Marked abnormalities in other electrolyte or urinalysis parameters were rare and generally not even numerically more common on active treatment than on placebo.

8.2.6. Hematologic system

8.2.6.1. Adequacy of hematologic assessment

Hematologic safety was assessed through red cell counts, while blood cell counts and differentials, platelet counts, and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.6.2. Hematologic events at least possibly drug-related

8.2.6.2.1. Hematologic deaths

There were no deaths attributed to hematologic events.

8.2.6.2.2. Serious hematologic adverse events

No serious hematologic adverse events were plausibly attributable to study drug.

8.2.6.2.3. Withdrawals for hematologic adverse events

Withdrawals for hematologic adverse events plausibly related to irbesartan are listed in Table 47 below.

Table 47. Withdrawals for hematologic adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	015/009	36	M	10	—	35	Discontinued with repeated episodes of epistaxis, possibly related to poor blood pressure control.
CV131-038	016/005	62	F	150	—	4 51	Complaint of palpitations, blurred vision, and dependent edema at day 4, resolved on treatment. Later discontinued for epistaxis, which resolved within 3 weeks. Causal relationship was not reported.
CV131-050	045/009	58	M	900	—	5	Discontinued with epistaxis, considered unlikely to be drug-related. Event resolved.
Long-term phase							
CV131-002	039/009	56	F	100	—	520	Discontinued with petechia on legs, abdomen, and back; platelet count was 232,000. Event was unresolved.
CV131-037	032/011	60	F	75	12.5	8	Discontinued with petechia on legs, considered possibly drug-related. Event did not resolve.
CV131-037	035/009	36	M	150	25	41	Discontinued for thrombocytopenia—decrease from 269 at baseline to 52/mm^3. Atenolol was substituted for HCTZ and event resolved.

8.2.6.3. Hematologic events unlikely to be drug-related

8.2.6.3.1. Hematologic deaths

There were no deaths attributed to hematologic events.

8.2.6.3.2. Serious hematologic adverse events

Serious hematologic adverse events unlikely to be attributable to study drug are summarized in Table 48 below. Hemorrhagic events were restricted to genito-urinary (Table 42, "Serious genito-urinary adverse events unlikely to be related to irbesartan.," on page 67) and gastrointestinal systems (Table 36, "Serious gastrointestinal adverse events unlikely to be related to irbesartan.," on page 62).

Table 48. Serious hematologic adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-029	001/003	51	M	75	—	109	Unremarkable history. Diagnosed with cervical lymphoma. Study drug was discontinued.
Long-term phase							
CV131-025	011/006	69	M	100	—	565	Hospitalized for inguinal lymphoma surgery. Study drug was discontinued prior to chemotherapy.

8.2.6.3.3. Withdrawals for hematologic adverse events

Withdrawals for hematologic adverse events unlikely to be related to irbesartan are listed in Table 49 below.

Table 49. Withdrawals for hematologic adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Long-term phase							
CV131-028	046/001	47	F	75	—	108	Discontinued for low hematocrit, not materially changed from baseline. Event did not resolve.

8.2.6.4. Common hematologic adverse events

Common hematologic adverse events from the double-blind periods in monotherapy studies are shown in Table 50 below. No hematologic events met criteria for tabulation from studies in combination with HCTZ.

Table 50. Hematologic adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Epistaxis	0.3	0.0	1.2	2.5	1.2	2.4	0.0	0.7	0.8	0.4	1.3	0.0	1.9	2.0	0.5
Decr neutrophils	0.0	0.0	1.2	1.2	1.2	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.2
WBC blood decr	0.0	0.0	1.2	1.2	1.2	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Lymphopenia	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Monocytes decr	0.0	0.0	0.0	1.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Decr hematocrit	0.0	0.0	1.2	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.2
Decr hemoglobin	0.0	0.0	1.2	0.0	1.2	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Anemia	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Ecchymosis	0.3	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	1.9	0.0	0.2

In open-label extensions, hematologic adverse events were reported for 13 subjects on irbesartan alone (0.7% or 7 subjects with events per 1000 subject-years) and by 9 subjects on irbesartan/HCTZ (0.5% or 8 subjects with events per 1000 subject-years). No event occurred in as many as 0.5% of subjects on irbesartan alone or in combination with HCTZ.

8.2.6.5. Hematologic laboratory findings

No systematic effects of treatment were seen for WBC, hemoglobin, hematocrit, or platelet counts.

The sponsor's analyses of marked abnormalities found lymphocytopenia was more common on irbesartan (1.2%) than on placebo (0.3%). None of the cases of lymphocytopenia were considered serious or resulted in any action.

The reviewers' analysis of neutrophil counts was prompted by the identification of a higher incidence of 'decreased neutrophils' as an adverse event in the pooled active treatment group (irbesartan alone; 0.2%) vs. placebo (0%). Thirty-eight subjects (Table 51 below) were identified who had neutrophil counts greater than 2.0/nL at baseline and a post-randomization value under 2.0/nL. Of these, 7 subjects on placebo (1.1%) and 12 subjects on irbesartan (0.6%) had the lowest neutrophil count on the last post-randomization assessment.

The sponsor's analyses of marked abnormalities found thrombocytopenia was more common on irbesartan (0.3%) than on placebo (0%). In consideration of possibly treatment-related epistaxis (1.6% incidence on irbesartan vs. 0% on placebo), the reviewers looked for cases of thrombocytopenia as indicated by a baseline value above the lower limit of normal and a final on-treatment value both below the lower limit of

Table 51. Neutropenia (reviewers' analysis).

	Study	Site	Subj	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt
Plcbo	CV131-004	1	5	-43	2.3	-8	2.4	33	1.9	—	—	—	—	—	—	—	—	—	—
	CV131-029	3	1	-29	2.1	-7	2.1	45	2.3	87	1.6	—	—	—	—	—	—	—	—
	CV131-029	3	9	-28	2.4	-7	2.4	43	3.0	84	1.8	—	—	—	—	—	—	—	—
	CV131-029	10	20	-42	4.1	-10	3.5	43	4.6	82	1.7	—	—	—	—	—	—	—	—
	CV131-037	13	3	-28	3.4	-6	3.4	33	2.9	61	1.5	—	—	—	—	—	—	—	—
	CV131-029	13	15	-28	1.7	-7	2.1	43	1.9	87	3.1	—	—	—	—	—	—	—	—
	CV131-050	14	5	-35	2.6	-8	2.4	27	1.5	—	—	—	—	—	—	—	—	—	—
	CV131-037	26	5	-28	1.8	-7	2.5	29	2.0	57	1.6	—	—	—	—	—	—	—	—
	CV131-025	29	3	-29	1.9	-7	2.4	12	1.9	—	—	—	—	—	—	—	—	—	—
	CV131-050	41	16	-27	2.8	-6	4.4	32	1.7	60	2.8	—	—	—	—	—	—	—	—
	CV131-038	60	2	-32	2.2	-8	2.5	43	1.8	85	2.3	—	—	—	—	—	—	—	—
	CV131-050	66	26	-29	1.4	-9	2.3	34	1.8	64	2.0	78	1.6	—	—	—	—	—	—
37.5 mg	CV131-037	19	8	<0	2.8	<0	3.1	32	1.8	60	3.0	—	—	—	—	—	—	—	—
	CV131-037	39	18	<0	1.7	<0	2.3	32	1.7	42	4.0	—	—	—	—	—	—	—	—
75 mg	CV131-029	11	10	-36	2.1	-8	2.1	42	2.3	85	1.7	—	—	—	—	—	—	—	—
	CV131-038	12	9	-34	1.9	-28	2.3	-7	2.0	-6	2.2	43	2.0	47	2.0	88	3.0	89	2.0
	CV131-029	14	2	-27	2.0	-7	3.8	45	2.4	87	1.9	—	—	—	—	—	—	—	—
	CV131-029	16	1	-27	3.4	-6	2.2	44	2.3	86	1.6	—	—	—	—	—	—	—	—
	CV131-038	24	9	-28	1.8	-7	2.2	43	1.9	85	1.8	—	—	—	—	—	—	—	—
	CV131-038	39	6	-28	2.6	-7	3.4	43	2.6	91	2.0	—	—	—	—	—	—	—	—
	CV131-038	49	7	-28	3.3	-7	2.4	43	1.9	87	2.9	—	—	—	—	—	—	—	—
100 mg	CV131-037	17	1	-28	2.3	-7	2.3	1	3.1	29	2.1	57	2.0	—	—	—	—	—	—
	CV131-037	21	12	-8	2.5	28	2.4	56	1.9	—	—	—	—	—	—	—	—	—	—
	CV131-037	39	2	-28	2.0	-7	2.2	28	2.9	57	2.0	—	—	—	—	—	—	—	—
150 mg	CV131-029	2	8	-29	2.3	-8	3.4	42	1.9	87	1.8	—	—	—	—	—	—	—	—
	CV131-050	4	9	-31	1.9	-8	2.2	30	2.3	56	2.0	63	4.5	—	—	—	—	—	—
	CV131-038	8	4	-27	3.1	-7	2.8	43	1.9	85	3.9	—	—	—	—	—	—	—	—
	CV131-029	9	2	-26	2.2	-6	2.4	1	2.2	24	1.8	—	—	—	—	—	—	—	—
	CV131-038	10	5	-27	1.9	-6	2.1	45	2.6	88	1.9	—	—	—	—	—	—	—	—
	CV131-029	14	9	-25	2.2	-7	2.2	43	1.9	85	1.9	—	—	—	—	—	—	—	—
	CV131-029	18	13	-28	2.7	-7	3.2	43	1.8	81	2.7	—	—	—	—	—	—	—	—
300 mg	CV131-037	31	24	-28	2.2	-9	2.9	34	1.5	63	2.8	—	—	—	—	—	—	—	—
	CV131-050	40	23	-28	3.0	-7	3.1	28	4.0	56	2.0	—	—	—	—	—	—	—	—
	CV131-050	65	2	-28	2.3	-7	2.2	29	1.6	55	2.1	—	—	—	—	—	—	—	—
600 mg	CV131-050	4	2	-38	2.4	-10	2.2	29	2.6	57	2.2	64	2.0	—	—	—	—	—	—
	CV131-050	36	15	-28	2.3	-7	2.3	29	2.2	43	2.0	—	—	—	—	—	—	—	—
	CV131-050	66	9	-33	3.6	-12	2.9	33	2.0	65	3.9	81	3.1	—	—	—	—	—	—

normal and 50/nL below baseline. Such subjects are listed in Table 52 below. Measured this way, the incidence rates by treatment groups were 0.5% on placebo, 1.2% on irbesartan 5 mg, 1.3% on 75 mg, 0.7% on 150 mg, 1.0% on 600 mg, and 0.5% on all irbesartan groups combined.

Table 52. Marked platelet abnormalities (reviewers' analysis).

	Study	Site	Subj	Platelet counts (/nL) by study day									
				Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt	Day	Cnt
Placebo	CV131-004	1	32	-42	268	-8	240	33	135	—	—	—	—
	CV131-025	25	5	-32	218	-10	216	25	221	60	202	75	131
	CV131-025	30	1	-31	231	-11	203	30	115	—	—	—	—
5 mg	CV131-002	3	6	-28	215	-7	219	30	190	59	100	—	—
75 mg	CV131-030	10	4	-34	212	-13	213	33	93	—	—	—	—
	CV131-029	4	9	-28	223	-7	236	43	208	85	113	—	—
	CV131-038	55	14	-24	266	-7	280	15	114	—	—	—	—
	CV131-038	59	14	-28	180	-10	194	44	150	87	140	—	—
150 mg	CV131-038	17	25	-27	221	-7	185	45	201	86	101	—	—
	CV131-038	40	11	-28	189	-6	214	48	136	91	143	—	—
	CV131-038	57	7	-29	185	-8	235	-1	252	42	215	84	198
600 mg	CV131-050	36	15	-28	207	-7	201	29	270	43	122	—	—

8.2.7. Immunologic system

8.2.7.1. Adequacy of immunologic assessment

Immunologic safety was assessed through adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.7.2. Immunologic events at least possibly drug-related

8.2.7.2.1. Immunologic deaths

No death attributable to immunologic events was considered to have any reasonably likely relationship to study drug.

8.2.7.2.2. Serious immunologic adverse events

One serious immunologic adverse event, described in Table 53 below, was possibly drug-related.

Table 53. Serious immunologic adverse events possibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-029	023/014	48	F	150	—	17	Allergic reaction—nausea, diarrhea, dizziness, tremor, fever, chills, and hives—treated with prednisone with discontinuation of study drug. Two days later, throat tightness, swollen tongue, and difficulty breathing treated with prednisone and epinephrine. Relationship to study drug cannot be excluded.

8.2.7.2.3. Withdrawals for immunologic adverse events

Withdrawals for immunologic events plausibly related to irbesartan are listed in Table 54 below

Table 54. Withdrawals for immunologic adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	011/006	70	M	25	—	2	Discontinued with generalized rash. Next day BUN and creatinine were elevated, but they resolved spontaneously within 2 weeks.
CV131-030	005/005	68	F	150	—	5	Discontinued with periorbital and hand edema, which resolved the day after discontinuation.
Long-term phase							
CV131-029	005/011	42	M	300	—	40	Discontinued with allergic rhinitis, bronchospasm, and wheezing. Event did not resolve.

8.2.7.3. Immunologic events unlikely to be drug-related

8.2.7.3.1. Immunologic deaths

There was one death attributed to an auto-immune disease.

Study CV131-031LT subject 008/005 was a 76 year old Caucasian male with a 2-year history of hypertension. He completed 24 weeks of double-blind treatment, despite complaints of chest pain, atrial flutter, and urinary tract infection. After 15 weeks on open-label irbesartan 75 mg, he was hospitalized with nausea, hemoptysis, acute renal failure, atrial fibrillation, and pneumonia. He required intubation and resuscitation following cardiac arrest. He developed electromechanical dissociation and died. His post-mortem diagnosis was Goodpasture's syndrome, an auto-immune disease producing glomerular nephritis and pulmonary hemorrhage. Relationship to study drug was considered unlikely.

8.2.7.3.2. Serious immunologic adverse events

Serious immunologic adverse events are described in Table 55 below.

Table 55. Serious immunologic adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-040	043/011	52	M	75	25	67	Hospitalized for mediastinal lymph node biopsy because of mass on baseline chest x-ray. Diagnosed as sarcoidosis; study drug was not interrupted.
Long-term phase							
CV131-038	063/019	47	F	75	12.5	7	Hospitalized with anaphylactic reaction. Study drug was continued.

8.2.7.3.3. Withdrawals for immunologic adverse events

No withdrawals for immunologic adverse events were considered implausibly related to treatment with irbesartan.

8.2.7.4. Common immunologic adverse events

Common immunologic adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 56 below and Table 57 below, respectively.

Table 56. Immunologic adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)												
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Allergy	0.6	0.0	0.0	0.0	0.0	2.4	1.2	0.3	0.4	0.7	1.3	0.8	0.0	1.0	0.6
Allergy environ agen	0.0	0.0	0.0	1.2	0.0	2.4	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.2
Allergic reaction	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Chemical allergy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.1
Edema head/neck	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Edema upp extremity	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	1.0	0.2
Edema upper extremity	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1

In open-label extensions, immunologic adverse events were reported for 41 subjects on irbesartan alone (2.3% or 40 subjects with events per 1000 subject-years) and by 33 subjects on irbesartan/HCTZ (1.9% or 28 subjects with events per 1000 subject-years). All such events are shown in Table 58 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 57. Immunologic adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300		
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
Allergy	0.0	0.0	0.0	0.6	4.8	0.0	2.2	4.9	0.0	0.0	0.8	2.4	2.3	0.0	0.0	0.5	0.7	2.3	2.5	2.3	2.2

Table 58. Immunologic adverse events with ≥0.5% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y
Allergy	26	1.5	26	17	1.0	14

a. Subjects with events per 1000 subject-years.

8.2.7.5. Immunologic laboratory findings No laboratory tests were considered in the evaluation of immunologic safety.

8.2.8. Metabolic and endocrine

8.2.8.1. Adequacy of metabolic and endocrine assessment Metabolic and endocrine safety was assessed through body weight, glucose, cholesterol, triglycerides, and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.8.2. Metabolic and endocrine events at least possibly drug-related

8.2.8.2.1. Metabolic and endocrine deaths There were no deaths attributed to metabolic or endocrine events.

8.2.8.2.2. Serious metabolic and endocrine adverse events No serious metabolic and endocrine adverse events were considered plausibly related to irbesartan.

8.2.8.2.3. Withdrawals for metabolic and endocrine adverse events Withdrawals for metabolic and endocrine adverse events plausibly related to irbesartan are listed in Table 59 below.

Table 59. Withdrawals for metabolic and endocrine adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Long-term phase							
CV131-038	047/016	65	F	75	12.5	28	Discontinued for hyperkalemia, considered possibly drug-related. Event resolved.
CV131-038	002/012	52	F	150	12.5	35	Discontinued for hypertriglyceridemia, considered possibly drug-related. Event did not resolve.

8.2.8.3. Metabolic and endocrine events unlikely to be drug-related

8.2.8.3.1. Metabolic and endocrine deaths There were no deaths attributed to metabolic or endocrine events.

8.2.8.3.2. Serious metabolic and endocrine adverse events Serious metabolic and endocrine adverse events unlikely to be related to study drug are listed in Table 60 below.

Table 60. Serious metabolic and endocrine adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-025	027/007	58	M	100	—	308	Subject diagnosed with adenocarcinoma of pancreas. Study drug was discontinued.
CV131-029	014/006	70	M	150	—	271	Hospitalization to set foot fracture sustained in fall. Study drug continued?
CV131-031	035/001	69	M	150	—	35	Hospitalized for repair of hip fracture. Study drug was continued.
Long-term phase							
CV131-038	010/006	57	F	75	12.5	18	Hospitalized for open reduction of fractured humerus. Study drug continued?
CV131-037	019/002	67	M	75	12.5	240	Hospitalized for decompressive laminotomy. Study drug was continued.
CV131-002	006/006	75	F	100	25	431	Hospitalized for thyroid micropapillary carcinoma. Study drug continued.
CV131-002	045/010	46	F	100	?	278	Hospitalized for laparoscopic disc surgery. Study drug continued.
CV131-002	006/006	78	F	100	?	434	Hospitalized for thyroid micropapillary carcinoma, surgically treated, and then, 3 days later, was found to be in atrial fibrillation. Study drug was discontinued.
CV131-037	026/003	72	M	150	12.5	353	Hospitalized with incarcerated inguinal hernia. Study drug was continued.
CV131-037	042/011	63	M	300	25	134	Visual disturbances led to diagnosis of pituitary adenoma, treated by surgery. Study drug was continued.
CV131-037	001/040	46	F	300	25	115	History of hip replacement. Hospitalized for hip replacement. Study drug was continued.
CV131-037	001/040	47	F	300	25	119	Hospitalized for hip replacement. Study drug was continued.
CV131-037	041/011	58	M	300	25	178	Hospitalized for laminectomy. Study drug continued?
CV131-037	042/011	64	M	300	25	135	Hospitalized for visual disturbance. Three weeks later, he underwent surgical removal of pituitary adenoma. Study drug was continued.
CV131-037	042/025	53	M	300	25	164	Hospitalized for (negative) cardiac work-up for left arm pain. Physician attributed event to study drug and discontinued. Investigator disagreed and restarted study drug.

8.2.8.3.3. Withdrawals for metabolic and endocrine adverse events

Withdrawals for metabolic and endocrine adverse events unlikely to be related to irbesartan are listed in Table 61 below.

Table 61. Withdrawals for metabolic and endocrine adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-040	012/001	63	M	75	25	58	Discontinued for hypokalemia, unchanged from baseline.

8.2.8.4. Common metabolic and endocrine adverse events

Common metabolic and endocrine adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Tables 62 and 63 below, respectively.

Table 62. Metabolic and endocrine adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)												
	0	1	5	10	25	37.5	50	75	100	150	200	300	600	900	Any
N=	641	82	82	81	83	42	82	297	242	451	79	240	105	99	1965
Serum glucose incr	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.8	1.0	2.0	0.5

Table 62. Metabolic and endocrine adverse events by dose in double-blind studies of irbesartan

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Breast disorder	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.4	1.0	0.0	0.3
Gout	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.7	1.3	0.0	0.0	0.0	0.3
Weight gain	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.4	0.0	0.0	1.0	1.0	0.3
Incr cholesterol	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Incr lipids	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.4	0.0	0.0	0.2

Table 63. Metabolic and endocrine adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300			
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
Sexual dysfunction	0.0	0.0	1.7	1.9	2.4	0.0	0.0	0.0	0.5	1.5	0.8	0.0	2.3	0.0	0.0	0.5	0.7	0.0	2.5	0.0	0.0
Gout	0.0	0.0	1.1	0.0	0.0	2.3	0.0	2.4	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.5	0.0	0.0	0.0	0.0	0.0

In open-label extensions, metabolic and endocrine adverse events were reported for 57 subjects on irbesartan alone (3.2% or 60 subjects with events per 1000 subject-years) and by 89 subjects on irbesartan/HCTZ (5.2% or 73 subjects with events per 1000 subject-years). All such events are shown in Table 64 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 64. Metabolic and endocrine adverse events with ≥0.5% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700				Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y		n	%	/KS-Y	n	%	/KS-Y
Sexual dysfunction	11	0.6	11	27	1.6	22	Libido change	6	0.3	6	11	0.6	9
Breast disorder	8	0.4	8	14	0.8	12	Diabetes	5	0.3	5	9	0.5	7
Gout	7	0.4	7	13	0.8	11							

a. Subjects with events per 1000 subject-years.

