CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20757 AND 20758

MEDICAL REVIEW(S)

1. Materials utilized in review

1.1. Materials from NDA/IND

NDA submissions reviewed are listed on the front cover. The material included conventional study reports for a total of 50 clinical studies, individually reviewed in Appendix A. The sponsor also provided an electronic submission of some study documents, all data from placebo-controlled studies and some biopharmaceutical studies, and page-images of CRFs for deaths and withdrawals for adverse events. These materials were all reviewed.

The clinical development programs for irbesartan and irbesartan plus HCTZ were undertaken under IND and IND respectively. These submissions were not utilized in this review.

1.2. Related reviews or consults

NDAs for several angiotensin II receptor antagonists, monotherapy and combination products, have been previously reviewed by the Division. Neither the original submissions nor the reviews of those materials were utilized in the review of NDAs 20-757 and 20-758.

1.3. Other resources

An NLM search was conducted to look for publications involving clinical trials of irbesartan. The results of this search are discussed in section 5.2.3 on page 13.

2. Background

2.1. Indication

The proposed indication for irbesartan and for the combination of irbesartan plus HCTZ is for the treatment of essential hypertension.

2.2. Information from related pharmacologically related agents

Irbesartan appears to have a mechanism of action similar to that of valsartan, previously approved for the same indication.

2.3. Administrative history

The development program for irbesartan was managed under IND filed in March of 1993, after some initial study in Europe. The sponsor met with the Division in September 1994 for an end-of-phase-II meeting. There have been no substantive administrative issues.

The development program for irbesartan plus HCTZ was managed under IND filed in September 1994. There have been no substantive administrative issues.

2.4. Proposed labeling

The proposed label is reviewed in section 9 on page 94.

2.5. Foreign marketing

As of the date of filing, irbesartan was not marketed in any country.

2.6. Other background information

None.

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3. Chemistry, manufacturing, and controls

3.1. Basis of review

This section of the review is based upon the chemistry review of NDA 20-757 dated 7 February 1997, by RD Mittal.

3.2. Structure

Irbesartan (SR 47436, BMS-186295) is 2-butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one, with molecular formula $C_{25}H_{28}N_6O$, molecular weight 428.5, and structure as shown in Figure 1 below.

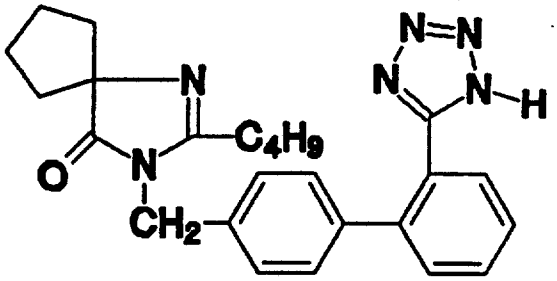

Figure 1. Structure of irbesartan.

3.2.1. Deficiencies

The chemistry review identified several minor deficiencies, the most serious of which is a lack of stability data to support a request for a 2-year expiry date. Approval with a 6-month expiry date appears feasible.

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4. Animal pharmacology

4.1. Basis of review

This section of the review is based upon draft pharmacology reviews by Drs. Jagadeesh (pharmacodynamics, pharmacokinetics, carcinogenicity, acute and long-term toxicology) and Stolzenberg (reproductive toxicology).

4.2. Mechanism of action

The data show that irbesartan is a potent and selective antagonist of the AT_1 angiotensin II receptor. This receptor is distributed in (a) blood vessels, where activation leads to vasoconstriction and smooth muscle growth, (b) adrenal cortex, where activation leads to aldosterone secretion and, via secondary effects of aldosterone on kidneys and the CNS, to salt and water retention, and (c) juxtaglomerular cells, where activation inhibits renin secretion.

4.2.1. Receptor affinity

Irbesartan displaces angiotensin II from AT_1 receptors on rat adrenal cortical membranes, rat liver cell membranes, cultured rat aortic smooth muscle, and human aortic smooth muscle, all with IC_{50}=0.5 to 2 x 10^{-9} M. Binding to rabbit aorta smooth muscle was characterized as competitive and insurmountable. Binding to receptor sites for other ligands—α_1- or α_2-adrenergic ligands, M_1- or M_2-muscarinic ligands, histamine, serotonin, bombesin, bradykinin, endothelin I, neurotensin, vasopressin, neuropeptide Y, imidazolines, CGRP, phencyclidine, cannabis—had at least 10^4-fold lower affinity.

Irbesartan failed to inhibit human or baboon renins and other aspartyl proteases.

4.2.2. Effects of exogenous angiotensin II

Irbesartan 3 mg/kg i.v., 30 mg/kg p.o., or 10 µg/kg intracerebroventricularly produced 80 to 100% inhibition of the pressor effect of exogenous angiotensin II in conscious rats. The antagonism of the pressor response in rabbit was characterized as non-competitive and insurmountable. The effect of exogenous angiotensin II on aldosterone secretion was affected over a similar irbesartan concentration range. Irbesartan 3 mg/kg had no effect on pressor responses to norepinephrine or vasopressin in rats.

Similar i.v. doses of irbesartan antagonized pressor effects of angiotensin II in dogs and monkeys.

4.2.3. Models of hypertension

Irbesartan reduced blood pressure in animals with a model system for high-renin hypertension—rats with a ligated renal artery—but not for models of low-renin hypertension—spontaneously or DOCA-salt hypertensive rats.

4.2.4. Screening for other activities

Doses of irbesartan several-fold greater than necessary to antagonize angiotensin II receptor-mediated actions failed to produce central or autonomic effects in mice.

4.3. Pharmacokinetics

Although fairly extensive studies of pharmacokinetics were performed, their relevance is now largely restricted to interpretation of toxicity studies. The following points, illuminated in animal studies, are of some interest.

4.3.1. Absorption

Estimated bioavailability is 11 to 22% in rats, 45 to 120% in monkeys, and >61% in man. Plasma levels increase less than dose-proportionally.

4.3.2. Distribution

The volume of distribution is large—on the order of 1 L/kg—in animals and man. Irbesartan is not taken up by red cells, but there is high, effectively non-saturable binding to plasma proteins, an observation that might have relevance to the treatment of drug overdose.

Radio-labelled irbesartan illustrates its principal metabolic pathway, with the bulk of the movement from the upper GI tract to the liver to bile to the lower GI tract.

4.3.3. Metabolism

Irbesartan is extensively metabolized, with no fewer than 14 metabolites identified, chiefly hydroxy and glucuronide derivatives. Mice metabolize irbesartan relatively quickly compared with rats, dogs, monkeys, and man, and the favored metabolic pathways are dissimilar in mice as well, suggesting that toxicological data from mice are of limited usefulness.

Work with hepatic microsomal preparations is consistent with metabolism by CYP2C9 and, to a lesser extent, CYP3A4. Irbesartan was neither an inducer nor an inhibitor of CYP 1A or 3A families in human hepatocytes.

Several metabolites have AT_1 receptor affinity comparable to that of the parent drug.

4.3.4. Excretion

The bulk of the recovered drug appears in feces, and relatively little (<10%) in urine. The main form of recovery in feces is as the parent drug, thought to represent in situ hydrolysis of the glucuronide metabolite from bile.

4.4. Toxicology

4.4.1. Acute toxicity

Acute toxicity was studied in mice and rats. There was no overt toxicity associated with single oral doses of irbesartan to 2000 mg/kg in either species. Combination of irbesartan/HCTZ to 2000/4000 mg/kg (mice) or 3000/500 mg/kg (rats) as a single oral dose was without overt toxicity. Intraperitoneal irbesartan 2000 mg/kg was 100% fatal in rats; doses up to 200 mg/kg were without overt toxicity. Mice and rats administered intravenous irbesartan to 50 mg/kg (solubility and volume limited) was associated with no overt toxicity.

4.4.2. Sub-chronic to chronic toxicity

Rats received oral doses of irbesartan 30 to 1000 mg/kg for 1 to 6 months. Findings thought to be treatment-related were small increases in blood glucose, urea, and creatinine, increases in urinary excretion of sodium and chloride, hyperplasia and hypertrophy of the juxtaglomerular apparatus, and mild to moderate anemia. Similar findings were obtained in rats maintained on irbesartan/HCTZ 10/10 or 90/90 mg/kg for 6 months. Rats had a *lower* than control incidence of murine progressive nephropathy, said to be like ACE inhibitors.

In a series of studies Cynomolgus monkeys received oral irbesartan 10 to 1000 mg/kg for 1 month, 10 to 90 mg/kg for 6 months, and 20 to 500 mg/kg for 1 year. There was no treatment-related mortality. Effects seen included anemia (decreased RBC, decreased hemoglobin), renal effects (increases in urea, and creatinine, hypertrophy of the juxtaglomerular apparatus), and decreases in heart weight. Monkeys were given oral irbesartan/HCTZ 10/10 to 90/90 mg/kg for 6 months, with a similar array of findings.

4.4.3. Special studies

Guinea-pigs were evaluated for development of phototoxicity in response to oral doses of irbesartan alone 100 mg/kg for 6 days. No phototoxicity was seen.

4.4.4. Carcinogenicity

Carcinogenicity studies were carried out in mice and rats at doses producing some mortality. Such high dose animals had acute tubular necrosis, focal necrosis of the liver, and single-cell necrosis of the spleen and thymus. Other effects observed in surviving animals included thinness, under-activity, salivation, reduced body temperature, and piloerection. Renal tissue examination revealed basophilic and dilated cortical tubules, vacuolation of tubular epithelial cells, and hyperplasia of the juxtaglomerular apparatus, reminiscent of effects seen with ACE inhibitors and other angiotensin II receptor antagonists.

The Carcinogenicity Assessment Committee convened to consider irbesartan on 24 June 1997. Its decision was that studies in mice and rats were adequate, and that, after appropriate consideration of laboratory historical control rates and multiple comparisons, there was no evidence of carcinogenicity in either species.

4.4.5. Mutagenicity

The Ames test looks for genotoxic agents causing histidine-dependent strains of *Salmonella typhimurium* to revert to histidine independence or tryptophan-dependent *E. coli* to revert to tryptophan independence, in the presence or absence of metabolic activation. Appropriate positive- and negative-controlled studies of irbesartan and equal (w/w) irbesartan/HCTZ, up to cytotoxic levels, revealed no genotoxic potential.

A DNA repair assay in isolated rat hepatocytes looks for unscheduled DNA synthesis. Positive-controlled studies revealed no increase in DNA synthesis with non-cytotoxic concentrations of irbesartan.

A gene mutation test in Chinese hamster fibroblasts (lung or ovary) looks for base-pair substitutions, frame-shift mutations, and deletions resulting in increased expression of HGPRT, in the presence or absence of metabolic activation. Positive-controlled studies revealed no increase in mutation frequency attributable to irbesartan or equal (w/w) irbesartan/HCTZ, up to cytotoxic levels.

A test of human lymphocytes in vitro looked for chromosomal aberrations (clastogenicity; gaps, breaks, translocations, etc.) in the presence or absence of metabolic activation. Two positive-controlled studies revealed numerical aberrations at doses of irbesartan within a factor of 2 or so of cytotoxic concentration. A similar study of equal (w/w) irbesartan/HCTZ revealed no clastogenic potential, up to cytotoxic levels.

The in vivo mouse micronucleus assay looks for polychromatic erythrocytes with micronuclei in marrow samples, an indication of clastogenicity or spindle poison activity. A positive- and negative-controlled study revealed no clastogenic potential of irbesartan or equal (w/w) irbesartan/HCTZ at doses higher than those employed in the carcinogenicity studies.

4.4.6. Reproductive toxicology

Studies of reproductive toxicology, undertaken in rates and rabbits, utilized doses that produced plasma drug levels roughly equivalent to blood pressure-reducing doses in man.

Male Sprague-Dawley rats were dosed from 71 days prior to mating and females were dosed from 15 days prior to mating to post-partum day 24. Females showed lower rates of weight gain and produced lower placenta and fetal weights. Fetuses exhibited hydroureter and renal pelvic cavitation, considered by the reviewer to represent mild and reversible retardation of development. Fetal lower weights persisted through weaning only; these animals went on to have normal second-generation litters.

Somewhat lower doses of irbesartan were administered during gestation in Sprague-Dawley rats, alone and in combination with HCTZ. The principal findings were again reduced weight gain in females and fetuses. Similar studies in New Zealand white rabbits showed reduced weight gain in does, and increased fetal resorption and decreased numbers of live births.

Tissue distribution of ^{14}C-labelled irbesartan was studied during gestation in rats and rabbits. Fetal levels were lower than maternal levels or placental levels, but fetuses did show appearance of label in the gall bladder and gastrointestinal tract, persisting for at least 48 hours.

Low concentrations of radiolabel appear in milk of Sprague-Dawley rats, following a single dose.

5. Description of clinical data sources

5.1. Primary source data

5.1.1. Study type and design and subject enumeration

5.1.1.1. Controlled studies Table 1 below lists controlled studies of effectiveness in hypertensive subjects. Each of these studies is the subject of a brief review in Appendix A. Most such studies were randomized, double-blind, placebo-controlled studies in a population with mild-to-moderate hypertension (SeDBP between 95 an 110 mmHg). A few studies were actively controlled, with amlodipine, atenolol, or enalapril. One study (CV131-032) was conducted with subjects have severe hypertension (SeDBP between 115 and 130 mmHg).

Table 1. Controlled clinical trials of effectiveness.

	Review	Design[a]	Weeks	Doses mg qd	N	Percentage		
						Female	>65 y	Black
Fixed-dose monotherapy								
ACT 1967: Dose-finding study of irbesartan in patients with mild to moderate hypertension.	page 129	R,DB,PC,II	1	1, 25, 100	87	10-33	—	0
CV131-001: A multicenter assessment of tolerability and antihypertensive activity of irbesartan in patients with mild to moderate hypertension.	page 135	R,DB,PC,II	1	5, 25, 100	77	23-40	—	20-24
CV131-004: Pharmacokinetics and pharmacodynamics of irbesartan in female and male patients with mild-to-moderate essential hypertension.	page 146	R,DB,PC,II	4	100	56	50-55	0	0
CV131-057: Pharmacodynamics (effects on renin angiotensin system, renal function and blood pressure) and pharmacokinetics of irbesartan in subjects with mild-to-moderate hypertension.	page 255	R,DB,PC,II	4	300	24	50-50	0	0
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).	page 138	R,DB,PC,II	8	1, 5, 10, 25, 50, 100	570	23-41	12-19	13-20
CV131-030: The antihypertensive activity of irbesartan as determined by 24-hour ambulatory blood pressure monitoring.	page 195	R,DB,PC,II	8	75, 150	215	28-40	18-21	0
CV131-025: Dose ranging study II: a multicenter trial of the antihypertensive activity and safety of 100 mg, 200 mg and 300mg irbesartan in mild-to-moderate hypertension.	page 172	R,DB,PC,II	8	100, 200, 300	319	26-35	10-16	7-18
CV131-050: A multicenter, 8 week study of the antihypertensive activity, tolerability, and safety of irbesartan in subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg).	page 246	R,DB,PC,II	8	150, 300, 600, 900	524	29-44	11-20	8-15
Fixed combination with HCTZ								
CV131-037: Factorial trial of the efficacy and safety of multiple dosages of irbesartan and hydrochlorothiazide in mild-to-moderate hypertension.	page 213	R,DB,PC,II	8	37.5, 100, 300	683	20-45	10-27	5-18
CV131-039: The antihypertensive efficacy of the combination of irbesartan and hydrochlorothiazide as determined by 24-hour ambulatory blood pressure monitoring.	page 227	R,DB,PC,II	8	75, 150	178	39-44	4-16	8-16
CV131-038: Double-blind, placebo-controlled, comparison of the combination of irbesartan and hydrochlorothiazide versus individual components in mild-to-moderate hypertension.	page 222	R,DB,PC,II	12	75, 150	815	41-47	12-19	8-14
Titrated dose								
CV131-029: Multicenter, randomized, double-blind, placebo-controlled trial of irbesartan for treatment of hypertension.	page 189	R,DB,PC,II	12	75, 150, 300	319	32-37	16-19	4-10
CV131-040: The efficacy and safety of irbesartan added to hydrochlorothiazide for the treatment of hypertension in subjects nonresponsive to hydrochlorothiazide alone.	page 234	R,DB,PC,II	12	75, 150	238	36-38	11-18	12-12
CV131-028: Multicenter, randomized, double-blind comparison of irbesartan and enalapril for treatment of hypertension.	page 184	R,DB,AC,II	12	75, 150, 300	202	46-51	28-30	0-1
CV131-032: The efficacy and safety of the angiotensin II receptor antagonist irbesartan in the treatment of patients with severe hypertension.	page 207	R,DB,AC,II	12	150, 300	182	37-44	10-11	31-33
CV131-027: Multicenter, randomized, double-blind comparison of irbesartan and atenolol for treatment of hypertension.	page 179	R,DB,AC,II	24	75, 150	231	38-45	18-23	0
CV131-031: Multicenter, randomized, double-blind comparison of irbesartan and amlodipine for treatment of hypertension in the elderly.	page 203	R,DB,AC,II	24	75, 150	188	54-56	100	0-13

a. R=randomized; DB=double-blind; PC=placebo-controlled; AC=active-control; II=parallel.

Not included in the table is one open-label study of irbesartan 150 to 300 mg in subjects (N=79) stratified by degree of renal impairment[1].

This set of studies was the primary basis for the evaluation of effectiveness of irbesartan alone and irbesartan plus HCTZ for the treatment of hypertension.

5.1.1.2. Clinical pharmacology

Studies of clinical pharmacology of irbesartan are listed in Table 2 below. Not included in this listing are those previously listed in Table 1 on page 7, but with pharmacokinetic data collected as well.

Table 2. Clinical pharmacology trials.

	Review	Design[a]	Doses mg qd	N	Purpose
Pharmacokinetics					
CV131-006: The effects of age and gender on the pharmacokinetics of irbesartan in healthy subjects following a single 50 mg oral dose.	page 153	OL,II	50	49	Single-dose PK in normal volunteers
CV131-011: Pharmacokinetics of SR 47436 (irbesartan) in subjects with renal impairment compared to subjects with normal renal function.	page 156	OL,II	100, 300	40	Repetitive-dosing PK and GFR in normal volunteers and renal impaired subjects
CV131-014: Single and multiple dose pharmacokinetics and pharmacodynamics of irbesartan in subjects with hepatic cirrhosis compared to healthy subjects	page 162	OL,II	300	20	Repetitive-dosing PK and GFR in normal volunteers and hepatic cirrhosis subjects
CV131-045: Safety, tolerance, pharmacokinetics and pharmacodynamics of irbesartan following single and multiple 150 to 900 mg doses in healthy subjects.	page 242	R,DB, PC,II	150, 300, 600, 900	36	Repetitive dosing PK in normal volunteers
CV131-058: Effects of age on the pharmacokinetics of irbesartan following a single 150 mg oral dose in healthy male subjects.	page 259	OL,II	150	24	Single-dose PK in normal volunteers
PPK 2198: Comparative pharmacokinetics of irbesartan in healthy young and elderly volunteers: single and repeated oral administration of 25 mg during 8 days.	page 290	OL,II	25	30	Single-dose PK in normal, elderly, and renally impaired subjects
TDR 1691: Tolerability assessment of SR47436 administered in repeated ascending doses to healthy volunteers.	page 295	R,DB, PC	10, 50, 100, 200	41	Single-dose PK in normal volunteers
TDU 1693: Tolerability assessment of irbesartan administration single ascending doses to healthy volunteers	page 301	R,DB, PC	5, 10, 25, 50, 100, 150, 200, 250, 300, 350, 375, 400	48	Single-dose PK in normal volunteers
Pharmacodynamics					
PDY 1692: Assessment of the inhibition of pressor response to exogenous angiotensin II by irbesartan in normotensive human subjects.	page 268	R,DB, PC,XO	5, 25, 50, 100	24	Single-dose response to AII in normal volunteers
PDY 2201: Effect of SR47436 on renal haemodynamics and on glomerular permselectivity in healthy humans. Double blind, placebo-controlled, crossover trial of a single 50mg oral dose.	page 271	R,DB, PC,XO	50	13	Single-dose renal effects in normal volunteers
PDY 2202: Hormonal profile and renal tubular effects of irbesartan in healthy volunteers after acute and repeated oral administration during 8 days of 10 or 50 mg.	page 274	R,DB, PC,II	10, 50	25	Repetitive dosing renal effects in normal volunteers
PDY 2203: Effects of irbesartan on blood pressure in healthy salt depleted normotensive male volunteers—exploration pilot study (single dose double-blind versus placebo dose ranging study)	page 277	R,DB, PC,XO	1, 5, 10, 25, 50, 100	12	Single-dose PD in normal salt-depleted volunteers
PDY 2204: Hormonal profile and hemodynamic effects of irbesartan in healthy volunteers.	page 280	R,DB, PC,XO	10, 50	9	Single-dose non-invasive hemodynamics in normal volunteers
PDY 2801: Assessment of the inhibition of pressor response to exogenous angiotensin II by irbesartan at single doses 75, 150, 300 mg in normotensive subjects.	page 285	R,DB, PC,XO	75, 150, 300	18	Single-dose AII antagonism in normal volunteers
Other indications					
CV131-003: Evaluation of the hemodynamic effects and safety of the angiotensin II antagonist irbesartan in patients with heart failure.	page 143	R,DB, PC,II	1, 5, 10, 50, 100, 200	96	Acute invasive hemodynamics in CHF

[1] *CV131-033: The safety and efficacy of irbesartan in patients with hypertension and renal insufficiency.* on page 210.

a. R=randomized; DB=double-blind; OL=open-label; PC=placebo-controlled; AC=active-control; ll=parallel; XO=cross-over.

5.1.2. Demographics

Figure 2 below shows the distribution of subjects' age by race and sex in placebo-controlled monotherapy studies[2], including the irbesartan-only and placebo arms of studies of irbesartan plus HCTZ.

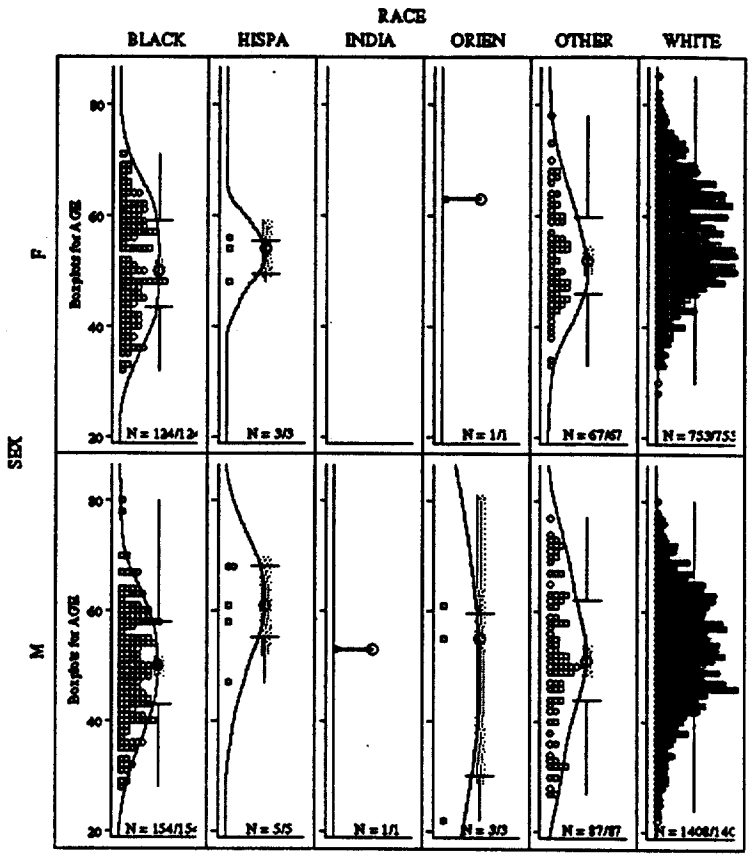

Figure 2. Demographics in placebo-controlled monotherapy trials.

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2. Studies CV131-002, CV131-004, CV131-025, CV131-029, CV131-030, CV131-037, CV131-038, CV131-050, and CV131-057.

Figure 3 below is a similar figure for studies of irbesartan plus HCTZ[3].

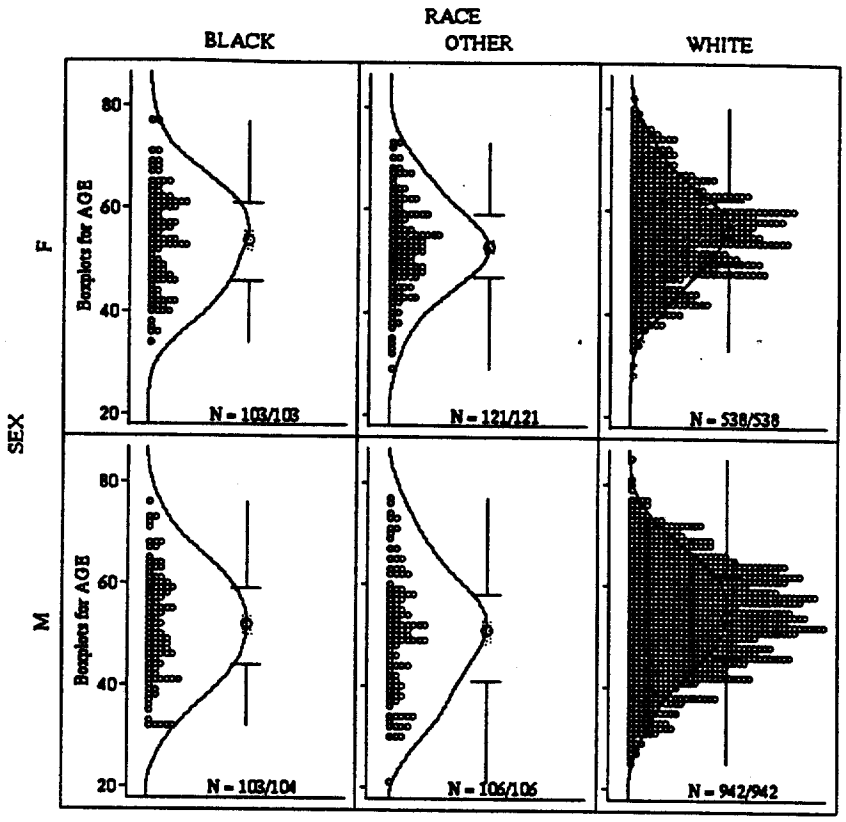

Figure 3. Demographics in placebo-controlled trials with HCTZ.

