				Irbesartan 37.5 mg				Irbesartan 100 mg				Irbesartan 300 mg			
HCTZ	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25
N	44	44	40	39	42	44	45	41	41	44	43	44	43	40	44	45
SeDBP (mean)	100	100	100	100	102	100	100	99	100	101	100	101	99	99	101	100
SD	4	4	5	4	5	4	5	4	4	5	4	5	4	4	4	4
>104 mmHg (%)	18	23	23	10	36	25	24	17	20	25	21	32	16	18	20	18
SeSBP (mean)	148	152	153	153	149	151	155	151	150	151	154	151	153	150	150	152
SD	13	17	15	13	13	14	15	14	12	15	12	19	14	14	20	14
SeHR (mean)	73	76	71	72	73	75	73	72	72	71	73	74	73	72	75	75
SD	8	10	8	10	8	9	9	9	9	8	9	11	9	9	12	12

The most common medical conditions among randomized subjects were hyperlipidemia, headache and diabetes mellitus. 557/683 randomized subjects had previously received antihypertensive medications within one month of enrollment.

A21.5.1. Pharmacodynamics

Changes from baseline in trough SeDBP and SeSBP (LOCF) are given in Table 220 below. The results are similar to the sponsor's for week 8. There was a significant baseline effect for SeSBP but not for SeDBP.

Table 220. Change in trough SeDBP and SeSBP (LOCF, CV131-037).

	Change in trough SeDBP (mean±SD) Irbesartan (mg)				Change in trough SeSBP (mean±SD) Irbesartan (mg)			
	0	37.5	100	300	0	37.5	100	300
HCTZ 0	-4±6	-7±7	-9±9	-10±6	-3±10	-8±10	-10±12	-15±10
HCTZ 6.25	-5±7	-8±8	-10±7	-13±6	-4±11	-11±11	-12±10	-17±12
HCTZ 12.5	-6±6	-9±6	-12±8	-15±8	-9±11	-15±16	-15±15	-16±13
HCTZ 25	-8±7	-12±7	-14±7	-14±8	-12±14	-17±12	-21±11	-22±14

The sponsor fit the change in blood pressure using a polynomial expression by the minimizing the least squares error and eliminating higher-order terms when their contribution to the overall result was small. The equation for the change in BP as a function of irbesartan and HCTZ is

$$\Delta BP = A + BI + CH + DI^2$$

where I is irbesartan (mg), H is the HCTZ (mg) and A, B, C and D are the fitted coefficients.

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Figure 54 below shows the data for the response surface for the change in SeDBP and SeSBP as a function of the dose of irbesartan and HCTZ.

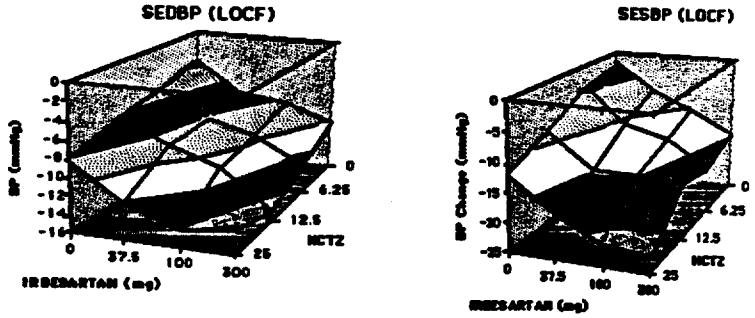

Figure 54. Response surface for the change in blood pressure (CV131-037).

Table 221 below gives the coefficients fitted for SeDBP, SeSBP, StDBP, and StSBP and their confidence intervals. The negative coefficient on A represented the fitted placebo response. The negative coefficients on B and C indicate the linear per-mg component of the blood pressure reduction attributable to irbesartan and HCTZ, respectively. The positive coefficient on D indicates that the response to irbesartan is plateauing, i.e. is less than linear with dose. No such effect is present for HCTZ.

Table 221. Coefficients for the fitted response surfaces (CV131-037).

	A (CI)	B (CI) x 10^2	C (CI) x 10	D (CI) x 10^4
SeDBP	-4 (-5, -3)	-6.4 (-8.6, -4.1)	-1.9 (-2.5, -1.3)	1.4 (0.6, 2.0)
Male	-3 (-5, -2)	-5.8 (-8.3, -3.2)	-1.9 (-2.6, -1.2)	1.0 (0.3, 1.8)
Female	-6 (-8, -3)	-7.1 (-12, -2)	-1.7 (-3, -0.3)	1.9 (0.3, 3.4)
SeSBP	-4 (-5, -2)	-1.0 (-1.3, 0.7)	-3.8 (-4.7, -2.8)	2.2 (1.2, 3.3)
StDBP	-3 (-4, -2)	-5.3 (-7.4, -3.3)	-2.1 (-2.7, -1.6)	1.0 (0.39, 1.7)
StSBP	-3 (-6, -1)	-8.6 (-13.5, -3.7)	-4.1 (-5.4, -2.8)	1.7 (0.18, 3.1)

The sponsor has mentioned that a global test (Hung, Chi and Lipicky, Biometrics, 49:85-94, 1993) was employed to test whether there was at least one combination that was superior to each of its components. But there are no details of the result of this test in the sponsor's report. The statistical reviewer performed the global test for the trough SeDBP LOCF data set. The average test gave a p-value <0.001, and the maximum test gave a p-value of 0.0011. The fitted coefficients for trough SeDBP calculated by the statistical reviewer were similar to the sponsor's coefficients.

The global test was also positive for all seated and standing blood pressures at all weeks with the exception of StDBP at Week 2.

Seated and standing mean heart rates changed by less than 5 bpm at trough for all treatment groups. However, there was a mild site effect with seated heart rate ($p<0.07$).

Dose-response plots for irbesartan (keeping HCTZ constant) for changes in SeDBP and SeSBP are shown in Figure 55 below.