8.2.8.5. Metabolic and endocrine laboratory findings

Glycosuria was somewhat more common on active treatment (1.6%) than on placebo (1.1%), but elevations in urinary ketones were more common on placebo. New onset or worsening of elevated fasting blood glucose was evaluated as the fraction of subjects with at least one value post-randomization >1x, >1.25x, or >1.5x the laboratory-specific upper limit of normal among subjects with a normal level at baseline and at least one value post-randomization. The rates (placebo vs pooled irbesartan alone) were, for >1xULN, 14.1% vs. 10.9%, for >1.25xULN, 2.4% vs. 1.9%, and for >1.5xULN, 0.6% vs. 0.4%.

About 10% of subjects had an abnormal fasting blood glucose level at baseline. The rates (placebo vs pooled irbesartan alone) for such subjects with at least one abnormal value after randomization were, for >1xULN, 84% vs. 81%, for >1.25xULN,51% vs. 42%, and for >1.5xULN, 25% vs. 26%. Subjects with abnormal fasting blood glucose at baseline were no more likely to have adverse events on active treatment than on placebo.

The sponsor evaluated the incidence of marked increases in triglycerides as 1.7% on irbesartan vs. 0.7% on placebo. The reviewers' analysis looked for the proportion of subjects with a post-randomization value >1.5x the upper limit of normal from a baseline below upper limit of normal or a 30% increase above a baseline greater than upper limit of normal. By these criteria, marked increases occurred among 19% of subjects randomized to placebo and 19% of subjects randomized to irbesartan alone.

8.2.9. Musculoskeletal system

8.2.9.1. Adequacy of musculoskeletal assessment Musculoskeletal safety was assessed through creatine phosphokinase and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.9.2. Musculoskeletal events at least possibly drug-related

8.2.9.2.1. Musculoskeletal deaths There were no deaths attributed to musculoskeletal events.

8.2.9.2.2. Serious musculoskeletal adverse events No serious musculoskeletal adverse events were considered plausibly related to irbesartan.

8.2.9.2.3. Withdrawals for musculoskeletal adverse events Withdrawals for musculoskeletal adverse events plausibly related to irbesartan are listed in Table 65 below.

Table 65. Withdrawals for musculoskeletal adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-045	001/011	29	M	150	—	1	Normal volunteer experienced asymptomatic rise in CPK from baseline 194 to 654 at 24 hours. CPK peaked at 2281 on day 11, and returned to baseline at 1 month.
CV131-050	029/013	44	M	300	—	45	Discontinued for muscle and joint pain. Also complained of hot flashes, sinusitis, nocturia, sleepiness, prostatitis, sore tongue, constipation, diarrhea, and headaches. Events were unresolved.
CV131-050	010/003	59	M	600	—	4	Discontinued with back pain, considered unlikely to be drug-related. Event resolved.
CV131-037	028/010	60	F	100	25	14	Discontinued for muscle ache, nervousness, dependent edema, all possibly drug-related. Events other than edema resolved.
CV131-032	016/004	55	M	150	?	55	Discontinued for hospitalization for back surgery. Event was unresolved.
Long-term phase							
CV131-029	020/001	68	F	75	—	57	Discontinued for myalgia and elevated CPK >458, considered likely to be drug-related. Myalgia resolved.
CV131-050	017/011	71	F	75	—	21	Discontinued with polymyalgia rheumatica, symptoms of which appeared during double-blind treatment on irbesartan 900 mg. Event, which did not resolve, was considered possibly drug-related.
CV131-025	005/005	52	M	100	—	154 196	Complaint of cramps in arms and legs. Later discontinued for decreased libido, considered possibly drug-related. Events resolved.
CV131-037	014/001	46	M	75	12.5	13	Discontinued with asymptomatic CPK elevation, considered probably drug-related. Event resolved within 2 weeks.
CV131-037	015/007	53	M	75	12.5	55	Discontinued with leg cramps and nocturia, both at least possibly drug-related. Neither event resolved.
CV131-038	018/008	59	M	150	12.5	37	Discontinued for severe knee pain, considered probably drug-related. Event resolved.
CV131-038	008/005	65	M	300	25	153	Discontinued for gouty arthritis, considered possibly drug-related. Event was unresolved.

8.2.9.3. Musculoskeletal events unlikely to be drug-related

8.2.9.3.1. Musculoskeletal deaths There were no deaths attributed to musculoskeletal events.

8.2.9.3.2. Serious musculoskeletal adverse events Serious musculoskeletal adverse events unlikely to be related to study drug are listed in Table 66 below.

Table 66. Serious musculoskeletal adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	032/005	53	F	25	—	34	History of hypertension, Grave's disease. Subject fell and dislocated patella, resulting in 3-day hospitalization. Subject completed double-blind phase.
CV131-028	034/001	71	F	75	—	76	History of knee arthrosis and rotator cuff problems. Hospitalized for knee arthroscopy. Subject completed double-blind phase.
CV131-031	014/004	68	M	75	—	8	Study drug was discontinued prior to planned knee surgery.
CV131-031	028/009	68	M	75	—	36	Hospitalized for repair of pre-existing inguinal hernia; study drug was not interrupted.
CV131-029	005/002	66	M	150	—	45	Hospitalized for lumbar disk surgery.
CV131-050	005/009	68	M	900	—	49	Hospitalized to correct deviated septum; study drug was not interrupted.
CV131-037	016/018	63	M	100	12.5	59	Hospitalized for CPK of 1023 (normal <221) and weak history of recent chest discomfort. CPK fell to 124 at discharge. Repeat CPK after 8-day rechallenge was 76; subject continued in open-label phase.
Long-term phase							
CV131-003	001/007	66	F	10 25	—	25 378	Hospitalized for compression fracture of the lumbar spine. Study drug was continued. Second hospitalization for nausea, vomiting, and abdominal pain; no further diagnosis given. Study drug was discontinued.
CV131-044	078/007	81	M	12.5	—	1	Hospitalized for fractured ankle. Study drug was interrupted.
CV131-025	011/004	35	F	50	—	125	History of back and neck pain secondary to injury. Hospitalized for anterior cervical dissection and fusion. Study drug continued.
CV131-028	034/002	53	M	75	—	222	Hospitalized following automobile accident with high blood alcohol.
CV131-029	022/003	43	M	75	—	159	History of osteoarthritis of knee. Hospitalized for knee surgery. Study drug continued?
CV131-047	002/004	58	F	75	—	61 140 212	History of diabetic nephropathy. Both hospitalizations were for infections of the foot, following amputation of the other foot during double-blind phase. Study drug was continued.
CV131-029	014/006	70	M	150	—	271	Hospitalization to set foot fracture sustained in fall. Study drug continued?
CV131-031	035/001	69	M	150	—	35	Hospitalized for repair of hip fracture. Study drug was continued.
CV131-031	006/008	76	F	150	—	~225	Hospitalized for dislocated shoulder. Study drug was continued.
CV131-025	018/010	56	M	200	—	145	History of arthritis and shoulder surgery. Hospitalized for shoulder replacement, study drug continued.
CV131-025	024/005	62	F	200	—	639	Hospitalized for repair of shoulder ligament. Study drug was interrupted.
CV131-027	010/005	62	F	300	—	49	Hospitalization for hip pinning. Study drug was not interrupted.
CV131-047	002/005	45	F	300	—	123	Hospitalized for carpal tunnel surgery. Study drug was continued.
CV131-037	034/002	68	M	75	12.5	314	Hospitalized for uvula reduction to treat pre-existing sleep apnea. Study drug was interrupted.
CV131-038	010/006	57	F	75	12.5	18	Hospitalized for open reduction of fractured humerus. Study drug continued?
CV131-037	019/002	67	M	75	12.5	240	Hospitalized for decompressive laminotomy. Study drug was continued.
CV131-038	036/003	55	M	75	12.5	269	Unremarkable history and no description of surrounding circumstances. Hospitalized for cardiac catheterization. Study drug was continued.
CV131-002	045/010	46	F	100	?	278	Hospitalized for laparoscopic disc surgery. Study drug continued.
CV131-038	008/002	61	M	150	12.5	278	History of hernia repair as child. Hospitalized for hernia repair. Study drug continued.
CV131-037	026/003	72	M	150	12.5	353	Hospitalized with incarcerated inguinal hernia. Study drug was continued.
CV131-037	001/040	46	F	300	25	115	History of hip replacement. Hospitalized for hip replacement. Study drug was continued.
CV131-038	038/012	65	M	300	25	204	Hospitalized for arthroscopic knee surgery. Study drug continued?
CV131-037	001/040	47	F	300	25	119	Hospitalized for hip replacement. Study drug was continued.
CV131-037	041/011	58	M	300	25	178	Hospitalized for laminectomy. Study drug continued?
CV131-037	042/025	53	M	300	25	164	Hospitalized for (negative) cardiac work-up for left arm pain. Physician attributed event to study drug and discontinued. Investigator disagreed and restarted study drug.

8.2.9.3.3. Withdrawals for musculoskeletal adverse events

Withdrawals for musculoskeletal adverse events unlikely to be related to irbesartan are listed in Table 67 below.

Table 67. Withdrawals for musculoskeletal adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-031	021/004	72	M	150	—	84	Discontinued with 18-day history of back and knee pain, attributed to osteoarthritis.
CV131-038	025/011	71	F	150	12.5	55	Discontinued for knee pain, which began during placebo withdrawal.
Long-term phase							
CV131-002	019/009	58	M	100	?	163	Discontinued for knee pain, attributed to osteoarthritis. Event was unresolved.

8.2.9.4. Common musculoskeletal adverse events

Common musculoskeletal adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 68 below and Table 69 below, respectively.

Table 68. Musculoskeletal adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Musc/skel pain	6.2	6.1	4.9	4.9	4.8	9.5	7.3	6.1	5.4	4.7	12.7	6.3	6.7	7.1	6.0
Muscle cramp	0.8	1.2	1.2	1.2	0.0	2.4	0.0	0.3	0.4	0.4	0.0	1.7	1.9	0.0	0.7
Muscle ache	1.1	0.0	0.0	1.2	0.0	0.0	0.0	1.0	0.0	0.4	0.0	0.4	1.0	0.0	0.4
Musculosk chest pain	0.5	1.2	0.0	0.0	0.0	0.0	0.0	0.7	0.8	0.0	0.0	0.0	1.0	1.0	0.4
Myalgia	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	1.3	0.0	1.0	0.0	0.2
Pain musculoskeletal	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Musculoskel trauma	0.5	0.0	1.2	1.2	2.4	4.8	0.0	2.7	0.8	1.1	3.8	2.9	2.9	2.0	1.8
Arthritis	0.0	0.0	1.2	0.0	1.2	2.4	0.0	0.0	0.0	0.4	3.8	0.0	1.0	0.0	0.5
Bursitis	0.0	0.0	0.0	2.5	0.0	0.0	0.0	0.3	0.4	0.0	1.3	0.0	0.0	1.0	0.3
Joint stiffness	0.0	0.0	0.0	0.0	1.2	0.0	1.2	0.0	0.4	0.4	0.0	0.0	1.0	0.0	0.3
Orthopedic surg	0.6	0.0	0.0	2.5	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Fracture bone	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.2	1.3	0.0	0.0	0.0	0.2
Musculoskeletal abn	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.3	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Weakness extremity	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.7	0.0	0.2	0.0	0.0	0.0	0.0	0.2
Muscle weakness	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Limitation movement	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.4	0.0	0.0	0.0	0.0	0.2
Disc disease	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Hernia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.1
Muscle contract	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Tendinitis	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Epicondylitis	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Joint swelling	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.1
Surgery nose	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Degener arthritis	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Stiffness back	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Surgery orthopedic	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

In open-label extensions, musculoskeletal adverse events were reported for 295 subjects on irbesartan alone (17% or 300 subjects with events per 1000 subject-years) and by 384 subjects on irbesartan/HCTZ (23% or 317 subjects with events per 1000 subject-years). All such events are shown in Table 70 below; the reviewers made

Table 69. Musculoskeletal adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300			
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
Myalgia	4.7	9.1	12.4	7.5	9.5	6.8	13.3	0.0	8.2	11.9	9.3	7.3	2.3	7.0	9.1	4.5	5.9	4.7	7.5	4.5	2.2
Cramp	1.3	4.5	1.7	1.9	2.4	0.0	0.0	0.0	0.0	0.7	2.5	2.4	2.3	4.7	0.0	1.5	0.0	0.0	0.0	0.0	0.0
Edema	0.8	0.0	1.1	0.6	7.1	2.3	2.2	0.0	0.5	0.0	1.7	0.0	0.0	2.3	0.0	1.0	1.5	0.0	0.0	0.0	0.0
Arthritis	0.8	2.3	0.0	0.6	2.4	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	2.3	0.0	0.5	0.7	0.0	0.0	2.3	2.2
Chest pain	0.4	0.0	0.0	0.6	0.0	2.3	2.2	0.0	1.0	0.0	0.8	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.0
Weakness	0.0	0.0	0.0	1.3	2.4	0.0	0.0	0.0	0.5	0.0	0.8	0.0	0.0	0.0	0.0	0.5	0.0	0.0	2.5	0.0	0.0

no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 70. Musculoskeletal adverse events with ≥0.5% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y
Musculoskeletal pain	154	8.6	154	187	11	154
Trauma	41	2.3	41	48	2.8	40
Muscle cramp	28	1.6	28	48	2.8	40
Arthritis	27	1.5	27	40	2.4	33
Extremity swelling	18	1.0	18	20	1.2	17
Orthopedic surgery	17	0.9	17	20	1.2	17

	Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y	n	%	/KS-Y
Muscle ache	13	0.7	13	13	0.8	11
Bone fracture	11	0.6	11	9	0.5	7
Chest pain	8	0.4	8	9	0.5	7
Musculoskel abnorm	9	0.5	9	8	0.5	7
Myalgia	4	0.2	4	13	0.8	11

a. Subjects with events per 1000 subject-years.

8.2.9.5. Musculoskeletal laboratory findings

The sponsor defined marked increases in CK as 4-fold elevation above baseline, and found abnormal increases among 10 subjects (1.7%) on irbesartan vs 2 subjects (0.7%) on placebo. None of these resulted in discontinuation, were thought to be serious, or were even considered treatment-related.

The reviewers evaluated the incidence of a rise in CK (any post-randomization measurement) from below the upper limit of normal to 1.5xULN or a 50% increase from an already elevated baseline, and found a rate of 2.2% on irbesartan vs. 2.1% on placebo. Among 206 subjects for whom adverse events of myalgia, muscle cramps, musculoskeletal pain, or muscle ache were reported, 80 subjects had CK values measured at baseline and at least once post-randomization. The ratio of CK on the last post-randomization visit to the value at baseline was 1.1±0.3 among 29 subjects randomized to placebo and 1.0±0.4 among 51 subjects randomized to irbesartan.

8.2.10. Nervous system

8.2.10.1. Adequacy of nervous system assessment

Nervous system safety was assessed through adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.10.2. Nervous system events at least possibly drug-related

8.2.10.2.1. Nervous system deaths

There were no deaths attributed to nervous events.

8.2.10.2.2. Serious nervous system adverse events

No serious nervous system events were considered plausibly related to irbesartan.

8.2.10.2.3. Withdrawals for nervous system adverse events

Withdrawals for nervous system adverse events plausibly related to irbesartan are listed in Table 71 below.

Table 71. Withdrawals for nervous system adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-003	004/006	79	F	1	—	1	Discontinued because of confusion, considered unrelated to study drug. Symptom resolved.
CV131-031	035/009	72	F	75	—	26	Discontinued with weakness and paresthesia of hands and feet, considered possibly drug-related. Events were unresolved.
CV131-029	018/013	52	F	150	—	49	Discontinued with jittery feeling, considered possibly drug-related.
CV131-030	013/006	54	M	150	—	4	Discontinued after severe panic attack, which resolved.
CV131-050	065/015	61	M	150	—	14	Discontinued with anxiousness, nausea, irritability, tinnitus, and weakness, all considered possibly drug-related. Events resolved within 1 to 4 days.
CV131-031	031/012	65	M	150	—	47	Discontinued for "thick head with mental vagueness", considered probably drug-related. Event resolved the next day.
CV131-038	017/004	48	M	75	12.5	16	Discontinued for insomnia, considered probably drug-related. Event unresolved.
CV131-038	019/012	55	M	75	12.5	4	Discontinued with headache, dizziness, and visual disturbance, considered possibly drug-related. Events resolved.
CV131-037	025/009	55	M	100	25	1	Discontinued for increased irritability and decreased ability to concentrate. Event unresolved.
Long-term phase							
CV131-002	027/001	54	M	10	—	35	Discontinued for agitation and tiredness. Event resolved.
CV131-029	019/012	66	F	75	—	1	Discontinued for nightmares, considered probably drug-related. Event did not resolve.
CV131-029	015/069	69	M	75	—	9	Discontinued with tremor and anxiety, considered possibly drug-related.
CV131-002	003/003	54	M	100	—	107	Discontinued for nightmares, insomnia, and irritability. Events were unresolved.
CV131-027	027/006	50	F	75	12.5	139	Discontinued for "vivid dreams", considered possibly drug-related. Event resolved.
CV131-037	002/004	67	F	75	12.5	142	Discontinued with vertigo and nystagmus, with dizziness considered possibly drug-related. Events did not resolve.
CV131-037	029/003	72	M	75	12.5	147	Discontinued with dizziness and slow speech, considered possibly drug-related. Events resolved.
CV131-038	032/004	79	F	75	12.5	36	Discontinued for somnolence and hyperhidrosis, considered possibly drug-related. Events resolved.
CV131-031	008/003	76	F	300	25	158	Discontinued with giddiness, considered possibly drug-related. Event resolved within 1 week.

8.2.10.3. Nervous system events unlikely to be drug-related

8.2.10.3.1. Nervous system deaths

There were no deaths attributed to nervous events.

8.2.10.3.2. Serious nervous system adverse events

Serious nervous adverse events unlikely to be related to irbesartan are listed in Table 72 below.

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Table 72. Serious nervous system adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	029/010	71	M	1	—	16	Medical history was unremarkable except for hypertension. Subject was randomized to irbesartan. Two weeks later, he had the flu, developed headache and subsequently suffered left eyelid droop. Diagnostic testing (brain MRI/ MRA) confirmed left carotid artery dissection. Study drug was subsequently discontinued. Concomitant medications: acetaminophen, bismuth subsalicylate, flurazepam and ibuprofen.
CV131-006	001/044	34	F	50	—	1	This subject received a single 50-mg dose. During the study she complained of chest discomfort. A physical exam and ECG were normal. The symptoms subsided and resolved by study completion. She was diagnosed with a teratoma of the lung with metastasis to the brain stem. Chemotherapy was advised but she refused treatment. The outcome is unknown.
CV131-038	047/006	74	M	75	—	57	Subject had headaches and orthostatic dizziness during treatment. He had sudden onset of nausea, vomiting, and unsteady gait lasting 12 hours. CT revealed bilateral cerebellar infarcts. He discontinued study drug and was started on antiplatelet therapy. Neurological symptoms resolved.
CV131-039	016/027	57	F	150	12.5	2	History includes migraines. Hospitalized and study drug interrupted for severe migraine and vertigo.
CV131-032	015/012	49	F	150	?	79	Subject reported transient ischemic attack, unconfirmed by MD. Subject also receiving atenolol and nifedipine.
Long-term phase							
CV131-002	006/014	57	M	25	—	26	Subject received 100 mg during 8-week double-blind phase. Subject was discontinued for CVA—weakness, poor coordination, slurred speech.
CV131-003	003/007	76	F	25	—	83	History of idiopathic dilated cardiomyopathy. Hospitalization for evaluation of a near-syncopal episode. Study drug was continued.
CV131-044	064/002	58	M	75	—	25	Hospitalized for CVA with global aphasia. Study drug was discontinued.
CV131-047	001/001	46	M	75	—	50	History of myocardial infarction and diabetic nephropathy. Hospitalized for CVA. Study drug continued?
CV131-002	016/005	54	F	100	?	712	Unremarkable history. Hospitalized for transient ischemic attack, BP "normal". Study drug continued.
CV131-032	022/001	48	F	150	—	21	Unremarkable history. Hospitalized for CVA. Study drug was discontinued.
CV131-044	004/001	41	M	150	—	32	History of idiopathic dilated cardiomyopathy. Hospitalized for vasovagal episode. Study drug was continued.
CV131-037	014/004	44	M	150	25	160	Hospitalization for severe depression. Study drug was discontinued.
CV131-037	015/014	38	M	150	25	146	History of migraine headaches. Hospitalized for headaches, blurred vision, lateralized weakness. Work-up showed no focal abnormalities. Study drug was continued.
CV131-029	020/014	41	M	300	12.5	170	History of cervical fracture. Hospitalized for syncope and right arm numbness, attributed to cervical muscle contusion. Study drug was continued.
CV131-038	001/006	52	M	300	25	58	Unremarkable history. Hospitalized for TIA. Study drug was continued.
CV131-038	047/002	55	M	300	25	293	Hospitalized for head and neck pain, diagnosed as brain tumor. Outcome unknown. Study drug continued?
CV131-038	013/004	61	M	300	25	187	History of alcohol abuse and depression. Hospitalized for substance abuse. Study drug was discontinued.
CV131-037	042/025	53	M	300	25	164	Hospitalized for (negative) cardiac work-up for left arm pain. Physician attributed event to study drug and discontinued. Investigator disagreed and restarted study drug.

8.2.10.3.3. Withdrawals for nervous system adverse events

Withdrawals for nervous system adverse events unlikely to be related to irbesartan are listed in Table 73 below.