Table 3 below is a tabular summary of demographic data for placebo-controlled studies of irbesartan alone and irbesartan plus HCTZ.

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[3] Studies CV131-037, CV131-038, CV131-039, and CV131-040.

Table 3. Demographics of subjects in placebo-controlled studies.

	Plcbo N=64	Irbe N=1965	Plcbo N=236	HCTZ N=380	Irbe N=400	Irbe/ HCTZ N=898
Age (%)						
20-30	1.4	1.8	1.3	1.1	0.8	0.8
31-40	8.9	8.9	5.9	7.6	10	9.7
41-50	27	29	24	26	28	25
51-60	36	33	43	37	34	35
61-64	11	13	10	12	12	13
65-74	14	14	14	15	14	14
≥75	1.7	1.5	1.3	1.3	1.5	2.3
Mean (y)	54	54	55	54	54	54
Male (%)	64	64	62	62	58	60
White (%)	83	83	73	80	74	79
Black	11	11	12	11	9.8	11
Other	6.7	6.3	14	8.9	16	11
Duration of HTN (%)						
<6 months	6.4	6.6	8.5	6.1	5.5	4.9
6-12 months	8.6	7.4	13	8.7	6.8	8.4
12-24 months	7.0	6.8	6.8	4.7	8.5	6.6
>24 months	73	77	72	80	79	80

5.1.3. Extent of exposure

5.1.3.1. Placebo-controlled experience

Planned exposure by dose in monotherapy studies is shown in Table 4 below. Planned exposure by dose in combination studies is shown in Table 5 below. Actual drug exposure during double-blind treatment was only somewhat less than predicted because only a small fraction of subjects withdrew for any cause.

Table 4. Drug exposure in placebo-controlled phases of monotherapy studies.

Weeks	Plcbo	Irbesartan (mg)												
		1	5	10	25	37.5	50	75	100	150	200	300	600	900
	Subjects on randomized doses for planned follow-up periods													
4	641	82	82	81	83	42	82	297	242	450	79	240	105	99
6	611	82	82	81	83	42	82	297	204	450	79	228	105	99
8	494	82	82	81	83	42	82	193	204	352	79	228	105	99
12	135	0	0	0	0	0	0	138	0	136	0	0	0	0
	Cumulative totals (subjects treated with at least this dose and duration)													
4	2616	1975	1893	1811	1730	1647	1595	1513	1216	973	523	444	204	99
6	2525	1914	1832	1750	1669	1586	1544	1462	1165	961	511	432	204	99
8	2206	1712	1630	1548	1467	1384	1342	1260	1067	863	511	432	204	99
12	409	274	274	274	274	274	274	274	136	136	0	0	0	0
	Cumulative totals (subjects treated with at least this dose and duration x weeks)													
4	10464	7900	7572	7244	6920	6568	6385	6052	4864	3892	2092	1776	816	396
6	15150	11484	10992	10500	10014	9516	9264	8772	6990	5766	3066	2592	1224	594
8	17648	13696	13040	12384	11736	11072	10736	10080	8536	6904	4088	3456	1632	792
12	4908	3288	3288	3288	3288	3288	3288	3288	1632	1632	0	0	0	0
Total	48170	36068	34892	33416	31958	30444	29673	28192	22022	18194	9246	7824	3672	1782

Table 5. Drug exposure in placebo-controlled phases of combination studies.

Weeks	Irbesartan (mg)																				
	0				37.5				75			100				150		300			
HCTZ	0	6.25	12.5	25	0	6.25	12.5	25	0	12.5	25	0	6.25	12.5	25	0	12.5	0	6.25	12.5	25
.	Subjects on randomized doses for planned follow-up periods																				
6	120	0	0	0	0	0	0	0	0	0	118	0	0	0	0	0	0	0	0	0	0
8	101	44	40	39	42	44	45	41	0	58	0	41	44	43	44	0	63	43	40	44	43
12	135	0	137	0	0	0	0	0	138	134	0	0	0	0	0	136	135	0	0	0	0
	Cumulative totals (subjects treated with at least this dose of irbesartan and HCTZ and duration)																				
6	1964	1125	979	285	1296	813	763	246	1124	682	205	676	839	395	130	504	372	170	127	87	43
8	1684	1008	866	167	1178	738	650	128	1006	564	87	756	444	265	87	369	285	170	127	87	43
12	812	406	406	0	540	269	269	0	540	269	0	271	135	135	0	271	135	0	0	0	0
	Cumulative totals (subjects x weeks / 100)																				
6	118	68	59	17	78	49	46	15	67	41	12	54	50	24	5.2	30	17	10	7.6	5.2	2.6
8	135	81	69	13	94	59	52	10	80	45	7.0	54	33	30	7.0	40	23	14	10	7.0	3.3
12	97	49	49	0	65	32	32	0	65	32	0	33	16	16	0	33	16	0	0	0	0
Total	350	197	177	30	237	140	130	25	213	118	19	141	100	70	12	103	0	24	18	12	5.9

There were approximately 930 subject-years of double-blind experience in monotherapy studies, of which 25% was on placebo, 15% was on doses of 1 to 75 mg, and 8% was on doses >300 mg.

There were approximately 670 subject-years of double-blind experience in combination studies with HCTZ, of which 68% was on non-zero doses of irbesartan (37.5 to 300 mg) and 56% was on non-zero doses of HCTZ (6.25 to 25 mg).

5.1.3.2. Open-label experience

Figure 4 below shows life table analyses of actual time in study by days for subjects in monotherapy and combination studies, including open-label exposure and placebo and all active doses[4].

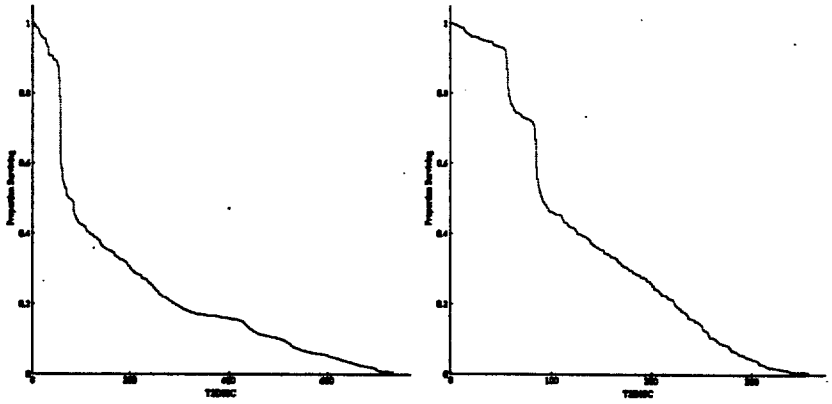

Figure 4. Time in study (days) for monotherapy and combination trials.

The sponsor's summary of long-term open-label exposure, through the cut-off date for the safety update is shown in Table 6 below.

[4] These graphs were developed from the electronic data supplied with the original NDA submission. They do not include open-label experience accrued to the closing date for the safety updates.

Table 6. Exposure to study drug in open-label studies.

	By gender				By age				By race					
	Irbesartan		Irbesartan /HCTZ		Irbesartan		Irbesartan /HCTZ		Irbesartan			Irbesartan /HCTZ		
N-	M 1123	F 668	M 1045	F 655	<65 1399	≥65 392	<65 1368	≥65 332	W 1555	B 152	Oth 84	W 1339	B 186	Oth 175
<90 days	444	270	278	116	560	154	313	81	564	97	53	315	43	36
91-180 days	219	111	151	71	245	85	162	60	301	21	8	290	18	14
181-270 days	97	87	100	59	137	47	123	36	166	10	8	130	20	9
271-365 days	151	95	288	229	193	53	423	94	233	6	7	387	55	75
366-545 days	123	62	173	153	153	32	278	48	173	9	3	254	33	39
546-730 days	45	25	34	19	64	6	42	11	65	3	2	42	10	1
>730 days	44	18	21	8	47	15	27	2	53	6	3	21	7	1
Total subject-years	641	359	712	501	792	205	997	219	907	61	31	945	142	131

5.1.3.3. Safety updates

The 4-month safety updates included no new controlled clinical data. The final safety updates included safety data from active-control study CV131-064. The total number of hypertension subjects exposed to irbesartan as of the cut-off date for the final safety update (15 March 1997) was approximately 5123. The number of subjects still in open-label studies as of the final cut-off date was 640, down from about 1300 at the cut-off date for the 4-month safety update. The sponsor estimates that the total exposure to irbesartan in open-label extensions as of the final cut-off date was 2948 subject-years.

Nine trials with irbesartan were still blinded as of the final cut-off date, estimated to include 775 subjects on irbesartan.

Enumerated events from the safety updates are listed in the review of safety. Estimates of incidence were based on the exposure for the original NDA submission only.

5.2. Secondary source data

5.2.1. Other studies

None applicable.

5.2.2. Post-marketing experience

Irbesartan (alone or in combination) is not approved for marketing in any country.

5.2.3. Literature

A search of the on-line catalog at NLM revealed only two published descriptions of clinical trials of irbesartan.

The first[5] appears to refer to pharmacodynamic study in normal volunteers PDY 2202[6].

The second[7] appears to correspond to an early dose-ranging study, ACT 1967[8].

Neither publication was reviewed in detail.

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5. Short-term and sustained renal effects of angiotensin II receptor blockade in healthy subjects. Burnier M et al., *Hypertension* 1995 Apr;25(4 Pt 1):602-9.
6. *PDY 2202: Hormonal profile and renal tubular effects of irbesartan in healthy volunteers after acute and repeated oral administration during 8 days of 10 or 50 mg.* on page 274.
7. Hemodynamic and biochemical effects of the AT1 receptor antagonist irbesartan in hypertension. van den Meiracker AH et al. *Hypertension* 1995 Jan;25(1):22-9.
8. *ACT 1967: Dose-finding study of irbesartan in patients with mild to moderate hypertension.* on page 129.

5.3. Adequacy of clinical experience

Development programs for antihypertensive agents are typically sized to provide some minimum level of safety data. This amount of clinical experience is generally far greater than is required to assess effectiveness.

The development program for irbesartan exposed 3100 subjects to study drug in short-term (4 to 12 weeks), fixed-dose studies, of whom 1125 received study drug in combination with HCTZ. Long-term (up to 2 years on irbesartan alone or 1 year on irbesartan plus HCTZ) open-label extensions to controlled studies substantially increased the number of subject-days of exposure.

Irbesartan is intended for life-long treatment of hypertension, typically many times the length of exposure obtained in the clinical development program. The expected (as opposed to established) benefits of treatment of hypertension are a reduction in fatal cardiovascular events on the order of 1 per 1000 subject-years. If there were no suspected drug-related fatal or life-threatening events in irbesartan-treated subjects, the available safety data would, with 95% confidence limits, rule out an undetected problem of about this magnitude.

In summary, although the development program cannot provide much assurance that there is a clinical benefit derived from treatment of hypertension with irbesartan or irbesartan plus HCTZ, it does meet the usual standards set for this indication.

5.4. Data quality and completeness

Full study reports have been provided for all pertinent clinical studies. Complete machine-readable data were provided for well-controlled and biopharmaceutical studies.

DSI audit of a sampling of centers in major studies uncovered no problems of a material nature.

Outside of the DSI audit, there was no attempt made as part of this review to reconcile datasets with case report forms.

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6. Human pharmacokinetics

6.1. Review

Four bioequivalence trials[1] were reviewed but study reports were not incorporated into this review. All pertained to formulations not intended for marketing.

6.2. Assays

Table 7 below summarizes irbesartan assays used in various clinical studies. All assays were considered satisfactory.

Table 7. Assay validation for irbesartan.

Method No.	Matrix	Method	Standard curve range (ng/mL)	Linearity	Specificity	Sensitivity (LOQ)	Precision %CV inter- & intra-day	Accuracy %CV inter- & intra-day	% Recovery
1	Plasma		0.25-2	Satisfactory	Satisfactory	0.25	≤7	≤8	99.2-115.1
2	Plasma		1-1000	Satisfactory	Satisfactory	1	≤7	≤7	98-105.2
3	Plasma		5-500	Satisfactory	Satisfactory	5	≤13	≤18.7	98.7-104.8
4	Plasma		1-1000 10-4000	Satisfactory	Satisfactory	1 10	≤8 ≤4	≤3 ≤5	94-103.5 98-102
5	Plasma		1-600 10-4000	Satisfactory	Satisfactory	1 10	≤9 ≤11	≤5.3 ≤8.7	98-102.5 98-102.7
6	Urine		5-1000	Satisfactory	Satisfactory	5	≤12	≤9	85-94
7	Urine		2.5-200	Satisfactory	Satisfactory	2.5	≤4	≤11	86-94
8	Urine		1-1000	Satisfactory	Satisfactory	1	≤6	≤5	90-111
9	Urine		1-500	Satisfactory	Satisfactory	1	≤6.3	≤5.4	91-96
10	Urine		1-800	Satisfactory	Satisfactory	1	≤5	≤8.2	96.2-108

6.3. Composition

6.3.1. Irbesartan

Composition of irbesartan tablets proposed for marketing is shown in Table 8 below.

[1] Studies BEQ 2275, CV131-026, CV131-051, and CV131-063.

Table 8. Composition of irbesartan tablets.

	Quantity (mg)			Function
Irbesartan[a]	75.00	150.00	300.00	Active
Lactose, monohydrate[b]				
Pregelatinized starch				
Croscarmelose sodium				
Poloxamer 188				
Silicon dioxide[c]				
Microcrystalline cellulose				
Magnesium stearate[d]				
Purified water[e]				
Tablet weight				

a. Amount at 100% chemical potency.
b. Amount of lactose varies with the actual potency of irbesartan.
c. The allowable range is of the theoretical tablet weight.
d. The allowable range is of the theoretical tablet weight.
e. Water is used for processing only; it does not appear in the final tablet.

6.3.2. Irbesartan/HCTZ

Composition of irbesartan/HCTZ tablets proposed for marketing is shown in Table 9 below.

Table 9. Composition of irbesartan/HCTZ tablets.

	Quantity (mg)		Function
Product identification number	186295-A999-096	186295-A999-097	—
Irbesartan[a]		150.00	Active
Hydrochlorothiazide[b]		12.50	Active
Lactose, monohydrate[c]			
Microcrystalline cellulose			
Pregelatinized starch			
Croscarmelose sodium			
Ferric oxide, red			
Ferric oxide, yellow			
Silicon dioxide[d]			
Magnesium stearate[e]			
Purified water[f]			
Tablet weight			

a. Amount at 100% chemical potency
b. Amount at 100% chemical potency.
c. Amount of lactose varies with the actual potency of irbesartan.
d. The allowable range is of the theoretical tablet weight.
e. The allowable range is of the theoretical tablet weight.
f. Water is used for processing only; it does not appear in the final tablet.

6.4. Dissolution

6.4.1. Methods and specifications

The proposed dissolution methods and specifications for irbesartan tablets (75, 150, and 300 mg) and the combination irbesartan/HCTZ tablets (75/12.5 mg and 150/12.5 mg) are shown in Table 10 below.

Table 10. Proposed product dissolution methods and specifications.

	Irbesartan	Irbesartan/HCTZ
Dosage form	Tablet	Tablet
Strengths	75, 150, 300	75/12.5, 150/12.5
Apparatus		
Media/temperature		
Volume		
Speed of rotation		
Sampling times		
Analytical method		
Specification	Not less thai	(Q) in 30 minutes

6.4.2. Media effects

Comparative dissolution profiles for irbesartan 75, 150 and 300 mg tablets in three media (0.1N HCl, pH 7.5 phosphate buffer, and pH 2.0 citrate buffer) are illustrated in Figure 5 below and summarized in Table 11 below.

Figure 5. Dissolution of irbesartan tablets in various media.

Table 11. Effect of medium on dissolution of irbesartan tablets.

	Percent dissolved								
	75 mg (lot 8MDH05)			150 mg (lot 8MDH06)			300 mg (lot 8MDH07)		
	0.1 N HCl	pH 2.0	pH 7.5	0.1 N HCl	pH 2.0	pH 7.5	0.1 N HCl	pH 2.0	pH 7.5
10 min									
20 min									
30 min									
45 min									
60 min									

6.4.3. Batch consistency

Dissolution profiles (mean±SD) from 4 different batches of each strength of the combination tablet are shown in Figure 6 below. Most of the error bars are smaller than the symbols. These data are summarized in Table 12 below.

75/12.5 mg **150/12.5 mg**

Figure 6. Combination tablet consistency of dissolution from 4 lots.

Table 12. Combination tablet batch assay.

	Batches of 75/12.5 mg				Batches of 150/12.5 mg			
	N95093	N95096	8MLJ143	8MLJ345	N95094	N95095	8MLJ142	8MLJ346
Date of manufacture	July 1995	July 1995	Nov 1995	Nov 1995	July 1995	July 1995	Nov 1995	Nov 1995
Manufacturing site								
Batch size (tablets)								
Irbesartan lot	5ARL002	5ARL003	5ARS012	5ARS009, 5ARS011	5ARL002	5ARL003	5ARS012	5ARS009, 5ARS011
HCTZ lot	G527G	G075G	2MLJ109	2MLJ109	G527G	G075G	2MLJ109	2MLJ109
Irbesartan potency								
mg	75.8	76.4	74.7	75.9	151.6	149.8	151.4	149.7
% of claim	101.0	101.8	99.5	101.2	—	—	—	—
HCTZ potency								
mg	12.9	12.8	12.6	12.8	—	—	—	—
% of claim	102.8	102.4	100.8	102.0	—	—	—	—
Impurities								
SR49498, I.I.	<0.1	<0.1	NE[a]	NE	<0.1	NE	NE	NE
SQ-8936, E.I.	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	0.11	<0.06
Total, I.I.	0.19	0.18	0.22	0.25	0.21	<0.1	0.11	0.14
Content uniformity								
Irbesartan								
Mean	75.8	76.2	76.7	77.1	152.6	151.1	152.9	151.5
Range								
RSD	1.21	1.57	1.59	1.18	1.19	1.26	1.16	0.98
HCTZ								
Mean	12.9	12.8	12.6	12.7	13.0	13.0	12.9	12.4
Range								
RSD	1.00	1.40	1.02	1.11	1.27	1.40	0.93	1.19
Dissolution[b]								
Irbesartan								
10 min								
20 min								
30 min								
45 min								
60 min								
HCTZ								
10 min								
20 min								
30 min								
45 min								
60 min								

a. None evident
b. Percentage; mean and range.

6.4.4. Conclusions

6.4.4.1. Irbesartan

An appropriate dissolution method and medium has been established. The release rates of the 75, 150 and 300 mg tablets are similar in the three media tested. The 75, 150 and 300 mg tablets are compositionally proportional. Thus, a biowaiver is granted for the 75 and 150 mg tablets.

The proposed dissolution specifications for all strengths is % (Q) in 30 minutes. A more appropriate specification would be % (Q) in 20 minutes.

6.4.4.2. Irbesartan/HCTZ

An appropriate dissolution method and medium has been established. The release rates across batches are similar.

The proposed dissolution specifications for each component is ≥ % (Q) in 30 minutes. A more appropriate specification for the combination tablet would be ≥ % (Q) in 20 minutes of irbesartan, and ≥ % (Q) in 30 minutes for HCTZ.

6.5. Summary

6.5.1. Bioavailability/Bioequivalence

6.5.1.1. Absolute bioavailability

Irbesartan is rapidly absorbed when administered orally as determined in two independent studies[2]. The mean T_{max} for the oral solution was 0.45 hours. The mean T_{max} for the oral capsule formulation was 1.35 hours, which is approximately 3 times longer than for the oral solution. Oral bioavailability is slightly higher for the capsule formulation, 87% compared to 82% for the oral solution[3]. In CV131-053 the absolute bioavailability (F) was 61%; this is considerably less than that observed in study CV131-043 where F was 82% for a 50 mg oral solution. The sponsor does not have an explanation for this discrepancy. The total radioactivity is greater than that of irbesartan alone, suggesting the existence of metabolites. Irbesartan accounts for 80% of total plasma radioactivity. The majority of the remaining radioactivity (~6%) corresponds to plasma irbesartan glucuronide. Mass balance is shown in Table 13 below.

Table 13. Mass balance.

	% of dose in			% of dose in	
	Urine	Feces		Urine	Feces
Irbesartan	2	—	M5, M6, M7	—	16
M8	2	20	M4	—	6
M1	5	—	Unidentified	8	23
M3	3	—	Total	20	65

6.5.1.2. Bioequivalence

6.5.1.2.1. Irbesartan

The pivotal bioequivalence study[4] compared the clinical capsule formulation (3x100 mg) to the irbesartan 300 mg tablet (market). The two formulations are bioequivalent with respect to C_{max} (90% CI 1.03-1.19) and AUC (90% CI 0.94-1.10).

6.5.1.2.2. Irbesartan/HCTZ

The combination tablet (150/12.5 mg) irbesartan/HCTZ is bioequivalent to irbesartan (2x75 mg) capsules with HCTZ 12.5 mg tablets. The 90% CI for irbesartan were C_{max} (1.06-1.20) and AUC (0.96-1.06); the 90% CI for HCTZ were C_{max} (0.94-1.07) and AUC (0.90-1.04)[5].

The combination tablet (75/12.5 mg) irbesartan/HCTZ is bioequivalent to irbesartan (75 mg) capsules with HCTZ 12.5 mg tablets. The 90% CI for irbesartan were C_{max} (0.97-1.14) and AUC (0.92-1.01); the 90% CI for HCTZ were C_{max} (0.82-0.96) and AUC (0.88-1.02)[6].

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2. *CV131-043: The disposition and bioavailability of irbesartan in healthy male subjects after intravenous and oral administration of [14C] irbesartan in solution, and oral administration of irbesartan capsule.* on page 240, and *CV131-053: Mass balance and absolute bioavailability of irbesartan in healthy male subjects after 50 mg intravenous and 150 mg oral administration of [14C]-irbesartan solution.* on page 249.
3. CV131-043.
4. *CV131-062: A bioequivalence study comparing the intended 300 mg commercial tablet formulation of irbesartan to the reference 100 mg BMS capsule formulation.* on page 262.
5. *CV131-054: A bioequivalence study comparing a 150/12.5 mg irbesartan/hydrochlorothiazide combination tablet to 2 x 75 mg irbesartan capsules and a 12.5 mg hydrochlorothiazide tablet.* on page 251.
6. *CV131-067: A bioequivalence study comparing 75/12.5 mg irbesartan/hydrochlorothiazide combination tablet to a 75 mg irbesartan capsule and a 12.5 mg hydrochlorothiazide tablet.* on page 264.

6.5.2. Food effect

6.5.2.1. Irbesartan

The effect of food (FDA standard meal) on the absorption of irbesartan 300 mg tablets (market) as a single morning dose[7] showed no statistically significant differences in AUC, C_{max}, T_{max} or $T_{1/2}$. In a separate study[8], the T_{max} of irbesartan capsules (25 mg) was delayed by 30 minutes (fed). However, C_{max} and AUC were unchanged.

6.5.2.2. Irbesartan/HCTZ

Food had no clinically relevant effect on the bioavailability of irbesartan/HCTZ (150/12.5 mg) combination tablets. The C_{max} of HCTZ is 21% less when this dosage form is administered with a high fat meal[9].

6.5.3. Pharmacokinetics

The pharmacokinetics of irbesartan was evaluated in double-blind, placebo-controlled, single and multiple dose studies[10] with doses ranging from 5 to 900 mg. Steady-state concentrations were reached within 3 days with doses from 10 mg to 900 mg administered once daily. T_{max} ranged from 1.5 to 2 hours, and $T_{1/2}$ from 11 to 25 hours[11]. The accumulation index ranged from 1.13 to 1.26 for AUC; and 0.91 to 1.12 for C_{max} for irbesartan 150 to 900 mg[12]. Following iv administration the mean V_{ss} of irbesartan was 53 to 93 L, Cl_T ranged from 157 to 176 ml/min, Cl_R was 3 to 3.5 ml/min[13].

6.5.3.1. Protein binding

Protein binding was investigated in vitro by an equilibrium dialysis method. Irbesartan is primarily bound to albumin and α-acid glycoprotein. Protein binding was approximately 90% and was constant over a range from 0.01 to 50 μg/ml.

6.5.3.2. Red blood cell partitioning

An in vitro study showed that >90% of the whole blood radioactivity was recovered in the plasma samples. Ex vivo binding of irbesartan to the cellular component of human blood was found to be negligible[14].