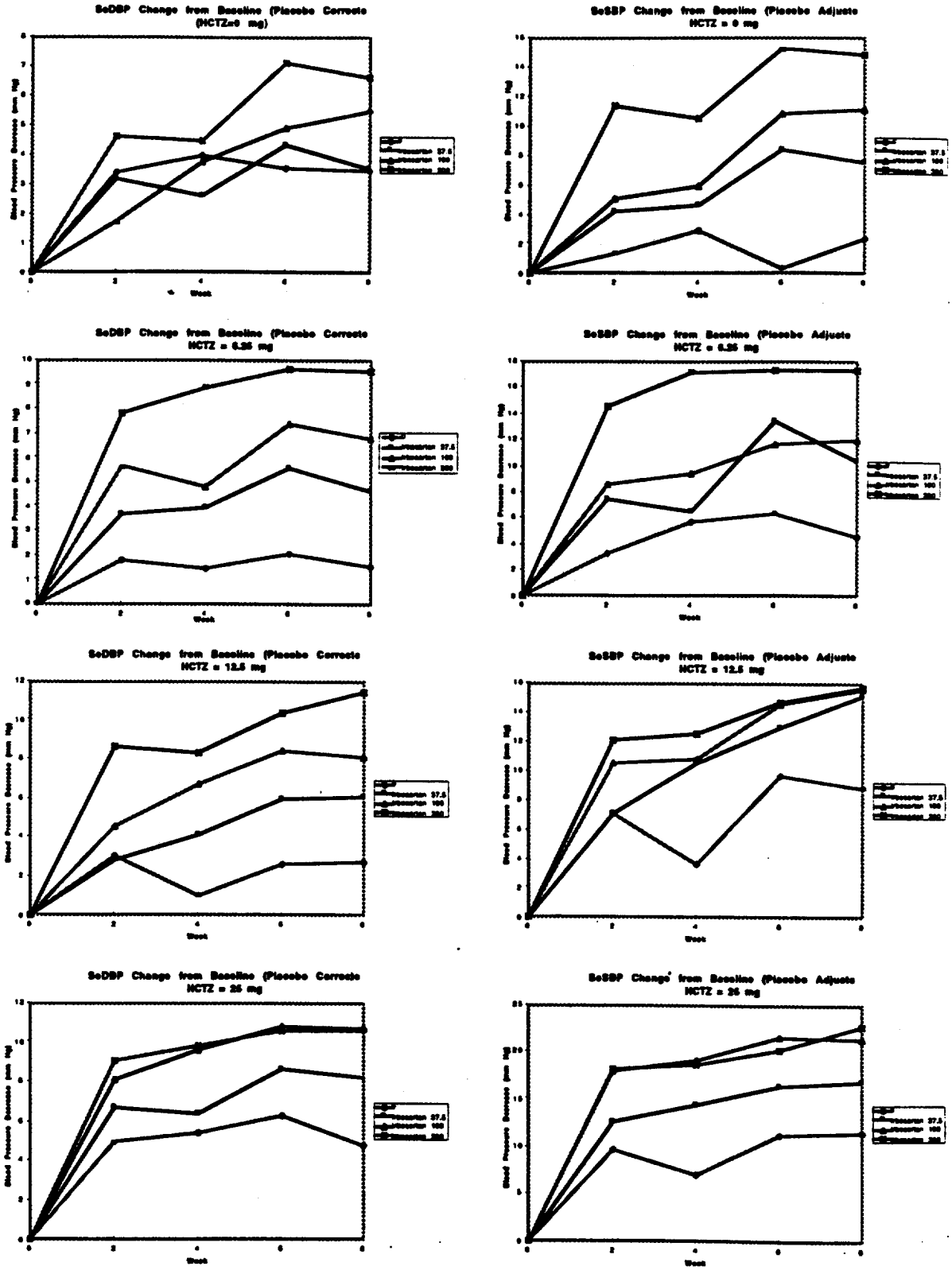

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Figure 55. Irbesartan dose-response curves (CV131-037).

Figure 56 below shows the percentage of normalized subjects and total responders (equal to normalized patients plus subjects change in baseline >10 mmHg).

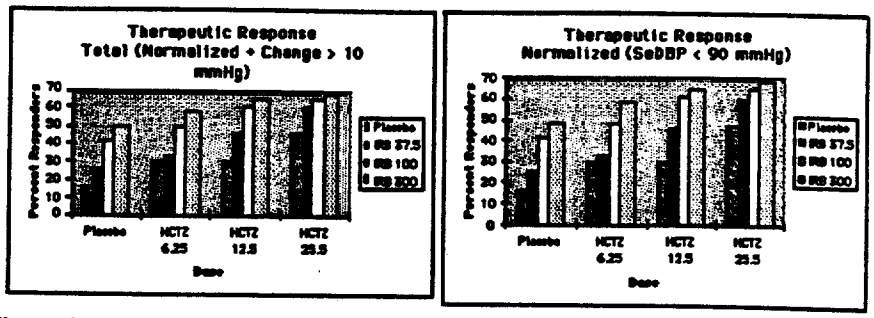

Figure 56. Percentage of normalized subjects and total responders (CV131-037).

The trough:peak ratio was calculated for subjects with valid data at 8 weeks post randomization, as is shown in Table 222 below.

Table 222. Trough:peak ratios (CV131-037).

	Irbesartan 0 mg				Irbesartan 37.5 mg				Irbesartan 100 mg				Irbesartan 300 mg			
HCTZ	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25	0	6.25	12.5	25
N	44	44	40	39	42	44	45	41	41	44	43	44	43	40	44	45
ΔSeDBP (trough)	—	-1.5	-2.7	-4.8	-3.6	-5.0	-5.5	-7.8	-5.5	-6.8	-8.1	-10.6	-6.6	-9.6	-11.4	-10.7
ΔSeDBP (peak)	—	-1.1	-3.7	-5.0	-5.0	-9.0	-8.2	-10.0	-9.0	-10.6	-11.2	-13.1	-11.1	-12.0	-14.4	-15.5
Ratio	—	1.39	0.75	0.95	0.71	0.56	0.67	0.78	0.61	0.64	0.72	0.80	0.59	0.80	0.79	0.68

Elderly patients (>65 yrs.) and non-caucasians were not analyzed separately since their numbers in the trial group were small within the treatment groups.

A21.5.2. Safety

There was a mean exposure to the study drug of approximately 55 days. More than 90% of subjects were exposed for greater than 31 days. No deaths were reported.

There were 22 (3.2%) dropouts in the 8-week double-blind period. Table 223 below shows the dose, subject, and adverse events during the double-blind period. There were no dropouts on irbesartan alone.

Table 223. Adverse events which resulted in discontinuation (CV131-037).

Irb/HCTZ	Day	Serious	Adverse event	Day	Serious	Adverse event
37.5/6.25	9/25	Y	Chest pain	9/25	Y	Cardiac cath; CABG re-do
37.5/6.25	2/7	N	Pruritus, muscle ache, edema	6/7	N	Constipation
	3/7	N	Depression	6/7	N	Abnormal urination
	6/7	N	Anxiety/nervousness	7/7	N	Chest pain
37.5/6.25	41/46	N	Heart failure			
37.5/12.5	28/35	N	AST, ALT, ALKPhos incr.	33/35	N	Rash, dizziness, hypotension
37.5/12.5	8/9	N	Hypertension			
37.5/25	43/48	N	Dizziness	47/48	N	Hypotension
I100/6.25	0/1	N	Dizziness			
100/6.25	17/21	Y	Anorectal disorder; peptic ulcer**			
100/12.5	1/11	N	Fatigue, weakness			
100/25	1/14	N	Anxiety/nervousness, constipation			

Table 223. Adverse events which resulted in discontinuation (CV131-037).*(Continued)*

Irb/HCTZ	Day	Serious	Adverse event	Day	Serious	Adverse event
I100/25	14/29 16/29 19/29	N N N	Muscle ache Sleep disturbance Anxiety/nervousness	20/29 29/29	N N	Edema Weight gain
300/6.25	7/12	N	Pruritic rash			
300/12.5	0/1	N	Headache; nausea/vomiting			
300/25	39/43	Y	Myocardial infarct			
300/25	1/2	N	ECG abnormal; dizziness			
0/6.25	1/1	Y	CVA			
0/6.25	3/14	N	Dizziness, headache, chest pain	9/14	N	Emotional lability
0/25	2/29	N	Sexual dysfunction			
0/25	2/4	N	Headache, chest pain			
0/25	0/42	N	Flushing			
Placebo	16/27	N	Dizziness/fatigue			
Placebo	41/42	N	Chest pain			

Dizziness and anxiety/nervousness were the most common adverse events on combination therapy. Edema caused withdrawal of 2 subjects on irbesartan/HCTZ. Both were women who weighed greater than 200 lbs. Hypotension caused 2 withdrawals. One subject experienced orthostatic hypotension which resolved after IV fluid administration. The other experienced elevated liver enzymes after 28 days of treatment. Five days later the subject presented with rash, dizziness, and hypotension. The events resolved within 2 weeks of discontinuation. Both subjects with muscle aches had a history of musculoskeletal problems. CPK levels were not markedly elevated. However, there was an increased incidence of CPK elevations (>4x baseline) in the combination (10 subjects; 2.6%) and irbesartan monotherapy (3 subjects; 2.4%).