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Table 73. Withdrawals for nervous system adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-050	066/003	62	F	900	—	2	Discontinued for moderate TIA, considered unlikely to be drug-related. Event resolved next day.
Long-term phase							
CV131-029	005/012	57	M	75	—	30	Discontinued with "feeling fuzzy", increased perspiration, and flushing, all considered unlikely to be drug-related. All events resolved.
CV131-029	016/001	68	M	75 225	—	13 41	Complaint of gait disturbance. Later discontinued for depression, both events considered possibly drug-related. Events resolved.
CV131-037	029/003	72	M	75	12.5	147	Discontinued with dizziness and slow speech, considered possibly drug-related. Events resolved.
CV131-037	037/002	70	M	75	12.5	14	Discontinued after CAT scan performed to 'rule out TIA' when subject developed left-sided weakness and clumsiness. Event resolved.
CV131-038	032/004	79	F	75	12.5	36	Discontinued for somnolence and hyperhidrosis, considered possibly drug-related. Events resolved.

8.2.10.4. Common nervous system adverse events

Common nervous system adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 74. and Table 75 below, respectively.

Table 74. Nervous system adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Dizziness	5.0	3.7	3.7	3.7	3.6	2.4	4.9	4.0	5.8	5.1	2.5	4.2	4.8	8.1	4.6
Anxiety/nervousness	0.9	0.0	0.0	1.2	0.0	2.4	1.2	1.7	0.0	1.6	1.3	0.8	1.0	1.0	1.0
Numbness	0.3	1.2	1.2	1.2	0.0	2.4	2.4	0.3	0.8	0.7	0.0	0.0	1.9	0.0	0.7
Sleep disturb	1.2	1.2	2.4	0.0	0.0	0.0	1.2	1.0	0.4	0.2	1.3	0.8	0.0	1.0	0.7
Disturbing dreams	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Insomnia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Somnolence	0.2	1.2	0.0	0.0	0.0	0.0	0.0	0.7	0.4	1.1	0.0	0.4	0.0	0.0	0.5
Depression	0.5	0.0	1.2	0.0	0.0	0.0	0.0	1.0	0.0	0.4	1.3	0.0	1.9	0.0	0.5
Emotion labil/distur	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.7	0.0	0.8	1.9	0.0	0.5
Paresthesia	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.4	0.0	0.4	1.0	0.0	0.3
Disturb sensation	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.1
Disorder stress rel	0.2	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.8	0.2	0.0	0.0	0.0	0.0	0.2
Entrapment neuropath	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Tremor	0.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	1.0	0.2

In open-label extensions, nervous system adverse events were reported for 299 subjects on irbesartan alone (17% or 300 subjects with events per 1000 subject-years) and by 351 subjects on irbesartan/HCTZ (21% or 289 subjects with events per 1000 subject-years). All such events are shown in Table 76 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

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Table 75. Nervous system adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300		
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
Headache	15.7	18.2	13.6	7.5	14.3	13.6	15.6	9.8	10.2	9.0	11.9	7.3	6.8	16.3	9.1	11.6	11.1	4.7	2.5	6.8	11.1
Dizziness	4.2	6.8	4.0	5.0	2.4	11.4	6.7	12.2	4.1	3.0	10.2	7.3	4.5	7.0	6.8	6.0	5.9	7.0	10.0	6.8	20.0
Anxiety	0.0	0.0	0.6	0.6	2.4	2.3	0.0	0.0	1.0	3.0	0.8	0.0	0.0	0.0	4.5	0.0	0.0	2.3	0.0	0.0	2.2
Numbness	0.0	0.0	0.6	0.6	2.4	0.0	0.0	4.9	0.0	0.0	1.7	0.0	2.3	0.0	0.0	1.0	0.7	0.0	2.5	0.0	0.0
Sleep disturbance	1.3	0.0	0.6	0.6	0.0	4.5	0.0	0.0	0.5	1.5	0.8	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	4.4
Vertigo	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.8	0.0	2.3	2.3	0.0	0.0	0.7	0.0	0.0	2.3	0.0
Depression	0.4	2.3	0.6	0.0	0.0	2.3	0.0	0.0	0.5	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	2.2
Paresthesia	0.4	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	0.0	2.3	0.0	0.5	0.7	0.0	0.0	0.0	0.0

Table 76. Nervous adverse events with ≥0.5% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700				Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y		n	%	/KS-Y	n	%	/KS-Y
Headache	131	7.3	131	122	7.2	101	Numbness	9	0.5	9	24	1.4	20
Dizziness	67	3.7	67	109	6.4	90	Paresthesia	15	0.8	15	21	1.2	17
Sleep disturbance	23	1.3	23	24	1.4	20	Anxiety/nervousness	15	0.8	15	18	1.1	15
Orthostatic dizziness	12	0.7	12	34	2.0	28	Vertigo	16	0.9	16	19	1.1	16
Depression	20	1.1	20	25	1.5	21	Entrapment neuropathy	10	0.6	10	11	0.6	9

a. Subjects with events per 1000 subject-years.

8.2.10.5. Nervous system laboratory findings — No laboratory tests were considered in the evaluation of nervous system safety.

8.2.11. Respiratory system

8.2.11.1. Adequacy of respiratory assessment — Respiratory safety was assessed through adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.11.2. Respiratory events at least possibly drug-related

8.2.11.2.1. Respiratory deaths — There were no deaths attributed to respiratory events.

8.2.11.2.2. Serious respiratory adverse events — No serious respiratory adverse events were considered plausibly related to irbesartan.

8.2.11.2.3. Withdrawals for respiratory adverse events — Withdrawals for respiratory adverse events plausibly related to irbesartan are listed in Table 77 below.

Table 77. Withdrawals for respiratory adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	005/002	45	M	50	—	14	Discontinued with shortness of breath beginning with first dose, and considered probably drug-related. Event reported as unresolved.
CV131-031	006/017	75	F	75	—	126	Discontinued with shortness of breath and wheezing, considered possibly drug-related. Unresolved.
CV131-038	025/022	59	M	75	12.5	1	Discontinued for cough, considered probably drug-related. No follow-up.
Long-term phase							
CV131-029	018/007	67	M	50	—	131	Discontinued for cough. Event resolved.
CV131-037	038/015	49	M	75	12.5	1	Discontinued with cough, considered possibly drug-related. Resolution is unknown.
CV131-002	042/004	69	F	100	?	306	Discontinued for shortness of breath. Event was unresolved.

8.2.11.3. Respiratory events unlikely to be drug-related

8.2.11.3.1. Respiratory deaths There were no deaths attributed to respiratory events.

8.2.11.3.2. Serious respiratory adverse events Serious respiratory adverse events unlikely to be related to irbesartan are listed in Table 78 below.

Table 78. Serious respiratory adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-006	001/044	34	F	50	—	1	This subject received a single 50-mg dose. During the study she complained of chest discomfort. A physical exam and ECG were normal. The symptoms subsided and resolved by study completion. She was diagnosed with a teratoma of the lung with metastasis to the brain stem. Chemotherapy was advised but she refused treatment. The outcome is unknown.
Long-term phase							
CV131-044	052/007	36	M	75	—	71	Hospitalized for pulmonary edema after becoming short of breath on an airplane. Hospitalized again 2 days later with atrial fibrillation. Study drug was continued.
CV131-044	045/001	61	M	75 150	—	15 48 99 112	Hospitalized for chest tightness; study drug was continued. Hospitalized again for shortness of breath and cough. Study drug was interrupted. Third and fourth hospitalizations were for nausea and shortness of breath. Study drug was discontinued.
CV131-025	003/004	58	M	100	—	27	Unremarkable history. Hospitalization for onset of heart failure and bronchitis. Study drug was discontinued.
CV131-025	003/009	65	F	150	—	20	History of smoking for 50 years. Subject diagnosed with lung cancer; study drug was discontinued.

8.2.11.3.3. Withdrawals for respiratory adverse events Withdrawals for respiratory adverse events unlikely to be related to irbesartan are listed in Table 79 below.

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Table 79. Withdrawals for respiratory adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Long-term phase							
CV131-038	064/005	29	M	75	—	37	Discontinued for upper respiratory tract infection and intermittent rash on hands, considered unlikely to be drug-related. Event resolved.
CV131-050	055/004	60	M	75	—	2	Discontinued with upper respiratory symptoms, considered possibly drug-related. Events resolved.
CV131-027	027/011	64	F	150	—	1	Discontinued for rhinitis, which began during double-blind phase, and was considered possibly drug-related. Event did not resolve.
CV131-025	013/021	64	F	200	—	111	Discontinued for upper respiratory infection, considered unlikely to be drug-related. Event resolved.
CV131-002	027/002	52	M	100	?	124	Discontinued for bronchial congestion. Event resolved over several months.
CV131-002	042/002	62	M	100	?	203	Discontinued for sinusitis. Event resolved.

8.2.11.4. Common respiratory adverse events

Common respiratory adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 80. and Table 81 below, respectively.

Table 80. Respiratory adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Sinus abnormality	5.0	0.0	3.7	4.9	2.4	2.4	3.7	4.4	2.5	3.3	2.5	3.3	2.9	5.1	3.3
Cough	2.7	1.2	2.4	3.7	1.2	2.4	3.7	3.7	2.5	1.8	3.8	1.3	8.6	2.0	2.7
Pharyngitis	2.3	2.4	0.0	1.2	2.4	2.4	3.7	1.3	3.3	2.4	2.5	2.1	1.9	2.0	2.2
Rhinitis	2.5	0.0	3.7	0.0	1.2	2.4	2.4	2.4	0.8	1.3	1.3	0.8	7.6	0.0	1.7
Tracheobronchitis	1.1	0.0	0.0	2.5	0.0	0.0	0.0	1.7	0.8	0.7	0.0	0.4	1.9	0.0	0.8
Congestion	0.9	0.0	0.0	3.7	0.0	0.0	0.0	0.3	0.8	0.9	0.0	0.8	1.0	0.0	0.7
Pulmonary congestion	0.6	0.0	1.2	2.5	0.0	2.4	0.0	0.3	0.8	1.1	0.0	0.0	1.0	0.0	0.7
Dyspnea	0.8	2.4	1.2	0.0	0.0	0.0	1.2	0.3	0.4	0.4	1.3	0.0	0.0	0.0	0.5
Wheezing	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	1.2	0.0	1.3	0.4	0.0	0.0	0.3

Table 81. Respiratory adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																				
	0				37.5				75			100				150		300			
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
URI	5.5	11.4	5.6	7.5	9.5	13.6	8.9	0.0	6.1	9.7	3.4	14.6	6.8	2.3	9.1	5.5	6.7	7.0	0.0	4.5	2.2
Sinus abnormality	4.7	4.5	3.4	2.5	2.4	6.8	0.0	0.0	4.6	1.5	0.8	2.4	4.5	11.6	0.0	3.0	2.2	4.7	5.0	4.5	8.9
Cough	3.0	4.5	4.0	0.6	2.4	4.5	4.4	2.4	3.6	3.0	0.8	0.0	6.8	2.3	0.0	2.0	1.5	2.3	0.0	0.0	0.0
Pharyngitis	1.7	2.3	3.4	2.5	2.4	0.0	2.2	2.4	2.0	2.2	2.5	2.4	0.0	0.0	6.8	3.5	1.5	0.0	0.0	2.3	2.2
Rhinitis	2.5	2.3	1.7	1.3	2.4	6.8	0.0	2.4	2.6	1.5	1.7	0.0	0.0	0.0	0.0	2.5	2.2	2.3	0.0	4.5	0.0
Pulmonary congestion	1.7	0.0	0.6	0.0	2.4	0.0	0.0	0.0	0.5	0.7	1.7	4.9	0.0	2.3	0.0	1.0	0.0	0.0	0.0	0.0	2.2
Tracheobronchitis	0.8	0.0	1.1	1.9	0.0	0.0	0.0	0.0	0.5	0.7	0.0	0.0	0.0	0.0	2.3	0.5	2.2	0.0	0.0	2.3	0.0
Dyspnea	0.8	0.0	0.6	0.0	0.0	0.0	2.2	0.0	0.5	0.0	1.7	0.0	2.3	0.0	2.3	0.5	0.7	0.0	0.0	0.0	0.0
Wheezing	0.4	0.0	1.1	0.6	0.0	2.3	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.5	1.5	0.0	0.0	0.0	0.0

In open-label extensions, respiratory adverse events were reported for 373 subjects on irbesartan alone (21% or 140 subjects with events per 1000 subject-years) and by 443 subjects on irbesartan/HCTZ (26% or 365 subjects with events per 1000 subject-years). All such events are shown in Table 82 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 82. Respiratory adverse events with ≥1% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700				Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y		n	%	/KS-Y	n	%	/KS-Y
Upper respir infection	158	8.8	158	186	11	153	Dyspnea	15	0.8	15	21	1.2	17
Sinus abnormality	62	3.5	62	91	5.4	75	Epistaxis	13	0.7	13	9	0.5	7
Cough	59	3.3	59	67	3.9	55	Congestion	12	0.7	12	9	0.5	7
Pharyngitis	53	3.0	53	74	4.4	61	Pulmonary infection	13	0.7	13	8	0.5	7
Rhinitis	57	3.2	57	55	3.2	45	Pulmonary congestion	12	0.7	12	5	0.3	4
Tracheobronchitis	47	2.6	47	51	3.0	42	Wheezing	5	0.3	5	11	0.6	9

a. Subjects with events per 1000 subject-years.

8.2.11.5. Respiratory laboratory findings — No laboratory tests were considered in the evaluation of respiratory system safety.

8.2.12. Special senses

8.2.12.1. Adequacy of special sense assessment — Special sense safety was assessed through adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.12.2. Special sense events at least possibly drug-related

8.2.12.2.1. Special sense deaths — There were no deaths attributed to special sense events.

8.2.12.2.2. Serious special sense adverse events — No serious special sense adverse events were considered plausibly related to irbesartan.

8.2.12.2.3. Withdrawals for special sense adverse events — Withdrawals for special sense adverse events plausibly related to irbesartan are listed in Table 83 below.

Table 83. Withdrawals for special sense adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-038	055/014	54	F	75	—	11	Discontinued with visual disturbance, which resolved.
Long-term phase							
CV131-002	034/008	56	M	100	—	67	Discontinued for visual disturbances. Event resolved.
CV131-038	001/003	38	F	75	12.5	75	Discontinued for tinnitus, of unassessable relationship to study drug. Event did not resolve.

8.2.12.3. Special sense events unlikely to be drug-related

8.2.12.3.1. Special sense deaths — There were no deaths attributed to special sense events.

8.2.12.3.2. Serious special sense adverse events — Serious special sense adverse events unlikely to be attributable to study drug are shown in Table 84 below.

Table 84. Serious special sense adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Long-term phase							
CV131-031	006/012	73	F	75	—	23	Hospitalized for cataract surgery, scheduled prior to randomization. Study drug continued.

8.2.12.3.3. Withdrawals for special sense adverse events

Withdrawals for special sense adverse events unlikely to be related to irbesartan are listed in Table 85 below.

Table 85. Withdrawals for special sense adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-031	023/007	71	F	150	—	91	Discontinued for worsening glaucoma, considered unlikely to be drug-related. Event did not resolve.
CV131-050	048/008	55	M	600	—	10	Discontinued for conjunctivitis, which did not resolve.
CV131-038	061/035	70	F	150	12.5	31	Discontinued with glaucoma, considered unlikely to be drug-related.

8.2.12.4. Common special sense adverse events

Common special sense adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 86. and Table 87 below, respectively.

Table 86. Special sense adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Vision disturbance	0.6	0.0	0.0	1.2	0.0	2.4	0.0	0.7	1.7	0.9	0.0	0.4	0.0	3.0	0.8
Abn visual field	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	1.0	0.1
Hearing abn	0.3	1.2	0.0	0.0	0.0	0.0	1.2	0.7	0.8	0.9	0.0	0.0	0.0	1.0	0.6
Abnormality hearing	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pain Ear	1.2	0.0	0.0	0.0	2.4	0.0	0.0	0.7	0.4	0.4	0.0	0.8	0.0	0.0	0.5
Vertigo	0.6	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.8	0.9	0.0	0.4	0.0	1.0	0.5
Inner ear disorder	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0	1.3	0.0	0.0	0.0	0.1
Abn conjunctiva	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.8	0.2	0.0	0.4	1.0	2.0	0.4
Disturb eye other	0.6	0.0	0.0	0.0	1.2	0.0	0.0	0.3	0.0	0.4	0.0	1.3	0.0	0.0	0.4
Eyelid abn	0.2	1.2	0.0	1.2	1.2	0.0	0.0	0.3	0.4	0.0	0.0	0.0	0.0	0.0	0.3
Ear abnormality	0.3	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.4	0.0	0.0	0.4	0.0	0.0	0.2
Eye surgery	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.8	0.0	0.0	0.2
Injury eye	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	1.0	0.2

In open-label extensions, special sense adverse events were reported for 88 subjects on irbesartan alone (4.9% or 90 subjects with events per 1000 subject-years) and by 125 subjects on irbesartan/HCTZ (7.4% or 103 subjects with events per 1000 subject-years). All such events are shown in Table 88 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 87. Special sense adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																					
	0				37.5				75			100				150		300			
HCTZ N=	0 236	6.2 44	12 177	25 159	0 42	6.2 44	12 45	25 41	0 196	12 134	25 118	0 41	6.2 44	12 43	25 44	0 199	12 135	0 43	6.2 40	12 44	25 45
Infection	0.8	2.3	1.1	0.6	2.4	0.0	0.0	0.0	1.0	0.7	2.5	0.0	0.0	0.0	0.0	0.5	2.2	2.3	0.0	0.0	0.0
Ear abnormality	0.0	0.0	0.0	0.6	0.0	0.0	2.2	2.4	0.0	0.7	3.4	2.4	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	0.0
Vision disturbance	1.3	0.0	0.6	1.3	2.4	0.0	0.0	0.0	0.5	1.5	1.7	0.0	0.0	0.0	2.3	1.0	0.7	0.0	0.0	0.0	0.0
Hearing abnormality	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.5	0.0	0.0	1.0	0.0	0.0	0.0	0.0	4.4
Ear pain	1.3	0.0	0.0	0.0	0.0	2.3	0.0	2.4	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	2.3	0.0	0.0	0.0

Table 88. Special sense adverse events with ≥0.5% open-label incidence.

	Irbesartan N=1791			Irbesartan/HCTZ N=1700				Irbesartan N=1791			Irbesartan/HCTZ N=1700		
	n	%	/KS-Y[a]	n	%	/KS-Y		n	%	/KS-Y	n	%	/KS-Y
Disturb eye other	18	1.0	18	22	1.3	18	Hearing abnormality	10	0.6	10	13	0.8	11
Vision disturbance	9	0.5	9	22	1.3	18	Conjunctival abnormality	6	0.3	6	15	0.9	12
Ear infection	8	0.4	8	17	1.0	8	Ear pain	10	0.6	10	7	0.4	6

a. Subjects with events per 1000 subject-years.

8.2.12.5. Special sense laboratory findings No laboratory tests were considered in the evaluation of special sensory safety.

8.3. Summary of key adverse findings

- There were no deaths plausibly related to study drug.
- There were few cases of hypotension, but as a pharmacological property of the drug, these were to be expected in fixed dose studies. Very few cases of orthostatic hypotension were reported as adverse events.
- There were several plausibly drug-related cases of rash. However, the overall rate was higher on placebo, so the rate of drug-related rash is probably too low to estimate.
- There were several plausibly drug-related cases of angioedema.
- Because epistaxis was a common adverse event, some additional attention was paid to platelets; the reviewers found no drug-related signal.
- Neutropenia was a more common adverse event on irbesartan than on placebo during double-blind treatment (0.2% vs. 0%), but laboratory observation of low neutrophil count, by the reviewers' analysis, was more common on placebo.
- Because another drug in the same pharmacological class appears to be associated with evidence of hepatotoxicity, some attention was given to hepatic enzymes; there was no evidence of drug-related elevations in hepatic enzymes.
- Hyperkalemia, by criteria set by the reviewers, was more common on irbesartan than on placebo. The incidence may be somewhat dose-related, with the excess appearing within the recommended dose range and continuing beyond the useful range.
- There were no observable effects on serum creatinine.
- The most common adverse events during double-blind treatment and more common on active treatment than on placebo are listed in Table 89 below.

Table 89. Common adverse events by dose in double-blind studies of irbesartan only.

