A25. CV131-043: The disposition and bioavailability of irbesartan in healthy male subjects after intravenous and oral administration of [^{14}C] irbesartan in solution, and oral administration of irbesartan capsule.

A25.1. Source documents

Study report: NDA 20-757, vol 1.92-1.93.

A25.2. Investigators

Miquel A. Zinny, M.D., Medical and Technical Research Associates, 320 Washington Street, Boston, MA 02135.

A25.3. Study design

The objective of the study was to determine the absolute bioavailability of an irbesartan oral solution and capsule formulation, determine mass balance, and identify the metabolites in plasma, urine and feces.

This was a single-center, open label, single dose, 3-way crossover in 12 healthy male subjects. Each subject received a 50 mg dose of irbesartan as ^{14}C-irbesartan i.v. solution infused over 30 minutes, ^{14}C-irbesartan oral solution or non-radiolabeled irbesartan capsules. Blood samples were collected at pre-dose, and 0.17, 0.33, 0.50, 0.67, 0.83, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144 and 168 hours after IV dosing. The blood sampling scheme was the same for oral dosing minus the 0.17, 0.50 and 0.83 time points. Sampling was stopped at 96 hours for oral capsule dosing. Urine samples were collected at pre-dose and 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours post-dose. Fecal samples were collected up to 168 hours post-dosing.

Assay of plasma and urinary irbesartan was performed according to methods 4 and 10, respectively, in Table 7. *Assay validation for irbesartan.* on page 15. Plasma, urine and feces were solubilized and measured for radioactivity of irbesartan and metabolites.

C_{max}, T_{max}, $T_{1/2}$, AUC_{∞}, MRT (mean residence time), Clr, %ABS, F, E (hepatic extraction ratio, and MAT (mean absorption time) were the pharmacokinetic parameters evaluated. No statistical tests were done.

A25.4. Results

The pharmacokinetic results for each formulation are summarized in Table 253 below.

Table 253. Pharmacokinetic parameters (CV131-043).

	Intravenous		Oral solution		Capsule
	Irbesartan	Total radioactivity	Irbesartan	Total radioactivity	Irbesartan
C_{max} (ng/mL)	4445±905	4384±704	2097±577	2001±538	1309±368
AUF_{∞} (ng.h/mL)	5589±1209	7247±1499	4581±1331	6555±1577	4968±1915
T_{max} (h)[a]	—	—	0.3 (0.3-1.0)	0.3 (0.3-1.0)	1.25 (0.7-2.0)
CL_T (mL/min)	157±40	—	—	—	—
V_{SS} (L)	53±15	—	—	—	—
$T_{1/2}$ (h)	12.6±6.2	16.3±7.7	12.1±4.6	18.5±11.0	14.4±8.7
CL_R (mL/min)	3.5±2.2	—	2.7±1.2	—	2.3±1.6
%UR	2.2±0.9	24.2±6.5	1.4±0.6	23.0±5.9	1.1±0.6
F (%)	—	—	82±17	—	88±20

a. Median (minimum, maximum)

Plasma profiles of unchanged irbesartan and total radioactivity following intravenous dosing or dosing with the oral solution are shown in Figure 65 below. The mean plasma concentration profiles for unchanged irbesartan and total radioactivity were superimposable up to 24 hours after intravenous dosing.

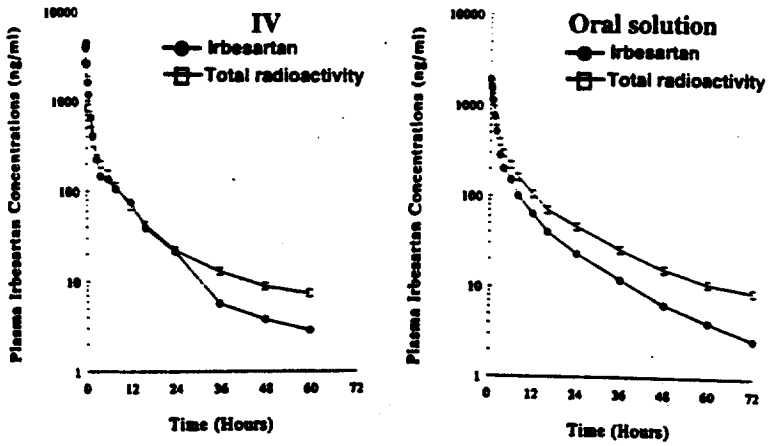

Figure 65. Plasma irbesartan and total radioactivity after i.v. and oral solution dosing (CV131-043).

The plasma profile following a 50 mg oral dose of unlabeled irbesartan is shown in Figure 66 below.

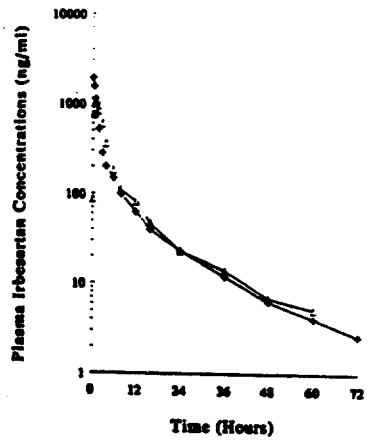

Figure 66. Plasma irbesartan after oral dosing (CV131-043).

A25.4.1. Safety

Not reviewed.

A25.5. Summary.