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7. *CV131-056: The effect of a high-fat meal on the oral bioavailability of irbesartan in healthy male subjects.* on page 253.
8. *PPK 1690: Pharmacokinetic study in a single dose assessment of the food effect on the SR47436 pharmacokinetics in healthy volunteers.* on page 288.
9. *CV131-069: Effect of a high-fat meal on the oral bioavailability of irbesartan/hydrochlorothiazide combination tablets in healthy male subjects.* on page 266.
10. *CV131-045: Safety, tolerance, pharmacokinetics and pharmacodynamics of irbesartan following single and multiple 150 to 900 mg doses in healthy subjects.* on page 242, *TDR 1691: Tolerability assessment of SR47436 administered in repeated ascending doses to healthy volunteers.* on page 295. and *TDU 1693: Tolerability assessment of irbesartan administration single ascending doses to healthy volunteers* on page 301.
11. Studies CV131-045 and TDU 1691.
12. Study CV131-045.
13. *CV131-043: The disposition and bioavailability of irbesartan in healthy male subjects after intravenous and oral administration of [14C] irbesartan in solution, and oral administration of irbesartan capsule.* on page 240, and *CV131-053: Mass balance and absolute bioavailability of irbesartan in healthy male subjects after 50 mg intravenous and 150 mg oral administration of [14C]-irbesartan solution.* on page 249.
14. *CV131-053: Mass balance and absolute bioavailability of irbesartan in healthy male subjects after 50 mg intravenous and 150 mg oral administration of [14C]-irbesartan solution.* on page 249.

6.5.3.3. Metabolism

Eight metabolites have been identified for irbesartan, as shown in Figure 7 below[15]. These metabolites are primarily formed by

6.5.3.4. Dose and dosage form proportionality

AUC and C_{max} were linear and dose proportional up to 200 mg. At higher doses irbesartan was 20-30% less than dose proportional. This may be the result of saturation of absorption processes[16].

6.5.3.5. Special populations

6.5.3.5.1. Renal impairment

Studies PPK 2198[17] and CV131-011[18] examined the pharmacokinetics of irbesartan in renally impaired patients. PPK 2198 compared the pharmacokinetics of irbesartan (25 mg) in young and elderly subjects. AUC was >50% higher in elderly patients with 45<CrCl<60 mL/min as compared to young patients with CrCl>90 mL/min. In CV131-011 (100 mg x 8 days qd) the accumulation ratio showed an increasing trend from 1.14/1.16 in normal/mild-moderate subjects to 1.24/1.39 in severe/hemodialysis subjects. However, variability was too great to determine statistical significance. A dosing adjustment may be required in patients with severe renal impairment. Irbesartan is not removed by dialysis.

6.5.3.5.2. Hepatic impairment

In a single-dose, multiple-dose (300 mg x 7 days) study[19] in hepatic impaired patients the pharmacokinetics of irbesartan were not significantly different. The ratio (normal/impaired) for C_{max} and AUC was 1.2 and 1.3, respectively.

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15. *Metabolism of irbesartan (from pharmacologist's review).* on page 312.
16. *CV131-045: Safety, tolerance, pharmacokinetics and pharmacodynamics of irbesartan following single and multiple 150 to 900 mg doses in healthy subjects.* on page 242 and *TDR 1691: Tolerability assessment of SR47436 administered in repeated ascending doses to healthy volunteers.* on page 295.
17. *PPK 2198: Comparative pharmacokinetics of irbesartan in healthy young and elderly volunteers: single and repeated oral administration of 25 mg during 8 days.* on page 290.
18. *CV131-011: Pharmacokinetics of SR 47436 (Irbesartan) in subjects with renal impairment compared to subjects with normal renal function.* on page 156.
19. *CV131-014: Single and multiple dose pharmacokinetics and pharmacodynamics of irbesartan in subjects with hepatic cirrhosis compared to healthy subjects* on page 162.

6.5.3.5.3. Age	Study CV131-006[20] (single dose) and study PPK 2198[21] (multiple dose) compared the pharmacokinetics of irbesartan in the young and elderly at doses up to 150 mg. The AUC and C_{max} were 20 to 50% greater in the elderly. A dose adjustment may be required in the elderly.
6.5.3.5.4. Gender	Study CV131-006[22] in healthy subjects showed no statistically significant gender related effects, in both young and elderly groups. Study CV131-057[23] showed no gender differences in AUC, C_{max}, and $T_{1/2}$ in mild to moderate hypertensive subjects. However, clearance was greater in males. In study CV131-004[24], of mild to moderate hypertensives, females had a statistically significant greater AUC for both single and multiple dose administration compared to males. This difference may indicate the need for dose adjustment in females. Females also showed an increase in $T_{1/2}$ from single (9.2±3.2 hours) to multiple (22.5±17.1 hours) dosing.
6.5.3.5.5. Race	Under fasted conditions, after a single 300 mg dose of irbesartan blacks had a 20 to 25% higher AUC and $T_{1/2}$, while C_{max} was comparable to that of whites. The differences in AUC and $T_{1/2}$ are not thought to be clinically significant[25].
6.5.3.6. Drug Interactions	
6.5.3.6.1. HCTZ	There were no statistically significant differences in the pharmacokinetics of irbesartan alone and irbesartan administered with HCTZ. However, the pharmacodynamics of irbesartan, a decrease in SBP and DBP, and increases in plasma levels of angiotensin II and plasma renin activity are potentiated with the co-administration of HCTZ. There was no change in heart rate[26].
6.5.3.6.2. Warfarin	Irbesartan does not alter the pharmacodynamics (PTR-values) of warfarin[27].
6.5.3.6.3. Nifedipine	Concomitant nifedipine administration does not alter the steady-state pharmacokinetics of irbesartan[28].
6.5.3.6.4. Digoxin	Irbesartan (150 mg qd) shows no significant effect on the steady-state pharmacokinetics of digoxin[29].
6.5.4. Pharmacokinetics/pharmacodynamics	The sponsor did not establish a pharmacokinetic-pharmacodynamic relationship for irbesartan.
6.5.5. Assay	The sponsor used . The analytical validation was satisfactory.

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20. *CV131-006: The effects of age and gender on the pharmacokinetics of irbesartan in healthy subjects following a single 50 mg oral dose.* on page 153.
21. *PPK 2198: Comparative pharmacokinetics of irbesartan in healthy young and elderly volunteers: single and repeated oral administration of 25 mg during 8 days.* on page 290.
22. *CV131-006: The effects of age and gender on the pharmacokinetics of irbesartan in healthy subjects following a single 50 mg oral dose.* on page 153.
23. *CV131-057: Pharmacodynamics (effects on renin angiotensin system, renal function and blood pressure) and pharmacokinetics of irbesartan in subjects with mild-to-moderate hypertension.* on page 255.
24. *CV131-004: Pharmacokinetics and pharmacodynamics of irbesartan in female and male patients with mild-to-moderate essential hypertension.* on page 146.
25. *CV131-056: The effect of a high-fat meal on the oral bioavailability of irbesartan in healthy male subjects.* on page 253 and *CV131-062: A bioequivalence study comparing the intended 300 mg commercial tablet formulation of irbesartan to the reference 100 mg BMS capsule formulation.* on page 262.
26. *CV131-005: Pharmacokinetic and pharmacodynamics of irbesartan when coadministered with hydrochlorothiazide compared to when administered alone to patients with mild to moderate hypertension.* on page 151.
27. *CV131-019: A report on the effect of concomitant administration of irbesartan on the steady-state pharmacodynamics of warfarin.* on page 168.
28. *CV131-017: Effect of concomitant administration of nifedipine on the steady-state pharmacokinetics of irbesartan in healthy subjects.* on page 165.
29. *CV131-024: Effect of concomitant administration of irbesartan on the steady-state pharmacokinetics of digoxin in healthy male subjects* on page 170.
30. Table 7. *Assay validation for irbesartan.* on page 15.

6.5.6. Formulation All to-be-marketed tablets are compositionally proportional[31].

6.5.7. Dissolution The proposed dissolution method—
are acceptable; the specification of ≥ (Q) at 30 minutes is unacceptable. A more appropriate specification would be ≥ % (Q) at 20 minutes for irbesartan.

6.6. Recommendation

The Division of Pharmaceutical Evaluation I (DPEI) recommends the following:

- The proposed dissolution specifications for all strengths is ≥ % (Q) in 30 minutes. Because dissolution is % for all strengths at 20 minutes, a more appropriate specification would be ≥ % (Q) in 20 minutes for irbesartan.
- The proposed dissolution specifications for each component of the combination tablet is ≥ (Q) in 30 minutes. Dissolution of both components is % across batches. A more appropriate specification for the combination tablet would be ≥ % (Q) in 20 minutes of irbesartan, and ≥ % (Q) in 30 minutes for HCTZ.
- A biowaiver is granted for the 75 and 150 mg tablets. This waiver is based on dissolution profiles in three media and in view of the fact that the tablets are compositionally proportional.
- Labeling changes are recommended as shown in section 9 on page 94.

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[31] Table 8. *Composition of irbesartan tablets.* on page 16 and Table 9. *Composition of irbesartan/HCTZ tablets.* on page 16.

7. Integrated review of effectiveness

7.1. Mechanism of action

Numerous studies included measurements of angiotensin II, active renin, and aldosterone, and the effects of exogenous angiotensin II, as summarized in Table 14 below.

Table 14. Studies of mechanism of action.

	Review	Pop'n[a]	N
ACT 1967: Dose-finding study of irbesartan in patients with mild to moderate hypertension.	page 129	HTN	86
CV131-004: Pharmacokinetics and pharmacodynamics of irbesartan in female and male patients with mild-to-moderate essential hypertension.	page 146	HTN	38
CV131-011: Pharmacokinetics of SR 47436 (Irbesartan) in subjects with renal impairment compared to subjects with normal renal function.	page 156	NV RI	40
CV131-014: Single and multiple dose pharmacokinetics and pharmacodynamics of irbesartan in subjects with hepatic cirrhosis compared to healthy subjects	page 162	NV HI	20
CV131-057: Pharmacodynamics (effects on renin angiotensin system, renal function and blood pressure) and pharmacokinetics of irbesartan in subjects with mild-to-moderate hypertension.	page 255	HTN	24
PDY 1692: Assessment of the inhibition of pressor response to exogenous angiotensin II by irbesartan in normotensive human subjects.	page 268	NV	24
PDY 2201: Effect of SR47436 on renal haemodynamics and on glomerular permselectivity in healthy humans. Double blind, placebo-controlled, crossover trial of a single 50mg oral dose.	page 271	NV	12
PDY 2202: Hormonal profile and renal tubular effects of irbesartan in healthy volunteers after acute and repeated oral administration during 8 days of 10 or 50 mg.	page 274	NV	25
PDY 2203: Effects of irbesartan on blood pressure in healthy salt depleted normotensive male volunteers—exploration pilot study (single dose double-blind versus placebo dose ranging study)	page 277	NV	12
PDY 2204: Hormonal profile and hemodynamic effects of irbesartan in healthy volunteers.	page 280	NV	9
PDY 2278: Assessment of acute and chronic renal hemodynamics following treatment with an AII antagonist (irbesartan) or an ACEI (enalapril) in essential hypertensive patients.	page 283	HTN	21
PDY 2801: Assessment of the inhibition of pressor response to exogenous angiotensin II by irbesartan at single doses 75, 150, 300 mg in normotensive subjects.	page 285	NV	18
PPK 2198: Comparative pharmacokinetics of irbesartan in healthy young and elderly volunteers: single and repeated oral administration of 25 mg during 8 days.	page 290	NV	30
TDR 1691: Tolerability assessment of SR47436 administered in repeated ascending doses to healthy volunteers.	page 295	NV	41
TDU 1693: Tolerability assessment of irbesartan administration single ascending doses to healthy volunteers	page 301	NV	48

a. Population: HI=hepatic impaired; HTN=hypertensive; NV=normal volunteers; RI=renally impaired

7.1.1. Angiotensin II receptor antagonism

In study PDY 1692, exogenous angiotensin II produced a pressor response in normal volunteers. Irbesartan doses 5 to 100 mg antagonized the pressor effect of exogenous angiotensin II in a dose-dependent manner, as shown by the placebo-subtracted responses in Figure 8 below[1].

These doses, it will be shown, represent the foot to the middle of the dose-response curve for the antihypertensive action. The 50 and 100 mg doses were the smallest producing a detectable receptor antagonism at the once-daily inter-dosing interval; this is also consistent with data on antihypertensive effects. By themselves, the data do not rule out other mechanisms of action, but these data are entirely consistent with the animal studies of mechanism.

[1] Same as Figure 81. on page 270.

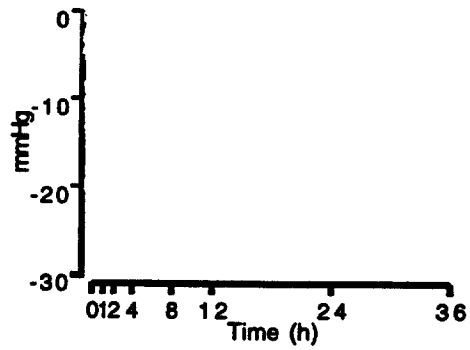

Figure 8. AII antagonism (PDY 1692).

In study PDY 1692, plasma levels of irbesartan were measured at some times corresponding to measurements of angiotensin II antagonism[2]. These data permit construction of hysteresis curves for angiotensin II receptor antagonism, as shown in Figure 9 below. These data demonstrate some clockwise hysteresis, indicating that some other process (diffusion of drug to receptor sites, formation of an active metabolite, or transduction of receptor-mediated effects into blood pressure effects) is rate determining.

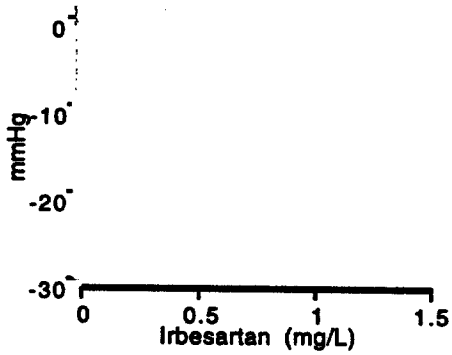

Figure 9. AII antagonism by plasma irbesartan (PDY 1692).

Somewhat longer-lasting angiotensin II antagonism was shown with higher doses (up to 300 mg) in Study PDY 2801.

7.1.2. Associated hormonal changes

Angiotensin II receptor antagonism would be expected to be associated with increases in renin and angiotensin II, and decreases in aldosterone. Such effects were sought in numerous clinical pharmacology studies. However, except in salt-depleted subjects[3], effects seen in normal volunteers were small and seldom statistically significant. Exceptional results were obtained in study TDR 1691, which showed the development of dose-related changes in angiotensin II and plasma renin activity over a 7-day course, as shown in Figure 10 below[4].

Effects on aldosterone were assessed in at least 6 studies, with varying results. No changes in urinary excretion of aldosterone were seen in normal volunteers in studies CV131-011, PDY 2202, and PDY 2204, while an increase in aldosterone was seen in normal volunteers in study CV131-014. Small decreases in aldosterone were seen in

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2. See Figure 80. on page 269.
3. Study PDY 2203.
4. Same as Figure 92. on page 298 and Figure 93. on page 299.

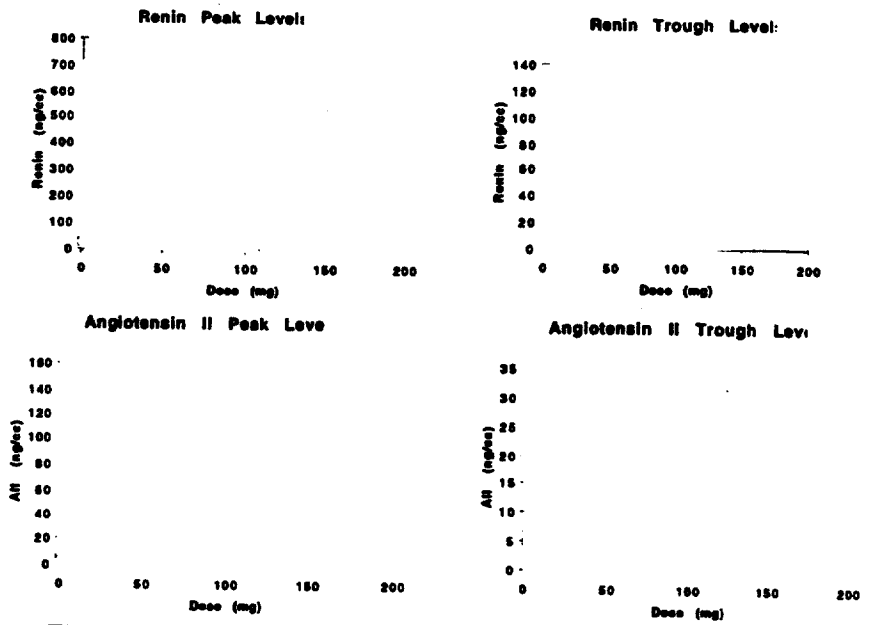

Figure 10. Peak and trough renin and angiotensin II levels (TDR 1691).

hypertensive subjects in studies CV131-004 and CV131-057, and in subjects with hepatic impairment in study CV131-014. Consistent changes in aldosterone also seem to be difficult to demonstrate with ACE inhibitors.

Study PDY 2204 also examined other hormonal effects in normal volunteers. No effect was demonstrated for plasma ACE, atrial natriuretic factor, or antidiuretic hormone.

7.1.3. Renal effects

In study PDY 2201, normal volunteers were challenged with exogenous angiotensin II. The observed effects were increases in filtration fraction and renal vascular resistance, and decreases in glomerular filtration rate, effective renal plasma flow, and urinary excretion of sodium and uric acid. These effects were somewhat attenuated by concomitant administration of irbesartan 50 mg. A similar study (PDY 2202), but with no angiotensin II challenge, contributed little.

Study PDY 2278 was an enalapril-controlled study in hypertensive subjects. It found no differences between groups in effects on glomerular filtration rate, renal plasma flow, or renal vascular resistance.

7.2. Antihypertensive effects

7.2.1. Monotherapy

7.2.1.1. Dose-response

Studies CV131-002[5], CV131-025[6], and CV131-050[7] were all randomized, parallel, placebo-controlled, multi-center studies in subjects with uncomplicated moderate hypertension. Among these studies, doses from 1 to 900 mg once daily were studied. Trough baseline- and placebo-subtracted dose-response data from these studies are shown in Figure 11 below.

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5. *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).* on page 138.
6. *CV131-025: Dose ranging study II: a multicenter trial of the antihypertensive activity and safety of 100 mg, 200 mg and 300mg irbesartan in mild-to-moderate hypertension.* on page 172.
7. *CV131-050: A multicenter, 8 week study of the antihypertensive activity, tolerability, and safety of irbesartan in subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg).* on page 246.

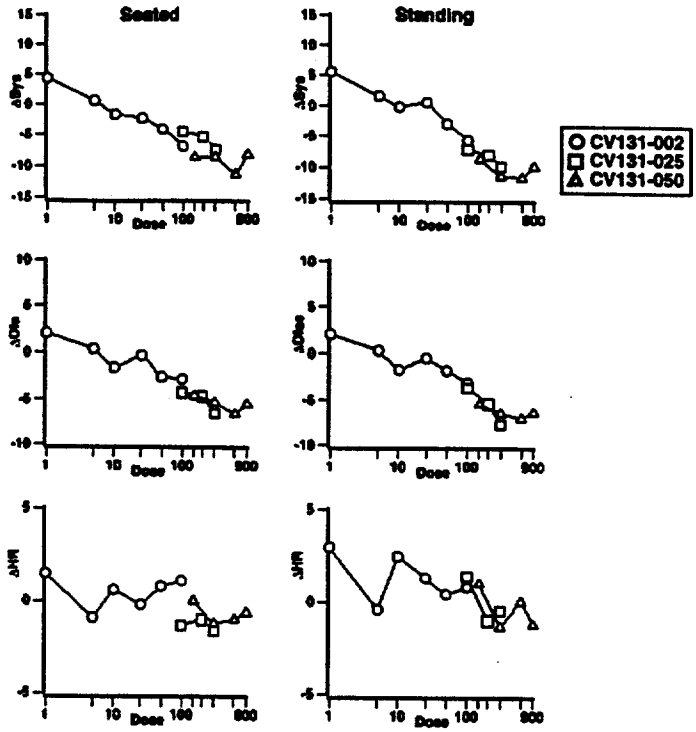

Figure 11. Dose-response data from parallel fixed-dose studies.

Dose-related effects were seen for seated and standing systolic and diastolic pressures. These results suggest that doses above 25 mg are active, about half of the maximum effect on blood pressure is obtained with a 100-mg dose, and doses above 300 mg are of no additional benefit. No dose-related effects were seen on seated or standing heart rate.

7.2.1.2. Dependence on plasma levels

Dependence of antihypertensive effects on plasma irbesartan levels was not well studied. The reviewers constructed hysteresis curves from a relatively low-dose trial in hypertensive subjects, as shown in Figure 12 below[8].

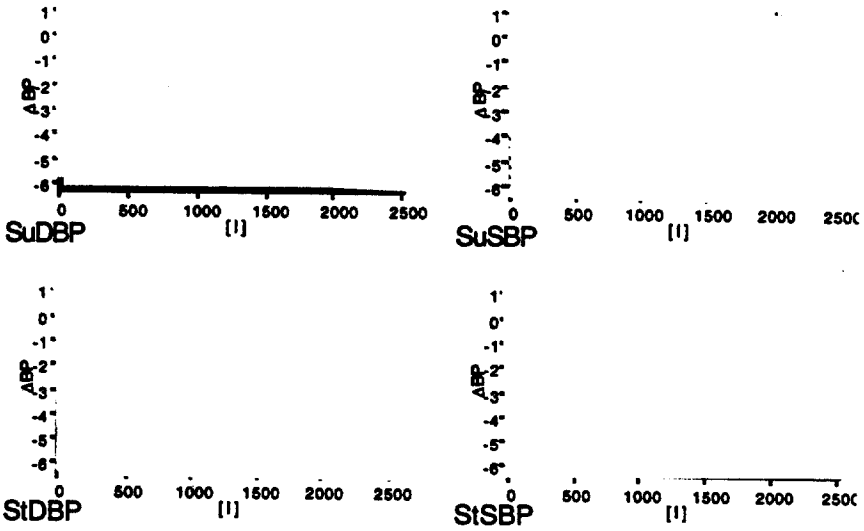

Figure 12. Antihypertensive effects by plasma irbesartan level (ACT 1967).

The data are consistent with there being an active metabolite of irbesartan, but data from a higher dose would have been helpful. For comparison, the hysteresis in Figure 12. can be compared with that for the intravenously administered active metabolite for losartan, shown in Figure 13 below. The amount of hysteresis in irbesartan is certainly no more than in this case, suggesting that some process with a fairly long time constant is actually rate limiting, but why, then, one obtains prompt pressor effects to exogenous angiotensin II remains unexplained.

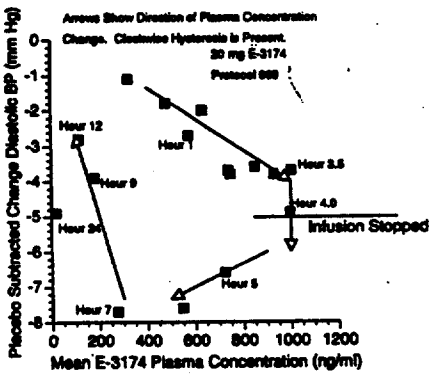

Figure 13. Antihypertensive effect by plasma level for the active metabolite of losartan.

7.2.1.3. Time course of effect

Several different time courses are noteworthy. The time course of antihypertensive effects in hours after a dose, and a comparison of once-daily vs. twice daily dosing give some information about the appropriate dosing interval. The time course of blood pressure changes in days or weeks from the onset of treatment provide some information about the how quickly a patient should have dosing adjustments to achieve the goals of treatment.

7.2.1.3.1. Time course of effect following a dose

Studies ACT 1967[9] and CV131-030[10] were randomized, double-blind, parallel, fixed dose studies with ABPM. ACT 1967 was a 7-day study (for which there is no figure

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8. Same as Figure 26. on page 133.
9. *ACT 1967: Dose-finding study of irbesartan in patients with mild to moderate hypertension.* on page 129.
10. *CV131-030: The antihypertensive activity of irbesartan as determined by 24-hour ambulatory blood pressure monitoring.* on page 195.

showing baseline- and placebo-subtracted treatment effects). Figure 14 below[11] shows baseline- and placebo-subtracted ABPM data from week 8 of CV131-030.

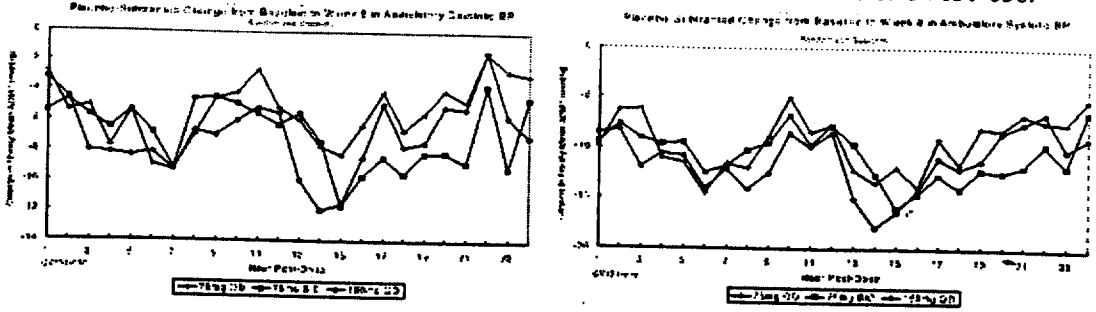

Figure 14. Baseline- and placebo-subtracted ABPM data (CV131-030).

With morning dosing and peak plasma concentrations a few hours later, the expected time of peak effects of blood pressure would be late morning. In fact, near minimum drug effects are observed then, with peak activity in the evening[12].