Two subjects who received combination therapy experienced adverse events after one dose. One subject (IRB 100/HCTZ 6.25) complained of dizziness without evidence of hypotension and asked to be withdrawn. The other subject complained of headache and nausea/vomiting after the first dose of IRB 300/HCTZ 12.5. Five hours later the subject was feeling better. The study medication was discontinued and he was sent to the ER. The investigator believed that the subject experience a vasodilatory response secondary to dehydration and study medication.

Serious adverse events which did not result in withdrawal of the study is given in Table 224 below.

Table 224. Serious Adverse Events which did not result in Discontinuation

Irb/HCTZ	Days	Adverse event	Irb/HCTZ	Days	Adverse event
100/12.5	59	Increased CPK	300/0	35	Ovarian abnormality
300/6.25	32	Renal calculus	Placebo	Post-tx	GI malignancy
300/6.25	27	Dermatologic procedure			

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events for irbesartan monotherapy were in the respiratory, nervous, musculo-skeletal and general body systems.

The most common treatment-emergent adverse events on irbesartan monotherapy were upper respiratory infection, headache, musculo-skeletal pain and dizziness.

The treatment-emergent adverse events during the first 24 hours of treatment with irbesartan monotherapy included headache, dizziness, and fatigue.

On irbesartan monotherapy, there were 3 subjects with increased WBC (>1.25 upper limit of normal), and one subject each with increased eosinophils (>750/mm^3) and decreased lymphocytes (<750/mm^3).

On irbesartan monotherapy there was one subject with a marked increase in BUN. However there were 12 (3.1%) subjects who received combination therapy who had marked elevations of BUN. This is in comparison to HCTZ monotherapy which had only 2 subjects (1.7%).

There was only one subject on combination therapy who had hypokalemia (0.9x lower limit of normal). There was only one subject on irbesartan monotherapy who had hyperkalemia (1.1x upper limit of normal). Statistically significant changes from baseline (sponsor's analysis) were observed in the HCTZ 25 (decreased K^+), IRB 37.5/HCTZ 25 (decreased K^+) and IRB 300 (increased K^+).

Triglycerides were markedly increased in 8 (2.6%) subjects taking combination therapy. One subject's triglycerides were markedly abnormal (>2.5x upper limit of normal). Values ranged from 3 to 7x baseline values.

Increased RBCs in urine were seen in HCTZ and irbesartan monotherapy and with combination therapy compared to placebo.

There were no changes in physical examination noted in the study.

A21.6. Summary

The study shows that irbesartan in combination with HCTZ lowers trough SeDBP and SeSBP and showed that there was at least one combination that was superior to each of its components. The response surface was fitted by a quadratic dependence on irbesartan and a linear dependence on HCTZ, because the response to irbesartan begins to plateau within the tested dose range, whereas the response to HCTZ does not. Although the model predicts a drop-off in blood pressure effect at some dose of irbesartan, this dose is beyond the dose range studied. The proportion of subjects normalized or showing at least a 10 mmHg change increases monotonically with dose of irbesartan or HCTZ.

There was an increased incidence of elevated BUN with combination therapy. This is expected since both irbesartan and HCTZ would be expected to produce dose-dependent increases in BUN based on their mechanism of action. There were also several cases of marked increases in triglycerides. Both observations will be discussed in the integrated review of safety.

A22. CV131-038: Double-blind, placebo-controlled, comparison of the combination of irbesartan and hydrochlorothiazide versus individual components in mild-to-moderate hypertension.

A22.1. Study documents

Study report: NDA 20-757, vols 1.288 - 1. 295.

A22.2. Investigators

This study was conducted at 63 sites by 53 US investigators and 10 Latin American investigators.

A22.3. Study dates

26 October 1994 to 19 September 1995.

A22.4. Study design

The study description was based on approved protocol dated 22 June 1993. This was a randomized, double-blind, placebo-controlled trial in subjects with mild-to-moderate hypertension (SeDBP 95 to 110 mmHg). Study design is shown in Figure 57 below. Following a 4-week single-blind placebo lead-in period (with an optional fifth week to meet blood pressure criteria), qualified subjects started a 12-week double-blind randomized treatment period with one of the following once-daily oral regimens: irbesartan 75 mg plus HCTZ 12.5 mg, irbesartan 150 mg plus HCTZ 12.5 mg, irbesartan 75 mg alone, irbesartan 150 mg alone; HCTZ 12.5 mg alone, or placebo. Subjects completing the double-blind phase of trial were eligible for enrollment in an optional one-year long-term open-label extension period.

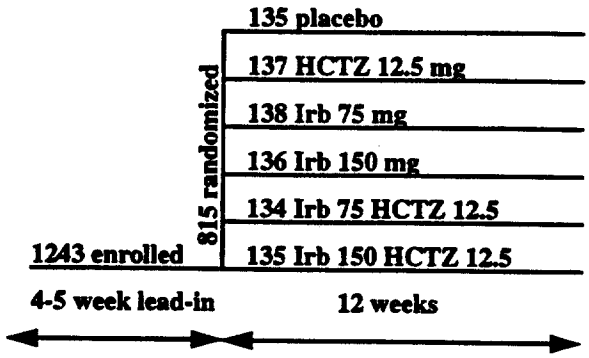

Figure 57. Study design (CV131-038).

Subjects were to be males or surgically sterile or post-menopausal, non-lactating females >18 years old, with SeDBP 95 to 110 mmHg.

Drug supplies are presented in Table 1.

Table 225. Drug supplies (CV131-038).

	Product	Lot		Product	Lot
Placebo irbesartan	186295-030	N94F098BC	Irbesartan 25 mg	186295-031	N94F095C
Placebo HCTZ	186295-026	N94G09BC	Irbesartan 50 mg	186295-032	N94G09bC
HCTZ 12.5 mg	186295-022	N94F08bC	Irbesartan 100 mg	186295-033	N94G097C

The primary objectives of this study were to compare effects of HCTZ and irbesartan alone and in combination on SeDBP at 12 weeks, and to assess the tolerability of the combination.

Secondary end points included comparisons of effects on StDBP, SeSBP, StSBP, response rates, serum potassium, and lipid levels.

Safety was assessed by medical history, physical examinations, changes in ECG, sponsor-defined laboratory analyses including fasting glucose and lipid levels, and monitoring for adverse events.

A22.5. Results

Individual sites enrolled 2 to 54 subjects.

The study screened 1243 subjects, of whom 815 subjects were randomized. Reasons for exclusion prior to randomization are shown in Table 226 below. Of the 815 randomized subjects, 724 (89%) completed the study. Demographic characteristics of randomized subjects are compared in Table 227 below. None of the differences among groups was statistically significant. About 81% of subjects had been on prior antihypertensive therapy. The ratios of subjects by age (<65:>65 years), sex (M:F), and race (Whites: Blacks: Others) were 5.6:1, 1.2:1, and ~7:1:2, respectively. There were no statistically significant differences among groups with respect to baseline vital signs.

Table 226. Exclusions prior to randomization (CV131-038).

	N		N		N
Subject did not qualify	255	Administrative reason	5	Others	2
Subject request	74	BP high (investigator opinion)	5	Investigator request	2
Adverse event	31	Poor compliance	4	Protocol violation	1
Lost to follow-up	27	Concomitant medication	3		
BP >protocol limit	15	Death	3		
Total	427				

Table 227. Demographics (CV131-038).