Irbesartan is rapidly absorbed when administered orally. The mean T_{max} for the oral solution was 0.45 hours, and the maximum concentration was generally achieved within 20 minutes. The mean T_{max} for the oral capsule formulation was 1.35 hours; this is approximately 3x as long as T_{max} for the oral solution. Oral bioavailability is slightly higher for the capsule formulation, 87% compared to 82% for the oral solution. It appears that the parent compound is the primary plasma circulating moiety of irbesartan. Biliary excretion is thought to be the main pathway for elimination of irbesartan and its metabolites. However, due to problems with fecal collection, this was not apparent from the data presented. This study was repeated[1]. The data show that approximately 25% of the radioactive dose is recovered in urine; less than 2% of the dose is recovered as unchanged irbesartan.

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[1] *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.

A26. CV131-045: Safety, tolerance, pharmacokinetics and pharmacodynamics of irbesartan following single and multiple 150 to 900 mg doses in healthy subjects.

A26.1. Source documents

Study report: NDA 20-757, vol 1.120-1.123.

A26.2. Investigator

Howard D. Uderman, M.D. The Clinical Pharmacology Unit of the Medical Center at Princeton, Princeton, NJ, USA.

A26.3. Study dates

4 November 1994 to 20 January 1995.

A26.4. Study design

The study objective was to assess the safety, tolerance, pharmacokinetics and pharmacodynamics of single, and multiple doses of 150, 300, 600, and 900 mg of irbesartan in healthy subjects. This study was a placebo-controlled, double-blind, sequential, ascending dose study of single and multiple doses. Within each cohort, subjects were randomized to placebo (N=3) or irbesartan 150, 300, 600, or 900 mg (N=9). Subjects received the randomized dose on day 1, placebo on days 2 to 4, randomized dose on days 5 to 11, and placebo on days 12 to 14. Table 254 below shows the schedule of events.

Table 254. Schedule of events (CV131-045).

	Screen	Day							
		-2	-1	1	2	3-10	11	12	13-14
Hematology, chemistry, urinalysis	X				X			X	X
Serum B-HCG	X	X							X
Drugs of abuse in urine	X	X							
Vital signs	X	X	X	X	X	X	X	X	X
ICG clearance									
24-h urinalysis	X				X			X	X
Dosing with irbesartan				X	X	X	X	X	X
Urine PD samples			X	X			X		
Blood PD samples			X	X			X		
Blood and urine PK samples			X	X			X		
C_{min} blood samples for irbesartan						X			
Adverse events		X	X	X	X	X	X	X	X
Discharge									X

Table 255 below shows drug supplies.

Table 255. Drug supplies (CV131-045).

Unit	Product number	Lot	Unit	Product number	Lot
Placebo	186295-R000-030	N94F090C	Irbesartan 50 mg	186295-R050-032	N94D063C
			Irbesartan 100 mg	186295-R100-033	N94G097C

Assay of plasma irbesartan was performed according to methods 2 and 5, and urinary irbesartan was assayed by methods 8 and 10, in Table 7. *Assay validation for irbesartan.* on page 15. Plasma, urine and feces were solubilized and measured for radioactivity of irbesartan and metabolites.

The single, and multiple dose pharmacokinetic parameters included AUC_t and AUC_∞, C_{max}, $t_{1/2}$, CL_R, T_{max}, %UR, and AI, with sampling as shown in Table 256 below.

Table 256. PK and PD sampling (CV131-045).

Time (h)	PK		PD		Meal	Time (h)	PK		PD		Meal
	Blood	Urine	AII/PRA	Vitals			Blood	Urine	AII/PRA	Vitals	
Before rising		-8-0	X	X		10	X	8-12		X	D
Pre-dose	X	-0.8-0	X	X		12	X	12-24	X	X	
0.5	X	0-2		X		24	X	12-24	X		
1	X	0-2	X	X		30	X	24-36			
1.5	X	0-2		X		36	X	24-36			
2	X	2-4	X	X	B	48	X	36-48	X	X	
3	X	2-4		X		60	X	48-60			
4	X	4-6	X	X	L	72	X	60-72	X	X	
5		4-6		X		84	X	72-96			
6	X	6-8		X		96	X	72-96	X	X	
8	X	8-12	X	X							

A26.5. Results

A26.5.1. Pharmacokinetics

The pharmacokinetics data of irbesartan measured after the first dose, and after 7 days of dosing (day 11), for each of the treatment groups and placebo groups are presented in Figure 67 below. Pharmacokinetics parameters are shown in Table 257 below. The C_{max} in the active treatment groups increased with ascending dosage but not in a linear fashion. Mean values for AUC_{τ} and AUC_{∞} also increased with ascending dose, but not in a linear fashion.

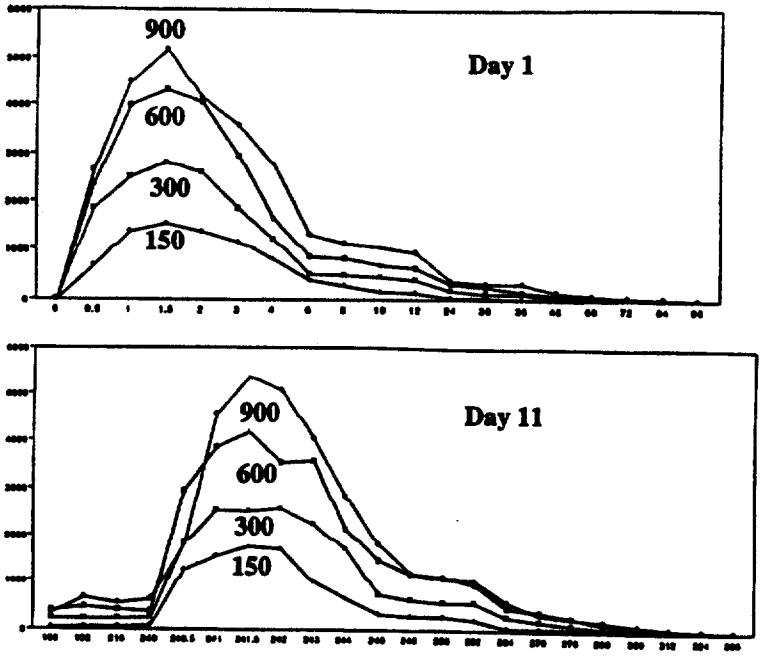

Figure 67. Mean drug levels on day 1 and day 11 (CV131-045).