7.2.1.3.2. **Once-daily vs twice-daily dosing**

Once-daily and twice-daily dosing were compared in only one trial. Study CV131-030[13] was a randomized, parallel, fixed-dose study in which subjects received placebo or irbesartan 75 mg qd, 150 mg qd, or 75 mg bid for 8 weeks. Hourly averaged diastolic pressures from week 8 are shown in Figure 15 below[14]. Mean changes (differences from baseline and placebo) in ambulatory diastolic pressure at trough were -6, -8, and -10 mmHg, on 75 mg qd, 150 mg qd, or 75 mg, respectively. The placebo-adjusted trough:peak ratios were 36%, 74%, and 66%, respectively.

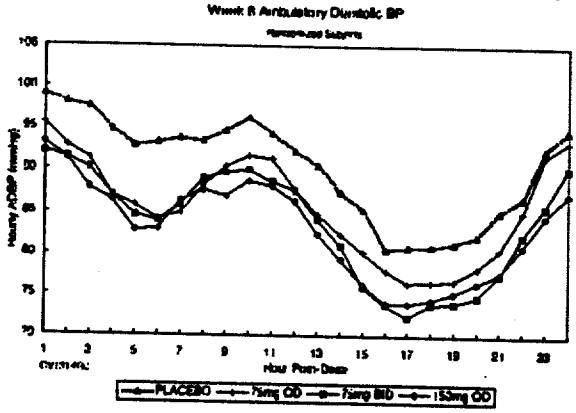

Figure 15. Week 8 hourly-averaged ABPM diastolic pressure (CV131-030).

Despite the observation that trough:peak ratios for once-daily dosing were, in this and other studies, significantly less than unity, the results of this study provide little empirical evidence of additional antihypertensive effect achieved by twice daily dosing.

11. Same as Figure 52. on page 199.
12. The peak drug effect with the combination of irbesartan plus HCTZ occurs later still; see Figure 22. *ABPM systolic and diastolic blood pressure at week 8 (CV131-039).* on page 37.
13. *CV131-030: The antihypertensive activity of irbesartan as determined by 24-hour ambulatory blood pressure monitoring.* on page 195.
14. Same as Figure 51. on page 199.

7.2.1.3.3. Time course of effect with repetitive dosing

Study CV131-025[15] was a randomized, double-blind, parallel, placebo-controlled, fixed-dose study of irbesartan 100, 200, and 300 mg, probably near the upper limit of useful doses. Time course data from that study are shown in Figure 16 below[16].

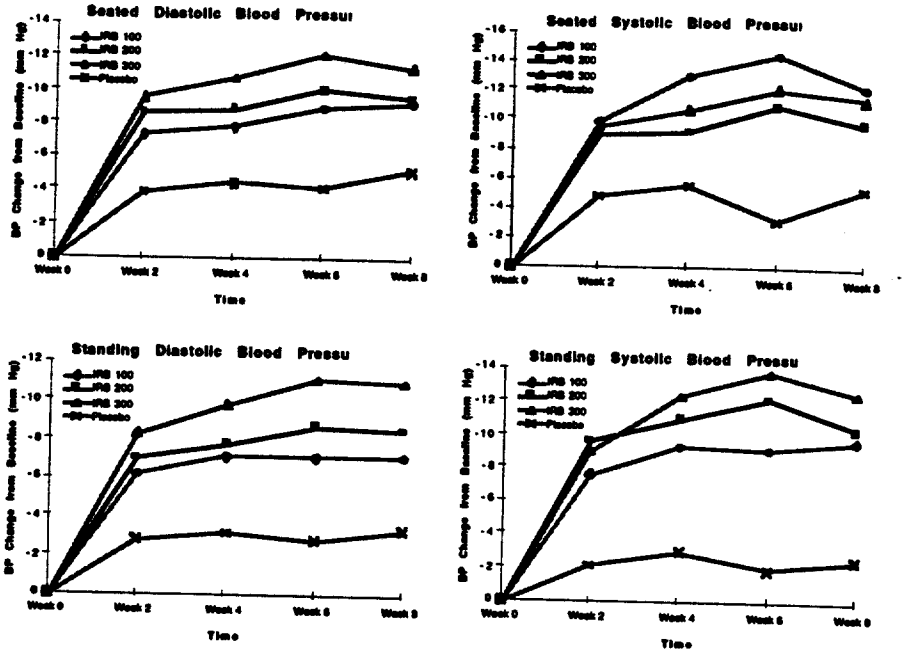

Figure 16. Time course of seated and standing blood pressure (CV131-025).

More than half of the placebo-subtracted treatment effect at theses doses in manifest by 2 weeks.

7.2.1.3.4. Long-term open-label experience

Long-term experience with irbesartan was summarized in 2 reports, covering open-label phases of controlled monotherapy studies[17] and studies in combination with HCTZ[18]. This long-term experience was all uncontrolled, open-label, and permitted use of other treatments (sustained release nifedipine and atenolol) as necessary to achieve blood pressure control goals. Consequently, this experience is of little value in determining long-term effects on blood pressure.

Withdrawal for lack of efficacy was not a prominent feature of the long-term experience, but most subjects who remained in the studies required other agents for blood pressure control.

7.2.1.3.5. Time course of recovery after repetitive dosing

When some of the major studies of effectiveness were reviewed, the sponsor was encouraged to include a double-blind, randomized, placebo-withdrawal phase at the end of 6 or 12 months of open-label treatment. The sponsor elected not to do such study, so what data there are to address the time course of recovery after repetitive

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15. *CV131-025: Dose ranging study II: a multicenter trial of the antihypertensive activity and safety of 100 mg, 200 mg and 300mg irbesartan in mild-to-moderate hypertension.* on page 172.
16. Same as Figure 44. on page 176.
17. *Long-term monotherapy: Six multicenter trials evaluating the long term antihypertensive activity, tolerability and safety of open label irbesartan monotherapy (CV131-002, CV131-025, CV131-029, CV131-027, CV131-028, and CV131-031).* on page 304.
18. *Long-term combination therapy: Two multicenter trials evaluating the long term antihypertensive activity, tolerability, and safety of open label irbesartan with hydrochlorothiazide (CV131-037, CV131-038).* on page 308.

dosing comes from the withdrawal phase at the end of one short-term controlled study[19]. Other controlled studies led directly into open-label phases.

This study was a parallel, fixed-dose, study of the low end of the dose-response relationship (1 to 100 mg). For the 100-mg group, about 2/3 of the baseline- and placebo-subtracted effect on blood pressure was present 1 week after withdrawal.

7.2.1.4. Subgroup analyses

7.2.1.4.1. Analysis by race

Figure 17 below is an analysis of dose-response broken down by race (Caucasian vs all non-Caucasian), but otherwise similar to Figure 11.

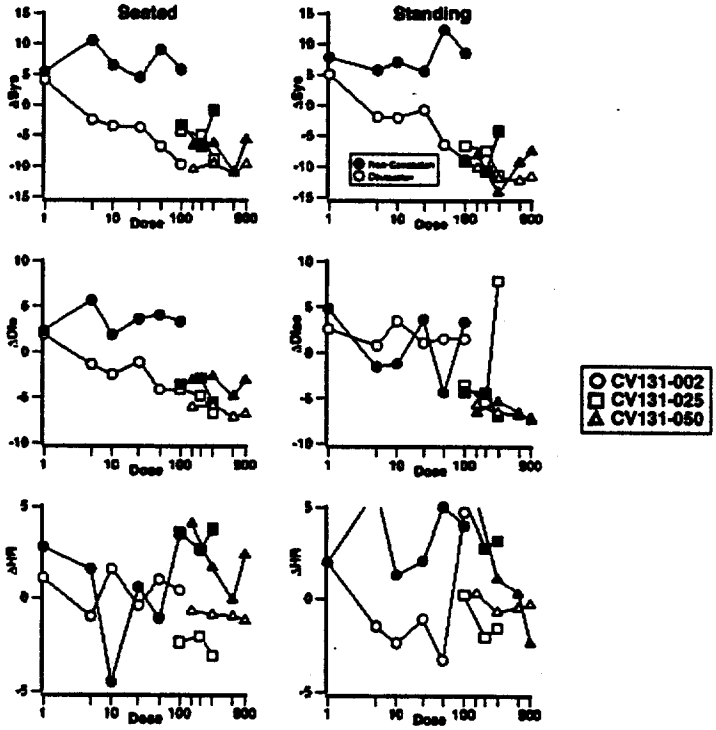

Figure 17. Dose-response by race in parallel fixed-dose studies.

The low end of the dose-response curves for studies CV131-025 (100 mg) and CV131-050 (150 mg) reveal no material difference between Caucasians and non-Caucasians. The results suggest that the low-dose study (CV131-002) was an outlier with respect to this subgroup analysis.

7.2.1.4.2. Analysis by sex

Figure 18 below shows the dose-response data in parallel, fixed-dose studies analyzed by sex. There is no evidence of a clinically significant difference in antihypertensive effects in males and females.

[19] *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).* on page 138.

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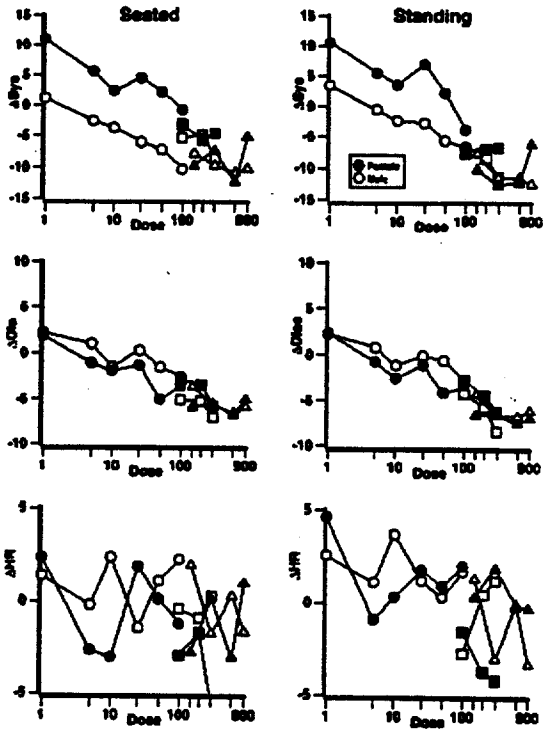

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Figure 18. Dose-response by sex in parallel fixed-dose studies.

7.2.1.4.3. Analysis by age

Figure 19 below shows the dose-response data in parallel, fixed-dose studies analyzed by age (using age 65 as a cut point). There is no evidence of a clinically significant difference in antihypertensive effects in the two age groups.

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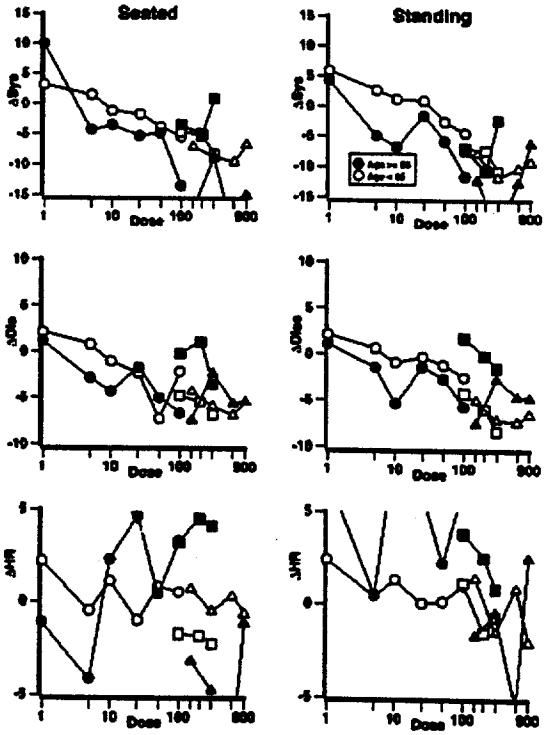

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Figure 19. Dose-response by age in parallel fixed-dose studies.

7.2.2. Combination with HCTZ

7.2.2.1. Dose-response surfaces

CV131-037[20] and CV131-038[21] were randomized, double-blind, parallel, placebo-controlled, fixed-dose, factorial studies of irbesartan plus HCTZ. CV131-037 utilized irbesartan 37.5, 100, and 300 mg and HCTZ 6.25, 12.5, and 25 mg (a total of 16 arms) and approximately 40 subjects per arm followed for 8 weeks. CV131-038 utilized irbesartan 75 and 150 mg and HCTZ 12.5 mg (a total of 6 arms) and approximately 135 subjects per arm followed for 12 weeks.

The response surfaces for the LOCF analyses of seated systolic and diastolic pressures in CV131-037 are shown in Figure 20 below[22]. When analyzed by fitting a polynomial to the response surface for seated diastolic pressure, there was a statistically significant contribution of both agents to the antihypertensive effects of the combination and a global test[23] was highly statistically significant.

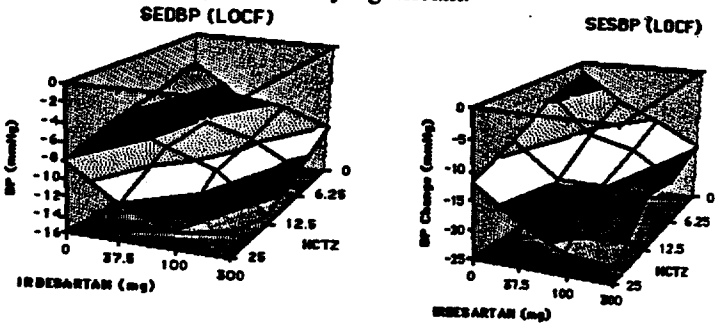

Figure 20. Response surface for the change in blood pressure (CV131-037).

Statistically significant effects were found for contributions of irbesartan and HCTZ to seated systolic pressure, standing diastolic pressure, and standing systolic pressure except for the effect of irbesartan on seated systolic pressure. Statistically significant effects were found for contributions of irbesartan and HCTZ to seated diastolic pressure in subgroups of males and females. No such analysis was performed for race because of the small size of the treatment groups and the low (5 to 18%) number of non-Caucasians studied. No treatment effects were observed for seated or standing heart rate.

Although not formally analyzed by fitting a polynomial to the response surfaces, the response rates for proportion of subjects with seated diastolic pressure (a) reduced to <90 mmHg, or (b) either reduced to <90 mmHg or reduced by 10 mmHg ordered in a manner highly consistent with both agents contributing to treatment effects, as shown in Figure 21 below[24].

Study CV131-038 was not analyzed by the polynomial technique, but statistically significant effects on blood pressure were observed with a reasonable ordering of treatment effects (change from baseline and placebo in seated diastolic pressure) by dose: irbesartan 150 mg plus HCTZ 12.5 mg > irbesartan 150 mg > irbesartan 75 mg plus HCTZ 12.5 mg > irbesartan 75 mg.

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20. *CV131-037: Factorial trial of the efficacy and safety of multiple dosages of irbesartan and hydrochlorothiazide in mild-to-moderate hypertension.* on page 213.
21. *CV131-038: Double-blind, placebo-controlled, comparison of the combination of irbesartan and hydrochlorothiazide versus individual components in mild-to-moderate hypertension.* on page 222.
22. Same as Figure 54. on page 217.
23. Hung J, Chi G, Lipicky RL, *Biometrics* 49:85-94; 1993.
24. Same as Figure 56. on page 219.

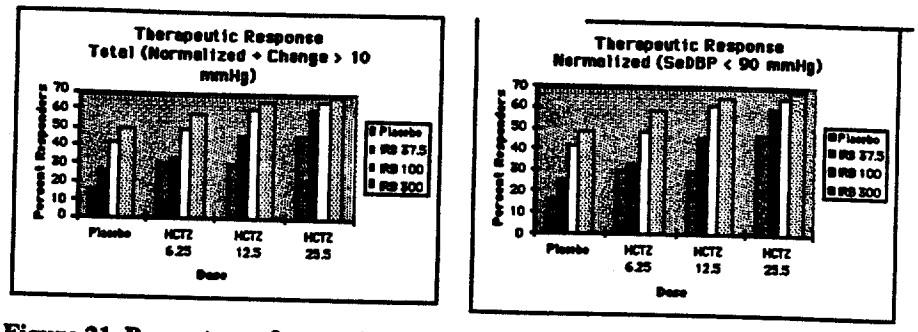

Figure 21. Percentage of normalized subjects and total responders (CV131-037).

Further evidence of the benefit of the combination comes from Study CV131-040[25], a trial enrolling subjects whose blood pressure was not adequately controlled on HCTZ 25 mg, randomizing them to placebo or irbesartan 75 mg for 12 weeks. Subjects still not adequately controlled at 6 weeks had their study drug dose doubled; about 1/3 of the irbesartan group went to the higher dose. The magnitude of treatment effect attributable to addition of irbesartan was -14/-11 mmHg, considerably larger than the estimated effect size for these irbesartan doses alone.

7.2.2.2. Dosing equivalence

The sponsor's proposed label for the combination product suggests its use might be to allow a patient experiencing dose-related side effects on HCTZ alone to back off the dose and add irbesartan. The specific proposal is that HCTZ 25 mg has about the same antihypertensive effect as does the combination of irbesartan 150 mg plus HCTZ 12.5 mg. In fact, none of the sponsor's clinical trials contain such a comparison. The reviewers took as the best estimate of the dose-response properties of the combination the fit to the surface shown above in Figure 20. The model and the fit parameters are described in the study report for Study CV131-037. Thus, the reviewers solved, by algebraic means, for the dose of irbesartan to pair with HCTZ 12.5 mg to give the same antihypertensive effect as HCTZ 25 mg, and used all of the data in Study CV131-037 to make the estimate. For seated diastolic pressure, the appropriate dose of irbesartan was 40 mg[26]. For seated systolic pressure, the analysis indicates there is no irbesartan dose capable of compensating for the reduction in HCTZ (both roots are imaginary), but that is probably a result of the poor fit of the model; inspection suggests that 40 mg is not a bad estimate for the irbesartan dose for effects on seated systolic pressure as well.

7.2.2.3. Analysis by race

Study CV131-038 also enrolled more non-Caucasian subjects (8 to 14% Black and 14 to 23% other) than did CV131-037. The treatment effects by race are shown in Table 15 below[27]. The results are consistent with there being smaller treatment effects in Blacks, even with treatment with irbesartan plus HCTZ, than in Caucasians or other races.

[25] *CV131-040: The efficacy and safety of irbesartan added to hydrochlorothiazide for the treatment of hypertension in subjects nonresponsive to hydrochlorothiazide alone.* on page 234.

[26] The model is quadratic with respect to irbesartan, so there is a second root for the irbesartan dose, but the other root (416 mg) lies outside the dose range studied in this trial.

[27] Reorganized from Table 229. on page 224.

Table 15. Efficacy data by race at week 12 (CV131-038).

		Irbesartan 0 mg		Irbesartan 75 mg		Irbesartan 150 mg	
	HCTZ	0	12.5	0	12.5	0	12.5
N	All	135	137	138	134	136	135
	White	99	102	93	88	98	100
	Black	16	16	13	19	14	11
	Others	26	19	32	27	24	24
SeDBP	All	-5.1	-8.0	-8.2	-11.2	-9.7	-11.6
	White	-3.5	-7.4	-8.4	-10.5	-9.7	-12.1
	Black	-5.2	-8.5	-4.9	-11.6	-7.2	-9.5
	Others	-9.9	-10.7	-9.2	-13.3	-10.7	-10.8
StDBP	All	-3.4	-5.8	-7.5	-10.4	-8.4	-11.1
	White	-2.5	-5.3	-8.2	-9.3	-8.3	-11.4
	Black	-3.3	-5.8	-5.3	-11.1	-5.9	-8.9
	Others	-5.9	-8.7	-7.3	-14.5	-10.1	-12.9
SeSBP	All	-3.3	-8.7	-7.6	-15.3	-12.3	-16.5
	White	-2.1	-7.8	-7.6	-15.1	-12.2	-17.3
	Black	-3.0	-10.1	-8.4	-13.6	-10.1	-7.7
	Others	-6.1	-11.9	-7.1	-17.1	-13.8	-17.2
StSBP	All	-2.5	-8.2	-8.2	-14.3	-11.5	-15.6
	White	-2.2	-7.0	-8.5	-13.8	-11.5	-16.1
	Black	-0.3	-9.6	-9.6	-12.8	-9.4	-9.5
	Others	-4.8	-11.9	-6.2	-17.8	-13.4	-17.8

7.2.2.4. Time course of effect

Duration of effect of the irbesartan/HCTZ combination through the once-daily interdosing interval was amply demonstrated in Study CV131-038[28], a parallel, fixed-dose comparison of placebo, irbesartan 75 mg plus HCTZ 12.5 mg, and irbesartan 150 mg plus HCTZ 12.5 mg, with about 60 subjects per group, by ABPM at the beginning and end of an 8-week treatment period. The placebo-subtracted ABPM results are shown in Figure 22 below[29]. Of note, the apparent peak drug effect (not just the lowest blood

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[28] *CV131-039: The antihypertensive efficacy of the combination of irbesartan and hydrochlorothiazide as determined by 24-hour ambulatory blood pressure monitoring.* on page 227.
[29] Same as Figure 61. on page 231.

pressure) occurred about 17 hours after morning dosing, probably sometime after midnight, somewhat later than the peak effect was seen with irbesartan alone[30].

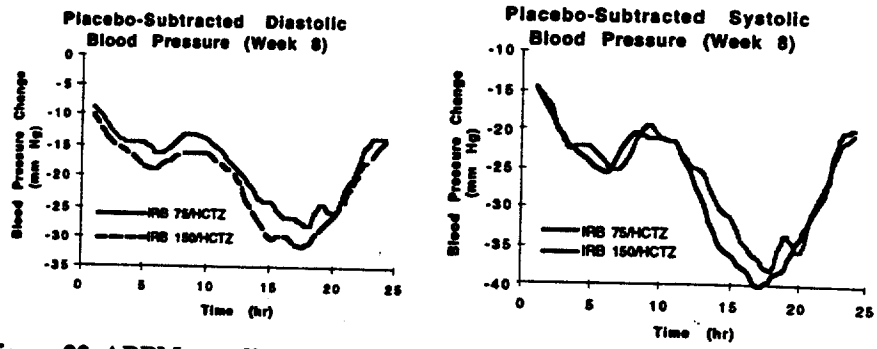

Figure 22. ABPM systolic and diastolic blood pressure at week 8 (CV131-039).

7.2.3. Active-controlled studies

Eight hundred and three subjects participated in 4 actively controlled studies of irbesartan, as shown in Table 16 below. These studies had double-blind treatment periods of 12 or 24 weeks.

Table 16. Actively-controlled clinical trials of effectiveness.

	Review	Design[a]	Weeks	Doses mg qd	N	Percentage		
						Female	>65 y	Black
CV131-028: Multicenter, randomized, double-blind comparison of irbesartan and enalapril for treatment of hypertension.	page 184	R,DB,AC,II	12	75, 150, 300	202	46-51	28-30	0-1
CV131-032: The efficacy and safety of the angiotensin II receptor antagonist irbesartan in the treatment of patients with severe hypertension.	page 207	R,DB,AC,II	12	150, 300	182	37-44	10-11	31-33
CV131-027: Multicenter, randomized, double-blind comparison of irbesartan and atenolol for treatment of hypertension.	page 179	R,DB,AC,II	24	75, 150	231	38-45	18-23	0
CV131-031: Multicenter, randomized, double-blind comparison of irbesartan and amlodipine for treatment of hypertension in the elderly.	page 203	R,DB,AC,II	24	75, 150	188	54-56	100	0-13

a. R=randomized; DB=double-blind; AC=active-control; II=parallel.

7.2.3.1. Comparison with atenolol

Study CV131-027 randomized subjects with mild-to-moderate hypertension to either atenolol 50 mg or irbesartan 75 mg. The dose of either agent could be doubled after 6 weeks. In the last 12 weeks, subjects not meeting blood pressure control criteria had HCTZ 25 mg and finally long-acting nifedipine added. A comparable number of subjects required some up-titration step. There was no difference between groups with respect to the degree of blood pressure control achieved.

7.2.3.2. Comparisons with enalapril

Study CV131-028 randomized subjects with mild-to-moderate hypertension to either enalapril 10 mg or irbesartan 75 mg. The dose of either agent could be doubled after 4 weeks, and then doubled again at 8 weeks, as necessary to achieve blood pressure control criteria. There was no difference between groups with respect to the degree of blood pressure control achieved.

A second study, CV131-032) randomized subjects with severe hypertension (SeDBP 115 to 130 mmHg) to enalapril 20 mg or irbesartan 150 mg. The dose could be doubled after 1 or 2 weeks, and, beginning at 4 weeks, HCTZ 25 mg, long-acting nifedipine 30 to 60 mg, and finally atenolol 50 to 100 mg could be added as needed to meet blood pressure control criteria. Fewer than 10% of subjects in either group were controlled on either agent alone; most subjects required treatment using all 4 agents.

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30. Compare with ABPM records for irbesartan alone, Figure 14. *Baseline- and placebo-subtracted ABPM data (CV131-030).* on page 30 and Figure 15. *Week 8 hourly-averaged ABPM diastolic pressure (CV131-030).* on page 30.

There was no difference between groups with respect to the degree of blood pressure control achieved.

7.2.3.3. Comparison with amlodipine

Study CV131-031 randomized subjects with mild-to-moderate hypertension to amlodipine 5 mg or irbesartan 75 mg. The dose of either agent could be doubled at 6 weeks, HCTZ could be added at 12 weeks, and atenolol 50 mg could be added at 20 weeks, as necessary to meet blood pressure control criteria. Significantly better antihypertensive effects were obtained at week 12 (prior to introduction of additional agents) in the amlodipine group.