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Upper resp infect	6.2	12.2	4.9	14.8	3.6	9.5	14.6	7.4	10.3	5.1	0.0	7.9	12.4	11.1	8.0
Pulmonary infection	0.2	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Influenza	2.0	3.7	3.7	4.9	2.4	2.4	3.7	1.0	2.5	3.1	0.0	0.0	1.9	2.0	2.2
Viral infection	0.5	1.2	0.0	0.0	0.0	2.4	1.2	0.7	0.4	0.2	0.0	0.8	1.0	0.0	0.5
Infection	0.3	1.2	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.4	0.0	0.0	1.0	0.0	0.3
Superficial fung inf	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.4	0.0	0.4	0.0	0.0	0.3
Infect skin bacteria	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Fungal infection	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Gynecologic infect	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Infec herpes simplex	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Infec varicella zost	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Infect upper resp	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Infect urinary tract	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Infection viral	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Seroprotein Hep B	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Trichomonas urine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.1
Gram (+) infection	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ear infection	1.4	0.0	0.0	0.0	0.0	2.4	0.0	1.3	0.0	0.7	1.3	0.4	0.0	0.0	0.5
Fatigue	3.3	4.9	1.2	1.2	2.4	4.8	3.7	3.7	4.1	3.5	6.3	5.4	4.8	4.0	3.9
Musculoskel trauma	0.5	0.0	1.2	1.2	2.4	4.8	0.0	2.7	0.8	1.1	3.8	2.9	2.9	2.0	1.8
Anxiety/nervousness	0.9	0.0	0.0	1.2	0.0	2.4	1.2	1.7	0.0	1.6	1.3	0.8	1.0	1.0	1.0
Vision disturbance	0.6	0.0	0.0	1.2	0.0	2.4	0.0	0.7	1.7	0.9	0.0	0.4	0.0	3.0	0.8
Abn visual field	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	1.0	0.1
Numbness	0.3	1.2	1.2	1.2	0.0	2.4	2.4	0.3	0.8	0.7	0.0	0.0	1.9	0.0	0.7
Pulmonary congestion	0.6	0.0	1.2	2.5	0.0	2.4	0.0	0.3	0.8	1.1	0.0	0.0	1.0	0.0	0.7
Allergy	0.6	0.0	0.0	0.0	0.0	2.4	1.2	0.3	0.4	0.7	1.3	0.8	0.0	1.0	0.6
Allergy environ agen	0.0	0.0	0.0	1.2	0.0	2.4	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.2
Allergic reaction	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Chemical allergy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.1
Hearing abn	0.3	1.2	0.0	0.0	0.0	0.0	1.2	0.7	0.8	0.9	0.0	0.0	0.0	1.0	0.6
Abnormality hearing	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Abdominal pain	0.0	0.0	2.4	1.2	1.2	0.0	1.2	1.3	1.7	1.1	0.0	1.3	1.0	2.0	0.5
Pain abdomen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Fever	0.3	0.0	0.0	1.2	2.4	0.0	1.2	0.0	0.4	0.4	1.3	0.4	1.0	0.0	0.5
Epistaxis	0.3	0.0	1.2	2.5	1.2	2.4	0.0	0.7	0.8	0.4	1.3	0.0	1.9	2.0	0.5
Somnolence	0.2	1.2	0.0	0.0	0.0	0.0	0.0	0.7	0.4	1.1	0.0	0.4	0.0	0.0	0.5
Emotion labil/distur	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.7	0.0	0.8	1.9	0.0	0.5
Arthritis	0.0	0.0	1.2	0.0	1.2	2.4	0.0	0.0	0.0	0.4	3.8	0.0	1.0	0.0	0.5
Libido change	0.0	0.0	0.0	1.2	0.0	0.0	1.2	0.3	0.4	0.0	0.0	0.4	1.0	1.0	0.4
Sexual dysfunction	0.3	0.0	0.0	0.0	2.4	2.4	0.0	0.3	1.2	0.0	0.0	0.8	1.0	2.0	0.4
Abn conjunctiva	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.8	0.2	0.0	0.4	1.0	2.0	0.4
Dizziness orthostatic	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.9	1.3	1.7	1.9	1.0	0.3
Orthostatic hypotens	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	1.9	0.0	0.2
Hypotension	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	1.0	0.1
Syncope	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Hypotension orthostatic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Bursitis	0.0	0.0	0.0	2.5	0.0	0.0	0.0	0.3	0.4	0.0	1.3	0.0	0.0	1.0	0.3

Table 89. Common adverse events by dose in double-blind studies of irbesartan only.*(Continued)*

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Joint stiffness	0.0	0.0	0.0	0.0	1.2	0.0	1.2	0.0	0.4	0.4	0.0	0.0	1.0	0.0	0.3
Incr bilirubin serum	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.7	0.0	0.2	0.0	0.4	1.0	1.0	0.3
Incr serum creatinine	0.2	0.0	1.2	0.0	1.2	2.4	0.0	0.0	0.0	0.2	0.0	0.4	1.0	0.0	0.3
Bite insect	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	2.5	0.0	0.0	0.0	0.3
Chills	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.4	0.2	0.0	0.4	0.0	0.0	0.3
Hot flashes	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.0	0.4	0.0	1.0	0.3
Flushing	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.8	1.3	0.0	0.4	0.0	1.0	0.3
Dermatitis	0.0	0.0	0.0	1.2	0.0	0.0	1.2	0.0	0.8	0.4	0.0	0.8	1.0	0.0	0.3
Distention abdomen	0.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	1.3	0.4	1.0	0.0	0.3
Serum potassium incr	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.9	0.0	0.8	0.0	2.0	0.3
Breast disorder	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.4	1.0	0.0	0.3
Gout	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.7	1.3	0.0	0.0	0.0	0.3
Weight gain	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.4	0.0	0.0	1.0	1.0	0.3
Eyelid abn	0.2	1.2	0.0	1.2	1.2	0.0	0.0	0.3	0.4	0.0	0.0	0.0	0.0	0.0	0.3
Decr neutrophils	0.0	0.0	1.2	1.2	1.2	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.2
WBC blood decr	0.0	0.0	1.2	1.2	1.2	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Lymphopenia	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.1
Monocytes decr	0.0	0.0	0.0	1.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Decr hematocrit	0.0	0.0	1.2	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.2
Decr hemoglobin	0.0	0.0	1.2	0.0	1.2	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Anemia	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Edema head/neck	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Edema upp extremity	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	1.0	0.2
Edema upper extremity	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Trauma	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.4	0.0	0.0	0.2
Trauma musculoskel	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Erythema face	0.0	0.0	1.2	0.0	0.0	0.0	0.0	1.0	0.0	0.2	0.0	0.0	0.0	0.0	0.2
Erythema extremity	0.2	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Weakness extremity	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.7	0.0	0.2	0.0	0.0	0.0	0.0	0.2
Muscle weakness	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.1
Dryness skin	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	1.0	0.2
Lesion oral	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	1.7	0.2	0.0	0.0	1.9	0.0	0.2
Oral pain	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.0	0.0	0.4	1.0	0.0	0.2
Irrit bowel syndr	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.2
Increased BUN	0.0	0.0	1.2	0.0	1.2	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	2.0	0.2
Musculoskeletal abn	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.3	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Limitation movement	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.4	0.0	0.0	0.0	0.0	0.2
Entrapment neuropath	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.4	0.2	0.0	0.0	0.0	0.0	0.2
Injury eye	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	1.0	0.2

Table 89. Common adverse events by dose in double-blind studies of irbesartan only.*(Continued)*

		Irbesartan (mg/day)													
N=	0 641	1 82	5 82	10 81	25 83	37.5 42	50 82	75 297	100 242	150 451	200 79	300 240	600 105	900 99	Any 1965
Disc disease	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Hernia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.1
Tendinitis	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Epicondylitis	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Joint swelling	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.1

32 pages

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(DRAFT Labeling)

10. Conclusions

10.1. Chemistry

The only issue concerns assignment of an appropriate expiration date. The available data appear to support only 6 months, but there is no reason not to approve with 6-months and allow that to amended on the basis of additional data when available.

10.2. Mechanism

Pharmacological data show the parent drug to be a potent and highly selective AT_1 angiotensin II receptor antagonist with expected antihypertensive effects in high-renin models of hypertension.

Studies in normal adult human males show that irbesartan antagonizes the hypertensive effects of exogenously administered angiotensin II.

Dose-related increases in endogenous angiotensin II and plasma renin were seen in one study. Changes in aldosterone were variable, as they are with ACE inhibitors.

10.3. Animal toxicology

Studies of acute and chronic toxicity were performed in multiple animal species. Toxic effects, appearing at doses high compared to expected exposure in man, were similar to those seen with other members of the class of angiotensin II receptor antagonists or ACE inhibitors.

The carcinogenicity and mutagenicity assessments were considered adequate and without important findings.

10.4. Pharmacokinetics

Animal data showed low bioavailability, a large volume of distribution, and multiple metabolites, some of which having angiotensin II receptor antagonist activity comparable to that of the parent drug.

The antagonistic effect of irbesartan on the hypertensive effects of exogenous angiotensin II in normal volunteers demonstrates clockwise hysteresis, consistent with the involvement of active metabolites.

Effects on blood pressure in hypertensive subjects also show clockwise hysteresis.

10.5. Clinical exposure

Clinical effectiveness was assessed in 9 adequate and well-controlled, randomized, parallel, double-blind, fixed-dose studies of irbesartan alone and 3 such studies of irbesartan plus HCTZ in subjects with uncomplicated mild-to-moderate hypertension. These studies included a reasonable proportion of subjects who were women, age >65 years, or of minority races. These studies explored irbesartan from 1 to 900 mg (37.5 to 300 mg in combination with HCTZ) daily dosing in placebo-controlled periods of 4 to 12 weeks, for a total of 930 subject-years on irbesartan alone and 670 subject-years on irbesartan plus HCTZ.

Open-label follow-on studies involved more than 3000 subjects for a total of 1000 subject-years on irbesartan alone and 1200 subject-years on irbesartan plus HCTZ.

10.6. Antihypertensive effectiveness of irbesartan alone

Antihypertensive effects of irbesartan alone were explored in 3 parallel, fixed dose studies covering doses from 1 to 900 mg q.d. Trough effects on blood pressure appear to plateau at approximately -10/-6 mmHg at the high end of the dose range studied. The half-maximal effect is observed at a dose of about 100 mg q.d.

Peak antihypertensive effects lag several hours behind the peak in the plasma concentration of irbesartan following a morning dose.

Evidence from a study with ambulatory blood pressure monitoring suggests there is little benefit from twice-daily dosing compared with once-daily dosing.

Repetitive once-daily dosing produces progressively larger antihypertensive effects, for at least the first 6 to 8 weeks of treatment. The majority of the antihypertensive effect develops within 2 weeks, suggesting that this is a reasonable interval between dosing adjustments in clinical practice. There are no good studies of the time course of recovery of blood pressure at the end of a period of repetitive dosing.

10.7. Antihypertensive effectiveness of irbesartan plus HCTZ

A response surface analysis of a factorial study of irbesartan 37.5 to 300 mg and HCTZ 6.25 to 25 mg demonstrated compelling evidence of a contribution by both agents to the observed antihypertensive effects.

10.8. Effectiveness in subpopulations

Across studies of irbesartan alone, analysis of the dose-response relationship for Caucasians vs. non-Caucasians (mostly Blacks), for males vs. females, and for age less than vs greater than age 65 revealed no compelling evidence of differences, but the data do not allow one to rule out differences among groups of 50%.

Analysis of one study of irbesartan plus HCTZ by race was consistent with there being somewhat smaller treatment effects in Blacks, even with HCTZ.

10.9. Safety

The irbesartan and irbesartan-HCTZ development programs were relatively large, but resulted in otherwise conventional safety databases.

There were no findings that distinguished irbesartan from other members of this class of drugs.

11. Recommendations

11.1. Irbesartan alone

Irbesartan is clearly effective in reducing blood pressure. Its development program did not uncover safety concerns that might mitigate against approval. Irbesartan should be approved, as alternative first-line treatment of hypertension, upon satisfactory amendment to the proposed label according to the marked-up draft contained in this review. This approval need not be predicated upon the sponsor's commitment to any post-marketing studies.

11.2. Irbesartan plus HCTZ

Irbesartan plus HCTZ is clearly effective in reducing blood pressure. Both components contribute to the observed effects on blood pressure. The combination product's development program did not uncover safety concerns that might mitigate against approval. Irbesartan plus HCTZ should be approved, as alternative second-line treatment of hypertension, upon satisfactory amendment to the proposed label according to the marked-up draft contained in this review. This approval need not be predicated upon the sponsor's commitment to any post-marketing studies.

A. Individual study reviews

A1. ACT 1967: Dose-finding study of irbesartan in patients with mild to moderate hypertension.

A1.1. Source documents

Study report: NDA 20-757, vol 1.239 to 1.252; electronic document: ACT1967.PDF.

A1.2. Investigators

Center 1: Professor A. Man In't Veld, University Hospital Dijkzigt, Department of Internal Medicine, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Center 2: Mr. T Schwarz, U. Gene Research, BV, Utrecht, The Netherlands.

A1.3. Study dates

10 February 1993 to 30 July 1993

A1.4. Study design

This study description was based upon the protocol dated 15 February 1994. There was one amendment 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<115 mmHg). In order to qualify for randomization, the subject's seated diastolic blood pressure variability was not to exceed 10 mmHg. After a 3-week lead-in period, the subjects were randomized to placebo, 1 mg, 25 mg or 100 mg qd for 7 days.

Drug supplies are shown in Table 90 below.

Table 90. Drug supplies (ACT 1967).

Dose	Lot	Dose	Lot
Placebo	J794M	1 mg	J854T
	J855S	25 mg	J885N

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects must 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 fundoscopic 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 NSAIDs were excluded. Subjects must have been able to wean other antihypertensives and vasoactive agents. All other comcominant medications were to be noted on the case report forms.

The primary efficacy variables in this study were (1) changes in supine DBP and SBP compared to baseline, (2) ABPM amplitude of blood pressure decrease on study drug versus placebo, (3) ABPM determination of the peak-trough ratio, and (4) mean values of day- and night-time measurements. Secondary objectives were to determine pharmacokinetic and pharmacodynamic measurements of the renin-angiotensin system.

Blood pressure readings were to be performed at 30 minutes and just prior to dose, and 1, 2, 4 hours post-dose on day 1. The blood pressure measurements prior to randomization and on day 7 were the same as day 1 with additional measurements at 6, 10 and 24 hours post-dose.

ABPM recordings were to be performed for a period of 24 hours prior to the first dose and 4 hours after dose. Also, a 24-hour recording was to be made on day 7. Measurements were to take place every 15 minutes during the day and every 30 minutes at night.

Baseline and study drug determinations on day 1 and 7 of total and inactive renin, angiotensin II and aldosterone were to be made.

Blood samples for plasma irbesartan levels were to be drawn at 0, 1, 2, and 4 hours post-dose on day 1 and at 0, 1, 2, 4, 6, 10, and 24 hours on day 7.

24-hour urine collection at baseline and on study days 1 and 7 were to be analyzed for sodium, potassium, creatinine, uric acid, and proteins.

The primary efficacy variable was analyzed using analysis of covariance by center and baseline.

Although there was no interim analysis planned in the original protocol, one was carried out to facilitate the planning of a definitive dose ranging phase III study. Summary statistics of office blood pressure were provided by dose group to the sponsor's trial physician. The physician was blind to dose and did not reveal any information to personnel directly involved with the study.

Safety assessments were done both in the single- and double-blinded period. Tests included (1) ECGs 0 and 6 h after dose, (2) laboratory tests (CBC, SMA20, urinalysis), and (3) physical examination. Clinical adverse events and their relationship to the study drug were recorded.

A1.5. Results

There were 105 subjects enrolled. Disposition of enrolled subjects is shown in Table 91 below.

Table 91. Subject disposition (ACT 1967).

Subject Disposition	N
Enrolled	105
Not Randomized	19
Randomized	86
Discontinued	0
Completed	86

Table 92 below shows reasons for exclusion prior to randomization.

Table 92. Reasons for exclusion (ACT 1967).

Reason	N	Reason	N
Did not qualify	15	Adverse event	1
Subject request	2	Other	1
Total	19		

There were only minor protocol deviations. Seven subjects had mean baseline supine diastolic pressures <95 mmHg (range 93 to 94 mmHg) on the last day of the lead-in phase. A large number of subjects (62) had their first blood pressure reading on day 1 just prior rather than 30 minutes prior to dosing. There were 15 samples of blood in 13 subjects that were collected outside ±10% of the theoretical sampling time.

Demographics of the 4 treatment groups are shown in Table 93 below. There was no statistical relationship between the groups in terms of gender, race, or age. The majority of subjects were male.

Table 93. Demographics (ACT 1967).

		Placebo N=21	Irbesartan		
			1 mg N=23	25 mg N=22	100 mg N=21
Gender	Male (%)	90	68	82	67
	Female (%)	10	32	18	33
Race	White (%)	100	100	100	100
Age	Mean (SD)	51 (11)	52 (9)	50 (11)	53 (8)
Previously treated HTN	(%)	86	86	82	76
No prior treatment	(%)	14	14	18	23
Uncontrolled HTN	N(%)	15(71)	17(77)	13(59)	15(71)
Despite Previous RX	N(%)	12(67)	14(74)	9(50)	10(63)

A1.5.1. Pharmacodynamics

Table 94 below shows seated baseline blood pressures and heart rate on day 4. There were no significant statistical differences among the 4 groups.

Table 94. Baseline blood pressure and heart rate (ACT 1967).

	Seated (mean±SD)				Standing (mean±SD)			
	Placebo N=21	Irbesartan			Placebo N=21	Irbesartan		
		1 mg N=23	25 mg N=22	100 mg N=21		1 mg N=23	25 mg N=22	100 mg N=21
DBP (mmHg)	104±6	106±6	107±7	103±7	107±8	108±7	108±8	107±9
SBP (mmHg)	161±16	162±17	165±11	159±19	161±17	160±17	163±12	163±22
HR (bpm)	70±8	69±9	68±11	68±6	75±10	76±11	76±12	75±8

Table 95 below shows the mean change in seated trough systolic and diastolic blood pressure and heart rate from baseline. There was no whole-model significance in either systolic or diastolic blood pressure in the dosage range studied. There was a statistically significant difference only between placebo and 100 mg irbesartan in all blood pressure measurements except StSBP.

Table 95. Mean change in seated blood pressure and heart rate (ACT 1967).

	Seated (mean±SE)				Standing (mean±SD)			
	Placebo N=21	Irbesartan			Placebo N=21	Irbesartan		
		1 mg N=23	25 mg N=22	100 mg N=21		1 mg N=23	25 mg N=22	100 mg N=21
DBP (mmHg)	-1±6	-3±7	-3±6	-6±7	-2±7	-3±6	-2±6	-6±7
SBP (mmHg)	-1±11	-4±11	-7±11	-12±13	-3±13	-6±13	-5±11	-13±13
HR (bpm)	-3±7	2±7	0±6	5±5	5±7	2±6	1±9	7±7

Mean ambulatory systolic and diastolic pressures on day 7 are shown in Figure 25 below. There were no statistical differences in the ABPM data between the groups prior to the start of study drug.

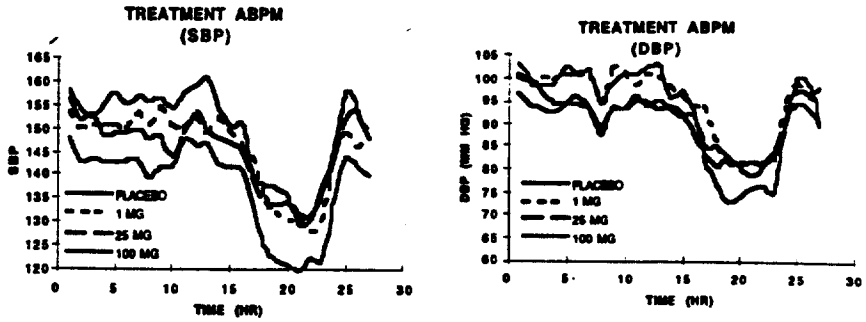

Figure 25. ABPM Data on day 7 (ACT 1967).

The mean changes from baseline in 24-hour ambulatory diastolic and systolic pressures is given in Table 96 below.

Table 96. 24-hour ABPM data (ACT 1967).

	Placebo	Irbesartan		
		1 mg	25 mg	100 mg
DBP				
BP (mean±SD)	-1±9	2±7	0±8	-3±10
AUC (mean±SD)	-83±111	-37±109	-149±119	-180±116*
SBP				
BP (mean±SD)	0±10	0±11	1±12	-7±10
AUC (mean±SD)	-82±118	-65±153	-179±152	-291±212*

*Statistically significant (*critical* $p<0.0192$) compared with placebo.

No dose was statistically significant, but the 100 mg dose approached significance. $AUC_{0\text{-}24h}$ for mean systolic and diastolic pressure are significantly reduced compared to placebo.

The reviewers investigated the relationship between plasma levels and irbesartan and Antihypertensive effects by plotting hysteresis loops for supine and standing systolic and diastolic pressure changes from baseline and placebo for the 25 and 100 mg doses, as shown in Figure 26 below. Although inconclusive, some of the graphs are demonstrate a significant amount of hysteresis, raising the possibility of an active metabolite.

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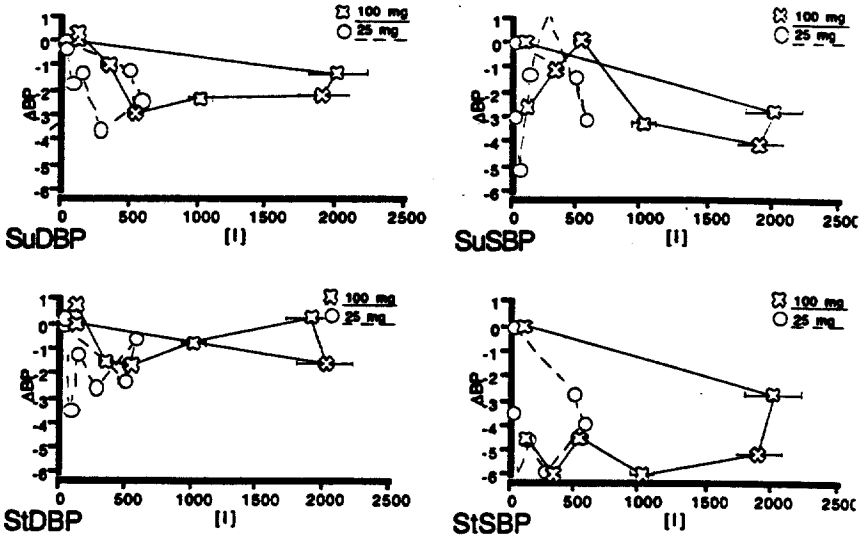

Figure 26. Antihypertensive effects by plasma irbesartan level (ACT 1967).

A1.5.2. Neurohormones

Active renin and angiotensin II levels at trough (day 7) for irbesartan 100 mg significantly increased compared to placebo. Peak active renin and angiotensin II on day 7 showed a slight negative correlation with supine blood pressure. Small positive correlations were observed between C_{max} and AUC versus total renin and angiotensin II.

A1.5.3. Pharmacokinetics

Pharmacokinetic profiles were similar to ones observed in the pharmacokinetic studies. The dose proportionate relationship between plasma concentrations at 1, 2, and 4 hours was observed.

The relationship between supine blood pressure and plasma levels at 24 hours were negative, but not statistically significant.

A1.5.4. Safety

There was a mean exposure of the study drug of approximately 7 days. No deaths or serious adverse events were reported.