	Irbesartan 0 mg		Irbesartan 75 mg		Irbesartan 150 mg	
	HCTZ 0 N=135	HCTZ 12.5 N=137	HCTZ 0 N=138	HCTZ 12.5 N=134	HCTZ 0 N=136	HCTZ 12.5 N=135
Age mean (y)	55	53	54	54	53	55
Min, max						
>65 (%)	19	15	17	12	13	17
>75 (%)	1	1	3	2	0	1
Male (%)	59	58	53	54	55	53
Female (%)	41	42	47	46	45	47
White (%)	69	74	67	66	72	74
Black (%)	12	14	9	14	10	8
Others (%)	19	14	23	20	18	18

The disposition of randomized subjects is shown in Table 228 below.

Table 228. Post-randomization withdrawals (CV131-038).

	Irbesartan 0 mg		Irbesartan 75 mg		Irbesartan 150 mg	
	HCTZ 0 N=135	HCTZ 12.5 N=137	HCTZ 0 N=138	HCTZ 12.5 N=134	HCTZ 0 N=136	HCTZ 12.5 N=135
Adverse events	10	8	7	5	5	4
BP>limit	2	0	1	0	0	1
BP high (investigator's opinion)	6	1	3	0	2	0
Concomitant medications	0	0	1	1	1	0
Death	0	0	0	1	0	0
Loss to follow-up	2	0	1	1	1	2
Total	25	17	15	12	13	9

Table 228. Post-randomization withdrawals (CV131-038). *(Continued)*

	Irbesartan 0 mg		Irbesartan 75 mg		Irbesartan 150 mg	
	HCTZ 0 N=135	HCTZ 12.5 N=137	HCTZ 0 N=138	HCTZ 12.5 N=134	HCTZ 0 N=136	HCTZ 12.5 N=135
Not qualified	0	1	0	0	0	0
Personal reasons	1	0	0	0	0	0
Poor compliance	0	0	0	0	0	1
Protocol violations	1	3	1	1	1	1
Subject request	3	4	1	3	3	0
Total	25	17	15	12	13	9

A22.5.1. Pharmacodynamics

Analysis of efficacy based on completing subjects is shown in Table 229 below. Irbesartan plus HCTZ was superior to the components alone for reducing SeDBP and SeSBP at weeks 6 and 12. LOCF analyses gave similar results.

Table 229. Efficacy data at week 12 (CV131-038).

		Irbesartan 0 mg		Irbesartan 75 mg		Irbesartan 150 mg	
		HCTZ 0	HCTZ 12.5	HCTZ 0	HCTZ 12.5	HCTZ 0	HCTZ 12.5
All	N	135	137	138	134	136	135
	SeDBP	-5.1	-8.0	-8.2	-11.2*#	-9.7#	-11.6*#
	StDBP	-3.43	-5.8	-7.5	-10.4	-8.4	-11.1
	SeSBP	-3.3	-8.7	-7.6	-15.3	-12.3	-16.5
	StSBP	-2.5	-8.2	-8.2	-14.3	-11.5	-15.6
	T:P SeDBP	N/A	1.73	0.63	0.66	0.64	0.68
	Normalized (%)	24	29	32	54	35	51
White	N	99	102	93	88	98	100
	SeDBP	-3.5	-7.4	-8.4	-10.5	-9.7	-12.1
	StDBP	-2.5	-5.3	-8.2	-9.3	-8.3	-11.4
	SeSBP	-2.1	-7.8	-7.6	-15.1	-12.2	-17.3
	StSBP	-2.2	-7.0	-8.5	-13.8	-11.5	-16.1
Black	N	16	16	13	19	14	11
	SeDBP	-5.2	-8.5	-4.9	-11.6	-7.2	-9.5
	StDBP	-3.3	-5.8	-5.3	-11.1	-5.9	-8.9
	SeSBP	-3.0	-10.1	-8.4	-13.6	-10.1	-7.7
	StSBP	-0.3	-9.6	-9.6	-12.8	-9.4	-9.5
Others	N	26	19	32	27	24	24
	SeDBP	-9.9	-10.7	-9.2	-13.3	-10.7	-10.8
	StDBP	-5.9	-8.7	-7.3	-14.5	-10.1	-12.9
	SeSBP	-6.1	-11.9	-7.1	-17.1	-13.8	-17.2
	StSBP	-4.8	-11.9	-6.2	-17.8	-13.4	-17.8

*P<0.05 by sponsor's analysis
#P<0.05 by reviewers' analysis—Pearson's χ^2 without Yates continuity correction.

The response rate was analyzed by comparison of the proportion of subjects who, at week 12, had either a reduction in SeDBP <90 mmHg or a reduction from baseline in SeDBP >10 mmHg. These data are shown in Table 230 below. Nominally statistically significant differences from placebo were found for irbesartan 150 mg alone and for

both combination treatment groups. In addition, nominally statistically significant differences were found for both combination arms compared with either HCTZ alone or irbesartan 150 mg alone.

Table 230. Response rate at week 12 (CV131-038).

HCTZ	Response rates (%)					
	Irb 0		Irb 75		Irb 150	
	0	12.5	0	12.5	0	12.5
SeDBP<90	30	33	35	59	39	56
↓SeDBP>10	3.6	8.8	8.0	6.4	11	8.8
Neither	66	59	57	34	50	36

The time course of changes in SeDBP by treatment group is shown in Figure 58 below. Placebo-subtracted treatment effects are largely manifest by 6 weeks.

There were no significant drug related changes in placebo-adjusted heart rate changes (SeHR and StHR).

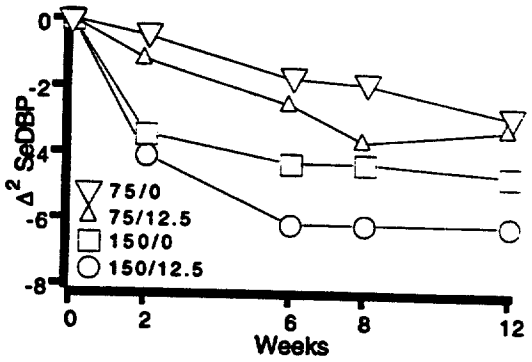

Figure 58. Change in SeDBP by time and dose (CV131-038).

The possible effects of age on treatment were analyzed by comparing blood pressure measurements in subjects below and above 65 years. Without placebo-adjustment, mean changes in SeDBP and SeSBP showed no significant differences.

The effect of placebo on SeDBP was smallest in Caucasians and largest in other non-blacks. Placebo-adjusted reductions in SeDBP was somewhat smaller in blacks than in Caucasians; treatment effects on other non-blacks was not different from placebo. Analyses of response rates showed similar results.

Analyses of SeDBP showed no significant differences in responses of males and females.

A22.5.2. Safety

Two subjects committed suicide and one subject died from myocardial infarction during the placebo lead-in phase. One subject died suddenly 6 days after discontinuation from the placebo lead-in period. One subject died from myocardial infarction after receiving irbesartan 75 mg plus HCTZ 12.5 mg for 28 days during the double-blind phase.

A total of 39 (4.8%) of the randomized subjects were discontinued because of drug-related adverse events or abnormal laboratory tests. Adverse events led to discontinuation of 9/269 (3.3%) subjects randomized to combination therapy, 12/274 (4.4%) subjects randomized to irbesartan monotherapy, 8/137 (5.8%) subjects randomized to HCTZ, and 10/135 (7.4%) subjects randomized placebo.

The proportion of subjects experiencing any adverse event ranged from 50% on placebo to 59% on irbesartan 150 mg plus HCTZ 12.5 mg. The most common adverse events in the pooled irbesartan treatment groups were headache, musculoskeletal pain, upper respirator infection, and dizziness. Of those, headache was more common on placebo.