Both comparisons with enalapril, studies CV131-028 and CV131-032, permitted titration to what is probably the highest useful dose of irbesartan (300 mg), but neither of these permitted twice daily use of enalapril. The other two studies, CV131-027 (atenolol) and CV131-031 (amlodipine), failed to utilize the full dose range of irbesartan, but they did use the highest recommended doses for the control agents.

No study was designed to show equivalence and no study demonstrated superiority of irbesartan. The sponsor seeks no claim derived from these actively controlled studies.

7.3. Summary

7.3.1. Mechanism of action

The clinical studies provide little evidence of a mechanism of action. Irbesartan antagonizes the pressor response to exogenous angiotensin II, but no clinical data shows that the antagonism takes place at the angiotensin II receptor.

There is hysteresis in the relationship between blood pressure effects and plasma levels of irbesartan, whether measured as antihypertensive activity or as antagonism of effects of exogenous angiotensin II. One possible explanation for the hysteresis is the formation of a more active metabolite.

7.3.2. Dose-response

The sponsor conducted parallel, fixed-dose studies covering a range of doses from 1 to 900 mg in subjects with mild-to-moderate hypertension. Population mean baseline- and placebo-subtracted effects are consistent with half-maximum effects at about 200 mg, little effect of doses below 100 mg, and little additional effect on blood pressure for doses above 300 mg.

These same trials included reasonable numbers of females, non-Caucasians, and people over age 65. However, sub-group dose-response analyses across studies were difficult to interpret. At best, such analyses provided no compelling evidence of an effect of age, gender, or race, but they can scarcely be said to have ruled out a clinically significant effect, either.

7.3.3. Time course of effects

Once-daily dosing with irbesartan produced antihypertensive effects which peak a few hours after dosing and have about 50% of the peak effect at 24 hours. One study compared dosing at 150 mg q.d. with 75 mg b.i.d., and found very similar effects on ambulatory blood pressure. There is a substantial clockwise hysteresis in the relationship between plasma levels of irbesartan and either antihypertensive effects or antagonism of pressor effects of angiotensin II.

With repetitive dosing, most of the population mean[31] placebo-subtracted antihypertensive effect of irbesartan is manifest at 2 weeks, making this a reasonable lower limit for the time between titration steps. Fixed-dose, placebo-controlled studies all lasted 8 weeks; there are no useful data pertaining to maintenance of antihypertensive effects for longer periods. Following repetitive dosing, about half of the placebo-subtracted antihypertensive effect of irbesartan remains at 1 week.

7.3.4. Use with HCTZ

Placebo-controlled 4x4-arm and 3x2-arm factorial trials with HCTZ clearly demonstrated antihypertensive contributions of both agents and the superiority of the

[31] One would expect individuals to be reach steady-state at least this quickly.

combination to either component alone. The data are consistent with antihypertensive effects of HCTZ and irbesartan being simply additive.

8. Integrated review of safety

8.1. Methodology

8.1.1. Deaths

For each death reported by the sponsor, the sponsor's narrative summary was compared with the case report form. The case report form was combed for indications of drug-relatedness of the immediate cause of death or associated problems. Deaths are summarized in section 8.2 on page 43, under the body system identified by the reviewers as most appropriate.

8.1.2. Serious adverse events

The sponsor identified serious adverse events as those that were fatal, life-threatening, permanently disabling, resulted in or prolonged hospitalization, associated with congenital anomaly, cancerous, or resulted from overdose of study drug. These events were allocated to one or more body systems and tabulated by appearance during double-blind or long-term phases, by sub-category of event, by use of irbesartan alone or with HCTZ, and by dose. Events plausibly attributable to study drug were tabulated separately from those for which no attribution is suspected.

The cited experience is from trials in subjects with hypertension, heart failure, or diabetic nephropathy, where the blind has been broken, and, because few events have any likelihood of being treatment-related and no events happened with enough frequency to make it possible to detect a safety concern by comparison of rates in control and treatment groups, it only includes experiences of subjects receiving irbesartan.

8.1.3. Withdrawals and other significant adverse events

The sponsor identified subjects withdrawn for adverse events. In some cases, the reviewers reassigned cases as serious adverse events. Subjects withdrawn for adverse events were allocated to one or more body system categories and tabulated by phase of study, use of irbesartan alone or with HCTZ, and by dose. Events plausibly attributable to study drug were tabulated separately from those for which the reviewers judged unlikely to be drug-related. In either case, the investigator's assessment of attribution was usually noted.

As with serious adverse events, the tables list only cases on active treatment. Events considered serious are not repeated in the tables of withdrawals.

8.1.3.1. Overall profile of withdrawals

Withdrawals were characterized by the primary associated event, as identified by the sponsor. The reviewers made no attempt to characterize other adverse events occurring in this sub-group. Nor was any attempt made to recategorize the causes for withdrawal.

8.1.3.2. Adverse events associated with withdrawal

Adverse events associated with withdrawal were analyzed separately for the double-blind and open-label periods, and for irbesartan alone (including appropriate arms of combination therapy trials) and irbesartan plus HCTZ.

8.1.3.3. Other significant adverse events

Common adverse events were analyzed separately for the double-blind and open-label periods, and for irbesartan alone (including appropriate arms of combination therapy trials) and irbesartan plus HCTZ.

In double-blind trials, the reviewers, working with the electronic datasets, identified unique 'preferred term entries' and made decisions about appropriate wording and categorization by body system. Some terms were combined and some were shifted from one body system category to another. The tabular summaries of adverse events during double-blind periods were prepared as a count of events (as opposed to subjects with events) divided by the number of subjects at risk and expressed as a percentage. The one b.i.d. dosing group was lumped with the subjects from the same total daily dose. A column allocated to event rates for any dose of irbesartan was produced from the unweighted averages of the various dose groups. The tables only show events for which the average on-treatment rate was >0.15% in studies of irbesartan alone or >0.35% in studies of irbesartan plus HCTZ. While in some cases adverse event terms were grouped together, no overall grouped event rate was calculated because of the difficulty in ascertaining unique subjects with a qualified event.

Open-label adverse events were characterized in a similar manner, but the rates are expressed as the number of events per 1000 years of exposure, rather than per subjects exposed.

The reviewers' estimated incidence rates for common events in open-label studies included only the experience documented in the original NDA submission.

8.1.4. Other search strategies

Adverse events were reviewed on case report forms for deaths and withdrawals.

8.1.5. Adverse event incidence

8.1.5.1. Approach to eliciting adverse events in the development program

Protocols all contained provision for the periodic ascertainment of adverse events from subjects through non-directive questioning. There is no reason to suspect bias or inadequate reporting of adverse events with this methodology.

8.1.5.2. Appropriateness of adverse event categorization and preferred terms

Rates for common adverse events were determined solely by the sponsor's categorization. There is, therefore, some possibility that some events were scattered among terms allocated, perhaps inappropriately, to multiple body systems. Little effort was spent by the reviewers to search the safety data systematically for such abuses. Categorization of events by body system and by likelihood of being related to study drug was performed by the reviewers. The resulting data are similar to common adverse events in other members of the class.

8.1.5.3. Identifying common and drug-related adverse events

Common adverse events in placebo-controlled studies were derived from the experience available electronically with the original submission.

Common adverse events in open-label extensions were tabulated by the sponsor in the 120-day safety update, by use of irbesartan monotherapy or irbesartan with HCTZ. The reviewers tabular summaries of common adverse events are shown as raw incidence rates (subjects with any reported event divided by the number of subjects exposed) and as rates adjusted for exposure (subjects with events per 1000 subject-years).

8.1.5.4. Additional analyses

No additional analyses of adverse events were performed.

8.1.6. Laboratory findings

8.1.6.1. Extent of laboratory testing

Clinical chemistry, hematology, urinalysis, and ECG were all routinely performed at the beginning and end of blinded treatment periods in major studies. Testing was also performed at follow-up visits during open-label studies. This level of monitoring is considered adequate for a drug of this class indicated for use in this population.

8.1.6.2. Selection of studies and analyses for drug-control comparisons

While serious event-related analyses covered all trial experience, analyses of trends in laboratory data focussed on previously identified collections of double-blind. placebo-controlled parallel-group studies of irbesartan alone and of irbesartan plus HCTZ.

8.1.6.3. Standard analyses

8.1.6.3.1. Analyses focussed on central tendency and outliers

Laboratory data were screened by graphical comparison of baseline and end point values, using a graphical tool written for S-plus. Figure 23 below is an example of such a plot, made from serum potassium data in monotherapy studies. Baseline (x) and end point (y) axes are scaled the same to encompass all of the data, so that a reference "no change" line can be drawn at 45°. Along the left and top are drawn kernel density functions (which can be treated as if they were smoothed histograms) by dose, with the median values shown as vertical bars, again by dose. In any such plot, one would

expect that a regression line for any particular dose would have a slope somewhat less than 45°, because of regression to the mean.

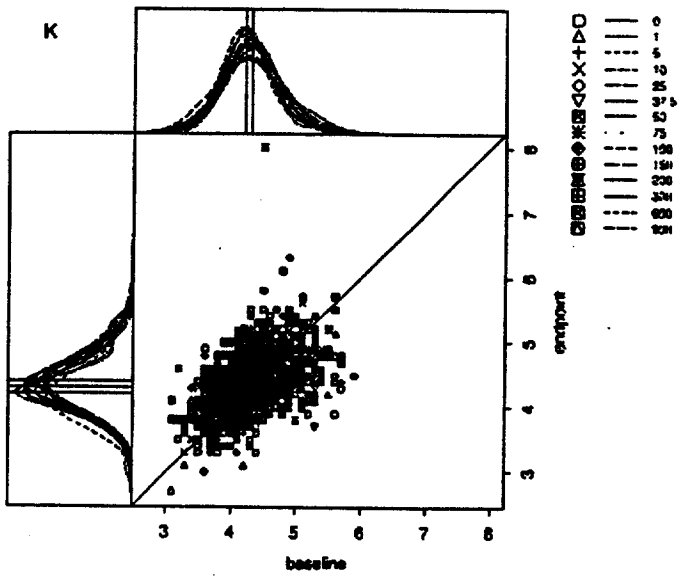

Figure 23. Changes in serum potassium (monotherapy studies).

Data from fixed-dose, monotherapy studies were reviewed separately from data from studies in combination with HCTZ.

Plots of this type were produced for any laboratory data for which there were more than 100 samples. These plots are only reproduced in the review where necessary to illustrate an apparent treatment effect.

Treatment effects producing outliers were assessed by comparing the incidence of such outliers in placebo and active treatment groups. In some cases, CRFs were examined to determine a broader picture of a subject's clinical course.

8.1.6.3.2. Withdrawals for laboratory abnormalities

Withdrawals for laboratory abnormalities are listed among withdrawals for other adverse events.

8.1.7. Vital signs

Vital signs were, in general, characterized under effectiveness. Outliers were characterized only to the extent they resulted in the generation of a reported adverse event.

8.1.8. ECGs

ECGs were analyzed in the same manner as other clinical laboratory data.

8.1.9. Special studies

The sponsor conducted studies in populations with renal[1] and hepatic[2] impairment, and in subjects with severe hypertension[3].

Some exploratory trials in heart failure are reported. Other trials in heart failure and diabetic nephropathy are underway.

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1. *CV131-011: Pharmacokinetics of SR 47436 (Irbesartan) in subjects with renal impairment compared to subjects with normal renal function.* on page 156; *CV131-033: The safety and efficacy of irbesartan in patients with hypertension and renal insufficiency.* on page 210.
2. *CV131-014: Single and multiple dose pharmacokinetics and pharmacodynamics of irbesartan in subjects with hepatic cirrhosis compared to healthy subjects* on page 162.
3. *CV131-032: The efficacy and safety of the angiotensin II receptor antagonist irbesartan in the treatment of patients with severe hypertension.* on page 207.

Drug-interaction studies are discussed elsewhere.

8.1.10. Withdrawal phenomena and abuse potential — Withdrawal effects on blood pressure were studied for 1 week at the end of studies CV131-002[4] and CV131-050[5]. Abuse potential is not a concern with this class of drugs.

8.1.11. Human reproduction data — All studies were conducted in a population at low risk of pregnancy.

8.1.12. Overdose experience — There is no known pertinent experience.

8.2. Review of systems

8.2.1. General body system

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

8.2.1.2. General events at least possibly drug-related

8.2.1.2.1. General deaths — No deaths were attributed to general adverse events.

8.2.1.2.2. Serious general adverse events — No serious general adverse events were plausibly attributable to study drug.

8.2.1.2.3. Withdrawals for general adverse events — Withdrawals for general adverse events plausibly related to study drug are listed in Table 17 below.

Table 17. Withdrawals for general adverse events plausibly related to study drug.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	005/008	50	M	1	—	1	Discontinued with dizziness and headache after 6 days of treatment.
CV131-002	042/033	61	M	1	—	27	Discontinued for headache and poor blood pressure control.
CV131-002	034/016	51	M	5	—	32	Discontinued for headache, considered probably drug-related.
CV131-002	001/004	38	M	25	—	16	Discontinued with flu-like symptoms and poor blood pressure control.
CV131-030	010/004	64	M	75	—	18	Discontinued with headache.
CV131-038	017/028	77	M	75	—	56	Discontinued with diarrhea, weakness, and malaise, which did not resolve.
CV131-038	017/028	77	M	75	—	56	Discontinued with 12-day history of diarrhea, weakness, and malaise, considered possibly drug-related. Event was unresolved.
CV131-027	027/008	51	M	75	—	3	Discontinued for malaise, weakness, fatigue, headache, and somnolence, all considered possibly drug-related.
CV131-031	002/003	74	F	75	—	11	Discontinued for headache, hot flushes, and ankle edema.
CV131-031	002/004	70	M	75	—	29	Discontinued for ankle edema and fatigue, considered probably drug-related. Event resolved.
CV131-031	008/014	65	F	75	—	15	Discontinued with headache and pharyngitis, both considered possibly drug-related.
CV131-031	013/002	73	F	75	—	39	Discontinued for drowsiness, which resolved the following day.
CV131-031	014/003	66	F	75	—	23	Discontinued for worsening headache, which resolved the next day.
CV131-033	002/004	52	F	75	—	16	Discontinued for headache, considered possibly drug-related. Event resolved the next day.
CV131-033	010/001	46	M	75	—	7	Discontinued for headache, considered probably drug-related. Event resolved.
CV131-033	010/002	72	M	75	—	7	Discontinued for headache, considered possibly drug-related. Event resolved.

[4] *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).* on page 138.

[5] *CV131-050: A multicenter, 8 week study of the antihypertensive activity, tolerability, and safety of irbesartan in subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg).* on page 246.

Table 17. Withdrawals for general adverse events plausibly related to study drug.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV133-033	023/012	46	M	75	—	20	Discontinued for viral hepatitis. Event was unresolved.
CV131-002	015/008	58	F	100	—	58	Discontinued with headache, considered related to blood pressure control. Event resolved within 2 days
CV131-029	007/007	43	F	150	—	8	Discontinued with headache and diastolic pressure of 107 mmHg, which resolved.
CV131-050	005/007	41	M	150	—	26	Discontinued with severe headaches, which resolved.
CV131-050	031/004	53	M	150	—	34	Discontinued with headache and weight gain dating from day 2. Events resolved 14 days later.
CV131-027	004/015	74	F	150	—	117	Discontinued with migraine, dyspnea, and fatigue, the latter two being considered probably drug-related.
CV131-027	031/014	43	M	150	—	56	Discontinued for headache, attributed to blood pressure (163/109 seated). Event was unresolved.
CV131-031	006/003	81	M	150	—	72	Discontinued for weakness, considered possibly drug-related. Event did not resolve.
CV131-032	016/009	63	M	150	—	20	Discontinued with uncontrolled hypertension, headache, and tachycardia, considered unrelated to study drug. Event resolved.
CV131-032	018/005	46	F	150	—	19	Discontinued with flu-like symptoms, considered related to study drug. Symptoms were unresolved.
CV131-025	012/007	58	F	200	—	8	History of migraines. Discontinued after migraine lasting 4 days.
CV131-050	052/006	71	M	300	—	8	Discontinued for headaches which began during placebo withdrawal. Event resolved.
CV131-050	012/007	25	M	600	—	4	Discontinued with chest pressure, considered unlikely to be drug-related. Event resolved.
CV131-050	039/003	55	M	900	—	32	Discontinued with chest pressure, considered possibly drug-related. Event unresolved.
CV131-050	055/010	53	F	900	—	1	Discontinued for facial flushing and body warmth. Events resolved.
CV131-050	065/005	45	M	900	—	13	Discontinued with weakness and tremors, considered possibly drug-related. Events resolved next day.
CV131-037	032/007	50	F	37.5	6.25	2	Discontinued for generalized itching, edema, muscle aches, and chest pain, all considered unlikely to be drug-related. Events resolved within 1 week.
CV131-039	013/020	65	M	75	12.5	13 37	Complaint of headaches, but study drug continued. Discontinued for feeling of missed beats and general malaise, considered possibly drug-related. Events resolved within 4 days.
CV131-039	020/018	50	M	75	12.5	26	Discontinued with headache and costochondral chest pain, the former being possibly drug-related. Both resolved within 2 weeks.
CV131-037	005/027	59	M	100	6.25	1	Discontinued for dizziness, considered unlikely to be drug-related. Event unresolved.
CV131-037	017/008	38	M	100	12.5	1	Discontinued for fatigue and weakness, considered possibly drug-related. Events unresolved.
CV131-038	039/002	57	F	150	12.5	3	Discontinued for worsening headaches, tightness in nasal passages, and chest pain, the first two considered possibly drug-related. Headache and chest pain resolved within 1 week.
CV131-039	007/016	41	M	150	12.5	1	Discontinued with headache, weakness, nausea, and rash, all considered drug-related. All resolved within 2 days.
CV131-037	010/011	45	M	300	12.5	1	Headache, nausea, and vomiting after first dose, considered possibly drug-related. Events resolved next day.
CV131-037	017/012	39	M	300	25	1	Discontinued with dizziness and PVCs, considered possibly drug-related. Events resolved.
Long-term phase							
CV131-002	037/007	48	F	50	—	21	Discontinued for headache. Event resolved.
CV131-025	016/008	54	M	50	—	1	Discontinued for headache, considered probably drug-related. Event did not resolve.
CV131-025	025/001	64	M	50	—	3	Discontinued for headache. Event resolved.
CV131-025	008/001	31	M	50	—	108	Discontinued for headache, considered unlikely to be drug-related. Event did not resolve.
CV131-029	007/014	33	M	75	—	1	Discontinued for fatigue, considered unlikely to be drug-related. Event resolved.
CV131-029	017/024	47	M	75	—	21	Discontinued for headache, considered possibly drug-related. Event resolved.
CV131-050	052/003	63	F	75	—	27	Discontinued for dizziness and uncontrolled hypertension, considered possibly drug-related. Events resolved.
CV131-025	012/005	67	M	100	—	29	Discontinued for tiredness, light-headedness, and occasional missed beat, all considered probably drug-related. Events did not resolve.
CV131-025	034/001	53	M	100	—	26	Discontinued for tiredness. Event did not resolve.
CV131-002	004/011	29	M	100	—	75	Discontinued for tiredness, back pain, and impotence. Events were unresolved.

Table 17. Withdrawals for general adverse events plausibly related to study drug.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-028	046/010	62	M	150 300	—	32 63	Complained of anxiety, but study drug continued. Later subject discontinued for hot flashes. Events resolved.
CV131-031	034/003	76	F	150	—	20	Discontinued for weakness and 'noticeable' heartbeat, considered possibly drug-related. Event resolved within 2 weeks.
CV131-032	011/003	58	M	150	—	10	Discontinued for dizziness, considered unlikely to be drug-related. Event did not resolve.
CV131-025	011/002	65	M	200	—	60	Discontinued for pruritus, constipation, fatigue, headache, fever, and generalized aches, all considered unlikely to be drug-related. Events resolved.
CV131-025	018/010	56	M	200	—	266	Discontinued with "hung over" feeling. Event did not resolve.
CV131-025	003/016	60	M	200	—	1	Discontinued with worsening edema, which resolved.
CV131-029	020/007	56	F	300	—	70	Discontinued with depression, fatigue, migraine, dizziness, and poor blood pressure control. Events did not resolve.
CV131-050	029/009	64	F	900	—	1	Discontinued for fatigue and blurred vision, both considered unlikely to be drug-related. Events did not resolve.
CV131-025	035/004	34	F	50	12.5	25	Discontinued for edema. Event resolved.
CV131-037	002/006	60	F	75	12.5	243	Discontinued for fatigue, considered unlikely to be drug-related. Event resolved.
CV131-037	005/026	53	F	75	12.5	4	Discontinued for malaise, considered possibly drug-related. Resolution is unknown.
CV131-037	024/006	37	M	75	12.5	2	Discontinued with fever, fatigue, and abdominal pain, all considered unlikely to be drug-related. Events did not resolve.
CV131-037	030/007	44	M	75	12.5	221	Discontinued with decreased libido, cold extremities, and chest pain, considered probably drug-related. Events resolved.
CV131-037	030/018	43	F	75	12.5	7	Discontinued with fatigue, headache, and light-headedness, all considered possibly drug-related. No events resolved.
CV131-038	012/016	56	M	75	12.5	5	Discontinued for fatigue, after almost 3 months on irbesartan alone or combination, considered possibly drug-related. Event was unresolved.
CV131-038	020/021	53	M	75	12.5	27 51	Complained of fatigue and urinary frequency. Discontinued for increased liver function tests, considered possibly drug-related. Event resolved.
CV131-002	027/015	74	F	100	?	124	Subject requested discontinuation for "funny feeling" 4 days after starting HCTZ.
CV131-002	039/026	57	M	100	?	313	Discontinued for weakness and light-headedness. The latter resolved.
CV131-002	016/006	37	M	100	?	464	Discontinued for nausea, weakness, and tight feeling in hands. Events were unresolved.
CV131-002	042/006	49	M	100	?	267	Discontinued for headaches. Event was unresolved.
CV131-025	013/003	41	M	200	25	345	Discontinued for weakness and dizziness. Events resolved.
CV131-038	037/007	54	M	300	12.5	88	Discontinued for fatigue, considered possibly drug-related. Event was unresolved.
CV131-029	012/012	72	M	300	25	209	Discontinued for headache, attributed to concomitant nifedipine. Event resolved.
CV131-037	021/058	63	F	300	25	56	Discontinued for malaise; relationship to study drug was not assessed. Event did not resolve.
CV131-038	023/005	58	F	300	25	30	Discontinued for fatigue and nausea, considered possibly drug-related. Events resolved.

8.2.1.3. General events unlikely to be drug-related

8.2.1.3.1. General deaths No deaths were attributed to general adverse events.

8.2.1.3.2. Serious general adverse events Serious general adverse events unlikely to be related to irbesartan are listed in Table 18 below. Cancer events were not uncommon, but the observed events were of several types, they were generally common (skin, breast, prostate) in the elderly population, and, in some cases, they were clearly discovered too soon after initiation of study drug to represent new, possibly drug-related phenomena.

Table 18. Serious general adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Cancer—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.
CV131-031	036/008	71	F	75	—	43	Hospitalized for mastectomy; final pathology report is "pending". Study drug was discontinued.
CV131-031	226/011	72	F	75	—	121	Subject discontinued with (pre-existing?) basal cell carcinoma.
CV131-025	035/010	48	F	100	—	43	Subject diagnosed with breast cancer, but completed double-blind phase and entered open-label.
CV131-050	059/002	68	F	300	—	43	Basal cell carcinoma; study drug not interrupted.
CV131-050	064/017	58	M	300	—	9	Throat malignancy; study drug was discontinued.
CV131-040	010/001	72	M	150	25	48	History of skin cancer. Hospitalized for removal of skin cancer; study drug was not interrupted.
Cancer—long-term phase							
CV131-002	045/026	64	M	10	—	53	Diagnosis of prostate cancer. Study drug was discontinued.
CV131-002	037/012	73	M	50	—	714	Hospitalized for removal of mandibular gland tumor. Study drug was continued.
CV131-025	023/014	70	M	50	—	22	Subject diagnosed with melanoma, treated by resection. Study drug continued.
CV131-029	001/003	51	M	75	—	109	Unremarkable history. Diagnosed with cervical lymphoma. Study drug was discontinued.
CV131-002	020/001	57	M	100	—	672	Unremarkable history. Hospitalized for prostate cancer. Stud drug was continued.
CV131-025	027/001	62	M	100	—	402	Subject was diagnosed with prostate/bladder cancer. Study drug was discontinued.
CV131-025	027/007	58	M	100	—	308	Subject diagnosed with adenocarcinoma of pancreas. Study drug was discontinued.
CV131-025	011/006	69	M	100	—	565	Hospitalized for inguinal lymphoma surgery. Study drug was discontinued prior to chemotherapy.
CV131-025	003/009	65	F	150	—	20	History of smoking for 50 years. Subject diagnosed with lung cancer; study drug was discontinued.
CV131-028	032/011	50	F	150	—	279	Breast cancer diagnosed by mammography. Study drug was discontinued.
CV131-029	020/012	43	M	300	—	197	Hospitalized for resection of renal carcinoma. Study drug was discontinued.
CV131-050	005/009	68	M	300	—	98	Diagnosed with prostate cancer. Study drug was continued.
CV131-038	037/023	52	M	75	12.5	11	Hospitalization for colon cancer. Study drug was discontinued.
CV131-038	039/005	64	F	75	12.5	62	Diagnosed with breast cancer. Subsequently underwent mastectomy. Study drug was continued.
CV131-038	057/029	55	F	75	12.5	34	Diagnosed with breast cancer. Subsequently underwent mastectomy. Study drug was discontinued.
CV131-038	060/012	66	M	75	12.5	46	Hospitalized for removal of squamous cell carcinoma. Study drug continued?
CV131-002	006/006	75	F	100	25	431	Hospitalized for thyroid micropapillary carcinoma. Study drug continued.
CV131-002	039/030	63	F	100	25	220 533	History of surgical treatment of skin cancer. Both hospitalizations for removal of squamous cell carcinomas. Study drug continued.
CV131-002	043/011	72	M	100	?	427	History of BPH. Diagnosis of adenocarcinoma of prostate. 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.
CV131-038	053/014	66	F	150	12.5	146	Hospitalized for uterine adenocarcinoma, treated by hysterectomy. Study drug continued?
CV131-038	053/023	58	F	150	12.5	110	Hospitalized for acute intestinal obstruction, diagnosed with bowel adenocarcinoma, and treated by colostomy. Study drug was discontinued.
CV131-025	024/003	66	M	200	25	169	Subject diagnosed with basal cell carcinoma, excised. 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.
CV131-038	047/002	55	M	300	25	293	Hospitalized for head and neck pain, diagnosed as brain tumor. Outcome unknown. Study drug continued?
CV131-037	027/030	57	F	300	25	102	History of multiple surgeries for basal cell carcinomas. Hospitalized for removal of basal cell carcinoma. Study drug was 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.