There were no dropouts in the 7-day double-blind period.

Treatment-emergent adverse events will be discussed as a group in the Integrated Review of Safety. There were a total of 30 adverse events reported by 25 subjects while on randomized treatment. The most frequently reported adverse events were fatigue, headache and lymphocytosis. Lymphocytosis is thought to be secondary to a viral infection in 3 of 4 subjects. None of the symptoms resulted in discontinuation of the study drug.

There were no clinically significant changes in physical exam findings.

There were a total of 6 ECG abnormalities seen in 6 subjects after randomization which had not been present prior to randomization. They were first degree block (2), atrial fibrillation (1), right bundle branch block (1), ventricular extrasystole (1) and superventricular extrasystoles (1).

As noted above, there were 4 subjects with lymphocytosis. There was no pattern with irbesartan dose.

Serum chemistry marked abnormalities were few. There were 4 subjects who had increased triglycerides after randomization. Three of 4 subjects had increased

triglycerides at baseline. There was no evident relationship of increasing triglycerides with dose.

Urinalysis showed no clinically significant changes.

A1.6. Summary

The study was a randomized, parallel, dose-ranging study of subjects on three doses of irbesartan versus placebo. There was a statistically significant treatment effect only with the 100 mg dose of irbesartan. Relative increases in renin and angiotensin were seen in irbesartan-treated subjects. There were no deaths or serious adverse events to comment upon.

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A2. CV131-001: A multicenter assessment of tolerability and antihypertensive activity of irbesartan in patients with mild to moderate hypertension.

A2.1. Source documents Study report: NDA 20-757, vol 1.253 to 1.254; electronic document: MAST001.PDF.

A2.2. Investigators Multi-center study with 10 investigators in the United States.

A2.3. Study dates 5 May 1993 to 16 July 1993.

A2.4. Study design This study description was based upon the amended protocol dated 22 April 1993. There were no amendments to the protocol after the start of enrollment.

This was a randomized, double-blind, placebo-controlled, parallel study in subjects with mild to moderate hypertension (95<SeDBP<110 mmHg). Subjects were to be randomized only if the last 2 consecutive weekly diastolic BP readings were within the entry range and the variation in diastolic BP was no greater than 8 mmHg. After a 4-week lead-in period, the subjects were randomized to placebo, 5 mg, 25 mg or 100 mg qd for 7 days.

Drug supplies are shown in Table 97 below.

Table 97. Drug supplies (CV131-001).

	Lot
Placebo	J797M
Irbesartan	
5 mg	J798M
25 mg	J855S

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 fundoscopic 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 NSAIDs, anticonvulsants, antibiotics, antacids or daytime H_2-antagonists, cimetidine, and bile acid binding resins were excluded. Subjects were to have been able to wean other antihypertensives and vasoactive agents. All other comcominant medications were to be noted on the case report forms.

Blood pressure readings during the double-blind period were performed just prior to dose, and 1, 2, 4, 6, and 8 hours post-dose on day 1 and day 7. Subjects were seen at 2 to 3 days and 6 to 7 days after discontinuation of double-blind treatment.

The primary efficacy variables in this study were (1) changes in trough supine DBP from baseline, (2) degree of therapeutic response, and (3) safety and tolerability. Secondary criteria were to determine changes in supine and standing BP and HR over the 8-hour measurement period (1st and 7th day of treatment).

The degree of therapeutic response during the active treatment period was characterized as follows: (1) normalized: SuDBP ≤90 mmHg; (2) responder: SuDBP not normalized but ≥10 mmHg from baseline, (3) partial responder: SuDBP not normalized but at least 5 to 10 mmHg from baseline, or (4) non-responder: neither normalized or responder.

The primary efficacy variable was analyzed using analysis of covariance by center and baseline.

Safety assessments were done both in the single- and double-blinded period. Tests included were (1) ECGs at screening and day 7,(2) laboratory tests (CBC, SMA20, urinalysis), and (3) physical examination. Clinical adverse events and their relationship to the study drug were recorded.

A2.5. Results

There were 114 subjects enrolled. Disposition of enrolled subjects is shown in Table 98 below.

Table 98. Subject disposition (CV131-001).

Subject disposition	N
Enrolled	114
Not randomized	37
Randomized	77
Discontinued	3
Completed	74

Table 99 below shows reasons for exclusion prior to randomization.

Table 99. Reasons for exclusion (CV131-001).

Reason	N		
Did not qualify	24	Adverse event	3
Subject request	5	Other	1
Sponsor request	4		
Total	37		

Protocol deviations included 7 subjects at one center (Center 10). The subjects were improperly dosed with supplies intended for the first day of withdrawal (placebo). Three subjects at separate centers were over-compliant by one dose. One subject was under-compliant by one dose. One subject with SuDBP difference ≤8 mmHg was randomized.

Demographics of the 4 treatment groups are shown in Table 100 below. There was no statistical relationship between the groups in terms of gender, race, or age. The majority of subjects were male.

Table 100. Demographics (CV131-001).

Subject		Placebo N=21	Irbesartan 5 mg N=19	Irbesartan 25 mg N=20	Irbesartan 100 mg N=17
Gender	Male (%)	62	12(63)	12(80)	13(77)
	Female (%)	38	7(37)	8(40)	4(23)
Race	White (%)	76	74	80	71
	Black (%)	24	21	20	29
	Other (%)	0	5.3	0	0
Age	(Mean±SD)	50±10	47±10	55±7	56±10

A2.5.1. Pharmacodynamics

Table 101 below shows baseline supine blood pressure. There were no significant statistical differences between the groups with respect to treatment arm.

Table 101. Baseline blood pressure and heart rate (CV131-001).

	Seated (mean±SE)				Standing (mean±SE)			
	Placebo N=21	Irbesartan			Placebo N=21	Irbesartan		
		5 mg N=19	25mg N=20	100mg N=17		5 mg N=19	25mg N=20	100mg N=17
DBP (mmHg)	99±1	98±1	98±1	98±1	100±1	99±1	99±1	99±1
SBP (mmHg)	150±3	146±3	153±3	149±3	147±3	142±3	149±3	146±3
HR (bpm)	72±2	73±2	73±2	74±2	78±2	77±2	78±2	79±2

Table 102 below shows the mean change in seated trough systolic and diastolic blood pressure and heart rate from baseline. As shown, there was no significant dose response on the dose range studied.

Table 102. Change in seated blood pressure and heart rate (CV131-001).

	Placebo N=21	Irbesartan		
		5 mg N=19	25mg N=20	100mg N=17
SeDBP (Mean±SE)	-5±1	-5±1	-4±1	-2±1
SeSBP (Mean±SE)	-3±2	0±2	-5±2	1±2
SeHR (Mean±SE)	0±1	1±2	-1±2	0±2

Secondary analyses of blood pressure and therapeutic response were not performed since the primary end point was not statistically significant.

A2.5.2. Safety

There was a mean exposure of the study drug of approximately 7 days. No deaths or serious adverse events were reported.

Treatment-emergent adverse events will be discussed as a group in the integrated review of safety. The most common treatment-emergent adverse events (irbesartan/total) were headache (9/12), dizziness (2/3) and ECG abnormalities (2/2).

Because of the small study size, adverse event differences between placebo and active treatments cannot be determined.

There were no clinically significant changes in physical exam findings.

Treatment-emergent ECG abnormalities were seen in two subjects. They were premature atrial contractions in the first subject and T-wave flattening in the second. The second subject's ECG was obtained after complaints of chest pain 12 minutes after the first double-blind dose of irbesartan 25 mg.

Serum chemistry marked abnormalities were few. One subject (0002/0010) had an increased CK (121 to 571 IU/cc). The subject was asymptomatic.

A2.6. Summary

The study is a randomized, placebo-controlled study evaluating the safety and tolerability of irbesartan. There was no statistically significant treatment effect in this study. There were no deaths or serious adverse events to comment upon.

A3. CV131-002: A multicenter, 8 week study of the antihypertensive activity, tolerability, and safety of irbesartan in subjects with mild-to-moderate hypertension (SeDBP 95-110mmHg).

A3.1. Source documents Study report: NDA 20-757, vols 1.255-1.268.

A3.2. Investigators This study was conducted at 44 sites in the US and Canada.

A3.3. Study dates 2 September 1993 to 17 June 1994.

A3.4. Study design This study description was based on the protocol dated 22 June 1993, modified and amended 5 times between 14 September 1993 and 2 November 1995, but no amendment impacted the study.

The study design is shown in Figure 27 below. Subjects were to have a history of mild to moderate hypertension (SeDBP 95 to 110 mmHg). Qualified subjects were to be given a 4- to 5-week, single-blind, placebo lead-in period prior to randomization to placebo or irbesartan 1, 5, 10, 25, 50, or 100 mg. At the end of the 8-week double-blind period, subjects were randomized in a 7-day, single-blind, placebo-withdrawal phase, following which they were eligible for open-label treatment.

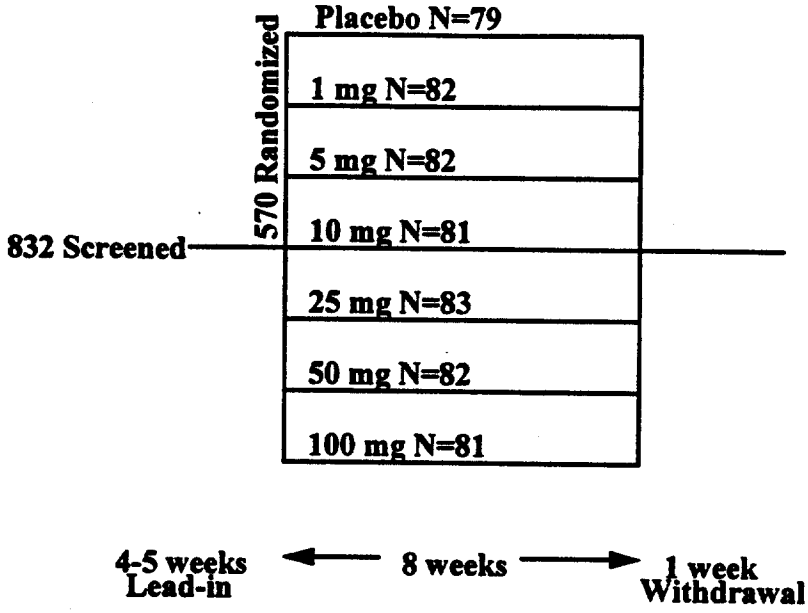

Figure 27. Study design (CV131-002).

Drug supplies are shown in Table 103 below.

Table 103. Drug supplies (CV131-002).

	Lot		Lot
Placebo	K9110J K926A	Irbesartan 1 mg	K936M
		Irbesartan 5 mg	K938M
		Irbesartan 25 mg	K940A K949A K965A

Exclusion criteria included (1) suspected or known causes of secondary hypertension, (2) recent MI, atherosclerotic, and obstructive valvular heart diseases, (3) dysrhythmias requiring medication, (4) insulin-dependent diabetes mellitus, (5)

women of child bearing potential, (6) psychiatric disorders, (7) obesity, (8) autoimmune disorders, (9) cerebrovascular incidents, (10) seizures (11) low output heart failure, (12) malabsorption, (13) abnormal hematologic profiles, and (14) abnormal chemistry profiles, including serum potassium, ALAT, ASAT, creatinine and blood urea nitrogen.

The primary efficacy end point was to be a change from baseline in trough SeDBP (>100 mmHg) at week 8 of double-blind treatment.

Secondary end points included trough-to-peak ratio and blood pressure at the end of the double-blind placebo-withdrawal period.

Safety assessments included identification of adverse clinical events, serious adverse events including death, evaluation of routine laboratory indices and parameters, and electrocardiograms after drug withdrawal.

A3.5. Results

The study enrolled 832 subjects into the placebo lead-in period. Individual sites enrolled 5 to 41 subjects. Of the 570 randomized subjects, 478 (84%) had been on antihypertensive therapy. The demographic characteristics of randomized subjects are shown in Table 104 below.

Table 104. Demographics (CV131-002).

	Placebo N=79	Irbesartan 1 mg N=82	Irbesartan 5 mg N=82	Irbesartan 10 mg N=81	Irbesartan 25 mg N=83	Irbesartan 50 mg N=82	Irbesartan 100 mg N=81
Age (mean±SD)	54±10	56±11	54±11	55±10	52±10	53±10	55±10
Range	31-75	33-77	28-81	28-78	28-74	29-74	29-76
>65 (%)	17	19	15	19	12	13	19
Male (%)	66	77	67	64	68	68	50
Female (%)	34	23	33	36	32	32	41
Weight (mean±SD)	87±17	88±16	87±15	88±20	89±17	90±18	87±17
White (%)	81	82	73	82	84	82	82
Black (%)	15	16	20	16	13	16	17
Other (%)	3.8	2.4	7.3	2.5	2.4	2.4	1.2
Duration HTN (mean±SD)	11±9	13±8	11±9	11±8	10±9	10±9	11±9

The disposition of the subjects is summarized in Table 105 below.

Table 105. Subject disposition (CV131-002).

	N	Withdrawals	N
Screened	832	Adverse event	23
Randomized	570	BP high*	20
Placebo	79	Subject request	8
Irbesartan	491	Protocol violation	7
Completed 8 weeks	499	Loss to follow-up	5
Placebo	73	Concomitant meds	2
Irbesartan	426	Administrative	1
Entered withdrawal phase	440	Investigator request	1
Placebo	62	Poor compliance	1
Irbesartan	378		

*By protocol or in investigator's opinion.

Compliance was estimated to be about 97%. A common protocol violation was variation in arm used for BP measurements.

A3.5.1. Pharmacodynamics

Summary effects on blood pressure are shown in Table 106 below, based on an intent-to-treat, LOCF analysis. Mean changes as differences from baseline and placebo, for subjects completing 8 weeks of treatment, are shown in Figure 28 below. For the 100-mg group, about 2/3 of the placebo- and baseline-subtracted effect on SeDBP and SeSBP seen at 8 weeks was still present at the end of the final 1-week placebo-withdrawal period.

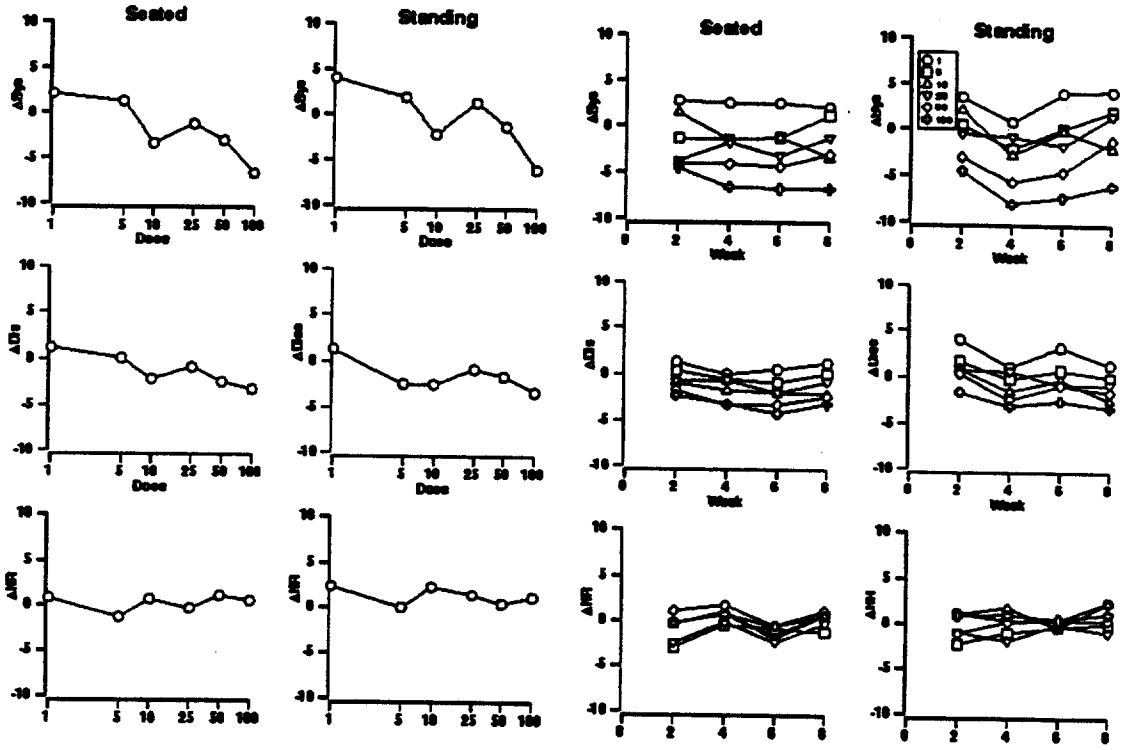

Figure 28. Changes in vital signs at 8 weeks (L) or by time (R) (CV131-002).

Table 106. Effects on blood pressure at week 8 (CV131-002).

	Plcbo	Irbesartan (mg)					
		1	5	10	25	50	100
All (N)	79	82	82	81	83	82	81
ΔSeDBP	-4.9	-3.7	-4.8	-6.7	-5.5	-7.3	-8.3
ΔSeSBP	-4.4	-2.4	-3.2	-7.0	-5.7	-7.6	-11.1
ΔStDBP	-3.7	-2.4	-3.7	-5.8	-4.3	-5.3	-7.1
ΔStSBP	-4.6	-0.5	-2.8	-5.5	-3.2	-6.0	-10.8
Trough:peak	0.0	0.7	0.1	<0	<0	<0	<0
Normalized (%)	22	16	19	35	20	29	32
Responders (%)	30	21	24	42	34	40	45

	Plcbo	Irbesartan (mg)					
		1	5	10	25	50	100
White (N)	64	67	60	66	70	67	66
ΔSeDBP	-4.4	-3.4	-5.9	-6.9	-6.1	-8.2	-8.9
ΔSeSBP	-3.5	-2.1	-5.0	-7.8	-6.5	-9.4	-12.7
ΔStDBP	-3.1	-3.2	-5.0	-5.7	-4.4	-6.5	-7.0
ΔStSBP	-3.0	-1.7	-4.8	-6.3	-1.6	-7.8	-10.7
Blacks (N)	12	13	16	13	11	13	14
ΔSeDBP	-5.6	-5.3	-2.9	-4.1	-1.0	-1.0	-5.2
ΔSeSBP	-9.1	-4.2	1.4	-3.0	1.3	2.3	-3.4
ΔStDBP	-4.6	-0.4	-2.0	-7.8	-5.2	-2.3	-6.8
ΔStSBP	-8.3	1.9	2.1	-8.8	-6.5	-0.9	-9.8

Figure 29 below shows the dose-response data for all subjects analyzed by last observation carried forward.

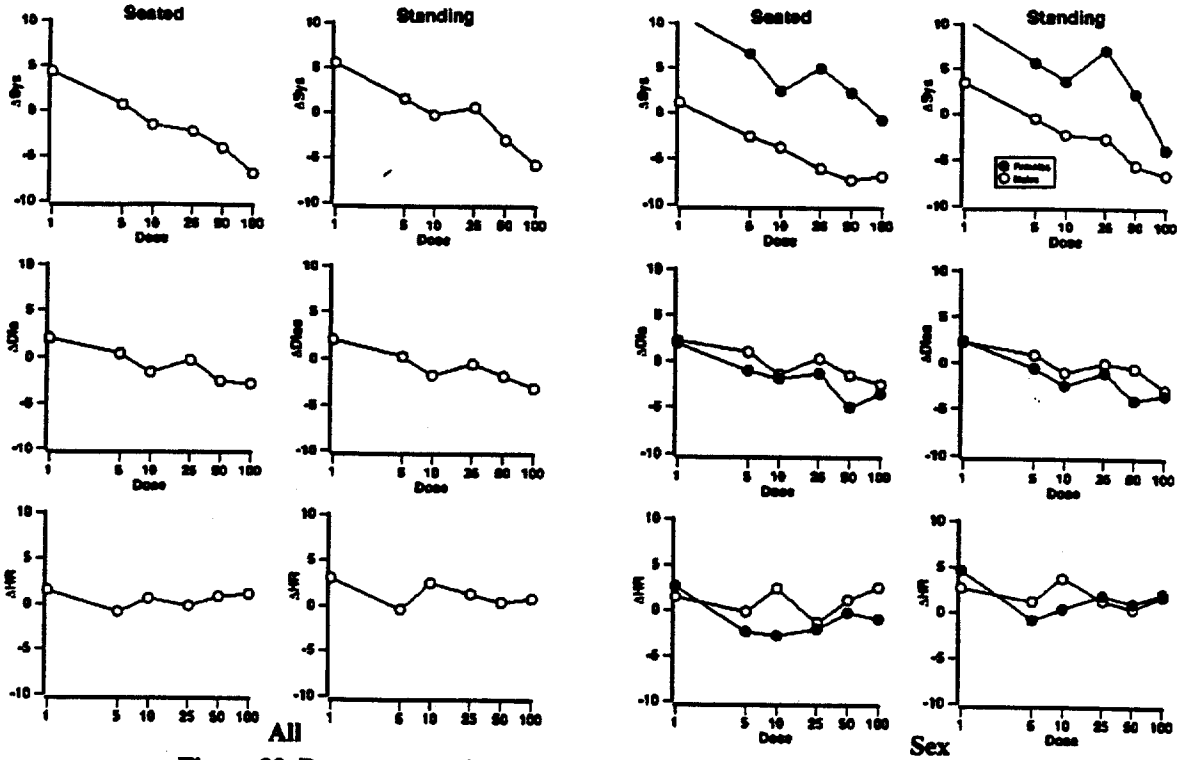

Figure 29. Dose-response by LOCF: all subjects and by sex (CV131-002).

A dose-response analysis by sex is shown in Figure 29. Analyses of dose-response by race and age are shown in Figure 30 below. Mean changes in SeDBP were larger in subjects over age 65 than in subjects under age 65. Mean changes in SeDBP were larger in males than in females. No effect of treatment was evident in a subgroup of non-Caucasian subjects.