One subject each had microscopic hematuria, proteinuria, and increased serum creatinine; otherwise there were no marked laboratory abnormalities.

A22.6. Summary

This was an adequate, and well controlled, double-blind, placebo-controlled study of HCTZ 12.5 mg and irbesartan 75 mg and 150 mg, in a population of mild-to moderate hypertensive subjects which included a modest number of Blacks, females and elderly. Modest, but statistically significant, blood pressure effects were seen with combination therapy compared to the components of the combination. Although there was no significant treatment difference between placebo and irbesartan 75 mg alone, reasonable dose-response curves suggest that irbesartan 75 mg plus HCTZ 12.5 mg is a useful dose. Irbesartan 150 mg alone was not as effective as either the combination of irbesartan 75 mg plus HCTZ 12.5 mg or irbesartan 150 mg plus HCTZ 12.5 mg. Placebo-subtracted effects on blood pressure developed over weeks of treatment.

A23. CV131-039: The antihypertensive efficacy of the combination of irbesartan and hydrochlorothiazide as determined by 24-hour ambulatory blood pressure monitoring.

A23.1. Source documents

Study report: NDA 20-758, vol 1.55 to 1.59; electronic document MAST039.PDF; CANDA.

A23.2. Investigators

This study was conducted at 20 sites in Australia, New Zealand and South Africa.

A23.3. Study dates

19 April 1995 to 4 March 1996.

A23.4. Study design

This study description was based upon the protocol dated 14 November 1994. There were only administrative amendments written after the start of enrollment.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (95 < SeDBP <110 mmHg). Figure 59 below shows a schematic of this trial. After a 4- to 5-week lead-in period, an ambulatory blood pressure monitor (APBM) was to be placed if the subject's seated diastolic blood pressure (SeDBP) was between 95 and110 mmHg on the last two successive visits. An ambulatory blood pressure monitor was placed on the subject for at least 24 hours for a baseline. Readings were taken every 15 minutes during waking hours and every 20 minutes during sleep. By an administrative amendment dated 11 July 1995, the night time readings decreased from every 20 minutes to every 30 minutes. If the average hourly diastolic blood pressure over the 24-hour period was greater than 85 mmHg (after checking for the adequacy of the data obtained) the subject was randomized to placebo, irbesartan 75 mg plus HCTZ 12.5 mg qd, or irbesartan 150 mg plus HCTZ 12.5 mg qd. There were routine visits at 1, 2, and 4 weeks. On week 8, an APBM was placed after ingestion of study drug.

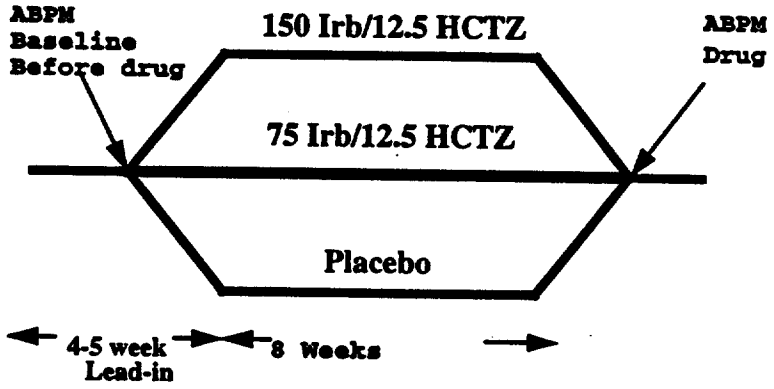

Figure 59. Study design (CV131-039).

Drug supplies are shown in Table 231 below.

Table 231. Drug supplies (CV131-039).

	Product code	Lot		Product code	Lot
HCTZ Placebo	186295-A000-062	M94L052C	IRB Placebo	186295-R000-030	L94F014C
HCTZ 12.5 mg	186295-R075-054	M94G041C	IRB 75 mg	186295-R075-054	L94F031C

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects must have had a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Subjects with renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded. If seated systolic blood pressure (SeSBP) or diastolic blood pressure was

>220 mmHg or >115 mmHg respectively, the subject was excluded. Subjects who were taking the following agents were not enrolled (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilators, or (8) NSAIDs greater than 7-day duration (low dose ASA excepted). Subjects must have been able to wean other antihypertensives and vasoactive agents.

The primary efficacy variable in this study was the change from baseline in hour-averaged ABPM data over a 24-hour period after the ingestion of study drug. Secondary end points were as follows: (1) the reduction in trough (i.e., 24±3 hours after the previous day's dose) office seated diastolic blood pressure, (2) the reduction in the mean daytime (i.e., the first 12 hours after the dose), (3) the reduction in the mean 24-hour and daytime ambulatory systolic BP, (4) the trough:peak ratios of ambulatory blood pressure (ABP) reduction and the ABP reduction during the 24th hour after the dose, (5) the reduction at week 8 in trough office seated systolic blood pressure and standing systolic and diastolic BP, (6) the proportions of subjects whose office SeDBP was normalized (decreased to <90 mmHg) or responds (decreased by 10 mmHg), and (7) safety and tolerability.

According to the original protocol, the sample size calculation of 50 per group was based on 90% power to detect a difference of 4.6 mmHg with a standard deviation of 7.0 mmHg and α=0.05. Changes in blood pressure from baseline would be compared between treatments using analysis of covariance (ANCOVA) with the baseline value as a covariate. Statistical significance was assessed using the protected LSD method.

In the original protocol, any hours with missing values were to be interpolated from the preceding and following hours. The final study report states that missing hourly averages were ignored.

Subjects who discontinued early were to go through the schedule of events at week 8, including ABPM.

Safety assessments were to include (1) ECG, (2) laboratory tests (CBC, SMA20, urinalysis), and (3) physical examination. Clinical adverse events and their relationship to the study drug were to be recorded.

A23.5. Results

There were 367 subjects enrolled. Disposition of enrolled subjects is shown in Table 232 below. Eleven 'completing' subjects did not have adequate ABPM at baseline or week 8.

Table 232. Subject disposition (CV131-039).

	N
Enrolled	367
Not Randomized	189
Randomized	178
Discontinued	13
Completed	165
Evaluable subjects at week 8	154

Table 233 below shows reasons for exclusion prior to randomization.

Table 234 below gives the reasons for discontinuations from study medication in the double-blind period. Eleven subjects were excluded from the primary analysis for insufficient data. Insufficient data was defined as not having at least one reading of ABP within at least 21 of the 24 post-dosage hours in both the baseline and 8-week ABPM records taken (>44 days after randomization).

Table 233. Reasons for exclusion (CV131-039).

	N		N
Did not qualify	117	Concomitant medication	7
Subject request	22	Poor compliance	1
Adverse event	19	BP high in opinion of investigator	1
Blood pressure above limit	15	Other	4
Lost to follow-up	3		
Total	189		

Table 234. Reasons for discontinuation (CV131-039).

	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63		Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
Adverse events	4	3	1	Poor BP control	0	1	0
BP↑ above limit	1	0	0	Failed entry criteria	0	1	0
Protocol violation	1	0	1				
Completed	51	53	61				

Demographics of the four treatment groups are shown in Table 235 below. There was no statistically significant differences among groups in terms of gender, race, or age. The majority of subjects were male.

Table 235. Demographics (CV131-039).

		Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63			Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
Gender	Male (%)	61	60	56	Age	Mean±SD	53±9	55±10	54±10
	Female (%)	39	40	44					
Race	White (%)	70	72	78		≥65 (%)	7	16	4
	Black (%)	16	14	8		≥75 (%)	2	3	0
	Other (%)	14	14	14					

There were no significant differences among groups with respect to baseline ABPM diastolic or systolic blood pressure, as shown in Table 236 below, or with respect to baseline seated and standing cuff blood pressures, as shown in Table 237 below.

Table 236. Baseline ABPM data (CV131-039).

	DBP, mmHg (mean±SE)			SBP, mmHg (mean±SE)		
	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
24-hour	93±1	93±1	93±1	147±2	149±2	152±2
Male	92±1	93±1	93±1	146±2	147±3	149±2
Female	94±1	93±1	93±1	152±3	152±3	157±2
Daytime	99±1	99±1	98±1	155±2	156±2	159±2
Trough	98±1	99±1	99±1	153±2	155±2	159±2

Table 237. Baseline cuff blood pressures (CV131-039).

	Seated (mean±SE)			Standing (mean±SE)		
	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
DBP	99±1	99±1	101±1	103±1	102±1	104±1
SBP	158±2	154±2	156±2	159±2	155±2	157±2

Baseline ABPM data for each treatment group is given in Figure 60 below.

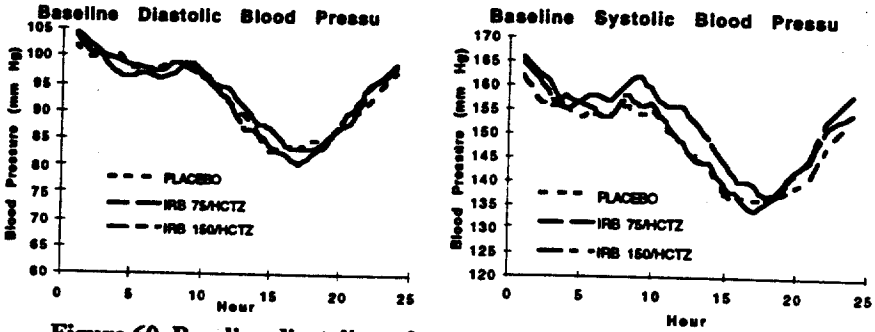

Figure 60. Baseline diastolic and systolic ABPM data (CV131-039).

A23.5.1. Pharmacodynamics

The mean changes from baseline in 24-hour ambulatory diastolic and systolic pressures are given in Table 238 below. Included were all available final ABPM data at week 8. No attempt to exclude data secondary to protocol deviations was made. Mean 24-hour SBP and DBP and mean 12-hour SBP had a significant baseline-by-treatment interaction. Active treatment groups were statistically significantly different from placebo for changes in DBP and SBP, for 24-hour averages, daytime averages, and trough measurements. The reviewers' and the sponsor's analyses gave similar results.

Table 238. Changes in ABPM data (CV131-039).

	24-hour average			Daytime average			Trough		
	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
DBP (mean±SE)	-3±1	-11±1	-14±1	-2±1	-12±1	-14±1	-1±2	-12±2	-12±2
Male	-2±1	-11±2	-13±1						
Female	-4±1	-11±2	-14±1						
SBP (mean±SE)	-5±2	-20±2	-22±2	-4±2	-22±2	-24±2	-2±2	-20±2	-20±2
Male	-3±2	-19±3	-19±2						
Female	-5±2	-22±3	-27±2						

Figure 61 below shows 24-hour ABPM data at week 8.

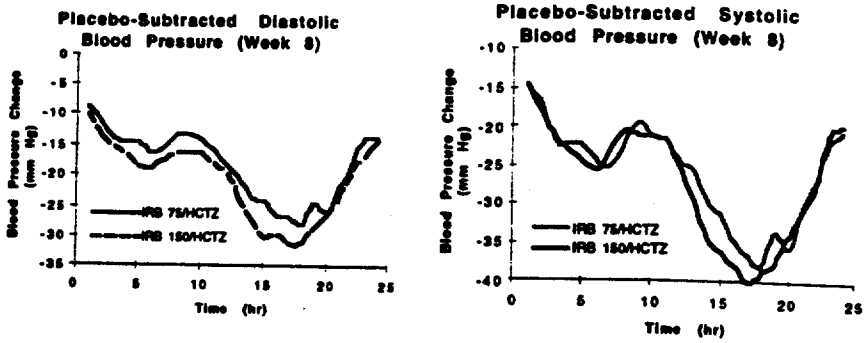

Figure 61. ABPM systolic and diastolic blood pressure at week 8 (CV131-039).

Mean change in trough seated diastolic and systolic blood pressure is given in Figure 62 below. For SeSBP and StDBP, there was a significant baseline by treatment interaction. There were no statistically significant treatment effects on trough seated or standing heart rate.

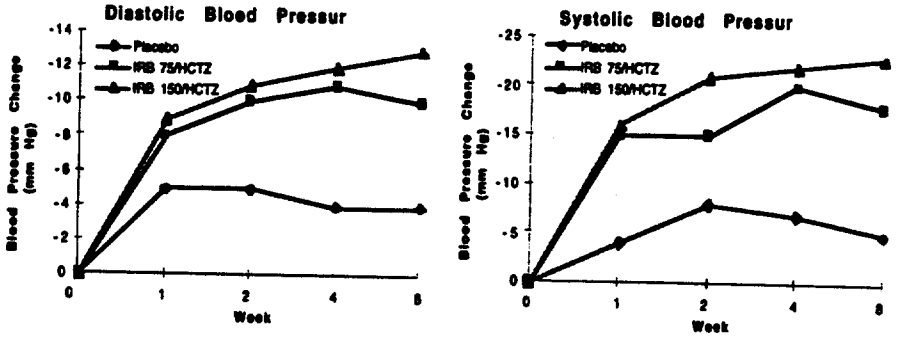

Figure 62. Changes in trough seated blood pressure (CV131-039).

A summary of response rates at week 8 is given in Table 239 below. Each active treatment group was statistically significantly superior to placebo for normalization or the total response rate.

Table 239. Response rate at week 8 (CV131-039).

	Placebo N=57	Irbesartan 75 mg N=58	Irbesartan 150 mg N=63
Normalized (%)	24	65	69
Total responders (%)	29	78	77

Elderly subjects were not analyzed separately since their numbers in the trial were small.

A23.5.2. Safety

There was a mean exposure of the study drug of approximately 56 days. No deaths were reported.

One subject randomized to irbesartan 150 mg plus HCTZ experienced a migraine headache after 2 days of treatment. The serious adverse event did not cause discontinuation of the study medication.

There were eight dropouts due to adverse events in the 8-week double-blind period. Table 240 below shows treatment duration and adverse event of the irbesartan subjects.

Table 240. Discontinuations due to adverse events (CV131-039).

Group	Days	Adverse event
IRB 75/HCTZ	13 7 37	Headache Palpitations Malaise
IRB 75/HCTZ	26	Headache, chest pain
IRB 150/HCTZ	1	Nausea, headache weakness, rash

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events occurred in the nervous, gastrointestinal, cardiovascular, and general body systems.

The most common treatment-emergent adverse event were fatigue, headache, nausea/vomiting, musculoskeletal pain, and dizziness. Seven events (headache, fatigue, nausea/vomiting, musculoskeletal pain, dizziness, influenza, and pharyngitis) tended to occur more frequently with irbesartan/HCTZ treatment compared to placebo.

One complaint of dizziness was secondary to hypotension after 40 days of study drug. The medication was reduced to every other day and symptoms resolved within 2 days. No blood pressure readings were taken at the time of the event.