Table 18. Serious general adverse events unlikely to be related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Drug abuse—long-term phase							
CV131-002	012/011	42	M	100	—	369	Unremarkable history. Hospitalized for alcoholism. Study drug was discontinued.
CV131-038	013/004	61	M	300	25	187	History of alcohol abuse and depression. Hospitalized for substance abuse. Study drug was discontinued.
Infectious disease—double-blind phase							
CV131-002	038/010	68	M	5	—	36	Subject with 17 year history of hypertension developed severe viral syndrome requiring 3-day hospitalization. Subject completed double-blind phase.
CV131-033	024/006	64	F	75	—	45	History of chronic glomerular nephritis and renal insufficiency. Hospitalized for flu symptoms and pneumonia. Study drug was subsequently discontinued.
CV131-033	006/005	38	M	150	—	38	Subject with nephrotic syndrome, glomerulonephritis, and muscular dystrophy. Hospitalized for viral vestibular neuronitis. Subject continued in open-label phase.
Infectious disease—long-term phase							
CV131-003	002/011	69	F	25	—	169	History of diabetes. Hospitalization for kidney infection. 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.
CV131-044	064/001	46	M	150	—	138	Hospitalized for flu-like symptoms. Study drug was continued.
CV131-029	015/012	51	M	300	—	282	Hospitalized for debridement of foot abscess. Study drug was continued.
CV131-037	042/013	40	F	75	12.5	126	Hospitalized for viral gastroenteritis. Study drug was interrupted.
CV131-029	015/023	72	F	150	25	195	History of emphysema. Hospitalized for pneumonia. Study drug was continued.
CV131-032	023/006	36	F	150	?	203	History of sterilization. Hospitalized for salpingitis, treated with antibiotics. Study drug was continued.
Trauma—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.
CV131-002	039/026	57	M	100	—	6	Subject hospitalized for gunshot, but completed double-blind treatment.
CV131-038	052/025	54	F	150	12.5	52	Hospitalized subsequent to injuries suffered in mugging; study drug was not interrupted.
Trauma—long-term phase							
CV131-044	078/007	81	M	12.5	—	1	Hospitalized for fractured ankle. Study drug was interrupted.
CV131-028	034/002	53	M	75	—	222	Hospitalized following automobile accident with high blood alcohol.
CV131-002	041/007	62	M	100	—	156	Hospitalized for surgical repair of injury inflicted with power tool.
CV131-002	044/009	59	F	100	—	120	Hospitalized for elective cosmetic surgery.
CV131-029	014/006	70	M	150	—	271	Hospitalization to set foot fracture sustained in fall. Study drug continued?
CV131-032	002/003	50	M	150	—	249	History of 2 hospitalizations following motor vehicle accidents. Hospitalized with broken back following motor vehicle accident. Study drug continued?
CV131-038	010/006	57	F	75	12.5	18	Hospitalized for open reduction of fractured humerus. Study drug continued?
CV131-038	009/007	41	F	150	12.5	196	Hospitalized for trauma in motor vehicle accident. Study drug was interrupted.

8.2.1.3.3. Withdrawals for general adverse events

Withdrawals for general adverse events unlikely to be related to study drug are listed in Table 19 below.

Table 19. Withdrawals for general adverse events unlikely to be related to study drug.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV133-033	023/012	46	M	75	—	20	Discontinued for viral hepatitis. Event was unresolved.

8.2.1.4. Common general adverse events

Common general adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 20 below and Table 21 below, respectively.

Table 20. General 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
Headache	15.0	20.7	12.2	13.6	12.0	14.3	14.6	9.1	7.4	10.2	7.6	11.7	12.4	10.1	10.9
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
Chest pain	1.7	2.4	1.2	1.2	1.2	2.4	1.2	1.7	0.4	1.6	2.5	0.8	2.9	3.0	1.5
Edema	2.3	1.2	1.2	0.0	1.2	0.0	0.0	1.3	0.8	1.6	2.5	2.1	2.9	0.0	1.3
Swelling extremity	0.6	0.0	0.0	1.2	0.0	7.1	0.0	0.7	0.0	0.7	2.5	0.0	0.0	0.0	0.6
Weakness	1.4	0.0	0.0	0.0	0.0	0.0	0.0	1.7	0.0	1.3	0.0	0.4	1.0	1.0	0.7
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
Wound	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.4	0.2	3.8	0.4	1.0	1.0	0.5
Pain	0.5	0.0	0.0	2.5	0.0	0.0	0.0	0.0	0.0	0.9	0.0	0.4	0.0	0.0	0.4
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
Malaise	0.3	1.2	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.4	0.0	0.0	0.3
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
Mal neopl head/neck	0.0	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
Neopl benign breast	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
Neopl malig derm	0.0	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
Neoplas malignant B	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
Neopl ben endocrine	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
Neoplasm unspec	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
Uns neopl endocrine	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

Table 21. General adverse events by dose in double-blind studies of irbesartan + HCTZ.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300		
HCTZ	0	6.2	12	25	0	6.2	12	25	0	12	25	0	6.2	12	25	0	12	0	6.2	12	25
N=	236	44	177	159	42	44	45	41	196	134	118	41	44	43	44	199	135	43	40	44	45
Fatigue	3.0	0.0	2.3	5.0	4.8	6.8	4.4	7.3	5.6	3.0	9.3	7.3	6.8	7.0	6.8	6.0	1.5	2.3	7.5	4.5	11.1
Infection	1.7	2.3	2.8	2.5	4.8	2.3	2.2	4.9	3.6	3.7	2.5	4.9	4.5	2.3	0.0	3.0	5.2	0.0	0.0	2.3	0.0
Trauma	1.3	4.5	0.0	3.1	4.8	6.8	2.2	2.4	2.6	1.5	1.7	2.4	0.0	0.0	0.0	1.0	2.2	0.0	2.5	0.0	4.4
Chest pain	1.3	6.8	1.1	0.6	2.4	0.0	2.2	0.0	0.5	0.7	2.5	0.0	4.5	9.3	0.0	2.5	0.7	2.3	0.0	2.3	0.0
Weakness	1.7	0.0	1.1	0.6	0.0	0.0	2.2	0.0	1.5	0.7	0.8	0.0	0.0	2.3	0.0	0.5	0.0	0.0	0.0	0.0	2.2
Hyperhidrosis	0.0	2.3	0.0	0.6	0.0	2.3	2.2	0.0	0.5	0.7	1.7	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0
Malaise	0.4	0.0	0.6	0.6	0.0	2.3	0.0	0.0	1.5	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	0.0
Chills	0.0	0.0	0.0	0.0	0.0	2.3	2.2	2.4	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Fever	0.4	0.0	1.7	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0

In open-label extensions, general adverse events were reported for 222 subjects on irbesartan alone (12% or 220 subjects with events per 1000 subject-years) and by 297 subjects on irbesartan/HCTZ (17% or 245 subjects with events per 1000 subject-years). All such events are shown in Table 22 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 22. General 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
Upper respiratory infection	158	8.8	158	186	11	153	Pain	13	0.7	13	16	0.9	13
Fatigue	69	3.9	69	88	5.2	73	Viral infection	6	0.3	6	19	1.1	16
Influenza	54	3.0	54	66	3.9	54	Hyperhidrosis	9	0.5	9	13	0.8	11
Chest pain	28	1.6	28	43	2.5	35	Weight gain	11	0.6	11	10	0.6	8
Fever	12	0.7	12	21	1.2	17	Wound	8	0.4	8	11	0.6	9
Weakness	9	0.5	9	23	1.4	19	Malaise	7	0.4	7	11	0.6	9

a. Subjects with events per 1000 subject-years.

8.2.1.5. General laboratory findings No laboratory tests were considered in the evaluation of general safety.

8.2.2. Cardiovascular system

8.2.2.1. Adequacy of cardiovascular assessment Cardiovascular safety was assessed through vital signs, ECG, and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.2.2. Cardiovascular events at least possibly drug-related

8.2.2.2.1. Cardiovascular deaths No cardiovascular deaths were judged by the sponsor or the reviewers to have any reasonable likelihood of being drug-related.

8.2.2.2.2. Serious cardiovascular adverse events Serious cardiovascular events plausibly related to study drug are shown in Table 23 below.

Table 23. Serious cardiovascular adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Hypotension—double-blind phase							
CV133-033	003/003	65	F	75	—	1	Discontinued for symptomatic hypotension, considered drug-related, and treated by hospitalization and fluids. Event resolved.
Heart failure—double-blind phase							
CV131-002	009/008	69	M	1	—	2	Discontinued for onset of heart failure (fatigue, shortness of breath, edema), which resolved by day 31. Investigator believed events unlikely to be related to study drug.
Rhythm disturbance—double-blind phase							
CV131-003	004/009	77	F	50	—	1	History including heart failure, myocardial infarction, and diabetes. Two hours after dosing, she had complete heart block and then runs of sustained and non-sustained ventricular tachycardia. Treated with lidocaine and temporary pacing.

8.2.2.2.3. Withdrawals for cardiovascular adverse events

Withdrawals for cardiovascular adverse events plausibly related to irbesartan are listed in Table 24 below.

Table 24. Withdrawals for cardiovascular adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Hypertension—double-blind phase							
CV131-033	024/002	51	F	75	—	1	Discontinued for increased blood pressure, considered unlikely to be drug-related. Event resolved.
CV131-033	001/007	63	F	75	—	8	Discontinued for uncontrolled hypertension without other symptoms.
CV131-033	007/005	55	M	300	—	57	Discontinued for uncontrolled hypertension, considered probably drug-related. Event did not resolve.
CV131-037	032/015	56	M	37.5	12.5	8	Discontinued for hypertension.
Hypotension—double-blind phase							
CV133-033	004/002	54	M	75	—	80	Discontinued for hypotension, dizziness, and weakness, considered drug-related. Event resolved.
CV131-033	013/002	63	M	75	—	62	Discontinued for hypotension, considered probably drug-related. Event was unresolved.
CV131-050	059/005	66	F	150	—	4	Discontinued with light-headedness, considered probably drug-related. Event resolved.
CV131-050	040/019	44	M	600	—	1	Discontinued with orthostatic hypotension (standing BP 72/46 mmHg 3 hours after first dose).
CV131-050	059/006	45	M	900	—	15	Discontinued for light-headedness, attributed to hypotension (BP 107/83 mmHg). Event resolved.
CV131-037	014/017	60	F	37.5	12.5	28	Discontinued with hypotension (standing BP 93/63 mmHg), rash, elevated lived enzymes. Events resolved within 2 weeks.
CV131-037	010/010	45	M	37.5	25	43	Discontinued for light-headedness and standing BP 91/67 mmHg. Treated by fluids; event resolved.
CV131-038	011/012	59	M	150	12.5	21	Discontinued after feeling of faintness 1 to 5 hours after dosing for 17 days, considered probably drug-related. Events resolved.
Hypotension—long-term phase							
CV131-027	016/006	60	F	75	—	79	Discontinued for symptomatic orthostatic hypotension, considered drug-related. Event resolved.
CV131-037	025/003	63	M	300	25	41	Discontinued for postural light-headedness, paresthesias, and headache, all considered probably drug-related. Events did not resolve.
Ischemia—double-blind phase							
CV131-002	017/009	51	M	1	—	61	Discontinued for chest tightness, considered possibly drug-related, and treated with nitroglycerin. Event resolved over 6 days.
CV131-039	019/004	73	M	75	—	11	History of angina. Discontinued with atypical chest pain and normal ECG.
CV131-002	012/004	60	F	100	—	37	Discontinued with moderate chest pain, treated with nitrates.
CV131-038	038/005	48	F	150	—	16	History of myocardial infarction and PTCA. Discontinued with chest pain, which resolved.
CV131-031	015/003	68	M	150	—	85	Discontinued for onset of angina, considered unlikely to be drug-related. Resolution is unknown.
Ischemia—long term phase							

Table 24. Withdrawals for cardiovascular adverse events plausibly related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-025	006/001	58	M	50	—	255	Discontinued for angina, requiring nitroglycerin. Event did not resolve.
CV131-029	012/025	58	M	75	—	203	Discontinued for exertional chest pain, considered unlikely to be drug-related. Event resolved.
CV131-028	020/001	69	F	150	—	205	Discontinued for onset of angina, considered unlikely to be drug-related. Event resolved.
CV131-029	007/010	50	F	150	—	29	Discontinued for chest pain, considered possibly drug-related. Event did not resolve.
CV131-037	033/007	52	M	300	25	109	Discontinued for chest pain, treated by isosorbide mononitrate and amlodipine. Event, which resolved, was considered unlikely to be drug-related.
Rhythm disturbance—double-blind phase							
CV131-002	016/008	33	F	1	—	8	Discontinued for increased palpitations, dizziness, and tachycardia, all considered at least possibly drug-related.
CV131-002	024/007	60	M	5	—	10	Discontinued for heart irregularity, light-headedness, vertigo, all considered possibly drug-related. Events resolved with 2 weeks.
CV131-031	006/023	66	M	75	—	4	Discontinued for palpitations and dizziness, which resolved the next day. Both resolved the following day.
CV131-031	015/008	78	F	75	—	93	Discontinued for atrial fibrillation, considered unlikely to be drug-related.
CV131-031	015/037	68	F	75	—	39	Discontinued with 'mild' ventricular tachycardia, considered possibly drug-related.
CV131-031	226/012	71	M	75	—	42	History of SVT. Discontinued for SVT, treated by i.v. verapamil, considered possibly drug-related. Event resolved.
CV131-033	003/002	33	M	75	—	8	Discontinued for palpitations, considered unlikely to be drug-related. Event resolved.
CV133-033	006/008	60	M	75	—	4	Discontinued for palpitations and dyspnea, considered unlikely to be drug-related. Events resolved the next day.
TDR 1691	001/022	29	M	100	—	3	Normal volunteer experienced asymptomatic right bundle branch block, which resolved by day 11.
CV131-050	058/001	58	M	300	—	9	Discontinued for paroxysmal ventricular tachycardia, considered unlikely to be drug-related. Events resolved over several weeks.
Rhythm disturbance—long-term phase							
CV131-002	018/001	63	M	10	—	5	Discontinued for palpitations. Event resolved.
CV131-025	023/013	69	M	50	—	22	Discontinued for tachycardia and weakness. Event resolved.
CV131-037	026/011	50	F	75	12.5	257	Discontinued for supraventricular tachycardia, considered unlikely to be drug-related. Event resolved.
CV131-037	016/004	61	M	150	12.5	39	Experienced intermittent atrial fibrillation, treated by quinidine. Discontinued 2 weeks later. Event resolved.
CV131-038	022/016	63	M	150	12.5	55	Discontinued for occasional PVCs and dizziness, considered possibly drug-related. Events resolved.
CV131-032	017/014	55	M	150	25	41	Discontinued for premature atrial contractions, considered possibly drug-related. Event resolved.
CV131-025	014/004	48	M	200	12.5	189	Discontinued for palpitations. Event resolved.

8.2.2.3. Cardiovascular events unlikely to be drug-related

8.2.2.3.1. Deaths

There were several sudden deaths—apparently arrhythmia, myocardial infarction, or ruptured aneurysm—among subjects in hypertension studies. None of these events were considered possibly related to study drug.

Study CV131-029 subject 026/014 was a 74 year old Caucasian male with a 20-year history of hypertension. On day 40 of treatment with irbesartan 150 mg, he experienced severe indigestion and heartburn, collapsed, arrested, and, despite attempts at CPR by neighbors, he died in the emergency room. His last reported blood pressure was 146/95 mmHg. Relationship to study drug was considered unlikely.

Study CV131-038 subject 021/003 was a 65 year old Caucasian male with a 42-year history of hypertension, most recently treated with nifedipine. After 4 weeks on irbesartan 75 mg plus HCTZ 12.5 mg, he suffered a myocardial infarction while playing tennis. CPR by a physician was unsuccessful and he was pronounced dead

at the hospital. Relationship to study drug was considered unlikely.

Study CV131-025LT subject 003/005 was a 64 year old male with a 16-year history of hypertension and a 41-year history of smoking. After 5 months of open-label treatment, he developed edema and deep vein thrombophlebitis, treated with coumadin. He died after 15 months on irbesartan 100 mg, while vacationing out of the country. He died from hemorrhagic, hypovolemic shock subsequent to a ruptured aortic aneurysm, considered unrelated to study drug.

Study CV131-031LT subject 015/007 was a 68 year old female. After 9 months on irbesartan 300 mg, HCTZ 50 mg, and atenolol 50 mg, she died suddenly, attributed to myocardial infarction. The investigator considered death possibly related to study drug.

Two subjects in hypertension studies died in motor vehicle accidents. In neither case was there a suspected relationship to study drug, but neither case history appears to rule out the possibility of a disabling sudden cardiac event precipitating the accident.

Study CV131-037LT subject 015/003 was a 65 year old Caucasian male with a 5-year history of hypertension. After 9 weeks on open-label irbesartan 75 mg plus HCTZ 12.5 mg, he died in a 2-vehicle motor vehicle accident. The investigator considered the event unlikely to be related to study drug, but the accident description does not attribute blame, nor does it appear to rule out sudden incapacitation of the subject prior to the accident.

Study CV131-025LT subject 003/006 was a 55 year old male with a 32-year history of hypertension. After 20 months on open-label irbesartan 200 mg plus HCTZ 50 mg, he died in a motor vehicle accident. Relationship to study drug was considered unlikely, but no description appears to rule out sudden incapacitation of the subject prior to the accident.

There were several sudden deaths among subjects in heart failure studies. Each such case appears typical of subjects with the underlying disease, and a relationship to study drug was not suspected in any case. One death occurred in a subject with no history of heart failure; this subject died from myocardial infarction in the open-label phase of the study of severe hypertension.

Study CV131-003LT subject 001/011 was a 72 year old Caucasian male with heart failure attributed to ischemic heart disease and treated with digoxin, asthma, and a 40-year smoking history. He received irbesartan 200 mg during double-blind treatment and then 25 mg during 2 weeks on open-label. He collapsed at home and was found to be in ventricular fibrillation. He died in hospital without regaining consciousness. Relationship to study drug was considered unlikely.

Study CV131-003LT subject 004/012 was a 57 year old Hispanic male with heart failure attributed to a 15-year history of hypertension. He had been on open-label irbesartan for 10 months when he died suddenly at home. There was no autopsy. Relationship to study drug was considered unlikely.

Study CV131-032LT subject 027/004 was a 42 year old Hispanic female with a 13-year history of hypertension. After 9 weeks on open-label irbesartan 300 mg plus nifedipine 60 mg, she was hospitalized for a myocardial infarction. She developed pulmonary edema and died in hospital. Death was attributed to heart failure with cardiomegaly and early cirrhosis. Events were considered unrelated to study drug.

Study CV131-044[6] subject 010/005 was a 31 year old male with history of heart failure and CVA. Blinded treatment was discontinued when he was hospitalized to undergo orthotopic heart transplant. Hospital course included right heart failure, respiratory arrest, brain stem failure, acute tubular necrosis, and perforated bowel. He died 8 days after transplant.

Study CV131-044LT subject 041/002 was a 57 year old male with a history of myocardial infarction, CABG, heart failure, diabetes, and hypercholesterolemia. After 11 weeks on open-label irbesartan 150 mg, he was found dead at home. Relationship to study drug was considered unlikely.

Study CV131-044 subject 045/005 was a 67 year old male with a history of heart failure, hypertension, arrhythmia, stroke, diabetes, and binge-drinking. He was found dead at home, having died after approximately 60 days on blinded treatment. Relationship to study drug was considered unlikely.

Study CV131-044 subject 046/006 was a 56 year old female with a history of heart failure and paroxysmal atrial tachycardia. She died suddenly in a restaurant after 19 days on blinded treatment. Because she initially had a pulse, the investigator rated this death as possibly the result of drug-related postural hypotension.

Study CV131-044LT subject 052/008 was a 48 year old male with a history of heart failure, myocardial infarction, smoking, and alcohol abuse. He was found dead at home after 9 months on irbesartan 150 mg. Relationship to study drug was considered unassessable.

Study CV131-044 subject 070/004 was a 77 year old male with history of coronary artery disease, hypertension, angina, claudication, diabetes, and hypothyroidism. He died in his sleep after 11 weeks on blinded treatment. Relationship to study drug was considered unlikely.

Study CV131-061 subject 034/012 was an 87 year old male with a history of heart failure, myocardial infarctions, CABG, CVA, and heavy smoking. On day 38 of blinded treatment, he was admitted to the hospital in cardiac arrest and died the following day. No other information is available.

Study CV131-061[7] subject 044/002 was a 78 year old male with a history of hypertension, heart failure, atrial fibrillation, and diabetes. He died suddenly at home after 6 days on double-blind treatment. Relationship to study drug was considered unlikely.

Study CV131-061 subject 058/004 was a 70 year old male with a history of myocardial infarctions, CABG, PTCA, and diabetes. He was brought to the hospital in cardiac arrest after 24 days on blinded treatment. Resuscitation was unsuccessful.

8.2.2.3.2. Serious cardiovascular adverse events

Serious cardiovascular events unlikely to be attributable to study drug are shown in Table 25 below.

Many of these events were derived from studies in subjects with underlying heart failure (studies CV131-003 and CV131-044), among whom ischemic events, arrhythmia, and progression of heart failure are not uncommon. The experience in such a population is inadequate to conclude whether such events are more or less common among subjects on irbesartan or other treatments.

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6. Ongoing trial in heart failure.
7. Completed, but unreported trial comparing irbesartan and lisinopril in heart failure.

Table 25. Serious cardiovascular adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Hypertensive crisis—double-blind phase							
CV131-038	063/023	42	F	150	—	51	Hospitalized for hypertensive crisis—BP 190/150, severe headache, tinnitus. Study drug was not discontinued; 2 days later BP was 160/98, asymptomatic.
CV131-033	026/003	70	F	150	—	57	History of chronic renal failure and hemodialysis. Hospitalized for "hypertensive peak" after subject had not taken study drug for 5 days. Subject continued in study.
CV131-033	024/005	51	F	150	—	35	Discontinued for 'hypertensive crisis'—BP 230/100 but no other symptoms noted. Event resolved.
CV131-028	003/008	55	F	300	—	69	Discontinued for hypertensive crisis (seated BP 252/153, headache, dizziness, fatigue, and weakness).
Hypertensive crisis—long-term phase							
CV131-029	015/002	58	F	75	12.5	147	Hospitalized for allergic reaction to lidocaine and hypertensive crisis, following dental procedure. Study drug continued.
Hypotension—double-blind phase							
PDY 2201	1003	30	M	50	—	<1	This subject was a healthy volunteer with no relevant medical history. Thirty minutes following the end of a 90-minute angiotensin II infusion, he developed postural hypotension (BP fell from 116/69 to 65/48 and HR increased 76 to 84/min) resulting in loss of consciousness, associated with clonic movements of the arms. HR fell to 43/min. No urination, no biting of the tongue. Neurological examination was without abnormality. Study drug discontinued. Corrective treatment: infusion of isotonic solution. The subject recovered.
Ischemia—double-blind phase							
CV131-037	025/017	61	M	37.5	6.25	9	History of myocardial infarction and CABG. Hospitalized for catheterization after experiencing precordial discomfort, shortness of breath, and diaphoresis, at which point study drug was discontinued. Received CABG 2 days later, during which he had CVA, symptoms of which largely resolved by discharge.
CV131-033	025/006	50	M	75	—	16	History of chronic renal failure and non-Q myocardial infarction. Hospitalized and discontinued for angina. Relationship to study drug given as "probable".
Ischemia—long-term phase							
CV131-002	028/007	50	F	10	—	667	Unremarkable history and double-blind experience. Chest pain, palpitations, and shortness of breath led to ECG diagnosis of non-ischemic chest pain. Dose increased to 25 mg and a few days later, subject was hospitalized with severe chest pain; catheterization showed significant stenosis. Study drug was interrupted.
CV131-002	026/008	48	F	50	—	329 426	Unremarkable history. Hospitalized for chest pressure, palpitations, and hypertension. Study drug was not interrupted. Subsequently hospitalized for angiogram and angioplasty. Study drug was interrupted.
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.
CV131-002	007/012	72	M	100	—	527	Unremarkable history. Hospitalized for angina and elective CABG. Study drug was not interrupted.
CV131-002	007/008	70	M	100	—	33	Unremarkable history. Hospitalized with non-specific ECG changes and ruled out myocardial infarction. Study drug was increased.
CV131-028	020/001	69	F	150	—	205	Hospitalized for new onset of angina pectoris. Event resolved. Study drug was discontinued.
CV131-044	034/001	52	M	150	—	76	History of myocardial infarction and CABG. Hospitalized for angina and worsening heart failure. Study drug continued?
CV131-044	081/001	50	M	150	—	69	History of PTCA. Hospitalized for PTCA was result of hemodynamics at end of double-blind phase. Study drug was continued.
CV131-029	007/003	50	F	300	—	288	Unremarkable history. Hospitalized for onset of angina, resulting in negative cardiac findings. Study drug continued?
CV131-038	022/010	65	M	75	12.5	17	History of myocardial infarction. Hospitalized for CABG; study drug was discontinued.
CV131-038	036/003	54	M	75	12.5	241	History of chest pain during double-blind phase. Hospitalized for shortness of breath and chest pain on exertion. Subsequently underwent catheterization. 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.
CV131-037	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.
Myocardial infarction—double-blind phase							
CV131-029	024/013	47	F	150	—	8	Hospitalized for severe chest pain, confirmed as myocardial infarction. Subject discontinued.