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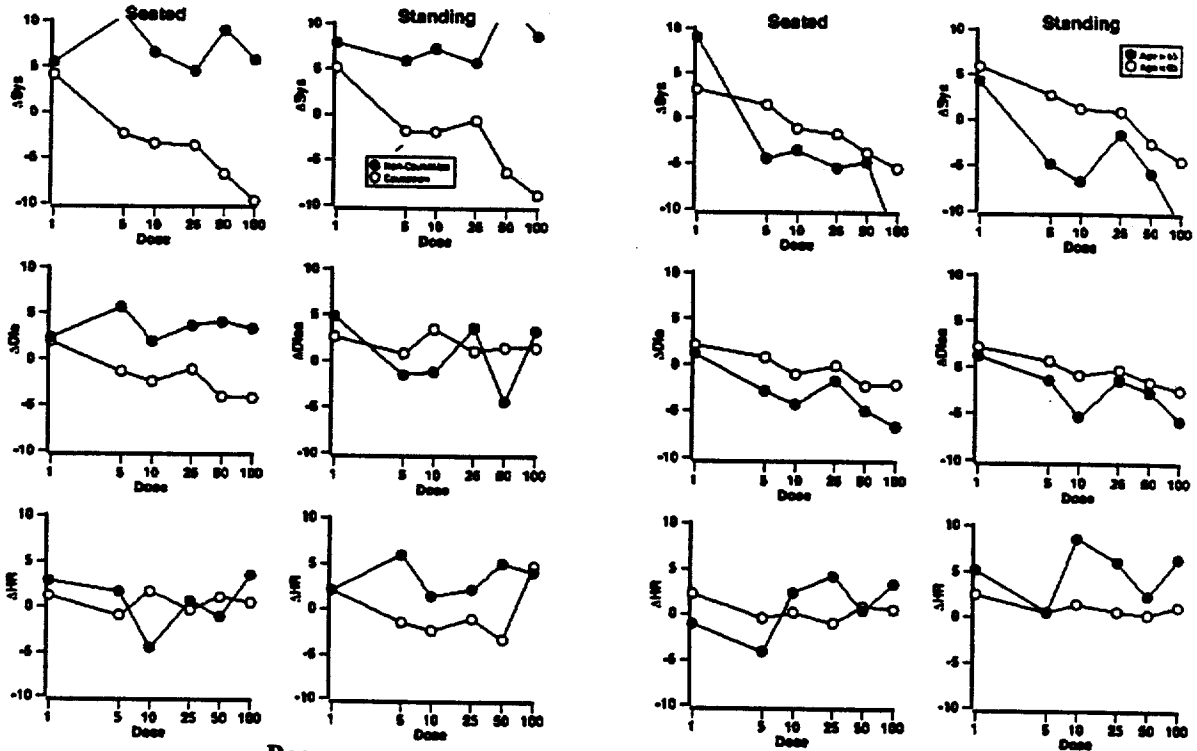

Figure 30. Dose-response (LOCF) by race and age (CV131-002).

A3.5.2. Safety

There were no deaths. The number of serious adverse events per group ranged from 0 on 50 mg to 5 on 5 mg. No serious adverse event was considered more than possibly related to study drug.

Treatment-emergent adverse events, laboratory findings, and physical abnormalities generally showed no dose-relatedness.

A3.6. Summary

This was an adequate and well-controlled 8-week study of fixed doses of Irbesartan in a population of mild-to moderate hypertensive subjects. Statistically significant changes in SeDBP were seen only with the 100-mg dose, but a reasonable dose response curve would suggest doses above 10 mg were active and that the 100-mg dose was not the plateau of the dose-response curve. The peak effect was at 2 to 6 hours after dosing. No significant postural effects or heart rate changes were observed.

There were no deaths and no serious safety problems in the dose range evaluated.

A4. CV131-003: Evaluation of the hemodynamic effects and safety of the angiotensin II antagonist irbesartan in patients with heart failure.

A4.1. Source documents Study report: NDA 20-757, vols 1.220-1.223.

A4.2. Investigators This study was conducted in 24 sites by 22 investigators in the US.

A4.3. Study dates 17 January 1994 to 10 May 1995.

A4.4. Study design The study design is illustrated in Figure 31 below. This was a prospective, double-blind, placebo-controlled, sequential-panel study in subjects with moderate-to-severe heart failure [(resting left ventricular ejection fraction (LVEF) <35%, and NYHA class II-IV]. There was a 4-day washout period for subjects on ACE inhibitor. Subjects were required to be on a diuretic. Qualifying subjects were randomized to receive a single dose of placebo or irbesartan 1, 10, 25, 50, 100, or 200 mg, followed by hemodynamic assessment over 24 hours.

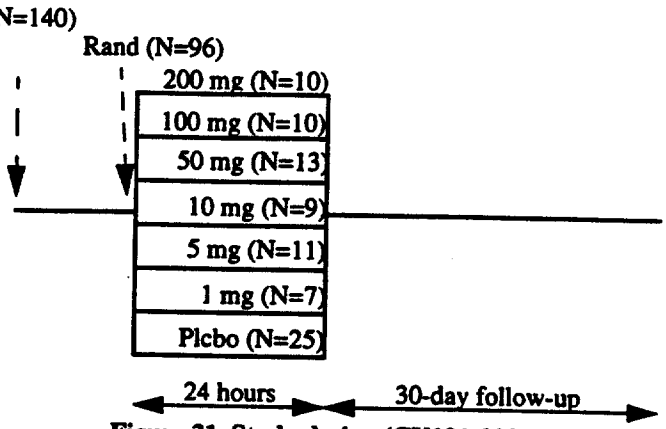

Figure 31. Study design (CV131-003).

Subjects were to be 18-80 years of age, on a diuretic, with a resting LVEF <35%, NYHA Class II-IV, SeSBP >90 mmHg, PCWP >18 mmHg, and a cardiac index <3.0 L/min/m^2.

Drug supplies are shown in Table 107 below.

Table 107. Drug supplies (CV131-003).

	Lot		Lot		Lot
Placebo	GEN-250/PH 186295R000-003 186295R000-030	Irbesartan 10 mg	186295-R025-001 186295-R005-047	Irbesartan 100 mg	186295-R025-001 186295-R025-031
Irbesartan 1 mg	186295-R005-005	Irbesartan 25 mg	186295-R025-001 186295-R025-031	Irbesartan 200 mg	186295-R100-033
Irbesartan 5 mg	186295-R005-005 186295-R005-047	Irbesartan 50 mg	186295-R025-001 186295-R025-031		

The primary objective of this study was to compare the efficacy of a single dose of irbesartan with placebo for inducing a decrease in pulmonary capillary wedge pressure and an increase in cardiac index in subjects with stable, moderate-to-severe heart failure.

Secondary objectives were (1) to determine whether irbesartan would induce other hemodynamic effects (SVR, MAP, HR, SVI, PAP, SBP, DBP, and RAP), and (2) to study safety and tolerability.

Drug safety was to be evaluated from clinical adverse events, physical examination, ECG, serum chemistry, urinalysis, and hematology.

A4.5. Results

Individual sites enrolled between 1 and 21 subjects.

The study enrolled 140 subjects of which 96 were randomized, and 93 completed the study. Demographics of randomized subjects are shown in Table 108 below. The subjects were between the ages of 39 and 80 years, with a mean±SD of 59.7±10.5 years. The ratios of subjects by sex (M:F), and race (whites: blacks: others) were 5:1, and ~2:1:1, respectively. The etiologic basis of the heart failure was ischemic heart disease (47%), cardiomyopathy (32%), and hypertension (20%).

Table 108. Demographics (CV131-003).

	Placebo N=25	Irbesartan						
		1 mg N=7	5 mg N=11	10 mg N=11	25 mg N=9	50 mg N=13	100 mg N=10	200 mg N=10
Age (y)	58.8	63.7	61.6	60.4	58.3	60.8	58.1	57.5
Male (%)	92	71	64	82	78	69	70	90
Female (%)	8	29	36	18	22	31	30	10
Race (%)				0				
White	56	71	36	36	44	46	70	40
Black	24	14	27	55	33	8	10	50
Hispanic	20	14	27	0	22	46	20	10
Others	0	0	9	9	0	0	0	0
NYHA (%)								
II	20	14	46	18	22	31	30	10
III	76	86	46	46	67	69	60	90
IV	4	0	9	36	11	0	10	0
LVEF (mean±SD)	0.23±0.07	0.20±0.06	0.22±0.06	0.23±0.05	0.21±0.07	0.24±0.07	0.17±0.03	0.20±0.04
Range								

Compliance was 100%.

A4.5.1. Pharmacodynamics

Analysis of efficacy was based on 93 completing subjects. This study showed maximal effects of irbesartan on pulmonary capillary wedge pressure (PCWP) at doses of 50 mg and 100 mg at 2, 3, and 4 hours post-dosing, as shown in Figure 32 below. At similar post dosing time points, significant effects were also seen on right atrial pressure at a dose of 100 mg compared to placebo ($p<0.05$). In contrast, no significant differences were seen on cardiac index between the treated and placebo groups, as shown in Figure 33 below.

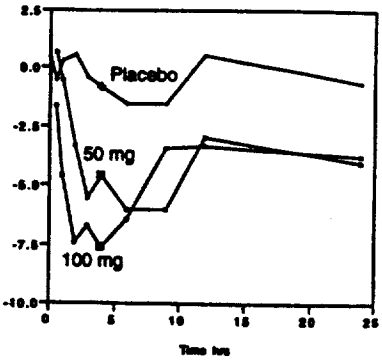

Figure 32. PCWP (CV131-003).

Statistically significant differences were observed for stroke volume index and systolic pulmonary artery pressure at 100 mg at 2 and 3 hours, and heart rate at 3 and 4 hours. No other consistent dose-related effects were observed on other parameters.

The possible effects of age, race and sex were analyzed by comparing the parameters evaluated in all randomized subjects. No significant differences were observed.

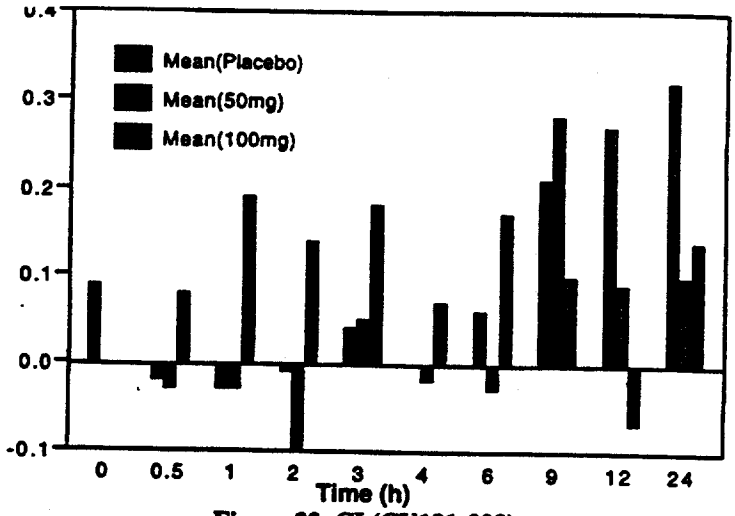

Figure 33. CI (CV131-003).

A4.5.2. Safety

No deaths occurred during the screening or double-blind treatment periods of study. Of the 6 deaths that occurred within 30 days after study completion, 2 were randomized to irbesartan (5 and 10 mg) and 4 were randomized to placebo. One additional death was reported (50 mg) >30 days after completion of study. All deaths were considered unrelated to study medication.

Other serious adverse events (during treatment included paroxysmal ventricular tachycardia and heart block in one subject given 100 mg and cholecystitis in another subject given 50 mg. Two subjects randomized to placebo experienced worsening of their heart failure which required prolonged hospitalization. Post-treatment serious adverse events included depression, post-catheterization subclavian vein thrombosis, ventricular tachycardia, and heart failure (Table 3).Treatment-emergent adverse events frequently reported in the treated group during the double-blind period affected the cardiovascular (10/71; 14%) and nervous systems (9/71; 13%). No other serious events were observed on laboratory tests, ECG, or physical examination.

Table 109. Serious adverse events (CV131-003).

	Day	Event	Relationship		Day	Event	Relationship
Placebo	10	Death; heart failure	Unrelated	5 mg	18	Death; heart failure	Unrelated
Placebo	17	Sudden cardiac failure	Unrelated	10 mg	14	Sudden cardiac death	Unrelated
Placebo	24	Sudden cardiac death	Unrelated	10 mg	6	Depression	Unrelated
Placebo	28	Death; heart failure	Unrelated	10 mg	4	Thrombosis	Unrelated
				25 mg	2	Ventricular tachycardia	Unrelated

A4.6. Summary

This was a small, placebo-controlled, single ascending-dose study in a population with stable, moderate-to-severe heart failure. Statistically significant effects were seen on PCWP. A reasonable dose-response curve would suggest doses above 10 mg were active and that the 100 mg dose showed maximal effect. Other hemodynamic effects were seen at some doses and time points. The study drug was well tolerated, and there were no significant issues of safety.

A5. CV131-004: Pharmacokinetics and pharmacodynamics of irbesartan in female and male patients with mild-to-moderate essential hypertension.

A5.1. Source documents

Study report: NDA 20-757, vol 1.124 to 1.128.

A5.2. Investigators

Wayne A. Colburn, Ph.D., Harris Laboratories, 4639 S. 36th St., Phoenix, Arizona.
James C. Kisicki, M.D., Harris Laboratories, 624 Peach St., Lincoln, Nebraska.

A5.3. Study dates

2 December 1993 to 27 September 1994.

A5.4. Study design

This study description was based upon the protocol dated 8 October 1993. There were no protocol amendments after the study date. The objectives of the study were (1) evaluate the pharmacodynamics and pharmacokinetics of 100mg qd irbesartan versus placebo in subjects with mild to moderate hypertension treated for up to four weeks, and (2) to compare the pharmacokinetics and pharmacodynamics of irbesartan in female versus male subjects.

This study was a randomized, double-blind, placebo-controlled, parallel-group study for which the design is shown in Figure 34 below. After a single-blind lead-in phase of 4 to 5 weeks, subjects were randomized to receive 100 mg of irbesartan or placebo if their seating diastolic blood pressure (SeDBP) was between 95 and 110 mmHg.

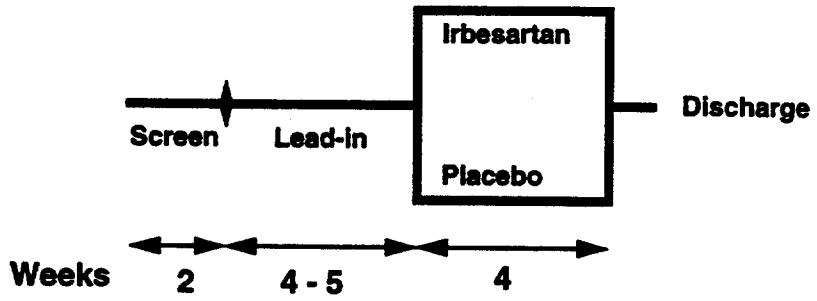

Figure 34. Study design (CV131-004).

The subjects were to be taken from a healthy non-obese and non-black population aged between 45 and 65 years old. 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 fundoscopic changes). Untreated SeDBP was to be between 95 and 110 mmHg in order to be randomized. Subject with renovasular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded.

Drug supplies are shown in Table 110 below.

Table 110. Drug supplies (CV131-004).

	Product number	Lot number
Placebo	186295-R000-003	K962A
Irbesartan 25 mg	186295-R025-001	K965A

PK and PD measurements were made 1 and 29 days after randomization. This schedule is shown in Table 111 below.

Physical exams, ECGs and clinical laboratory tests were performed during screening, the single-blind period and at the end of the double-blind period. Subjects were continually monitored throughout the study for the occurrence of any adverse events.

Table 111. Schedule for PK and PD procedures at day 1 and 29 (CV131-004).

Time (hr)	PK	Pharmacodynamics			Time (hr)	PK	Pharmacodynamics		
		RAS	Urine	Vitals			RAS	Urine	Vitals
within -60 min		X		X	4	X	X	X	X
Pre-Dose	X*	X	X	X*	6	X		X	X
0.5	X		X	X	8	X	X	X	X
1.0	X	X	X	X	10	X		X	X
1.5	X		X	X	12	X	X	X	X
2	X	X	X	X	24	X**	X	X	X
3	X		X	X					

*Procedures done on Day 15 only.; **PK measurements extended to 96 hrs Day 29.

Assay of plasma irbesartan was performed according to method 2 in Table 7. *Assay validation for irbesartan.* on page 15.

A5.5. Results

There were a total of 157 subjects screened, of whom 101 subjects were discontinued prior to randomization. Reasons for exclusion are given below in Table 112 below.

Table 112. Reasons for exclusion prior to randomization (CV131-004).

	N		N
Did not qualify	79	Adverse event	3
Subject request	6	Subject on prohibited medication	1
BP exceeded protocol criteria	3	Other	9

There were two dropouts after randomization. One subject on irbesartan had a systolic blood pressure exceeding 200 mmHg. The other subject on placebo was discontinued secondary to new onset of atrial fibrillation.

Nine subjects reported use of prohibited medications. One subject had blood pressure readings that were outside the protocol's inclusion criteria. None were excluded from the data analysis.

Forty-two subjects received anti-hypertensives prior to study.

Demographics of the two treatment groups are shown in Table 113 below.

Table 113. Demographic Characteristics in CV131-004

	Placebo		Irbesartan	
	Male N=9	Female N=9	Male N=18	Female N=20
Age (mean±SD) Range	55±7.2	57±5.9	52±6.7	54±6.3
Race (%)	White (100%)	White (100%)	White (100%)	White (100%)
Weight, kg Mean±SD Range	89±16	72±12	91±13	72±10
Height, cm Mean±SD Range	179±9	167±6	179±6	164±7

At the end of the placebo lead-in period, seated systolic and diastolic blood pressure and heart rate did not differ between the treatment groups. There was a mild increase in SBP in females compared to males in both the placebo and irbesartan groups.

There were no AII data for the first 4 subjects at Site 1 because the samples were not drawn appropriately.

A5.5.1. Pharmacokinetics

Mean pharmacokinetic data of irbesartan measured on days 15 and 29 are given in Table 114 below.

Table 114. Pharmacokinetic parameters on days 1 and 29 (CV131-004).

	Day 1		Day 29	
	Male N=18	Female N=20	Male N=18	Female N=19
C_{max} (ng/cc); M±SD	1615±539*	2088±639*	1795±536	2252±816
T_{max} (h; median) Range	1.0*	1.5*	1.75	1.5
$T_{1/2}$ (h)	10.1±5.6	9.2±3.2	14.1±7.8	22.5±17.3*
Cl_T/F (mL/h)	12735±4206	9884±3268	12118±3239	8761±3191*
Wt-adj Cl (mL/h/kg)	144.8±68.9	136.7±38.9	137.0±49.7	122.4±40.5
AUC (ng-h/cc),M±SD)	8632±2278*	11123±3417*	8857±2489*	12789±4475*
Normalized by Weight	96.7±36.5*	160.2±65.7*	98.7±29.2*	185.4±79.1*

*Statistically significant between genders

Pharmacokinetic profiles of males and females on Days 1 and 29 are given in Figure 35 below.

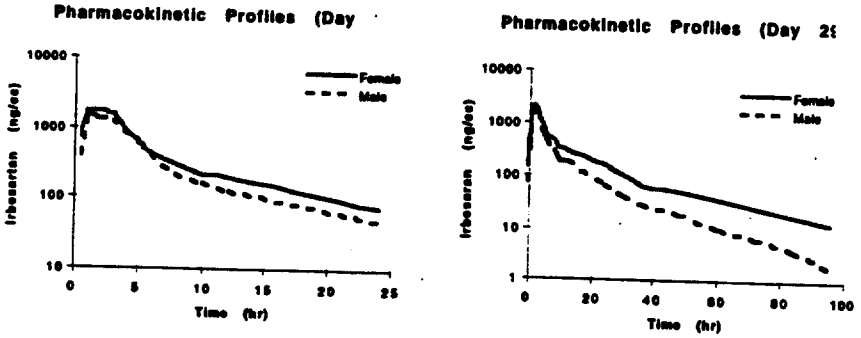

Figure 35. Pharmacokinetic profiles on days 1 and 29 (CV131-004).

Weight-adjusted clearance rates showed no difference between males and females. After 29 days of dosing there was some accumulation. $AUC_{Day\ 29}$ / $AUC_{Day\ 1}$ was 1.23 in males and 1.13 in females.

A5.5.2. Pharmacodynamics

Males and females treated with irbesartan showed decreases in SeSBP and SeDBP compared to placebo on both days 1 and 29. The mean AUC change from baseline is shown in Table 115 below.

The irbesartan group AUCs for blood pressure were decreased compared to placebo on days 1 and 29. Only on day 29 was this decrease statistically significant. There were no significant gender differences. Trough/Peak ratio was calculated as 0.991 on day 29.

Table 115. Change in seated diastolic and systolic blood pressure (CV131-004).

	SeDBP (24-h AUC; mmHg*h)				SeSBP (24-h AUC; mmHg*h)			
	Placebo		Irbesartan		Placebo		Irbesartan	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1 Mean±SD Range	-150±85	-183±108	-218±120	-137±164	-223±158	-261±261	-274±171	-223±218
Day 29* Mean±SD Range	-141±70	-194±76	-330±159	-244±243	-303±129	-257±215	-445±201	-393±371

*Statistically significant day and treatment effect.

There were no significant changes in heart rate between placebo and irbesartan as assessed by AUC over a 24-hour period.

A5.5.3. Neurohormones

Statistically significant differences in AUC for renin and angiotensin II were seen between placebo and irbesartan on both study days, as shown in Table 116 below.