The C_{max} and AUC_{τ} increased with ascending dosage, but not in a linear fashion. The C_{max} and AUC of irbesartan are proportional to dose over the 150 to 600 mg dose range. AI (the ratio of results on day 11 to the results on day 1) based on AUC ratio or C_{max} ratio showed no significant differences among treatment groups.

Table 257. Pharmacokinetic parameters (CV131-045).

	Day	Irbesartan			
		150 mg N=8-9	300 mg N=9	600 mg N=9	900 mg N=9
C_{max} (ng/mL)	1	1854±360	2981±943	4940±1211	5348±1918
	11	2039±370	3151±788	4440±683	5601±2184
T_{max} (h) (median and range)	1	1.5 (0.5-3.0)	1.5 (1.5-3.0)	1.5 (1.0-2.0)	1.5 (0.5-3.0)
	11				
AUC (ng.h/mL)	1	9715±3039	20027±5157	32616±11908	44826±20008
	11	9278±3024	19846±5843	31961±9716	34234±9345
$T_{1/2}$ (h)	1	16±7	14±7	14±8	17±7
	11	11±4	11±5	15±7	14±6
%UR	1	0.9±0.4	0.9±0.3	0.8±0.3	0.6±0.3
	11	1.2±0.5	1.1±0.3	0.7±0.3*	0.5±0.2*
AI based on C_{max}		1.12 (0.97-1.30)	1.07 (0.94-1.23)	0.91 (0.80-1.04)	1.08 (0.94-1.25)
AI based on AUC		1.14 (0.95-1.36)	1.21 (1.03-1.43)	1.26 (1.07-1.49)	1.13 (0.95-1.36)

Mean values for percent urinary excretion of the drug was higher in the 600 and 900 mg doses than in the 150 and 300 mg doses.

A26.5.2. Pharmacodynamics

There were no significant differences among treatment groups with respect to heart rate, SeSBP, and SeDBP.

A26.5.3. Hormones

On day 11, there were clearly dose-related increases in angiotensin II and plasma renin activity, as shown in Figure 68 below. Dose-related changes in urinary aldosterone levels were not seen.

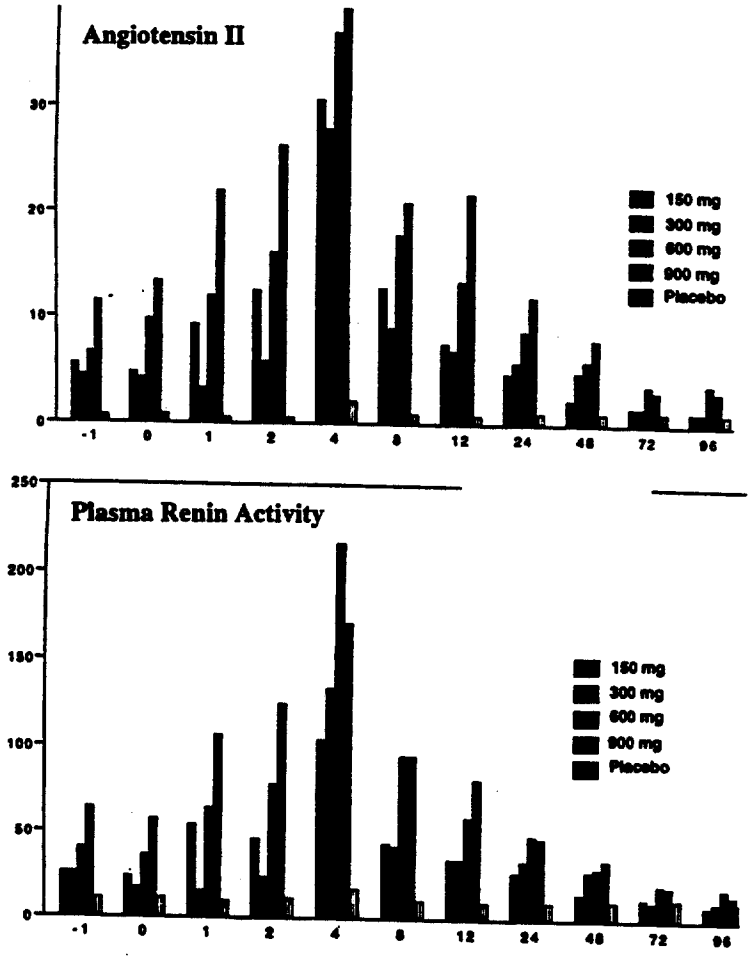

Figure 68. AII and plasma renin activity by dose and time (CV131-045).

A26.5.4. Safety

There were no deaths. Two subjects discontinued after enrollment. The frequencies of drug-related adverse events were not different in the active treatment groups compared to placebo. Nervous and gastrointestinal systems were most commonly affected by adverse events.