Table 25. Serious cardiovascular adverse events unlikely to be related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-031	015/025	78	F	150	25	152	Hospitalized and discontinued for myocardial infarction. Relationship to study drug was "possible".
CV131-037	014/003	60	F	300	25	39	Hospitalized with 3-day history of chest pain, diagnosed as myocardial infarction. Study drug was discontinued.
Myocardial infarction—long-term phase							
CV131-002	007/004	73	M	25	—	92	Hospitalization for atypical chest pain diagnosed as non-Q wave myocardial infarction. Subsequent catheterization led to CABG. Study drug was discontinued 1 month after CABG.
CV131-003	003/009	68	M	25	—	351	History of myocardial infarction. Hospitalized for non-Q wave myocardial infarction. Study drug was continued.
CV131-002	010/018	41	M	50	—	286 379	History of diabetes. Subject hospitalized for chest pain, catheterization, and angioplasty. Study drug was interrupted. Subsequently hospitalized for chest pain, diagnosed as myocardial infarction, and treated by angioplasty. Study drug was discontinued 2 weeks later.
CV131-002	020/002	44	M	50	—	202	Unremarkable history. Hospitalized for chest pain, diagnosed as myocardial infarction, and treated by angioplasty. Study drug was discontinued.
CV131-025	020/003	35	M	50	—	28	Unremarkable history. Hospitalized for myocardial infarction, angioplasty. Study drug was discontinued.
CV131-025	024/009	50	F	50	—	11	Unremarkable history. Hospitalized for myocardial infarction. Study drug was discontinued.
CV131-025	028/009	59	M	50	—	18	Unremarkable history. Hospitalized for myocardial infarction and pulmonary edema, treated with CABG. Study drug was discontinued.
CV131-029	009/013	57	M	75	—	27	History of diabetes. Hospitalized for myocardial infarction, treated by PTCA. Study drug was discontinued.
CV131-029	015/020	69	M	75	—	2	Discontinued with ECG evidence of myocardial infarction, considered unlikely to be drug-related. Event said to be resolved with residual effects.
CV131-002	034/019	45	F	100	—	156	History of normal catheterization 7 years earlier. Hospitalized for chest pain, diagnosed as myocardial infarction, with history of cocaine use the day before event. Study drug was discontinued.
CV131-029	002/019	70	M	150	—	144	Unremarkable history. Hospitalization for myocardial infarction. Study drug was discontinued.
CV131-027	005/008	55	M	150	—	299	Unremarkable history. Hospitalized for myocardial infarction, outcome unknown. Study drug was discontinued.
CV131-031	028/011	71	M	300	—	31	Three days after titration to 300 mg, hospitalized with 3-day history of chest tightness, shortness of breath, and orthopnea, confirmed as myocardial infarction. Study drug was discontinued.
CV131-037	030/020	59	M	75	12.5	18	History of atypical chest pain. Hospitalized for chest pain, diagnosed with myocardial 'injury', and treated by PTCA. Study drug was discontinued.
CV131-038	037/008	65	M	150	12.5	121	Unremarkable history. Hospitalized for myocardial infarction. Study drug was discontinued.
CV131-025	022/001	43	M	200	12.5	301	Unremarkable history. Hospitalized for myocardial infarction, treated by angioplasty. Study drug was discontinued.
CV131-025	025/003	50	F	200	12.5	261	Unremarkable history. Hospitalized for myocardial infarction, treated by angioplasty. Study drug was discontinued.
CV131-027	011/011	51	F	300	12.5	90	Unremarkable history. Hospitalization for myocardial infarction. Study drug was discontinued.
CV131-037	024/018	52	M	300	25	272	Unremarkable history. Hospitalized for myocardial infarction. Unclear whether study drug was discontinued.
CV131-038	014/014	56	M	300	25	162	Unremarkable history. Hospitalized with chest pain, diagnosed as non-Q wave myocardial infarction, treated by PTCA. Study drug was continued.
Heart failure—double-blind phase							
CV131-002	032/015	63	F	25	—	2	Unremarkable history. Discontinued and hospitalized with heart failure and bronchitis.
CV131-037	040/009	69	F	37.5	6.25	41	Discontinued for onset of heart failure, considered unlikely to be drug-related. Event resolved.
Heart failure—long-term phase							
CV131-003	001/010	67	M	10	—	103	History of diabetes and myocardial infarction. Hospitalized for heart failure, acute renal failure, and atrial fibrillation. Study drug was discontinued. He died 44 days later.
CV131-044	041/003	52	M	12.5	—	4	History of heart failure, 3 myocardial infarctions, COPD, renal insufficiency, and diabetes. Hospitalized for worsening heart failure. Study drug was discontinued.
CV131-003	003/008	78	F	25	—	11	Hospitalized for acute pulmonary edema. Event resolved and study drug was continued.
CV131-003	003/014	77	M	25	—	54	History of idiopathic dilated cardiomyopathy. Hospitalized for worsening heart failure. Study drug was discontinued.

Table 25. Serious cardiovascular adverse events unlikely to be related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-003	024/004	62	M	25	—	63 83 173	History of myocardial infarction and angina. Hospitalized for worsening heart failure, but study drug was continued. Subsequently hospitalized for chest pain, but study drug was continued. Third hospitalization was also for worsening heart failure. Study drug continued?
CV131-044	011/006	58	M	37.5	—	14	History of myocardial infarction, 6 PTCA. Hospitalized for unstable angina. Study drug was interrupted.
CV131-044	035/003	45	M	75	—	47 154	Hospitalized for worsening heart failure; study drug was interrupted. Second hospitalization for catheterization and evaluation for possible CABG. Study drug was continued.
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 75 150	—	15 48 112	Hospitalized for chest pain and weakness, which resolved, and study drug continued. Later hospitalized for dyspnea and study drug was interrupted. Third hospitalization for dyspnea and nausea and study drug discontinued. Events resolved.
CV131-025	003/004	58	M	100	—	27	Unremarkable history. Hospitalization for onset of heart failure and bronchitis. Study drug was discontinued.
CV131-028	039/004	69	F	150	—	140	History of alcoholism. Hospitalized for heart failure. Study drug was continued.
CV131-044	034/001	52	M	150	—	76	History of myocardial infarction and CABG. Hospitalized for angina and worsening heart failure. Study drug continued?
Rhythm disturbance—double-blind phase							
CV131-031	024/012	75	F	75	12.5	155	Hospitalized for fast atrial fibrillation and ischemic ST-T wave changes. She was cardioverted and discontinued study drug. Relationship to treatment was considered "possible".
CV131-032	007/003	56	F	150	—	2	History of atrial fibrillation. Hospitalized and discontinued for atrial fibrillation.
CV131-032	005/004	59	M	300	?	47	Hospitalized and discontinued for atrial fibrillation with rapid ventricular response.
Rhythm disturbance—long-term phase							
CV131-003	001/010	67	M	10	—	103	History of diabetes and myocardial infarction. Hospitalized for heart failure, acute renal failure, and atrial fibrillation. Study drug was discontinued. He died 44 days later.
CV131-003	003/006	54	M	10	—	13	History of idiopathic dilated cardiomyopathy. Hospitalized after implantable defibrillator discharged. Study drug was continued.
CV131-003	022/004	68	M	25	—	15	History of myocardial infarction, CABG, orthopnea. Hospitalized for intermittent heart block, treated by implanted pacemaker. Two days later, BUN and creatinine were elevated and study drug was discontinued.
CV131-003	001/004	76	M	25	—	182	History of myocardial infarction and CABG. Hospitalized for pre-syncopal episode, diagnosed with atrial fibrillation, treated by cardioversion. Study drug was continued.
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	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.
CV131-002	022/029	62	M	100	—	822	Hospitalized for atrial fibrillation. Study drug was continued.
CV131-044	011/003	60	M	150	—	142	Hospitalized for electrolyte disturbance and renal mass, not biopsied. Next day, he developed atrial fibrillation. Study drug was discontinued.
CV131-044	041/001	73	M	150	—	99	History of myocardial infarction and CABG. Hospitalized for shortness of breath and atrial fibrillation. Six days later, hospitalized with chest pain, and was cardioverted. Study drug was continued.
CV131-044	064/004	57	F	150	—	195	History of CABG, myocardial infarction, and heart failure. Hospitalized for atrial fibrillation. Study drug was discontinued.
CV131-029	020/009	70	F	300	—	200	History of paroxysmal atrial fibrillation. Hospitalized for atrial fibrillation, treated by cardioversion. Study drug was discontinued.
CV131-038	060/009	49	M	75	12.5	139	Hospitalized for atypical chest pain, diagnosed with non-sustained ventricular tachycardia. Study drug continued.
CV131-038	063/030	56	F	75	12.5	57	History of supraventricular arrhythmia at baseline. Hospitalized for atrial fibrillation. Study drug was interrupted. Subsequently hospitalized again for atrial fibrillation and study drug was discontinued.
Peripheral vascular disease—long-term phase							
CV131-031	027/003	65	M	75	—	222	Hospitalized for treatment of deep venous thrombus. Although considered "possibly" drug related, study drug was continued.

In contrast, most of the myocardial infarctions shown derived from studies of uncomplicated hypertension. There were 3 myocardial infarctions during double-blind

treatment among 3945 subjects (<0.1%) receiving irbesartan in placebo-controlled studies vs. 0 among 1257 subjects receiving placebo.

8.2.2.3.3. Withdrawals for cardiovascular adverse events

None of the non-serious adverse events leading to withdrawal were considered implausibly related to study drug.

8.2.2.4. Common cardiovascular adverse events

Common cardiovascular adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 26 below and Table 27 below, respectively.

Table 26. Cardiovascular 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
Tachycardia	0.8	2.4	0.0	1.2	0.0	0.0	1.2	0.3	0.0	1.6	0.0	0.8	2.9	5.1	0.4
Disturb rhythm subj	0.6	1.2	0.0	0.0	0.0	0.0	1.2	0.7	0.0	0.4	1.3	0.8	0.0	2.0	0.4
Disturb card rhythm	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.3	0.4	0.2	1.3	0.0	0.0	1.0	0.3
Disturb rhythm ventr	0.6	0.0	0.0	0.0	0.0	0.0	1.2	0.3	0.0	0.0	1.3	0.4	0.0	1.0	0.3
Atrial rhythm distur	0.0	1.2	1.2	0.0	0.0	0.0	0.0	0.0	0.4	0.0	1.3	0.0	0.0	0.0	0.2
Bradycardia	0.3	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.4	0.0	0.0	0.2
Conduction disorder	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
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
ECG abnormality	0.3	0.0	0.0	0.0	1.2	0.0	0.0	0.3	1.2	0.4	0.0	0.0	1.0	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
Cardiac murmur	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.8	1.0	2.0	0.3
Hypertension	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.8	1.1	0.0	0.4	0.0	1.0	0.3

Table 27. Cardiovascular 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
Edema	2.5	4.5	1.1	1.3	0.0	4.5	4.4	2.4	1.0	3.0	6.8	0.0	0.0	2.3	2.3	2.0	3.0	2.3	5.0	0.0	2.2
Orthostatic dizziness	0.4	0.0	0.0	1.9	0.0	2.3	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	2.3	2.0	2.2	2.3	5.0	0.0	2.2
Tachycardia	0.4	0.0	0.6	0.6	0.0	2.3	0.0	0.0	0.0	0.0	1.7	0.0	0.0	0.0	0.0	2.0	0.7	0.0	2.5	4.5	4.4
ECG abnormality	0.0	4.5	0.6	1.3	0.0	0.0	4.4	0.0	0.0	0.0	0.0	4.9	0.0	0.0	0.0	1.0	0.0	0.0	2.5	0.0	0.0
Arrhythmia	0.8	0.0	0.6	1.3	0.0	0.0	2.2	0.0	2.0	0.7	1.7	0.0	0.0	0.0	2.3	1.5	0.0	0.0	0.0	2.3	0.0
Flushing	0.0	0.0	1.1	0.6	0.0	2.3	0.0	0.0	0.5	0.7	1.7	0.0	0.0	2.3	0.0	1.5	0.0	0.0	0.0	2.3	0.0
Hypertension	1.7	2.3	1.7	0.0	0.0	0.0	2.2	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	1.0	0.0	2.3	0.0	0.0	0.0
Ventricular arrhythmia	0.4	0.0	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0	2.5	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0	2.2

In open-label extensions, cardiovascular adverse events were reported for 135 subjects on irbesartan alone (7.5% or 140 subjects with events per 1000 subject-years) and by 163 subjects on irbesartan/HCTZ (9.6% or 134 subjects with events per 1000 subject-years). All such events are shown in Table 28 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 28. Cardiovascular 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
Edema	41	2.3	41	45	2.6	37	Angina pectoris	10	0.6	10	9	0.5	7
Arrhythmia	27	1.5	27	35	2.1	29	Myocardial infarction	11	0.6	11	4	0.2	3
Tachycardia	8	0.4	8	12	0.7	10	Syncope	2	0.1	2	8	0.5	7

a. Subjects with events per 1000 subject-years.

8.2.2.5. Cardiovascular laboratory findings

ECG data appear not to have been systematically assessed by the sponsor. ECG interval data were in the electronic submission for two studies[8]; the reviewers combined the data from these studies to assess systematic changes from baseline. The results are shown in Table 29 below. These data do not suggest a systematic treatment effect of irbesartan on ECG intervals.

Table 29. ECG interval data (±SE; Studies CV131-002 and CV131-025).

	Placebo N=143	Irbesartan (mg) 1 N=71	5 N=75	10 N=71	25 N=72	50 N=73	100 N=146	200 N=72	300 N=72
ΔHR (bpm)	-0.6±0.8	-1.9±0.9	0.7±1.1	-0.8±1.2	-0.8±0.9	0.3±1.2	0.8±0.8	-0.9±1.0	-1.0±1.1
ΔQRS (ms)	7±6	-1±1	-1±1	1±2	0±1	1±1	9±6	1±1	4±5
ΔQT (ms)	1±3	4±3	5±5	-4±4	4±4	-2±3	-2±3	1±5	-3±3
ΔQTc (ms)	-1±3	-3±3	5±4	-7±3	2±4	-2±3	0±2	-2±6	-6±3

8.2.3. Dermatologic system

8.2.3.1. Adequacy of assessment

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

8.2.3.2. Dermatologic events at least possibly drug-related

8.2.3.2.1. Dermatologic deaths

There were no deaths attributed to dermatologic events.

8.2.3.2.2. Serious dermatologic adverse events

No serious dermatologic events were plausibly attributable to study drug.

8.2.3.2.3. Withdrawals for dermatologic adverse events

Withdrawals for dermatologic adverse events plausibly related to study drug are listed in Table 30 below.

Table 30. Withdrawals for dermatologic adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose Irb	Dose HCTZ	Days	History
Double-blind phase							
CV131-038	052/010	61	M	150	—	62	Discontinued with edema, cutaneous flushing, and pruritus, all considered at least possibly drug-related. Event was unresolved.
CV131-050	036/011	42	M	900	—	1	Discontinued with rash, considered possibly drug-related. Event resolved 8 days later.
CV131-040	022/006	52	F	75	25	3	Discontinued with rash on face, arms, and abdomen, considered possibly drug-related. Event unresolved.
CV131-040	024/007	49	F	75	25	10	Some signs predate exposure to irbesartan, but discontinued for rash on arms and legs, with at least possible relationship to study drug. Events resolved.

8. Studies CV131-002 and CV131-025.

Table 30. Withdrawals for dermatologic adverse events plausibly related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-037	020/033	56	M	300	6.25	7	Interrupted for pruritic rash; resolved within 2 days. Rechallenge positive; subject discontinued.
Long-term phase							
CV131-029	006/003	38	F	75	—	1	Discontinued for pruritus, with unassessable relationship to study drug. Event resolved the next day.
CV131-029	009/022	66	F	75	—	42	Discontinued for facial and neck swelling, dizziness, and headache, only the latter two considered possibly drug-related. Events did not resolve.
CV131-002	045/016	47	F	100	—	1	Discontinued for worsening hair loss. Event resolved.
CV131-031	022/011	71	F	150	—	14	Discontinued with rash, considered probably drug-related. Event did not resolve.
CV131-027	009/007	72	F	300	—	87	Discontinued for rash, considered possibly drug-related. Event resolved.
CV131-037	020/043	72	F	75	12.5	12	Discontinued with rash and cold feet and ankles, both considered unlikely to be drug-related. Neither event resolved.
CV131-038	031/010	63	F	75	12.5	81	Discontinued with paresthesias and rash, considered possibly drug-related. Events resolved.
CV131-038	037/005	64	M	150	12.5	37	Discontinued with macular rash, considered possibly drug-related. Event did not resolve.

8.2.3.3. Dermatologic events unlikely to be drug-related

8.2.3.3.1. Dermatologic deaths There were no deaths attributed to dermatologic events.

8.2.3.3.2. Serious dermatologic adverse events Serious dermatologic adverse events unlikely to be attributable to study drug are shown in Table 31 below. Most events were skin cancers or tumors, for which no attribution to study drug was suspected.

Table 31. Serious dermatologic adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-031	226/011	72	F	75	—	121	Subject discontinued with (pre-existing?) basal cell carcinoma.
CV131-050	059/002	68	F	300	—	43	Basal cell carcinoma; study drug not interrupted.
CV131-031	015/065	74	F	150	12.5	132	Hospitalized for biopsy of non-cancerous labial lesion. Study drug was not interrupted.
CV131-040	010/001	72	M	150	25	48	History of skin cancer. Hospitalized for removal of skin cancer; study drug was not interrupted.
CV131-032	005/001	53	M	150	?	65	Hospitalized for removal of pre-existing benign lipoma. Study drug was not interrupted.
CV131-037	027/027	58	M	300	6.25	27	Hospitalized for removal of pre-existing cyst on finger.
Long-term phase							
CV131-025	023/014	70	M	50	—	22	Subject diagnosed with melanoma, treated by resection. Study drug continued.
CV131-031	023/017	69	F	75	—	9	History of mastectomy and radiation treatment. Hospitalized for excision of benign axillary lesion. Study drug was continued.
CV131-025	023/001	51	F	100	—	553	Hospitalization for surgery for bunions. Study drug was continued.
CV131-029	015/012	51	M	300	—	282	Hospitalized for debridement of foot abscess. Study drug was continued.
CV131-047	001/005	51	M	300	—	123	History of diabetic nephropathy. Hospitalized for cellulitis, during which hospitalization he went into acute renal failure, requiring dialysis and suffered altered mental status, which did not improve with dialysis. Study drug was discontinued.
CV131-038	060/012	66	M	75	12.5	46	Hospitalized for removal of squamous cell carcinoma. Study drug continued?
CV131-002	039/030	63	F	100	25	220 533	History of surgical treatment of skin cancer. Both hospitalizations for removal of squamous cell carcinomas. Study drug continued.
CV131-025	024/003	66	M	200	25	169	Subject diagnosed with basal cell carcinoma, excised. Study drug was continued.

8.2.3.3.3. Withdrawals for dermatologic adverse events

No withdrawal for dermatologic causes was considered implausibly related to study drug.

8.2.3.4. Common dermatologic adverse events

Common dermatologic adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 32 below and Table 33 below, respectively.

Table 32. Dermatologic 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
Rash	1.9	1.2	0.0	0.0	1.2	0.0	0.0	0.7	1.2	0.9	1.3	2.9	0.0	2.0	0.4
Urticaria	0.3	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
Pruritic rash	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
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
Hyperhidrosis	0.8	0.0	1.2	0.0	0.0	0.0	0.0	0.7	0.4	0.4	1.3	0.0	1.0	0.0	0.3
Pruritus	0.3	0.0	0.0	0.0	2.4	2.4	0.0	0.7	0.0	0.7	2.5	0.8	0.0	0.0	0.3
Dermatologic proc	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.2	1.3	0.4	0.0	0.0	0.3
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
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
Scalp hair abnm	0.2	0.0	0.0	1.2	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	1.0	0.2

Table 33. Dermatologic 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
Rash	2.1	2.3	4.5	1.9	0.0	2.3	4.4	0.0	0.5	0.0	2.5	2.4	0.0	0.0	4.5	1.0	0.7	9.3	5.0	0.0	0.0
Pruritus	0.4	2.3	0.6	1.3	2.4	4.5	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	2.3	0.5	1.5	2.3	0.0	0.0	0.0
Dermatitis	0.4	0.0	0.6	1.3	0.0	0.0	0.0	0.0	0.0	0.7	2.5	0.0	0.0	0.0	0.0	0.0	0.7	2.3	0.0	2.3	0.0
Infection	0.4	0.0	0.0	0.6	0.0	2.3	0.0	0.0	0.0	0.0	0.8	2.4	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0
Insect bite	0.0	0.0	0.6	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.5	2.3	0.0

In open-label extensions, dermatologic adverse events were reported for 127 subjects on irbesartan alone (7.1% or 130 subjects with events per 1000 subject-years) and by 185 subjects on irbesartan/HCTZ (11% or 153 subjects with events per 1000 subject-years). All such events are shown in Table 34 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 34. Dermatologic 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
Rash	28	1.6	28	46	2.7	38	Ecchymosis	8	0.4	8	15	0.9	12
Dermatitis	20	1.1	20	28	1.6	23	Dermatologic proc	5	0.3	5	10	0.6	9
Superficial fungal infect	9	0.5	9	15	0.9	12	Insect bite	3	0.2	3	11	0.6	9
Pruritus	10	0.6	10	14	0.8	12	Xeroderma	3	0.2	3	8	0.5	7

a. Subjects with events per 1000 subject-years.

8.2.3.5. Dermatologic laboratory findings No laboratory tests were considered in the evaluation of dermatologic safety.

8.2.4. Gastrointestinal system

8.2.4.1. Adequacy of gastrointestinal assessment Gastrointestinal safety was assessed through liver transaminases, alkaline phosphatase, total bilirubin, and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.4.2. Gastrointestinal events at least possibly drug-related

8.2.4.2.1. Gastrointestinal deaths There were no deaths attributed to gastrointestinal events and plausibly attributable to study drug.

8.2.4.2.2. Serious gastrointestinal adverse events No serious gastrointestinal events were plausibly attributable to study drug.

8.2.4.2.3. Withdrawals for gastrointestinal adverse events Withdrawals for gastrointestinal adverse events plausibly related to irbesartan are listed in Table 35 below.

Table 35. Withdrawals for gastrointestinal adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	040/021	49	M	5	—	5	Discontinued for dyspepsia and chest pain, considered possibly drug-related. Events resolved within 2 days.
CV131-002	017/012	64	M	10	—	76	Experienced epigastric distress, and discontinued for cholecystectomy.
CV131-002	045/025	40	M	25	—	22	Treated in emergency room and discontinued for severe dyspepsia, considered possibly drug-related.
CV131-002	032/010	49	M	50	—	18	Discontinued after 2 weeks of nausea after dosing.
CV131-027	031/022	46	M	75	—	32	Discontinued with moderate abdominal pain; unresolved.
CV131-029	003/012	35	F	150	—	1	Discontinued with abdominal pain and weight loss, which did not resolve. Events were considered possibly related to study drug.
CV131-040	032/013	75	F	75	25	17	Discontinued for abdominal pain, which resolved the following day; event was considered probably drug-related.
Long-term phase							
CV131-002	006/003	61	F	25	—	39	Discontinued for epigastric discomfort and uncontrolled hypertension. Events resolved.
CV131-027	008/001	53	F	150	—	17	Discontinued for abdominal pain, considered unlikely to be drug-related. Event was unresolved.
CV131-038	041/002	52	F	150	12.5	194	Discontinued with mild elevation in LFTs, considered unlikely to be drug-related. Event did not resolve.

8.2.4.3. Gastrointestinal events unlikely to be drug-related

8.2.4.3.1. Gastrointestinal deaths

There was one death attributed to gastrointestinal hemorrhage.

Study CV131-038LT subject 019/005 was a 44 year old male with a history of hypertension and viral hepatitis. His double-blind and open-label experience was event-free until he was hospitalized after 189 days for massive hemorrhage from esophageal varices. He died from a second hemorrhage 2 days later. Autopsy showed a nodular cirrhotic liver.