Table 116. Change in Angiotensin II and Plasma Renin Activity

	Angiotensin II (24-h AUC)				Plasma renin activity (24-h AUC)			
	Placebo		Irbesartan		Placebo		Irbesartan	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1* Mean±SD Range	34.±42.3	-10±175	241±334	63.4±242	6.8±5.3	10.3±17.6	50.8±75.1	31.1±69.5
Day 29* Mean±SD Range	34.5±71.3	-10.3±169	403±491	141±301	7.3±5.4	6.5±24.3	96.2±132	53.7±70.2

*Statistically significant day and treatment effect.

Males tended to have larger AUCs for both renin and angiotensin II, in both the placebo and irbesartan groups. Neither difference was statistically significant. A significant gender effect was detected in angiotensin II at baseline. There was also a treatment-by-gender effect at baseline of both angiotensin II and renin, with the female placebo group having higher levels.

Aldosterone secretion was significantly lower among irbesartan subjects than placebo subjects on both study days (Table 117 below)

Table 117. Urinary excretion of aldosterone

	Urinary Aldosterone (µg/24 h)			
	Placebo		Irbesartan*	
	Male	Female	Male	Female
Day 1 (Mean±SD) Range	9.5±4.8	12.2±3.6	9.1±4.4	8.7±3.8
Day 29 (Mean±SD) Range	9.9±4.7	15.6±6.0	7.7±3.4	8.4±3.1

*Statistically significant ($p<0.05$) treatment and treatment-by-day effect.

No statistically significant differences in urinary sodium excretion between irbesartan and placebo subjects was seen. However, sodium excretion was significantly lower in females than males.

A5.5.4. Safety

There were no deaths during the study. There were two serious adverse events reported. One subject died of stomach cancer 9 months after completion of study. The other had atrial fibrillation on day 1.

Headache and fatigue were the most commonly reported adverse events. There was no treatment-emergent cough, angioedema or orthostatic hypotension reported in any subject. Subjective reports of cardiac rhythm disturbances possibly related to the study medication were reported in two irbesartan-treated females. Both screening and discharge ECGs showed no results which would explain the symptoms. Two subjects reported dizziness. One subject had atrial fibrillation. The other had a gradual decrease in BP over the 29-day study period. Mild to moderate nasal congestion or upper respiratory infection was reported in four irbesartan subjects and none in the placebo-group.

There were two marked laboratory values found on discharge; 2 female subjects who received irbesartan had urine WBCs. There were no consistent changes in physical exam findings between placebo and irbesartan groups. ECG findings were consistent with those found in a hypertensive population.

A5.6. Summary

The study is a double blind placebo controlled trial of irbesartan versus placebo. In addition to BP and HR measurements, the sponsor measured other pharmacodynamic and pharmacokinetic parameters. There is some concern that the baseline data used in the calculation of AUC for SeSBP, SeDBP, heart rate, angiotensin II and renin were not adequately obtained. Upon review, there are two concerning issues. On day 15, according to the raw data, vital signs and blood work were only measured at one time point. It would be difficult to calculate a 24-hour AUC based on one time point. It is unclear whether this would affect the validity of the sponsor's data. In addition, irbesartan has a half-life of 10 to 22 hours based on their study. A 24-hour wash-out would remove at most 2 time constants or 75% of the drug. The sponsor states that the trough-to-peak ratio is close to one which indicates minimal or no decline of BP on the average compared to placebo within the 24-hour period. This suggests that there is still bioactivity of irbesartan. There was a large difference in half-life between day 1 and day 29. Differences in the AUC normalized by weight were seen with males and females on both single- and multiple-dosing. This would indicate that there may be a need for dosing adjustments depending on gender. There were no overall safety concerns with this study.

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A6. CV131-005: Pharmacokinetic and pharmacodynamics of irbesartan when coadministered with hydrochlorothiazide compared to when administered alone to patients with mild to moderate hypertension.

A6.1. Source documents

Study report: NDA 20-757, vol 1.165-1.168.

A6.2. Investigators

Kenneth C. Lasseter, M.D., Clinical Pharmacology Associates, 2060 N.W. 22nd Ave., Miami, FL.

A6.3. Study design

This study description was based upon the final study report.

The objective of the study was to compare the pharmacokinetics and pharmacodynamics of irbesartan with concomitant HCTZ versus irbesartan alone in mild to moderate hypertension.

This was a randomized, double-blind, placebo controlled study in 36, Caucasian, mild to moderate hypertensive men and women. Following a 4- to 5-week single-blind placebo lead-in phase (period A), qualifying subjects were randomized to either:

1) Period B—irbesartan 150 mg qd x 7 days followed by
Period C—irbesartan 150 mg + HCTZ 25 mg x 7 days, or

2) Period B—irbesartan 150 mg qd x 7 days followed by
Period C—irbesartan 150 mg + placebo x 7 days.

Blood samples were taken for pharmacokinetic measurements on Days B7 and C7 at pre-dose 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose. Blood samples for pharmacodynamic measurements were taken on Days B7 and C7 before rising, pre-dose, 1, 2, 4, 8, 12 and 24 hours post-dose.

Drug supplies are shown in Table 118 below.

Table 118. Drug supplies (CV131-005).

	Lot number		Lot number
HCTZ placebo	GEN-110-H/PDA1	HCTZ 25 mg[a]	N93K089C
Irbesartan placebo	N95F090C	Irbesartan 50 mg	N94G096C

a. Manufactured by BMS; not a marketed product.

Assay of plasma irbesartan was performed according to method 5 in Table 7. *Assay validation for irbesartan.* on page 15.

The difference in Day B7 and C7 irbesartan T_{max} were determined using the Wilcoxon Rank Sum Procedure. $LogC_{max}$ and $logAUC_t$ were analyzed using ANCOVA. Day B7 and C7 pharmacodynamic measures were calculated for the 24-hour AUC values and analyzed using ANCOVA.

A6.4. Results

There were no statistically significant differences in the pharmacokinetics of irbesartan + HCTZ versus irbesartan + placebo. The data are summarized in Table 119 below and Figure 36 below.

Irbesartan + HCTZ showed a significant decrease in SPB and DPB, HR was not changed. These data are summarized in Table 120 below.

Levels of AII and PRA were significantly greater with the combination of irbesartan + HCTZ versus irbesartan + placebo, as shown in Table 121 below.

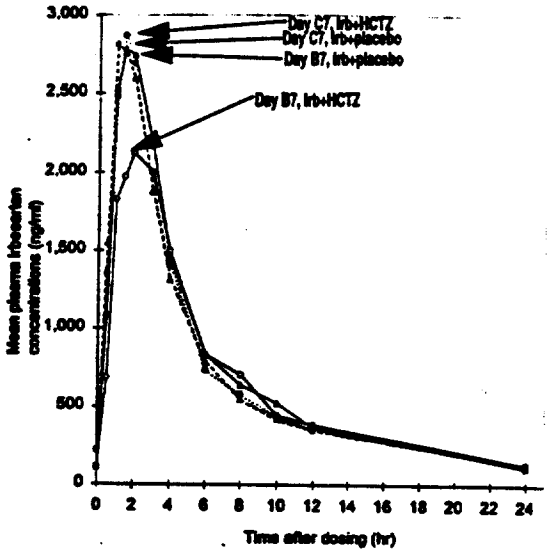

Figure 36. Plasma profiles for irbesartan (CV131-005).

Table 119. Pharmacokinetic parameters (±SD; CV131-005).

	Irbesartan + placebo (period C; N=18)			Irbesartan + HCTZ (period C; N=18)			P
	Day B7	Day C7	Ratio (95% CI)	Day B7	Day C7	Ratio (95% CI)	
C_{max} (ng/mL)	3296±1216	3115±868	1.04 (1.07-1.14)	2639±632	3192±868	1.18 (1.07–1.30)	NS
AUC_t (ng.mL/h)	16569±4967	15892±4229	0.99 (0.91-1.07)	15245±5479	16281±5261	1.07 (0.99-1.16)	NS
T_{max}* (h)	1.5 (1.0-3.0)	1.5 (0.5-3.0)	—	2.0 (1.0-4.0)	1.75 (1.0-4.0)	—	NS

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

Table 120. Vital sign AUC parameters (±SD; CV131-005).

	Irbesartan + placebo (period C; N=18)			Irbesartan + HCTZ (period C; N=18)			P
	Day B7	Day C7	C7-B7	Day B7	Day C7	C7-B7	
SBP (mmHg.h)	3334±392	3367±391	33	3330±325	3095±307	-235	<0.001
DBP (mmHg.h)	2115±135	2078±106	-38	2149±158	2008±128	-141	0.004
HR (bpm.h)	1810±119	1833±110	23	1795±189	1862±139	66	NS

Table 121. Angiotensin II and plasma renin activity AUC parameters (±SD; CV131-005).

	Irbesartan + placebo (period C; N=18)			Irbesartan + HCTZ (period C; N=18)			P
	Day B7	Day C7	C7-B7	Day B7	Day C7	C7-B7	
AII (pg.h/mL)	465±358	504±380	24	313±204	1095±1224	556	0.001
PRA ($ng.h^2/mL$)	72±106	88±105	17	75±115	192±248	114	0.008

A6.4.1. Safety Not reviewed.

A6.5. Summary. HCTZ given concomitantly with irbesartan does not appear to alter the mean pharmacokinetics of irbesartan. However, the pharmacodynamics of irbesartan, a decrease in SBP and DBP, and increases in the plasma levels of AII and PRA are significantly changes with the co-administration of HCTZ. There was no change in HR.

A7. CV131-006: The effects of age and gender on the pharmacokinetics of irbesartan in healthy subjects following a single 50 mg oral dose.

A7.1. Source documents

Study report: NDA 20-757, vol 1.141-1.45.

A7.2. Investigators

J.C. Doane, M.D., Besselaar Clinical Research Units, Inc. 900 Osceola Drive, West Palm Beach, FL 33409.

A7.3. Study dates

25 October 1993 to 7 December 1993.

A7.4. Study design

This study description was based upon the protocol dated 21 September 1993. There were no protocol amendments to this study.

The objective of the study was to compare the pharmacokinetics of irbesartan 50 mg in healthy, elderly males and females.

This study was a single-center, open-label, parallel-group study. The subjects were taken from a healthy non-obese population with normal physical exam findings and laboratory values. There were four demographic groups: (1) young males (18 to 40 y), (2) elderly males (65 to 80 y), (3) young females (18 to 40 y), and (4) elderly females (65 to 80 y).

Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, renal (other than age related decreases in creatinine clearance), pulmonary, endocrinologic, neurologic or psychiatric disease were excluded.

Drug supplies are shown in Table 122 below.

Table 122. Drug supplies (CV131-006).

Unit	Batch Number
Irbesartan 25 mg	K965A

At the screening visit, each subject was to undergo a complete medical history and physical examination. A complete laboratory evaluation (SMA20, CBC, urinalysis, hepatitis B and HIV ELISA), ECG and chest X-ray was to be done for potential candidates meeting initial screening medical histories and age.

The subjects were asked to return to the center two weeks later and were to be given irbesartan 50 mg. Pharmacokinetic profiles and urine specimens were obtained according to the following schedule (see Table 123 below).

Table 123. Schedule for PK and PD data on days 1 and 11 (CV131-006).

Time (h)	Blood	Urine	Vitals	Time (h)	Blood	Urine	Vitals
Pre-Dose	X	X	X	12	X	12 - 24	X
0.33	X	0 - 4	X	24	X	24 - 36	X
0.67	X		X	30	X		X
1	X		X	36	X	36 - 48	X
1.5	X		X	48	X	48 - 60	X
2	X		X	60	X	60 - 72	X
3	X		X	72	X	72 - 96	X
4	X	4 - 6	X	84	X		X
6	X		X	96	X		X
8	X	8 - 12	X				

Physical exams, ECGs and safety laboratory tests were performed during screening and at study end (Day 14).

Assay of plasma and urinary irbesartan was performed according to methods 2 and 8, respectively, in Table 7. *Assay validation for irbesartan.* on page 15.

The following pharmacokinetic parameters were to be determined and compared within each group on Day 1: C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, and Cl_R.

The pharmacokinetic parameters were evaluated using analysis of variance.

A7.5. Results

There were a total of 48 subjects entered into this study. There were no deaths or dropouts.

Demographics of the three treatment groups are shown in Table 124 below

Table 124. Demographics (CV131-006).

	Males		Females	
	18 to 40 y N=12	65 to 80 y N=12	18 to 40 y N=13	65 to 80 y N=12
Age (mean±SD)	30±6.7*	72±3.5*	31±6.8	69±4.3
Race				
White	10	12	7	11
Black	0	0	2	1
Other	2	0	3	0
Weight (kg; mean±SD)	75.9±7.5	71.3±9.5	61.3±9.8	61.3±9.8
Height (cm; mean±SD)	179.9±5.4	171.2±6.1	166.9±6.2	162.6±6.3

There were no significant protocol deviations or violations which would affect the results of this study.

A7.5.1. Pharmacokinetics

The mean pharmacokinetic profiles of the four groups is given in Figure 37 below.

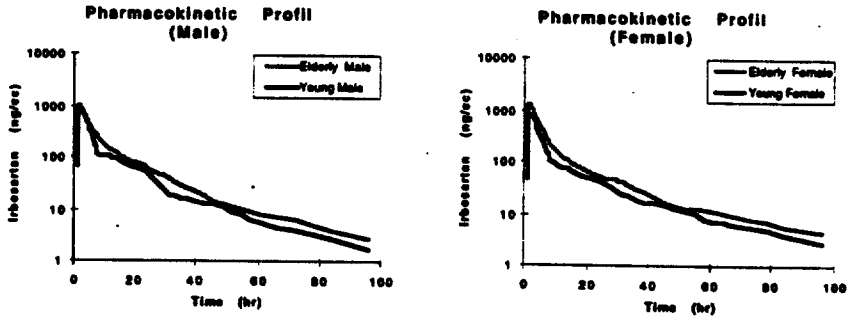

Figure 37. Pharmacokinetics in males and females (CV131-006).

Mean pharmacokinetic data of irbesartan measured is given in Table 125 below.

Analysis of covariance of C_{max}, AUC and CL/R using age and gender as covariates showed statistical differences with respect to age. There was no effect of gender on any of the parameters.

Table 125. Pharmacokinetic parameters (CV131-006).

	Males		Females	
	18 to 40 y N=12	65 to 80 y N=12	18 to 40 y N=13	65 to 80 y N=12
C_{max} (mg/L; mean±SD)	942±358	1310±454	1096±752	1623±445.33
T_{max} (h; median)	2	1	1.5	1
$AUC_{0-\infty}$ (mg-h; mean±SD)	5571±2165	7523±2546	5640±1288	8531±2348
Cl/R (ml/h; mean±SD)	84±72	85±64	101±60	47±31
$t_{1/2}$ (h; mean±SD)	20±12	18±7	18±10	21±10
% Dose in urine (96 h)	0.74±0.47	1.10±0.57	1.13±0.54	0.74±0.39

A7.5.2. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event.

One elderly subject developed atrial fibrillation with a moderate ventricular response (100 bpm) at the time of discharge. Other ECG abnormalities observed included nonspecific ST-T changes, first degree AV block, and right bundle branch block. ECG abnormalities observed in young subjects were premature ventricular beats, nonspecific ST-T changes, intraventricular conduction delay and poor R-wave progression.

There were a total of 19 adverse events reported by 13 subjects. The most frequently reported symptom was headache and muscular/skeletal pain (4/48). Other events that were reported are dizziness, somnolence, pharyngitis and upper respiratory tract infection.

There was one patient with a markedly decreased (<0.85 baseline) hemoglobin and hematocrit compared to baseline.

There were no significant differences in laboratory blood chemistry or urine compared to baseline.

A7.6. Summary

This is an open-label study of the effects age and gender on irbesartan pharmacokinetics. The over-65 subjects had roughly 50% higher values for C_{max} and AUC than did subjects under age 40. No gender-specific differences were observed. There were no major safety issues in this trial to comment upon.

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A8. CV131-011: Pharmacokinetics of SR 47436 (Irbesartan) in subjects with renal impairment compared to subjects with normal renal function.

A8.1. Source documents Study report: NDA 20-757, vol 1.148 - 1.149.

A8.2. Investigators Domenic A. Sica, M.D., Division of Nephrology, Medical College of Virginia, MCV Station Box 160, Richmond, VA 23298

A8.3. Study dates 10 August 1994 to 14 June 1995.

A8.4. Study design This study description was based upon the protocol dated 11 April 1994. There was one amendment after the start of the study. During the study it was found that irbesartan 100 mg did not adequately control diastolic blood pressure in hemodialysis subjects and the dose was increased to 300 mg. In addition, nifedipine was allowed as a concurrent medication in hemodialysis subjects.

The objective of this study was to assess the single dose and steady-state pharmacokinetics of irbesartan in subjects with varying degrees of renal impairment to those with normal renal function.

This study was an open-label, parallel group study. Four groups were to be selected on the basis of renal impairment (see Table 126 below). Non-obese (within 25% of Metropolitan Life Insurance Tables) male and female subjects (10 per group) were able to participate in this study.

Table 126. Renal impairment eligibility (CV131-011).

Group	Renal impairment	Definition
1	None	Cr_{Cl} >75 cc/min
2	Mild - Moderate	Cr_{Cl} 34 to 74 cc/min
3	Severe	Cr_{Cl} <30 and not requiring dialysis
4	Dialysis	On hemodialysis

Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, pulmonary, endocrinologic, neurologic, or psychiatric disease were excluded. Subjects with acute renal disease or evidence of rapidly declining renal function were excluded.

Drug supplies are shown in Table 127 below.

Table 127. Drug supplies (CV131-011).

Unit	Product ID	Lot number
Irbesartan 100mg	186295-R100-015	N93M116C

At the screening visit, each subject was to undergo a complete medical history and physical examination. A complete laboratory evaluation (SMA20, CBC, urinalysis, hepatitis B and HIV ELISA), ECG and chest X-ray was to be done for potential candidates meeting initial screening medical histories.

Glomerular filtration rates at screening was to be determined by two 24-hour urinary creatinine clearance measurements for Groups 1-3. If the two measurements differed by >20%, a third measurement was made. Categorization of the subject was made based on the mean of the creatinine clearance measurements.

The subjects were asked to return to the center within 2 weeks. Groups 1 to 3 received irbesartan 100 mg per day for a total of 8 days. On study days 1, 2, 3, 6, and 8 the study

drug was administered at the study center and measurements were made according to Table 128 below).

Table 128. Schedule for PK and PD procedures on days 1 and 8 (CV131-011).

Time (h)	PK	Procedures		Time (h)	PK	Procedures	
		Renin AII	Urine collection Aldo and Creatinine			Renin AII	Urine collection Aldo and Creatinine
Pre-Dose	X	X	X	4	X	X	4 - 8 hours X
0.5	X		0 - 4 hours X	6	X		
1.0	X			8	X		8 -12 hours X
1.5	X			10	X		
2	X			12	X		12 -24 hours X
3	X			24	X		

Glomerular filtration rate and renal blood flow were measured by inulin and para-aminohippourate respectively in the blood and urine on days 1 and 8.

Hemodialysis subjects were dosed with irbesartan 100 mg before January 1995 and 300 mg after January 1995. Dosing was scheduled 4 hours prior to dialysis time. On days 2 and 9 paired arterial and venous blood samples were collected 4, 6, and 8 hours post-dose. Dialysis time and flow rates were kept constant.

Physical exams, ECGs and safety laboratory tests were to be performed during screening and at study end (day 9 for Groups 1 to 3 or day 10 for Group 4). Vital signs and assessments for adverse events were to be done at regular intervals and on days 3 and 6, when trough blood samples for irbesartan were taken.

The following parameters were to be determined and compared within each group: C_{max}, T_{max}, $T_{1/2}$, AUC (single dose and repeated dose), C_{min}, accumulation index, angiotensin II, renin, renal blood flow, creatinine clearance, tolerability, and safety.

Assay of plasma irbesartan was performed according to method 2 and urine irbesartan was assayed by methods 5 and 10 in Table 7. *Assay validation for irbesartan.* on page 15.

Linear curve fitting of creatinine clearance versus AUC was performed. Scatter plots of creatinine clearance versus other pharmacokinetic parameters were inspected for possible relationships. Analysis of variance on repeated samples was used on C_{min} to determine whether steady state was reached. On each study day the dependence of C_{max} and AUC on the creatinine clearance was assessed by sequentially testing linear, quadratic and cubic terms with F tests based on Type I sum of squares.

A8.5. Results

A total of 43 subjects were considered eligible and signed consent to participate in the study. Three subjects discontinued from the study prior to dosing with the study drug. A total of 40 subjects received at least one dose of irbesartan. One hemodialysis subject dropped out after receiving irbesartan 100 mg since her diastolic blood pressure was inadequately controlled.

Demographics of the three treatment groups are shown in Table 129 below.

There were no major deviations from the protocol. There were two subjects with >125% of ideal body weight. One subject took irbesartan prior to reporting to the study unit for a blood draw. The study coordinator was unable to obtain a venous blood sample in one hemodialysis subject.

Table 129. Demographics (CV131-011).

	Normal N=10	Renal impairment		
		Mild- Mod N=10	Severe N=10	Dialysis N=10
Age (mean±SD)	52±6	53±12	52±15	49±14
Weight (kg; mean±SD)	86±15	80±13	71±16	85±24
Height (cm; mean±SD)	173±13	172±10	167±10	170±8
Gender (%)				
Male	50	60	70	50
Female	50	40	30	50
Race (%)				
White	60	70	30	10
Black	40	30	50	90
Hispanic	0	0	10	0
Asian	0	0	10	0

Two subjects were excluded in the pharmacokinetic analysis. One subject had mild-moderate renal impairment based on 24-hour creatinine clearances. Inulin measurements indicated normal GFR. Another subject was excluded because the subject discontinued prior to study completion.