A26.6. Summary

This was an adequate, and well controlled, randomized study in which oral doses of irbesartan from 150 to 900 mg were administered to healthy male subjects in single and multiple doses (7 days). Irbesartan concentrations reached a quasi-steady state after 3 days. Plasma AUC and C_{max} were less than dose-proportional. There was no significant accumulation of the drug during the once-daily dosing to steady state during the 7-day period. Plasma angiotensin II and renin were significantly elevated in the active treatment groups compared to placebo. Urinary aldosterone excretion showed no dose-related pattern. The drug was well tolerated, with no dose-limiting side effects.

A27. 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).

A27.1. Source documents

Study report: NDA 20-757, vols 1.268 to 1.275; electronic document MAST050.PDF; CRFs.

A27.2. Investigators

This study was conducted at 54 sites by 55 investigators in the US.

A27.3. Study dates

25 April 1995 to 26 February 1996.

A27.4. Study design

The study description was based on the revised protocol, #1, dated 23 February 1995, with one later amendment (22 May 1995) that did not affect the study.

The study design is shown in Figure 69 below. This was a randomized, multicenter, double-blind, placebo-controlled, parallel study in subjects with mild-to-moderate essential hypertension. Following a 4- to 5-week single-blind placebo lead-in period, qualifying subjects were randomized to receive 8 weeks of double-blind treatment with once daily oral irbesartan 150, 300, 600, or 900 mg or placebo. Subjects then entered a 1-week single-blind placebo washout period. An open-label, long-term extension of this study will be the subject of a separate report.

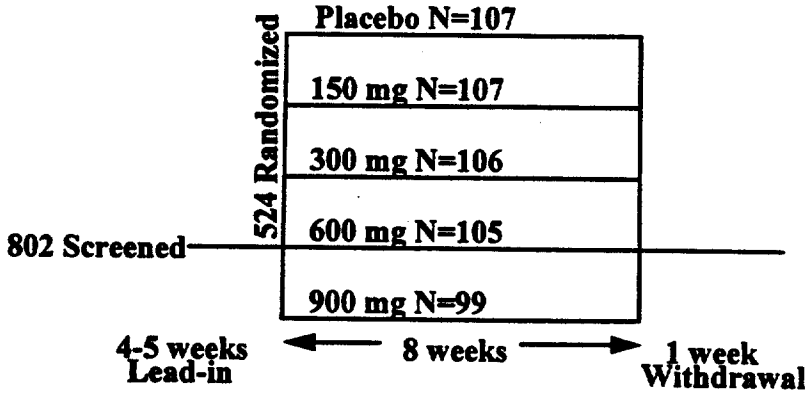

Figure 69. Study design (CV131-050).

Drug supplies are shown in Table 258 below.

Table 258. Drug supplies (CV131-050).

	Lot		Lot
Placebo	N94M142C	Irbesartan 150 mg	N95002 N95027

Subjects were to be consenting males, and post-menopausal or surgically sterile females who were not nursing, 18 years of age or older, with mild-to-moderate essential hypertension (SeDBP 95 to 110 mmHg). Exclusions included (1) suspected or known causes of secondary hypertension, (2) recent MI, atherosclerotic, and obstructive valvular heart diseases, (3) dysrhythmias requiring medication, (4) insulin-dependent diabetes mellitus, (5) women of child bearing potential, (6) psychiatric disorders, (7) obesity, (8) autoimmune disorders, (9) cerebrovascular incidents, (10) seizures, (11) low output heart failure, (12) malabsorption, and (13) abnormal hematologic or chemistry profiles, e.g. serum potassium, ALAT, ASAT, creatinine, and blood urea nitrogen.

The primary end point was change from baseline in trough SeDBP at week 8 of double-blind treatment.

Secondary end points were change from baseline in trough seated systolic blood pressure (SeSBP), standing diastolic blood pressure (StDBP), standing systolic blood pressure (StSBP), and seated and standing heart rate (HR) at week 8 of double-blind treatment, change from baseline at weeks 1 and 2 (trough) and week 8 (peak) in seated and standing diastolic and systolic BP and HR, trough-to-peak ratio for SeDBP after first dose and at week 8 of double-blind treatment, response rate at week 8, change from baseline in trough SeDBP and SeSBP at 3 and 7 days of placebo washout following double-blind treatment, assessment of trough and peak plasma drug concentrations at week 8, and trough and peak renin angiotensin system (RAS) components at baseline and weeks 2 and 8.

Drug safety assessment was to be based on frequencies of clinical adverse events (AEs), changes in physical examination, changes in ECG, sponsor-defined marked laboratory abnormalities, and 24-hour Holter monitoring.

The sponsor used Cochran-Mantel Haenszel χ^2 test, stratified by site for the analysis of response rate.

A27.5. Results

Individual sites enrolled 4 to 31 subjects. The study screened 802 subjects into the placebo lead-in period. Of the 524 randomized subjects, 450 (86%) completed the study. Demographic characteristics of randomized subjects are shown in Table 259 below. Baseline vital signs were comparable among groups.

Table 259. Demographics (CV131-050).