One subject on irbesartan/HCTZ experienced orthostatic hypotension. Two subjects on irbesartan combination therapy experienced symptoms of orthostatic dizziness. Blood pressures taken showed no evidence of orthostasis. No orthostatic symptoms caused discontinuation of the study drug.

Syncope was reported in one subject on irbesartan/HCTZ 17 days after randomization. Emergency room evaluation was negative including ECG, neurological exam, and blood pressure testing. The subject continued with the trial to completion. Further testing, if done, was not reported by the sponsor.

The number (%) of subjects reporting at least one adverse event within the first 24 hours of randomization was greater in the irbesartan 150 mg/HCTZ 12.5 mg dosing group (12/63; 19%) than in the placebo (6/57; 11%) or irbesartan 75 mg/HCTZ 12.5 mg (3/58; 5%) dosing groups. Symptoms reported more frequently in the irbesartan groups compared to placebo were headache, fatigue, nausea/vomiting, and cough.

Marked hemotologic abnormalities in this trial were minimal.

Serum chemistry marked abnormalities were few. Two subjects had hypokalemia in the irbesartan 150/HCTZ group. One subject had transient hyperkalemia on irbesartan 75 mg/HCTZ.

No significant changes in physical exam or ECG were noted.

A23.6. Summary

The study was a randomized, placebo-controlled ABPM study with combination irbesartan and HCTZ. There was a significant baseline effect. APBM analysis was done with all subjects with ABPM data at week 8. Irbesartan 75 mg and 150 mg, in conjunction with HCTZ, were effective in reducing ambulatory blood pressure. Consistent and statistically significant treatment effects were also seen for seating and

standing office blood pressures. The 75-mg and 150-mg doses were not distinguishable from one another.

There were no deaths or serious adverse events to comment upon.

A24. CV131-040: The efficacy and safety of irbesartan added to hydrochlorothiazide for the treatment of hypertension in subjects nonresponsive to hydrochlorothiazide alone.

A24.1. Source documents

Study report: NDA 20-757, vol 1.334 to 1.339; electronic document MAST040.PDF.

A24.2. Investigators

This study was conducted at 44 sites in the US and Canada.

A24.3. Study dates

17 January 1995 to 05 December 1995.

A24.4. Study design

This study description was based upon the protocol dated 20 October 1994. There was no protocol amendment after the start of randomization. There were minor changes in the entry criteria to allow subject >75 years to enter the study and was liberalized slightly to allow for mild elevations of serum creatinine and urine protein. The protocol amendment allowed a shortened single-blind lead in period to allow subjects to enter the HCTZ single-blind phase after two measurements. It also allowed addition of K^+ as necessary to keep subjects normokalemic.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (93 < SeDBP <110 mmHg and SeSBP ≤200 mmHg) who did not normalize after administration of HCTZ 25 mg. Figure 63 below shows a schematic of this trial. After a single-blind two-week lead-in period, eligible subjects entered into the 4-week HCTZ phase if 111≤SeDBP≤120 on 2 occasions 1 to 3 days after entry or after 2 weeks if 95≤SeDBP≤120. After the 4-week HCTZ phase, the subject was to be randomized to receive irbesartan 75 mg or placebo. If the subject's SeDBP>90 at the end of 6 weeks, the dose was doubled. The subjects were followed for an additional 6-week period. The intent was to randomize approximately 95 subjects equally between the treatment groups for a total of 190 subjects. The total double-blind period was 12 weeks.

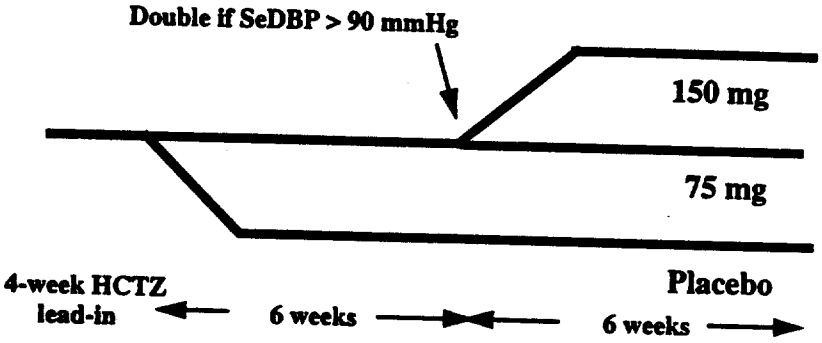

Figure 63. Study design (CV131-040).

Drug supplies are shown in Table 241 below.

Table 241. Drug supplies (CV131-040).

	Product Code	Lot		Product Code	Lot
Placebo Irbesartan	186295-R000-030	N94F090C	Irbesartan 75 mg	186295-R075-054	N94K136C
Placebo HCTZ	186295-A000-026	N94G098C	HCTZ 25 mg	186295-AXXX-013	N94G099C

The subjects were taken from a healthy, non-obese population aged over 18 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild funduscopic changes). Subject with significant renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, cerebrovascular disease, or abnormal laboratory values (with exception of mild

increases in serum creatinine and urine protein) prior to randomization were excluded. Subjects who were taking the following agents were excluded: (1) immunosuppressive agents, (2) neuropsychiatric or anticonvulsant agents, (3) digitalis, (4) bile-acid binding resins, (5) omeprazole or cimetidine, (6) steroids with exception of low-dose estrogen replacement therapy, (7) bronchodilators, or (8) NSAIDs greater than 7-day duration (low dose ASA excepted). Subjects must have been able to wean antihypertensives and other vasoactive agents.

The primary efficacy variable in this study was the change from baseline to week 12 in trough SeDBP. Secondary end points are as follows: (1) trough SeDBP at 6 weeks, (2) trough StDBP at 6 and 12 weeks, (3) trough SeSBP and StSBP at 6 and 12 weeks, and (4) degree of therapeutic response at 6 and 12 weeks. The subjects' blood pressure during the double-blind period was measured at weeks 2, 6, 8, and 12.

The datasets used for the primary and secondary analysis were intent-to-treat (primary data set) and one which excludes protocol violations (secondary data set). Statistical significance was determined by analysis of covariance using baseline and center as covariates.

Safety assessments to be done in the single- and double-blinded period included ECG and laboratory tests (CBC, SMA20, urinalysis). Clinical adverse events and their relationship to the study drug were recorded.

A24.5. Results

There were 478 subjects enrolled. Disposition of enrolled subjects is shown in Table 242 below.

Table 242. Subject disposition (CV131-040).

	N
Enrolled	489
Not randomized	251
Randomized	238
Discontinued	19
Completed	219
Evaluable subjects at week 12	221

Table 243 below shows reasons for exclusion prior to randomization.

Table 243. Reasons for exclusion

Reason	Lead-in period	HCTZ period	Reason	Lead-in period	HCTZ period
Did not qualify	92	66	Blood pressure above limit	3	2
Subject request	17	5	Lost to follow-up	8	6
Adverse event	2	15	Unknown	3	0
Concomitant Meds	9	1	Lab abnormality	0	1
Investigator request	1	0	Other	12	5
Poor compliance	0	3			
Total	147	104			

Table 244 below gives the reasons for discontinuations from study medication during the double-blind period.

There were a total of 22 subjects with significant protocol deviations. These were excluded from the secondary dataset but were included in the primary (ITT) dataset.

Table 244. Reasons for discontinuation (CV131-040).