A8.5.1. Pharmacokinetics

The mean pharmacokinetic profiles at days 1 and 8 for the 4 groups is given in Figure 38 below. Hemodialysis subjects received irbesartan 300 mg.

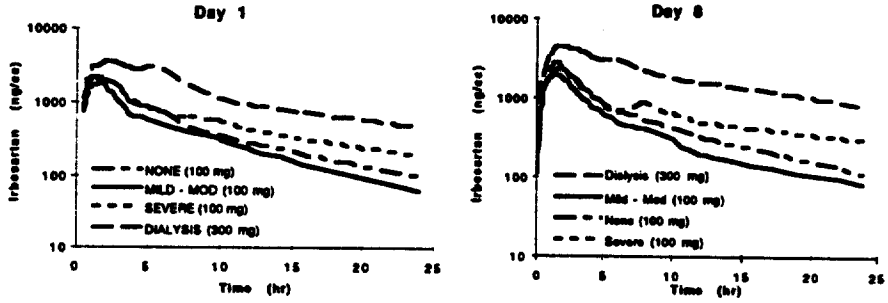

Figure 38. Pharmacokinetic profiles on days 1 and 8 (CV131-011).

Mean pharmacokinetic data for irbesartan is given in Table 130 below. Scatter plots (see Appendix) showed no obvious correlation between creatinine clearance and any of the pharmacokinetic parameters. Three subjects who had no renal impairment had significantly longer time constants on day 1. The same three subjects did not have significantly elevated time constants on day 8.

A plot of C_{min} on days 2, 4, 6, and at study end are shown in Figure 39 below. This curve was constructed after deletion of one outlier value on day 6 (3012 ng/cc, Subject 24). This was secondary to incorrect dosing on day 6.

Steady-state was reasonably achieved in subjects with no, mild-moderate and severe renal impairment. The steady state levels on day 9 were higher in the hemodialysis and severe group than in subjects with no or mild-moderate renal impairment. For hemodialysis subjects, a partial explanation is the higher

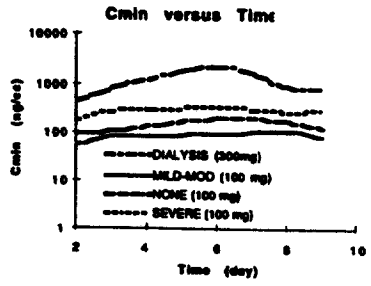

Figure 39. C_{min} versus time in study (CV131-011).

Table 130. Pharmacokinetic parameters (CV131-011).

	Normal N=10	Renal impairment		
		Mild- Mod N=10	Severe N=10	Dialysis* N=10
C_{max} (ng/cc; mean±SD)				
Single dose	2401±719	2322±871	2943±1449	1545±334
Repeated dose	2680±998	2214±860	3123±1882	1842±312
$t_{1/2}$ (h; mean±SD)				
Single dose	9±5	6±1	10±6	12±6
Repeated dose	8±3	8±4	22±22	20±20
T_{max} (h; mean, limits)				
Single dose	1.8 (1.0, 6.0)	1.5 (1.0, 2.0)	1.5 (0.5, 8.0)	3.0 (1.0, 6.0)
Repeated dose	1.8 (0.5, 3.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	1.5 (1.0, 6.0)
Cl/F (mL/h; mean±SD)				
Single dose	1.59±0.53	1.47±0.36	2.22±0.69	—
Repeated dose	—	—	—	—
Cl_T/F (mL/h; mean±SD)	8316±2704	11760±5640	7392±4799	7188±1917
Cl_R (mL/h; mean±SD)	49.5±44.9	54.0±44.7	14.0±10.9	—
AUC (ng-h/cc; mean±SD)				
Single dose	11742±3129	9663±4132	14544±5822	12020±3403
Repeated dose	13564±5111	10226±2289	17440±9073	15686±2350
Accumulation ratio				
Based on C_{max}	1.14±0.38	0.99±0.22	1.09±0.56	1.24±0.30
Based on AUC	1.14±0.22	1.16±0.31	1.24±0.30	1.38±0.39

*Dose normalized to 100 mg.

dose. There was a transient accumulation of irbesartan in the hemodialysis group over 2 to 3 days.

Pharmacokinetic parameters varied greatly in the severely impaired and hemodialysis subjects. The use of a higher dose in dialysis subjects is a confounding factor, making it difficult to ascribe observed effects to renal impairment rather than dose.

The percentage of unchanged irbesartan excreted in the urine was less than 1% for subjects with none, mild-moderate or severe renal dysfunction.

Samples taken from dialysis subjects during dialysis showed no differences in arterial or venous irbesartan concentration at 4, 6, and 8 hours post-dosing.

A8.5.2. Neurohormones

Table 131 below shows plasma angiotensin II levels, plasma renin activity, and aldosterone pre-dose and at 4 hours on days 1 and 8.

There was no consistent change in mean urinary aldosterone excretion across the groups.

Table 131. Angiotensin II, plasma renin, and plasma aldosterone (CV131-011).

	Normal N=10	Renal impairment		
		Mild- Mod N=10	Severe N=10	Dialysis N=10
AII (pg/ml; mean±SD)				
Day 1, pre-dose	13±6	13±3	16±8	16±5
Day 1, 4 h	20±8	16±5	43±66	21±19
Day 8, pre-dose	16±6	15±4	22±20	23±19
Day 8, 4 h	21±9	19±5	23±19	23±22
PRA (pg/ml-h; mean±SD)				
Day 1, pre-dose	0.7±7.0	0.4±0.2	2.2±2.4	0.6±0.7
Day 1, 4 h	1.5±2.0	1.0±0.7	9.0±15	1.7±3.1
Day 8, pre-dose	1.0±1.0	1.0±0.6	2.6±3.5	1.6±2.6
Day 8, 4 h	1.5±1.7	1.6±0.9	4.3±5.7	2.0±3.3
Aldo (ng/dl; mean±SD)				
Day 1, pre-dose	8±5	9±5	18±14	18±12
Day 1, 4 h	8±5	9±4	14±7	16±10
Day 8, pre-dose	9±4	6±4	12±5	13±7
Day 8, 4 h	6±3	6±2	11±4	12±8

A8.5.3. Pharmacodynamics

GFR (determined by inulin method) and effective renal plasma flow (determined by PAH) trended downward from baseline to post dose in all groups.

There was a 2 to 10 mmHg decrease in seated systolic and diastolic blood pressure between 4 and 12 hours post dose in subjects with none, mild-moderate, and severe renal dysfunction. There was no significant change in hemodialysis subjects. There was no significant change in heart rate in any of the groups.

A8.5.4. Safety

A total of 40 subjects were exposed to irbesartan, of whom 39 (98%) completed the study. One hemodialysis subject discontinued because her diastolic blood pressure was not controlled adequately by irbesartan 100 mg. There were no deaths reported in this study. No subjects were withdrawn due to an adverse event.

One serious adverse event (hypoglycemia) occurred in a hemodialysis subject with NIDDM.

The treatment-emergent adverse events included edema (1), tachycardia (1), hypoglycemia (1), nausea/vomiting (2), headache (4) and phrenologist (2).

There were no significant laboratory abnormalities of note.

A number of electrocardiogram abnormalities were noted either at baseline or screening. Most consisted non specific ST-T wave changes, intraventricular conduction delay, right and left ventricular hypertrophy and right and left atrial enlargement. The investigator considered the change in findings unrelated to study drug.

No significant changes in physical exam were observed except for edema in one subject.

A8.6. Summary.

This was a open-label study of irbesartan 100 and 300 mg (in hemodialysis subjects only) and pharmacokinetics with respect to renal function. None of the treatment groups were distinguishable by pharmacokinetic parameters. However, pharmacokinetic parameters tended to vary greater in the subjects with severe renal impairment. Labelling should reflect that the pharmacokinetics of severely impaired

patients had greater intersubject variability than either normal or mild to moderately impaired.

Hemodialysis subjects are difficult to compare to the other groups. It is uncertain whether irbesartan pharmacokinetics in hemodialysis subjects differ compared to other groups. Differences in C_{max} and $t_{1/2}$ in hemodialysis subjects compared to the other groups may indicate the differences.

The accumulation ratio did show an increasing trend from 1.14/1.16 in normal/mild-moderate subjects to 1.24/1.39 in severe/hemodialysis subjects. Because of the increased intersubject variability in the severe and probably the hemodialysis group, there is not enough statistical power to discern whether there is a difference. The difference, if any, is mild and will most likely not need any significant dosage adjustment in severe or hemodialysis patients.

Irbesartan does not appear to be dialyzable, so labeling should indicate this is not a satisfactory treatment for overdose.

There were no major safety issues in this trial to comment upon.

A9. CV131-014: Single and multiple dose pharmacokinetics and pharmacodynamics of irbesartan in subjects with hepatic cirrhosis compared to healthy subjects

A9.1. Source documents

Study report: NDA 20-757, vol 1.150-1.151.

A9.2. Investigator

Kenneth C Lasseter, M.D., Clinical Pharmacology Associates, 2060 N.W. 22nd Avenue, Miami, FL, 33142, USA

A9.3. Study dates

11 May 1995 to 15 September 1995.

To assess and compare the single dose and steady-state pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects and in subjects with hepatic impairment.

A9.4. Study design

The study design was based on the approved protocol dated 4 May 1995.

This study was an open-label, multiple dose, parallel group study in which irbesartan 300 mg was administered, orally, once daily for 7 consecutive days to 2 groups of subjects. One group (n=10) had normal liver morphology and function tests, whereas the other group (n=10) had histologically verified hepatic cirrhosis (Childs-Pugh class A or B=mild-to-moderate).

Drug supplies are shown in Table 132 below.

Table 132. Drug supplies (CV131-014).

	Product number	Lot		Product number	Lot
Placebo	186295-R000-030	L94F013C	Irbesartan 75 mg	186295-R075-054	N94J126C

A total of 20 eligible subjects were to be enrolled. A schedule of study events is shown in Table 133 below.

Table 133. Study schedule (CV131-014).

	Screen	Day							
		-2	-1	1	2-6	7	8	9	10
Hematology, chemistry, urinalysis	X	X						X	X
Serum B-HCG	X	X						X	X
Drugs of abuse in urine	X	X							
Vital signs	X	X	X	X	X	X	X	X	X
ICG clearance		X							
24-h urinary creatinine clearance		X							
Dosing with irbesartan				X	X	X			
Urine PD samples		X		X		X			
Blood PD samples				X		X	X	*X	
Blood and urine PK samples				X		X	X	*X	
C_{min} blood samples for irbesartan					X	X			
Adverse events		X	X	X	X	X	X	X	X
Discharge								X	X

*Hepatically impaired subjects only

Assay of plasma irbesartan was performed according to method 5 in Table 7. *Assay validation for irbesartan.* on page 15. Urine samples were collected for aldosterone,

creatinine, and electrolytes. The single dose and steady state irbesartan pharmacokinetic parameters included AUC_∞ and AUC_τ, C_{max}, $t_{1/2}$, CL_R, T_{max}, %UR, Cl_T/F, with sampling as shown in Table 134 below.

Table 134. Timing of PK and PD sampling (CV131-014).

Time (h)	PK	AII/ PRA	Urine	Vitals	Time (h)	PK	AII/ PRA	Urine	Vitals
Pre-dose	X	X	-0.8-0	X	8	X		8-12	X
1	X		0-2	X	10	X	X	8-12	X
1.5	X	X	0-2	X	12	X		12-24	X
2	X		2-4	X	24	X	X	12-24	X
3	X	X	2-4	X	36	X	X	24-36	
4	X		4-6	X	48	X	X	36-48	X
5		X	4-6	X	60 (hepatic only)	X	X	48-60	
6	X		6-8	X	72 (hepatic only)	X	X	60-72	X

A9.5. Results

The healthy group consisted of 10 subjects (9 Whites, 1 Black; 7 males, 3 females) were healthy, non-obese, between 34 and 68 (mean 55) years old, and had mild-to-moderate hypertension. The hepatic-impaired group of 10 subjects (8 Whites, 2 Blacks; 7 males, 3 females) were cirrhotics of undetermined etiology, with impairment of liver function tests, aged 38 to 65 (mean 54) years old.

A9.5.1. Pharmacokinetics

The PK data of irbesartan measured on days 1 and 7 are presented in Table 135 below. The sponsor excluded 2 'outliers' while calculating $T_{1/2}$ in healthy subjects, and as a result found no significant difference between the two groups. With the inclusion of the 2 'outliers', the estimated half-life on day 7 was about twice as long in normals as in cirrhotics. Less than 1% of the drug was cleared through the renal route. There was no statistically significant difference between groups with respect to C_{max}, AUC_∞, or AUC_τ. The accumulation ratio, based on either C_{max} or AUC, was indistinguishable from unity in both groups.

Table 135. Pharmacokinetic parameters (CV131-014).

	Day 1			Day 7		
	Normal N=10	Impaired N=10	Ratio	Normal N=10	Impaired N=10	Ratio
C_{max} (ng/mL)	3703	4555	1.2	3783	4562	1.2
AUC	18008	23448	1.3	18024	23276	1.3
$T_{1/2}$ (h)	10.0	9.0	0.89	25	12	0.47
UR (%)	0.31	0.80	2.6	0.37	0.91	2.5
CL_R (mL/h)	74	122	1.7	63	109	1.7
CL_T/F	18001	12042	0.67	18528	13742	0.74

A9.5.2. Pharmacodynamics

There was no significant difference between groups with respect to heart rate, SeSBP, or SeDBP.

A9.5.3. Neurohormones

As shown in Figure 40 below, both PRA and angiotensin II showed significantly higher baseline levels in cirrhotics compared to healthy subjects; cirrhotics also showed increases in mean values of AII compared to healthy subjects. In contrast PRA showed a greater increase in healthy subjects compared to cirrhotics at 4 hours on day 7. Urinary aldosterone excretion decreased 28% in the hepatically impaired group and increased 26% in healthy subjects.

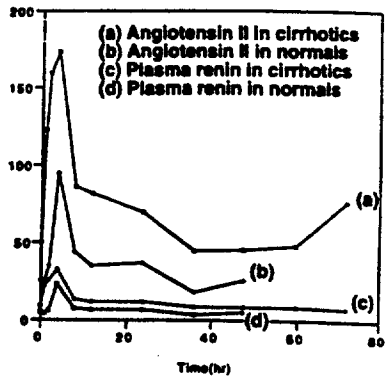

Figure 40. Angiotensin II and plasma renin activity (CV131-014).

A9.5.4. Safety

There were no deaths or discontinuations. The 3 drug-related adverse events reported by cirrhotic subjects included dyspepsia, diarrhea, and flatulence. Lymphopenia, low platelet counts, and low sodium levels, observed in cirrhotic subjects could be due to chronic liver disease, but a drug-related cause cannot be firmly ruled out. No significant differences were observed between groups for sodium, potassium, chloride, or creatinine. Physical examination, electrocardiograms, and other vital signs showed no abnormalities.

A9.6. Summary

This was an open-label, multiple dose, parallel group study in which irbesartan 300 mg was administered orally once daily for 7 days to 10 healthy and 10 cirrhotic subjects. Based on the analysis of the PK and PD data, there is no need to recommend dosing adjustment for mild to moderate hepatic impairment.

A10. CV131-017: Effect of concomitant administration of nifedipine on the steady-state pharmacokinetics of irbesartan in healthy subjects.

A10.1. Source documents

Study report: NDA 20-757, vol 1.169-1.170.

A10.2. Investigators

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

A10.3. Study design

The objective of the study was to assess the effect of nifedipine on the steady state pharmacokinetics of irbesartan and losartan in healthy subjects. A 20% change in AUC and C_{max} at steady-state of irbesartan, losartan or EXP3174 (active metabolite) after concomitant administration of nifidepine was considered to be of clinical relevance.

This was an open label, 4 period crossover study in 13 healthy male subjects. Subjects remained at the clinical site for the 4 treatment days of each period. Treatment periods were separated by a 7 to 10 day washout period. Subjects received each of the following treatments q.d. x 4 days: (a) irbesartan 300 mg, (b) irbesartan 300 mg plus nifedipine 30 mg, (c) losartan 100 mg, and (d) losartan 100 mg plus nifedipine 30 mg. On day 4 of each treatment period blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose. Blood pressure and heart rate were measured at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hour post-dose.

Drug supplies are shown in Table 136 below.

Table 136. Drug supplies (CV131-017).

	Lot number		Lot number
Losartan 100 mg	JAO22C	Irbesartan 300 mg	N95067
Nifedipine 30 mg (Procardia XL)	47P122A		

Assay of plasma irbesartan was by see method 5 in Table 7.*Assay validation for irbesartan.* on page 15. Other assays are described in Table 137 below. Both assays were satisfactory.

Table 137. Assays (CV131-017).

Assay	Sample	Technique	Linearity	Specificity	Sensitivity LOQ	Accuracy %CV inter-day	Precision %CV inter-day intra-day
Losartan	Plasma		Satisfactory	Satisfactory	5 ng/ml	≤4	≤5.6 ≤3.3
EXP 3174	Plasma		Satisfactory	Satisfactory	5 ng/ml	≤5	≤4.3 ≤7.7

The plasma pharmacokinetic parameters evaluated for irbesartan, losartan and EXP 3174 were C_{max}, AUC, T_{max} and C_{min}.

Pharmacodynamic assessments included BP, HR and PRA.

A10.4. Results

Eleven subjects completed all 4 treatment periods. Subject #2, discontinued due to an adverse event, received 3 doses of 100 mg losartan plus 30 mg nifedipine. Subject #6, discontinued due to an adverse event, completed 3 of 4 treatment periods.

There were no significant changes in the steady-state pharmacokinetics of irbesartan, losartan and EXP 3174[1] with concomitant nifedipine. The mean plasma concentration-time plot for irbesartan, losartan and EXP 3174 alone and with concomitant nifedipine are illustrated in Figure 41 below.

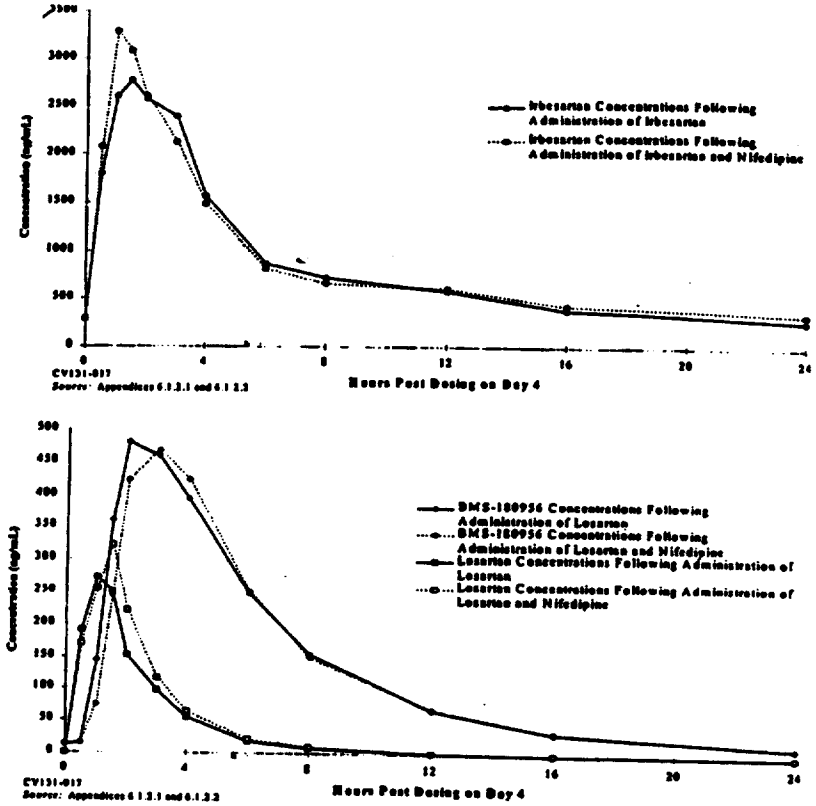

Figure 41. Plasma profiles of study drugs (CV131-017).

Table 138 below summarizes the mean pharmacokinetics results of this study.

Table 138. Pharmacokinetic parameters (±SD; CV131-017).

	Irbesartan		Losartan		EXP 3174	
	Alone N=11	+nifedipine N=11	Alone N=12	+nifedipine N=12	Alone N=12	+nifedipine N=12
C_{max} (ng/mL)	3255 (666)	3384 (751)	404 (186)	504 (275)	562 (196)	612 (160)
AUC (ng.h/mL)	19992 (4261)	19560 (4671)	705 (141)	824 (290)	3106 (742)	3069 (816)
T_{max}* (h)	1.5 (0.5-3.0)	1.0 (1.0-3.0)	1.0 (0.5-2.0)	1.5 (0.5-20)	2.5 (1.5-4.0)	2.5 (1.5-4.0)

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

The mean plasma renin activity, seated SBP and seated DBP are shown in Table 139 below.

[1] EXP 3174 or BMS-180956 is the active metabolite of losartan.

Table 139. Pharmacodynamic parameters (AUC±SD; CV131-017).

	Irbesartan		Losartan	
	Alone N=11	+nifedipine N=11	Alone N=12	+nifedipine N=12
DBP (mmHg.h)	1475 (198)	1506 (186)	1557 (150)	1575 (183)
SBP (mmHg.h)	2874 (207)	2929 (150)	2975 (156)	3000 (150)
PRA (ng.h^2/mL)	284 (244)[a]	356 (217)[b]	172 (138)	211 (134)

a. P=0.022 compared with losartan alone.
b. P=0.002 compared with losartan plus nifedipine.

A10.4.1. Safety Not reviewed.

A10.5. Summary. Concomitant nifedipine does not significantly alter the pharmacokinetics or pharmacodynamics of irbesartan or losartan and its active metabolite.