	Placebo N=107	Irbesartan 150 mg N=107	Irbesartan 300 mg N=106	Irbesartan 600 mg N=105	Irbesartan 900 mg N=99
Age (mean±SD)	53±11	51±11	55±11	53±11	53±11
Range					
>65 (%)	16	11	20	12	17
Male (%)	56	58	71	62	61
Female (%)	44	42	29	38	39
Weight (mean±SD)	88±19	90±19	90±19	90±17	88±18
White (%)	88	76	88	82	77
Black (%)	8.4	15	8.5	13	14
Other (%)	3.7	9.3	3.8	4.8	9.1
Duration HTN (mean±SD)	9.1±8.9	9.9±11	11±12	9.5±8.8	11±9.3

The disposition of the randomized subjects is shown in Table 260 below.

Table 260. Subject disposition (CV131-050).

	N	Withdrawals	N
Screened	802	Adverse event	28
Randomized	524	BP high*	13
Placebo	107	Subject request	15
Irbesartan	417	Administrative	10
Completed 8 weeks	416	Loss to follow-up	3
Placebo	92	Concomitant meds	2
Irbesartan	371	Lab abnormality	1
Completed withdrawal phase	450		

*By protocol or in investigator's opinion.

Compliance was estimated to be about 98%. Notable protocol violations included variation in arm used for BP measurements.

A27.5.1. Pharmacodynamics

shows a summary of effects on vital signs at week 8. Blood pressure effects in all active dose groups were statistically significantly different from placebo. Comparison of effects among active treatment groups showed no significant differences; the plateau effect on blood pressure, for once-daily dosing, is approximately reached with 150 mg. With once-daily dosing, the effects of treatment increased over the first 4 weeks, but changed little from weeks 4 to 8. At the end of the one-week washout period, effects on SeDBP in all active dose groups were back to baseline. There were no statistically significant effects on heart rate.

9.2 – 11.8 / 5.2 – 6.7

Table 261. Antihypertensive effects at 8 weeks (CV131-050).

	Plcbo	Irbesartan mg					Plcbo	Irbesartan mg			
		150	300	600	900			150	300	600	900
All (N)	107	107	106	105	99	Whites (N)	94	81	93	86	76
SeDBP	-4.1	-9.3	-9.4	-10.8	-9.8	SeDBP	-4.6	-10.2	-10.2	-11.5	-11.0
SeSBP	-2.1	-11.3	-11.5	-13.9	-11.0	SeSBP	-2.9	-13.1	-12.6	-14.3	-12.8
SeHR	-0.1	0.5	-0.4	-0.7	-0.6	StDBP	-3.0	-8.7	-9.6	-9.9	-10.1
StDBP	-2.4	-8.1	-8.8	-9.3	-9.2	StSBP	-1.8	-11.9	-13.8	-14.0	-13.4
StSBP	-1.4	-10.5	-13.2	-13.5	-11.4	Blacks (N)	9	16	9	14	14
StHR	-0.4	1.3	-0.6	0.6	-0.9	SeDBP	0.4	-7.2	-2.5	-5.3	-0.3
Normalized (%)	21	39	42	49	48	SeSBP	6.0	-9.0	1.4	-8.4	1.2
Responder (%)	27	53	56	63	58	StDBP	3.6	-7.4	-1.6	-4.3	-3.3
						StSBP	6.3	-7.7	-8.7	-3.7	-1.4

Subjects over age 65 had slightly larger responses to treatment than did younger subjects. Placebo-subtracted effects on SeDBP in Blacks were smaller than the effects in Caucasians at doses of 300 and 900 mg, but larger than Blacks for doses of 150 and 600 mg; there were probably too few Blacks to distinguish even clinically relevant effects of race. Mean changes from baseline and placebo in SeDBP were somewhat larger in males than in females.

A27.5.2. Safety

One subject died from myocardial infarction 23 days after completing 8 weeks on irbesartan 600 mg. This event was not considered drug-related.

Two subjects on irbesartan 150 and 600 mg experienced orthostatic hypotension after the first dose, and one of them discontinued for this cause. The incidence of hypotension generally was about 2%, with no apparent dose-relatedness. One subject in each active dose experienced musculoskeletal pain; in the one case (900 mg) associated with elevation in CK >3x ULN, the subject continued on treatment with spontaneous resolution.

Abnormalities in clinical laboratory assessments, ECG, Holter monitoring, and physical exam were rare and not obviously treatment-related.

A27.6. Summary

This was an adequate, and well controlled study of fixed doses of irbesartan in a population of mild-to moderate hypertensive subjects. Statistically significant blood pressure effects were seen with 150 to 900 mg dose range. A reasonable dose response curve would suggest doses above 150 mg were active, and that the 600-mg dose was on the plateau of the dose-response curve. Near maximum effects are seen by 4 weeks of treatment, and effects dissipated over 1 week after the last dose. There was one death unrelated to the drug; no other serious safety problems were observed.

A28. CV131-053: Mass balance and absolute bioavailability of irbesartan in healthy male subjects after 50 mg intravenous and 150 mg oral administration of [^{14}C]-irbesartan solution.

A28.1. Source documents

Study report: NDA 20-757, vol 1.94-1.95.

A28.2. Investigators

R.M. Dixon, M.D., Corning Besselaar Clinical Research Units, Inc., 309 West Washington Avenue, Madison, WI 53703.

A28.3. Study design

The objective of the study was to determine the mass balance following i.v. and oral administration of [^{14}C]-irbesartan.

This was an open label, randomized, single center, single dose, balanced 2-way crossover study in 6 healthy male volunteers. Each received a 50 mg i.v. dose of [^{14}C]-irbesartan solution over 30 minutes; and a 150 mg oral dose a [^{14}C]-irbesartan aqueous solution on two different occasions. Subjects were fasted 10 h before and 4 h after dose administration. Blood samples were taken at pre-dose, 0.17, 0.33, 0.50, 0.67, 0.83, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 168 h post-dose. Urine samples were collected at pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48 72, 72-96, 96-120, 120-144 and 144-168 hours post-dose. Fecal samples were collected up to 168 h post-dose.