8.2.4.3.2. Serious gastrointestinal adverse events

Serious gastrointestinal adverse events unlikely to be attributable to study drug are shown in Table 36 below

Table 36. Serious gastrointestinal adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-038	040/003	68	F	75	—	42	Hospitalization for rectal bleeding attributed to hemorrhoids and diverticuli. Treatment was not interrupted.
CV131-037	039/017	69	M	100	6.25	17	Hospitalized for syncopal episode at home. Screen Hgb was 11 vs 6 at admission. Was worked up for GI hemorrhage, peptic ulcer disease. Study drug was discontinued.
Long-term phase							
CV131-002	037/012	73	M	50	—	714	Hospitalized for removal of mandibular gland tumor. Study drug was continued.
CV131-029	017/020	59	M	75	—	32	Hospitalized for surgery on pre-existing hemorrhoids. Study drug was not interrupted.
CV131-029	018/017	53	F	75	—	115	Gallstones diagnosed prior to enrollment. Hospitalized for laparoscopic cholecystectomy. Study drug continued?
CV131-002	025/006	57	M	100	—	241	History of colon polyps and peptic ulcer disease. Diagnosed with colon carcinoma. Study drug was continued.
CV131-025	027/007	58	M	100	—	308	Subject diagnosed with adenocarcinoma of pancreas. Study drug was discontinued.
CV131-027	020/004	56	F	150	—	78	Hospitalized for hemorrhoidectomy. Study drug was continued.
CV131-033	006/003	64	M	150	—	147	Hospitalized for bleeding duodenal ulcer. Study drug was interrupted.
CV131-028	003/002	69	F	300	—	285	History of gastric ulcers. Hospitalized for antral gastritis. Study drug was continued.

Table 36. Serious gastrointestinal adverse events unlikely to be related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-037	017/015	43	M	75	12.5	122	Unremarkable history. Hospitalized for substernal/epigastric pain, diagnosed as probable gastroesophageal reflux. Study drug was continued.
CV131-037	042/013	40	F	75	12.5	126	Hospitalized for viral gastroenteritis. Study drug was interrupted.
CV131-038	037/023	52	M	75	12.5	11	Hospitalization for colon cancer. Study drug was discontinued.
CV131-038	038/010	48	F	75	12.5	39	Hospitalized for abdominal pain, treated by cholecystectomy. Study drug was interrupted.
CV131-002	022/031	64	F	100	?	355 400	Unremarkable history. Hospitalized for chest pain; myocardial infarction ruled out. Subsequently hospitalized for elective gall bladder surgery. Study drug continued.
CV131-038	013/003	52	M	150	12.5	26	Polyps removed by sigmoidoscopy. Subsequently hospitalized for bowel resection for malignancy. Study drug was discontinued.
CV131-038	053/023	58	F	150	12.5	110	Hospitalized for acute intestinal obstruction, diagnosed with bowel adenocarcinoma, and treated by colostomy. Study drug was discontinued.
CV131-038	059/023	58	F	150	12.5	33	Hospitalized for cholecystectomy. Study drug was continued.
CV131-038	037/029	37	M	225	25	53	Hospitalized for acute cholecystitis. Study drug was discontinued.
CV131-038	013/016	56	M	300	12.5	275	History of healed peptic ulcers. Hospitalized for diverticulitis. Study drug was continued.
CV131-037	013/007	74	M	300	25	90	Study drug was discontinued for elevated liver enzymes. Subsequently hospitalized with abdominal pain, nausea, vomiting, and diagnosed with gallstone, surgically treated.
CV131-038	037/038	58	M	300	25	82	Hospitalized for acute cholecystitis and cholelithiasis. Study drug was continued.

8.2.4.3.3. Withdrawals for gastrointestinal adverse events

Withdrawals for gastrointestinal adverse events unlikely to be related to irbesartan are listed in Table 37 below.

Table 37. Withdrawals for gastrointestinal adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	043/003	67	M	5	—	48	Experienced epistaxis on day 47, lower GI bleed on day 48. Diagnosed with colon polyps and extensive diverticulitis
Long-term phase							
CV131-038	040/007	46	M	75	12.5	1	Discontinued for epigastric pain, considered probably drug-related, although double-blind period (on irbesartan 150 mg plus HCTZ 12.5 mg) was accompanied by a set of different transient symptoms. Event resolved.
CV131-002	011/007	56	M	100	?	209	History of rectal incontinence. Discontinued for rectal incontinence, headaches, and dysphagia. Events were unresolved.
CV131-037	004/006	54	M	300	25	79	Alcoholic discontinued for pancreatitis, considered possibly drug-related. Event resolved.

8.2.4.4. Common gastrointestinal adverse events

Common gastrointestinal adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 38 below and Table 39 below, respectively.

Table 38. Gastrointestinal adverse events by dose on double-blind treatment.

		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
Dyspepsia/heartburn	1.1	2.4	2.4	1.2	3.6	0.0	3.7	0.3	0.4	2.7	1.3	2.1	1.9	1.0	0.6
Diarrhea	2.2	1.2	0.0	0.0	3.6	2.4	4.9	3.0	2.5	2.9	7.6	3.3	2.9	4.0	0.6
Nausea/vomiting	2.7	1.2	0.0	2.5	2.4	0.0	3.7	2.7	1.2	1.8	1.3	1.3	3.8	1.0	0.6
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

Table 38. Gastrointestinal adverse events by dose on double-blind treatment.*(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
Dental abn	0.9	1.2	1.2	0.0	1.2	2.4	1.2	0.7	0.8	0.2	1.3	0.0	0.0	2.0	0.5
Constipation	0.5	1.2	0.0	1.2	0.0	0.0	0.0	0.7	1.2	0.4	0.0	1.7	0.0	1.0	0.4
ASAT increased	0.2	1.2	0.0	1.2	0.0	0.0	1.2	0.0	0.0	0.2	0.0	0.0	1.0	0.0	0.3
ALAT increased	0.3	0.0	0.0	1.2	0.0	0.0	1.2	0.0	0.0	0.7	0.0	0.4	0.0	0.0	0.2
Incr CPK	0.2	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.8	0.4	0.0	0.0	0.0	0.0	0.2
Incr alk phosphatase	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	1.0	0.0	0.1
GGTP increased	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
Liver func test incr	0.5	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
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
Flatulence	0.3	1.2	0.0	1.2	0.0	0.0	0.0	0.7	0.0	0.4	0.0	0.4	0.0	0.0	0.3
Gastroenteritis	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.7	0.0	0.4	1.0	0.0	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
Anorectal disorder	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.4	0.0	1.0	0.2
Dental procedure	0.2	0.0	0.0	0.0	0.0	2.4	0.0	0.3	0.0	0.2	0.0	0.0	0.0	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

Table 39. Gastrointestinal adverse events by dose on double-blind combination treatment.

	Irbesartan (mg/day)																			
	0				37.5				75			100				150		300			
HCTZ	0	6.2	12	25	0	6.2	12	25	0	12	25	0	6.2	12	25	0	12	0	6.2	12	25
N=	236	44	177	159	42	44	45	41	196	134	118	41	44	43	44	199	135	43	40	44	45
Nausea/vomiting	0.4	0.0	2.8	2.5	0.0	4.5	2.2	2.4	3.6	0.0	4.2	0.0	0.0	0.0	2.3	4.0	3.7	0.0	0.0	11.4	0.0
Diarrhea	3.4	0.0	1.1	1.3	2.4	0.0	0.0	0.0	4.1	0.7	2.5	0.0	2.3	2.3	0.0	2.0	3.0	2.3	2.5	6.8	4.4
Dyspepsia	0.8	0.0	2.8	0.6	0.0	0.0	0.0	2.4	0.5	2.2	1.7	0.0	6.8	0.0	2.3	1.0	1.5	2.3	5.0	2.3	0.0
Abdominal pain	0.8	0.0	1.7	1.9	0.0	0.0	2.2	0.0	2.6	0.0	4.2	2.4	2.3	2.3	0.0	1.5	1.5	0.0	5.0	0.0	0.0
Dental abnormality	0.4	0.0	0.6	2.5	2.4	0.0	0.0	0.0	1.5	0.0	1.7	4.9	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0
Anorectal disorder	0.4	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.5	1.5	1.7	0.0	2.3	0.0	2.3	0.5	0.0	2.3	0.0	0.0	0.0
Oral lesion	0.0	0.0	0.6	1.3	0.0	0.0	0.0	2.4	1.0	0.0	0.0	2.4	2.3	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
Constipation	0.4	0.0	0.0	0.0	0.0	2.3	0.0	0.0	1.0	1.5	1.7	0.0	0.0	2.3	0.0	0.0	0.7	0.0	0.0	0.0	0.0
Rectal bleeding	0.8	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.8	0.0	2.3	0.0	0.0	0.0	0.7	0.0	0.0	2.3	0.0
Flatulence	0.4	0.0	0.0	0.0	0.0	4.5	0.0	0.0	0.5	0.0	0.0	0.0	0.0	2.3	0.0	0.5	0.0	0.0	0.0	0.0	0.0
Epigastric pain	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	1.7	0.0	0.0	0.0	2.3	0.0	0.7	0.0	2.5	0.0	0.0

In open-label extensions, gastrointestinal adverse events were reported for 220 subjects on irbesartan alone (12% or 220 subjects with events per 1000 subject-years) and by 312 subjects on irbesartan/HCTZ (18% or 254 subjects with events per 1000 subject-years). All such events are shown in Table 40 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 40. Gastrointestinal 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
Diarrhea	28	1.6	28	73	4.3	60	Oral lesion	10	0.6	10	12	0.7	10
Dyspepsia	23	1.3	23	59	3.5	49	Anorectal disorder	9	0.5	9	12	0.7	10
Nausea/vomiting	33	1.8	33	53	3.1	44	Gastritis	7	0.4	7	11	0.6	9
Abdominal pain	34	1.9	34	40	2.4	33	Dental abscess	9	0.5	9	8	0.5	7
Dental abnormality	20	1.1	20	17	1.0	14	Dental procedure	9	0.5	9	8	0.5	7
Gastroenteritis	12	0.7	12	16	0.9	13	Flatulence	9	0.5	9	6	0.4	5
Constipation	13	0.7	13	12	0.7	10	Oral surgery	3	0.2	3	10	0.6	9

a. Subjects with events per 1000 subject-years.

8.2.4.5. Gastrointestinal laboratory findings

Hepatic enzymes were evaluated for systematic treatment related shifts, and no such shifts were in evidence for either irbesartan alone or irbesartan plus HCTZ.

Because of concerns of possibly treatment-related elevations in hepatic enzymes seen in studies of another angiotensin II receptor antagonist, additional attention was given to placebo-controlled and long-term studies of irbesartan alone. During double-blind treatment, two subjects were identified with elevations in hepatic enzymes. Both subjects had enzyme levels below the upper limit of normal at baseline, but had elevation of either AST or ALT above 3x ULN on the first day. Both of these subjects were randomized to placebo and neither was terminated from study. No subject randomized to active treatment had a level of hepatic enzyme below ULN at baseline and a subsequent rise to 2x ULN reported. One subject randomized to placebo had elevated ALT >3x ULN on the first day of open label treatment; he was not discontinued. Two subjects on irbesartan plus HCTZ are noted in Table 35, "Withdrawals for gastrointestinal adverse events plausibly related to irbesartan.," on page 62 and Table 36, "Serious gastrointestinal adverse events unlikely to be related to irbesartan.," on page 62 as having discontinued for elevations in hepatic enzymes; one of these subjects was subsequently diagnosed with gall bladder disease.

8.2.5. Genito-urinary system

8.2.5.1. Adequacy of genito-urinary assessment

Genito-urinary safety was assessed through electrolytes, uric acid, BUN, creatinine, routine urinalysis, and adverse events. This evaluation is considered adequate for a drug of this class studied in a hypertensive population.

8.2.5.2. Genito-urinary events at least possibly drug-related

8.2.5.2.1. Genito-urinary deaths

No death attributable to genito-urinary events was considered to have any reasonably likely relationship to study drug.

8.2.5.2.2. Serious genito-urinary adverse events

No serious genito-urinary adverse events were plausibly attributable to study drug.

8.2.5.2.3. Withdrawals for genito-urinary adverse events

Withdrawals for genito-urinary adverse events plausibly related to irbesartan are listed in Table 41 below.

Table 41. Withdrawals for genito-urinary adverse events plausibly related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-029	024/008	52	F	75	—	1	Discontinued after 2 weeks of increased urinary frequency, which resolved.
CV131-038	044/001	63	M	75	—	14	Baseline complaint of impotence. Discontinued with worsening sexual dysfunction, thought possibly drug-related.
CV131-027	019/005	31	M	75	—	21	Discontinued for impotence; unresolved.
CV131-038	014/006	42	M	150	—	13	Discontinued with onset of proteinuria, considered unlikely to be drug-related. Event did not resolve.
CV131-038	057/042	40	F	150	—	13	Discontinued with metrorrhagia, of unknown relationship to study drug. Event resolved.
CV131-038	008/014	38	M	75	12.5	14	Discontinued for moderate hematuria, considered unlikely to be drug-related. Event resolved within 2 months.'
CV131-031	015/070	84	M	150	25	165	Discontinued for increase in serum creatinine, considered possibly drug-related. Resolution is unknown.
Long-term phase							
CV131-002	034/013	54	F	25	—	72	Discontinued for edema. Event was unresolved.
CV131-046	001/204	61	M	37.5	—	1	Discontinued with acute renal failure and asymptomatic postural hypotension, both considered at least possibly drug-related. Events resolved.
CV131-029	005/003	43	M	75	—	268	Discontinued for erectile dysfunction, considered possibly drug-related. Event did not resolve.
CV131-046	003/002	54	M	75	—	137	Discontinued for increased serum creatinine, considered possibly drug-related. Event resolved.
CV131-025	019/004	50	M	100	—	51	Discontinued for impotence, considered possibly drug-related. Event did not resolve.
CV131-033	007/001	58	F	150	—	155	History of chronic glomerular nephritis. Discontinued for elevated serum potassium and serum creatinine, considered possibly drug-related. Events did not resolve.
CV131-025	032/015	59	M	200	—	87	Discontinued for proteinuria, increased serum creatinine, and poor blood pressure control. Resolution is unknown.
CV131-038	050/012	36	M	75	12.5	111	Discontinued for decreased libido, considered unlikely to be drug-related. Event resolved.
CV131-038	060/007	54	M	75	12.5	28	Discontinued for increased urinary frequency, considered probably drug-related. Event resolved.
CV131-031	008/010	71	F	300	12.5	149	Discontinued with creatinine elevation from 124 to 132 mM, considered drug-related. BUN remained within normal limits. Creatinine was WNL one month later.
CV131-031	015/036	73	M	300	25	115	Discontinued with creatinine increased from 1.4 to 1.6, considered possibly drug-related; BUN remained WNL. Resolution is unknown.
CV131-031	015/039	72	M	300	50	105	Discontinued with creatinine elevation from 1.5 to 2.0 mg/dL, BUN from 22 to 39 mg/dL, considered possibly drug-related. Resolution is unknown.

8.2.5.3. Genito-urinary events unlikely to be drug-related

8.2.5.3.1. Genito-urinary deaths

There was one death attributed, in part, to an auto-immune glomerular nephritis.

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.

8.2.5.3.2. Serious genito-urinary adverse events

Serious genito-urinary adverse events unlikely to be attributable to study drug are summarized in Table 42 below. This listing includes some events from studies of subjects with pre-existing renal impairment (study CV131-033) or heart failure (study CV131-003).

Table 42. Serious genito-urinary adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-027	017/001	71	F	75	—	65	Hospitalized for post-menopausal vaginal bleeding, and treated with dilation and curettage. Study drug was not interrupted.
CV131-027	017/007	68	F	75	—	190	Hospitalized for post-menopausal vaginal bleeding, and treated with dilation and curettage. Study drug was not interrupted.
CV131-028	041/003	77	M	75	—	72	History of prostatectomy and urethroplasty. Hospitalized for endoprostatectomy and urethrotomy. Subject completed double-blind phase.
CV131-031	036/008	71	F	75	—	43	Hospitalized for mastectomy; final pathology report is "pending". Study drug was discontinued.
CV131-033	003/003	65	F	75	—	1	History of renal calculi and baseline creatinine clearance of 44 mL/min. Baseline BP 187/106 fell to 100/60, HR 80 bpm after first dose. Hospitalized for fluids; study drug was discontinued.
CV131-033	004/004	67	M	75	—	30	History of chronic renal failure. Hospitalized for start of dialysis, without further decline in creatinine clearance. Study drug was discontinued.
CV131-033	026/001	65	M	75	—	41	History of chronic renal failure and hemodialysis. Hospitalized for thrombosed vascular access. Study drug was continued.
CV131-031	034/002	78	M	150 75	—	51 80	Hospitalized first for acute urinary retention and then for prostate surgery. Study drug was not interrupted.
CV131-032	019/007	43	M	150	—	23	Hospitalized for acute renal failure attributed to herbal remedy. Study drug was discontinued.
CV131-028	003/005	64	M	150	—	68	History includes vesical cancer, cystectomy, and BPH. Hospitalized for post-surgical urethral stenosis. Subject completed double-blind phase.
CV131-025	011/002	65	M	200	—	36	Hospitalized with renal calculus, but continued into open-label phase.
CV131-037	045/001	40	F	300	—	35	Hospitalization to rule out ovarian cyst. Study drug was interrupted.
CV131-037	001/055	53	M	300	6.25	32	History of renal calculi. Hospitalized for renal calculus; study drug was not interrupted.
Long-term phase							
CV131-002	045/026	64	M	10	—	53	Diagnosis of prostate cancer. Study drug was discontinued.
CV131-003	002/011	69	F	25	—	169	History of diabetes. Hospitalization for kidney infection. Study drug continued?
CV131-025	016/024	45	M	50	—	149	History of impotence. Hospitalized for penile implant. Study drug continued.
CV131-027	009/006	59	F	75	—	52	Hospitalization for removal of cervical polyp. Study drug was interrupted.
CV131-033	027/005	38	M	75	—	132	History of hemodialysis. Hospitalized for renal transplant. Study drug was discontinued.
CV131-002	020/001	57	M	100	—	672	Unremarkable history. Hospitalized for prostate cancer. Stud drug was continued.
CV131-025	027/001	62	M	100	—	402	Subject was diagnosed with prostate/bladder cancer. Study drug was discontinued.
CV131-027	001/002	60	F	150	—	256	History of post-menopausal bleeding. Hospitalized for post-menopausal bleeding, treated by hysterectomy. Study drug was continued.
CV131-027	014/001	68	F	150	—	73 195	First hospitalization for vaginal prolapse; study drug was continued. Subsequently hospitalized twice for asthma, once with chest infection. Study drug was continued.
CV131-028	032/011	50	F	150	—	279	Breast cancer diagnosed by mammography. Study drug was discontinued.
CV131-044	011/003	60	M	150	—	142	Hospitalized for electrolyte disturbance and renal mass, not biopsied. Next day, he developed atrial fibrillation. Study drug was discontinued.
CV131-025	014/015	37	F	200	—	356	History of tubal ligation. Hospitalized for pelvic mass, dysmenorrhea, and severe dyspareunia, treated by hysterectomy. Study drug was continued.
CV131-025	023/010	40	M	200	—	284 459	History of pyelonephritis and urethral stricture. Hospitalized for renal calculi. Study drug was continued. Subsequently re-hospitalized for nephrolithiasis. Study drug was continued.
CV131-029	001/001	53	M	225	—	343	Hospitalized for urinary tract infection and pyelonephritis. Study drug continued?
CV131-028	003/005	66	M	300	—	284	History of benign vesicular tumor. Hospitalized for vesicular tumor recurrence, treated by resection. Study drug was interrupted.
CV131-028	029/002	66	M	300	—	355	History of renal lithiasis. Hospitalized for renal colic crisis. Study drug was continued.
CV131-029	020/012	43	M	300	—	197	Hospitalized for resection of renal carcinoma. Study drug was discontinued.
CV131-050	005/009	68	M	300	—	98	Diagnosed with prostate cancer. Study drug was continued.
CV131-050	028/015	69	M	300	—	906	Hospitalized for transurethral resection of prostate for benign prostate hyperplasia. Study drug was interrupted.

Table 42. Serious genito-urinary adverse events unlikely to be related to irbesartan.*(Continued)*

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
CV131-038	022/012	44	F	75	12.5	141	History of surgical treatment of ulcer disease and hysterectomy. Hospitalized for pyoperitoneum, ruptured diverticulum, hydrosalpinx, and necrotic ovary, resulting in salpingo-oophorectomy and colostomy. Study drug was discontinued.
CV131-038	039/005	64	F	75	12.5	62	Diagnosed with breast cancer. Subsequently underwent mastectomy. Study drug was continued.
CV131-038	057/029	55	F	75	12.5	34	Diagnosed with breast cancer. Subsequently underwent mastectomy. Study drug was discontinued.
CV131-038	059/025	59	M	75	12.5	56	Hospitalized for prostatectomy. Study drug was continued.
CV131-002	043/011	72	M	100	?	427	History of BPH. Diagnosis of adenocarcinoma of prostate. Study drug continued.
CV131-032	023/006	36	F	150	?	203	History of sterilization. Hospitalized for salpingitis, treated with antibiotics. Study drug was continued.
CV131-038	053/014	66	F	150	12.5	146	Hospitalized for uterine adenocarcinoma, treated by hysterectomy. Study drug continued?
CV131-038	018/029	48	F	300	25	133	History of menorrhagia and tubal ligation. Hospitalized for total abdominal hysterectomy with bilateral salpingoopherectomy. Study drug was continued.

8.2.5.3.3. Withdrawals for genito-urinary adverse events

Withdrawals for genito-urinary adverse events unlikely to be related to irbesartan are listed in Table 43 below.

Table 43. Withdrawals for genito-urinary adverse events unlikely to be related to irbesartan.

Study	Subject	Age	Sex	Dose		Days	History
				Irb	HCTZ		
Double-blind phase							
CV131-002	004/001	45	F	5	—	29	History of diabetes; baseline proteinuria, elevated BUN and creatinine. Discontinued for abnormalities in renal function not materially changed.
CV131-038	024/006	46	M	75	—	14	Baseline creatinine elevated, attributed to dehydration. Discontinued with creatinine unchanged.
CV131-038	037/040	63	M	75	12.5	22	Discontinued for impotence, apparently starting during placebo withdrawal. Event said to improve after withdrawal.
Long-term phase							
CV131-050	020/008	51	M	150	—	1	Discontinued for impotence, which did not appear during double-blind period on irbesartan 900 mg. Event, which resolved, was considered possibly drug-related.

8.2.5.4. Common genito-urinary adverse events

Common genito-urinary adverse events from the double-blind periods in monotherapy studies and studies in combination with HCTZ are shown in Table 44 below and Table 45 below, respectively.

Table 44. Genito-urinary 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
Abn urination	0.6	1.2	1.2	0.0	2.4	2.4	0.0	1.0	0.0	0.2	0.0	0.8	2.9	0.0	0.4
UTI	1.4	0.0	1.2	0.0	0.0	2.4	0.0	1.0	0.8	1.6	0.0	1.7	1.0	1.0	0.4
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
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
Menstrual disorder	0.3	1.2	1.2	0.0	1.2	0.0	0.0	0.3	0.0	0.0	0.0	0.8	0.0	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
Urine protein incr	0.5	2.4	1.2	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.0	0.0	1.0	0.0	0.3

Table 44. Genito-urinary 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
Urine RBC incr	0.6	2.4	0.0	1.2	0.0	0.0	0.0	0.3	0.0	1.1	1.3	0.0	0.0	0.0	0.3
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
Pain kidney	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.4	1.0	0.0	0.2
WBC urine incr	0.2	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.4	0.0	0.0	0.2
Prostate disorder	0.2	0.0	0.0	0.0	0.0	2.4	0.0	0.3	0.0	0.2	0.0	0.8	0.0	0.0	0.2

Table 45. Genito-urinary 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	2.5	4.5	2.3	1.9	2.4	0.0	0.0	2.4	1.5	0.7	0.8	0.0	0.0	4.7	4.5	1.0	3.0	0.0	0.0	6.8	0.0
Urinary abnormality	0.8	0.0	4.0	1.3	2.4	2.3	2.2	0.0	0.5	0.7	0.0	0.0	4.5	2.3	4.5	1.0	2.2	0.0	5.0	0.0	4.4

In open-label extensions, genito-urinary adverse events were reported for 110 subjects on irbesartan alone (6.1% or 110 subjects with events per 1000 subject-years) and by 100 subjects on irbesartan/HCTZ (5.9% or 82 subjects with events per 1000 subject-years). All such events are shown in Table 46 below; the reviewers made no attempt to separately tabulate events according to the likelihood of their being drug-related.

Table 46. Genito-urinary 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
Urinary tract infection	23	1.3	23	40	2.4	33	Prostate disorder	9	0.5	9	6	04	5
Abnormal urination	32	1.8	32	26	1.5	21	Kidney pain	10	0.6	10	4	0.2	3

a. Subjects with events per 1000 subject-years.

8.2.5.5. Genito-urinary laboratory findings

The proportion of subjects having a baseline potassium below the upper limit of normal and at least one post-randomization measurement who had a post-randomization value above the upper limit of normal was 3.9% on irbesartan and 2.7% on placebo. As shown in Figure 24 below, there is at least a suggestion of dose-relatedness to the incidence of hyperkalemia[9].

Few subjects had a rise from below the upper limit of normal for creatinine to above the ULN: 0.7% on placebo and 0.7% on all doses of irbesartan.

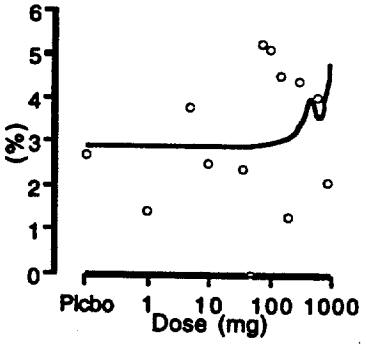

Figure 24. Incidence of hyperkalemia by dose.

[9] The line was drawn by a non-parametric fitting procedure (loess).