	Placebo N=120	Irbesartan N=118		Placebo N=120	Irbesartan N=118
Adverse event	4	4	Concomitant medication	1	0
BP above limit	1	0	Lost to follow-up	1	0
BP high in investigator opinion	0	1	Protocol violation	1	1
Death	0	0	Subject request	3	1
Did not qualify	1	0			
Completed	99	98			

Demographics of the two treatment groups are shown in Table 245 below. There were no statistically significant differences between treatment groups.

Table 245. Demographics (CV131-040).

		Placebo N=120	Irbesartan N=118			Placebo N=120	Irbesartan N=118
Gender	Male (%)	62	64	Age	Mean±SD	55±11	53±10
	Female (%)	38	36				
Race	White (%)	81	84		≥65 years (%)	18	11
	Black (%)	12	12		≥75 years (%)	2	3
	Other (%)	8	4				

There were no significant differences between treatment groups with regard to baseline seated blood pressure or heart rate (see Table 246 below). There were site interactions among some of the baseline variables.

Table 246. Baseline vital signs (CV131-040).

	Seated		Standing	
	Placebo N=120	Irbesartan N=118	Placebo N=120	Irbesartan N=118
DBP (mean±SE)	99±0.4	99±0.4	100±1	100±1
90<DBP<95 (%)	27	28		
95≤DBP≤100 (%)	39	45		
>100 (%)	34	27		
SBP (mean±SE)	149±1.5	148±1.4	149±1.5	147±1.5
HR (mean±SE)	74±1	73±1	78±1	76±1

A24.5.1. Pharmacodynamics

Analysis of seated and standing blood pressure using the LOCF dataset is given in Table 247 below. ANOVA analysis showed a number of site and baseline interactions with this data set. There was no significant difference in seated or standing heart rate. Mean changes in trough SeDBP and SeSBP showed no significant difference between male and female subjects.

Trough SeDBP and SeSBP mean change showed a smaller reductions in the black population. There was a larger placebo effect in black subjects. However, since there was a small number of non-white subjects, any conclusion from the data is problematic.

Trough SeDBP and SeSBP mean change showed similar response of seated blood pressures between subjects aged <65 and >65. However, since there were relatively

Table 247. Change in blood pressure (CV131-040).

	Diastolic		Systolic	
	Placebo N=120	Irbesartan N=118	Placebo N=120	Irbesartan N=118
Seated (mean±SE)	-5±1	-12±1*	-3±1	-14±1*
Male	-3±1	-11±1	-3±2	-13±2
Female	-6±1	-10±1	-5±2	-11±2
White	-4±1	-11±1	-3±1	-13±2
Black	-6±2	-9±2	-7±3	-14±3
<65 years	-4±2	-11±1	-3±1	-13±1
≥65 years	-5±2	-11±1	-5±4	-15±5
Standing (mean±SE)	-3±1	-10±1*	-2±1	-13±1*

*Irbesartan was statistically significant (p<0.01) compared to placebo

few older subjects in each treatment group, the power is not adequate enough to draw any conclusions.

Placebo subtracted seated and standing blood pressures as a function of time is given in Figure 64 below.

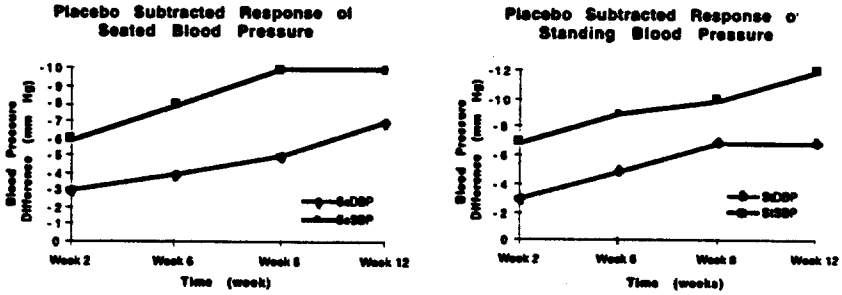

Figure 64. Placebo-subtracted blood pressure changes (CV131-040).

Referring to Table 248 below, there was a similar significant treatment effect on peak vital signs ($p<0.01$) compared to placebo (evaluable subjects with valid data).

Table 248. Changes in peak SeDBP and SeSBP (CV131-040).

	Peak seated diastolic		Peak seated systolic	
	Placebo N=120	Irbesartan N=118	Placebo N=120	Irbesartan N=118
Baseline (mean±SD)	99±5	99±5	147±14	145±14
Change from baseline	-7±1	-18±1	-6±1	-20±1
Difference from placebo		-11*		-14*

*p<0.01

A summary table of the sponsor's analysis of therapeutic response is shown in Table 249 below.

The effect of titration on changes from baseline are given in Table 250 below.

Table 249. Response rate (CV131-040).

	Placebo N=120	Irbesartan N=118
Normalized (%)*	29	67
Relative benefit (95%CI)**		2.3 (1.7, 3.0)
Total responders (%)***	32	77

*Normalized defined as trough SeDBP <90 mmHg
**Proportion responders on drug / proportion responders placebo
***Subjects normalized or SeDBP decreased at least 10 mmHg

Table 250. Changes in trough BP for subjects titrated at week 6 (CV131-040).

	Change in SeDBP (mmHg)		Change in SeSBP (mmHg)	
	Placebo	Irbesartan	Placebo	Irbesartan
Titrated subjects (%)	65	41	65	41
Week 6 (mean±SD)	-2±1	-6±1	-1±2	-8±2
Week 12 (mean±SD)	-3±1	-10±1	-4±2	-12±2

A24.5.2. Safety

There was a mean exposure of the study drug of approximately 83 days. There was no significant statistical difference between the treatment groups.

No deaths occurred during the study.

There were 19 dropouts in the 12-week blind period. Eight subjects discontinued for adverse events as shown in Table 251 below.

Table 251. Discontinuations due to adverse events (CV131-040).

	Days	Adverse event		Days	Adverse event
Placebo	2	Stroke	Irbesartan	58	Hypokalemia
Placebo	90	C5 radiculopathy	Irbesartan	3	Rash
Placebo	46	Elevated CK	Irbesartan	10	Petechiae/rash
Placebo	25	Ovarian cancer	Irbesartan	17	Abdominal pain

Eight subjects experienced a total of 8 serious adverse events, as shown in Table 252 below.

Table 252. Serious adverse events (CV131-040).

	Days	Adverse event		Days	Adverse event
Placebo	10	Nonspecific ST; neg cath	Irbesartan	48	Skin cancer
Placebo	2	Stroke	Irbesartan	79	Pancreatitis; H/O in past
Placebo	41	Skin cancer	Irbesartan	67	Sarcoidosis
Placebo	13	Skin cancer			
Placebo	25	Ovarian cancer			

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events were headache, dizziness, fatigue, musculoskeletal pain, edema, abdominal pain and nausea/vomiting. Syncope was reported in 3 subjects on irbesartan but none on placebo. One subject fainted during a blood draw and the other following heat exposure. The latter subject was titrated to irbesartan 150 mg at week 6. Ten weeks

after randomization, the subject experienced intermittent syncope which resolved after reduction back to 75 mg.

Marked hematologic abnormalities observed were high leukocytes (2 IRB, 1 PLA), eosinophillia (3 IRB, 1 PLA) and lymphopenia (3 IRB, 1 PLA).

Four placebo subjects had marked serum chemistry abnormalities.

Marked abnormalities of urine were comparable between irbesartan and placebo.

No significant changes in physical exam or ECG were noted.

A24.6. Summary

The current study demonstrates that the addition of irbesartan 75 or 150 mg is efficacious in reducing trough SeDBP and SeSBP in subjects not adequately treated by HCTZ alone.