Assay of plasma and urinary irbesartan was performed according to methods 2 and 8, respectively, in Table 7. *Assay validation for irbesartan.* on page 15. Plasma, urine and feces were solubilized and measured for radioactivity of irbesartan and metabolites.

C_{max}, T_{max}, $T_{1/2}$, AUC_{∞}, MRT (mean residence time), Clr, %ABS, F, E (hepatic extraction ratio, and MAT (mean absorption time) were the pharmacokinetic parameters evaluated. No statistical tests were done.

A28.4. Results

The pharmacokinetic results for i.v. and oral irbesartan are summarized in Table 262 below.

Table 262. Pharmacokinetic parameters (CV131-053).

	Intravenous		Oral solution	
	Irbesartan	Total radioactivity	Irbesartan	Total radioactivity
C_{max} (ng/mL)	3817±624	4432±848	3325±1047	4153±1211
AUC_{0-T} (ng.h/mL)	4988±1664	6473±1948	9322±4174	12611±5375
AUF_{∞} (ng.h/mL)	5136±1630	—	9538±4124	—
T_{max} (h)[a]	—	—	0.3 (0.2-0.5)	0.6 (0.2-0.7)
CL_T (mL/min)	176±55	—	—	—
V_{SS} (L)	93±56	—	—	—
Vd_{β} (L)	260±198	—	—	—
MRT (h)	8.5±3.8	—	3.0±5.2	—
$T_{1/2}$ (h)	16±10	—	20±12	—
CL_R (mL/min)	3.0±1.7	—	3.0±2.3	—
%UR	1.9±1.1	20±5	1.0±0.5	20±6
Fecal recovery (%)	—	65±4	—	54±9
Total recovery (%)	—	85±4	—	74±10
F (%)	—	—	61±10	—

a. Median (minimum, maximum)

Plasma profiles of unchanged irbesartan and total radioactivity following intravenous dosing or dosing with the oral solution are shown in Figure 70 below.

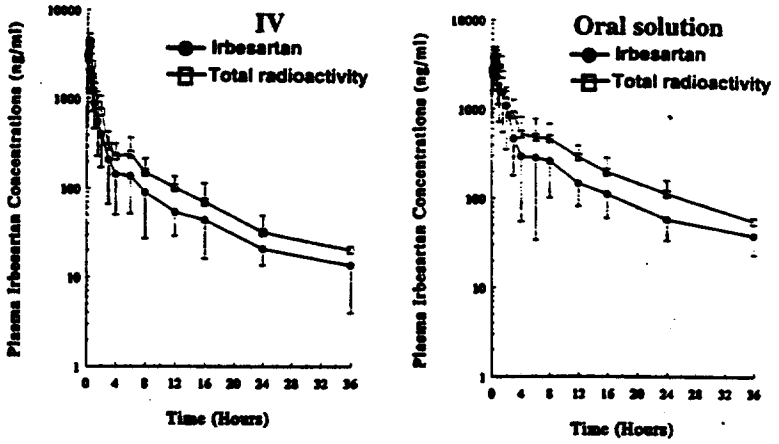

Figure 70. Plasma irbesartan and total radioactivity after i.v. and oral solution dosing (CV131-053).

A28.4.1. Safety

Not reviewed.

A28.5. Summary.

The absolute bioavailability (F) was 61%; this is considerably less than that of study CV131-043[1] 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 radioactivity. The majority of the remaining radioactivity (~6%) corresponds to plasma irbesartan glucuronide.

1. *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.

A29. 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.

A29.1. Source documents

Study report: NDA 20-757, vol 1.25-1.28.

A29.2. Investigators

Randall Stoltz, M.D., GFI Pharmaceutical Services Inc., 800 St. Mary's Dr., Evansville, IN.

A29.3. Study design

This study description was based upon the final study report of 8 July 1996.

The objective of the study was to assess the bioequivalence of a combination tablet formulation of irbesartan and hydrochlorothiazide (150/12.5 mg) relative to the individual irbesartan capsule (2 x 75 mg) and HCTZ tablet (12.5 mg) taken in combination.

This was a single center, open-label, single-dose, balanced, 2-period crossover study in 36 healthy males subjects. Each subject received a single 150 mg dose of irbesartan and 12.5 mg dose of HCTZ as either a combination tablet or a combination of each monotherapy on two separate study days separated by at least a 7 day washout period. Blood samples were collected at pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours after dosing.

Drug supplies are shown in Table 263 below.

Table 263. Drug supplies (CV131-054).

	Lot number	Lot size
Irbesartan 75 mg capsule	N95067	—
HCTZ 12.5 mg tablet	N94F086C	—
Irbesartan/HCTZ 150/12.5 mg tablet	8MLJ142	300,000

Assays are described in Table 264 below. Both assays were satisfactory.

Table 264. Assays (CV131-054).

Assay	Sample	Technique	Linearity	Specificity	Sensitivity LOQ	Accuracy %RSD interday	Precision %RSD intraday
Irbesartan	Plasma		Satisfactory	Satisfactory	3.0 ng/ml	≤1.0	≤7.0
HCTZ	Plasma		Satisfactory	Satisfactory	3.0 ng/ml	≤2.5	≤4.5

AUC_{∞}, C_{max}, T_{max}, and $T_{1/2}$ were analyzed using ANOVA. Bioequivalence was assessed using the 90% CI for AUC and C_{max}.

A29.4. Results

The 90% confidence intervals for the 150/12.5 mg combination tablet compared to individual irbesartan and HCTZ are described in Table 265 below. AUC and C_{max} were within the 80-125% CI for bioequivalence.

The mean plasma concentration time profiles for the combination tablet and the individual monotherapies, shown in Figure 71 below, were superimposable.

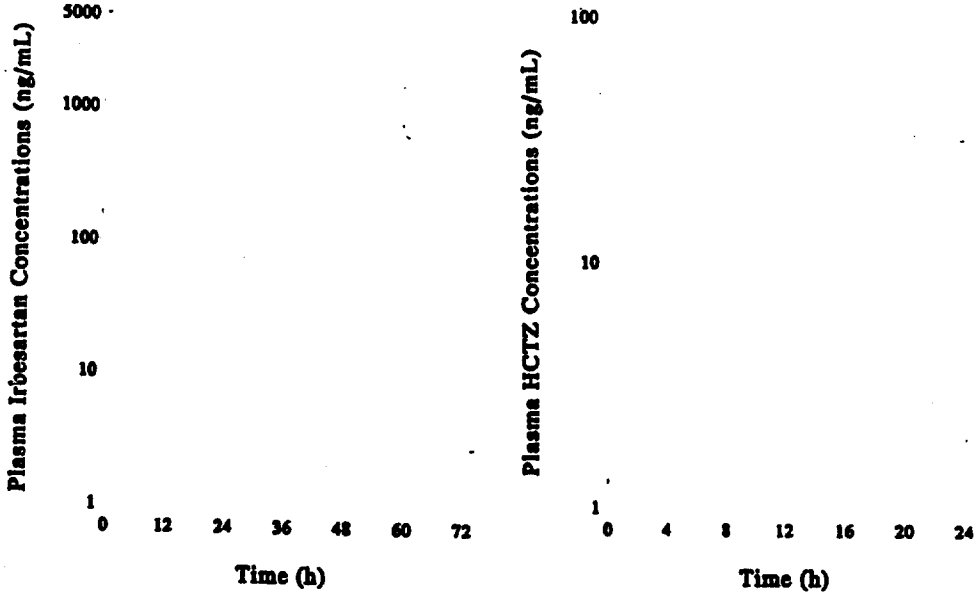

Figure 71. Plasma profiles for irbesartan and HCTZ (CV131-054).

Table 265. Pharmacokinetic parameters (±SD; CV131-054).

	Irbesartan			HCTZ		
	Reference capsule	Combination tablet	Ratio* (90% CI)	Reference tablet	Combination tablet	Ratio* (90% CI)
C_{max} (ng/mL)	2384 (693)	2691 (821)	1.13 (1.06-1.20)	65 (17)	65 (17)	1.00 (0.94-1.07)
AUC_{∞} (ng.mL/h)	12990 (4353)	13110 (4275)	1.01 (0.96-1.06)	417 (128)	409 (133)	0.97 (0.90-1.04)
T_{max}* (h)	1.5 (0.7-4.0)	1.5 (0.3-4.0)	NS	1.5 (0.7-4.0)	2.0 (1.0-4.0)	NS

*Ratio of test to formulation. Confidence limits obtained from analysis of variance of log-transformed data after correction of potency. For T_{max}, the values are the median and the minimum and maximum values are shown parenthetically.

A29.4.1. Safety Not reviewed.

A29.5. Summary. The combination tablet (150.12.5 mg) irbesartan/HCTZ is bioequivalent to irbesartan 2 x 75 mg capsules with HCTZ 12.5 mg tablets.

A30. CV131-056: The effect of a high-fat meal on the oral bioavailability of irbesartan in healthy male subjects.

A30.1. Source documents

Study report: NDA 20-757, vol 1.160-1.161.

A30.2. Investigators

Joel Morganroth, M.D., Premier Research Worldwide, 124 South 15th Street, Philadelphia, PA.

A30.3. Study design

The objective of the study was to investigate the effects of a high fat meal on the oral bioavailability of a 300 mg irbesartan tablet in healthy male subjects.

This was a randomized, open-label, single-center, single-dose, crossover study in 16 young, healthy male subjects. Each subject received a single 300 mg oral tablet of irbesartan under fasted or fed (standard FDA meal) conditions, separated by at least a 7 day washout period. Blood samples were collected at pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours after dose administration.

Drug supplies are shown in Table 266 below.

Table 266. Drug supplies (CV131-056).

	Lot number
Irbesartan 300 mg tablet	8MFJ140-300

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

Log-AUC_∞ and Log-C_{max} and $T_{1/2}$ were evaluated using ANOVA. T_{max} was analyzed by a 2x2 crossover design as described by Koch.

A30.4. Results

Subjects #4 and 12 were both randomized to be fed for the first treatment period. The plasma irbesartan levels were consistent with the other subjects under fed conditions. However, for subjects #4 and 12 under fasted conditions plasma irbesartan levels were not detectable. These subjects were excluded from pharmacokinetic analysis and were replaced by subjects #104 and 112.

There were no statistically significant effect of a high fat meal on the C_{max}, AUC, T_{max}, and $T_{1/2}$ for irbesartan.These data are summarized in Table 267 below.

Table 267. Irbesartan pharmacokinetics under fasted and fed conditions (CV131-056).

	Fasted	Fed	Fed/Fasted[a]
C_{max} (ng/mL)	2988±929	3277±1103	1.09 (0.94-1.26)
AUC (ng.h/mL)	22841±7239	24611±12143	1.07 (0.92-1.17)
$T_{1/2}$ (h)	15.0±5.3	18.3±9.8	NS
T_{max} (h)[b]	1.0 (0.3-4.0)	1.75 (1.0-8.0)	NS

a. Point estimate and 90% CI.
b. Median (min-max).

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The mean plasma concentration-time profiles for irbesartan 300 mg tablet under fed vs. fasted conditions are shown in Figure 72 below.

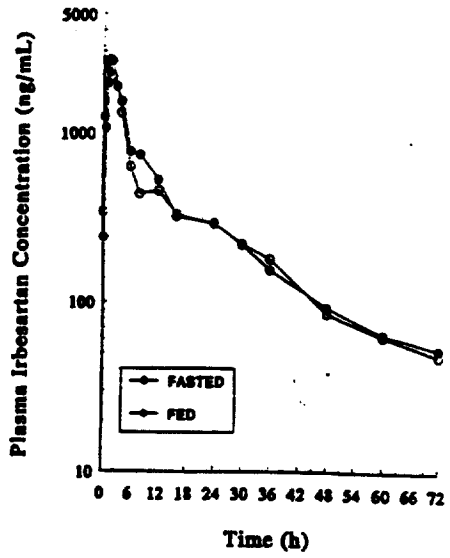

Figure 72. Plasma irbesartan under fasted and fed conditions (CV131-056).

A30.4.1. Safety Not reviewed.

A30.5. Summary. The were no statistically significant differences in the pharmacokinetics of irbesartan 300 mg tablets under fed versus fasted states.

A31. CV131-057: Pharmacodynamics (effects on renin angiotensin system, renal function and blood pressure) and pharmacokinetics of irbesartan in subjects with mild-to-moderate hypertension.

A31.1. Source documents

Study report: NDA 20-757, vol 1.129-1.131.

A31.2. Investigators

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

A31.3. Study dates

15 August 1995 to 20 December 1995.

A31.4. Study design

This study description was based upon the protocol dated 21 June 1995. There were 3 changes to the protocol made after the first enrolled subject. None of these amendments affected the basic pharmacokinetic measurements or biased the study.

The objective of the study was to compare the pharmacodynamics of irbesartan 300 mg qd with placebo in subjects with mild to moderate hypertension treated for up to 4 weeks and to evaluate the pharmacokinetics of irbesartan for the same time period.

This study was a randomized, double-blind, placebo-controlled, parallel-group study for which the design is shown in Figure 73 below. After a single-blind lead-in phase of 4 to 5 weeks, subjects were randomized to receive irbesartan 300 mg or placebo if their seated diastolic blood pressure (SeDBP) was between 95 and 110 mmHg.

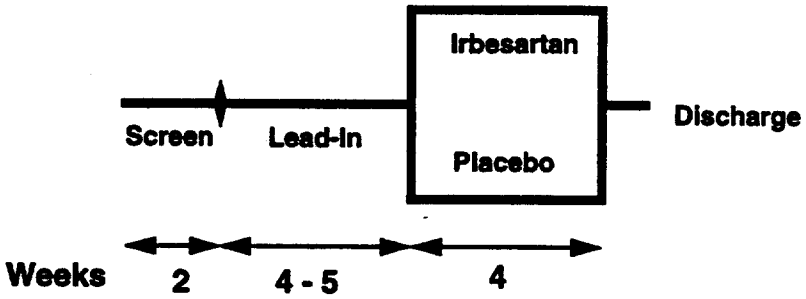

Figure 73. Study design (CV131-057).

The subjects were taken from a healthy, non-obese and non-black population aged between 45 and 65 years. Subjects were to have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage; mild funduscopic changes excepted). Untreated SeDBP must have been between 95 and 110 mmHg to be randomized. Subjects with renovascular disease, cardiovascular disease, diabetes, CHF, collagen-vascular disease, renal disease, or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded.

Drug supplies are shown in Table 268 below.

Table 268. Drug supplies (CV131-057).

	Product Number	Lot Number		Product Number	Lot Number
Placebo	186295-R000-030	L94F013C	Irbesartan 75 mg	186295-R075-054	L95008

Vital signs, plasma levels of angiotensin II and drug, renin and catecholamines were measured over 24 hours at specified intervals. A 24-hour urine specimen was obtained and amounts of aldosterone, creatinine, catecholamines, electrolytes, and metabolites of prostacyclin and thromboxane were determined. The measurements were obtained

prior to randomization as a baseline and at 15 and 29 days after randomization. A time schedule for these procedures is shown in Table 269 below

Table 269. Schedule for PK and PD sampling on day 1, 15 and 29 (CV131-057).

Time (h)	PK	Pharmacodynamics			Time (h)	PK	Pharmacodynamics		
		RAS	Urine	Vitals			RAS	Urine	Vitals
-1		X		X	4	X	X	X	X
Pre-dose	X	X	X	X	6	X		X	X
0.5	X		X	X	8	X	X	X	X
1.0	X	X	X	X	10	X		X	X
1.5	X		X	X	12	X	X	X	X
2	X	X	X	X	24	X	X	X	X
3	X		X	X					

Using standard radiochemical techniques, glomerular filtration rate and renal blood flow were measured prior to randomization and on day 30.

Assay of plasma irbesartan was performed according to method 5 in Table 7. *Assay validation for irbesartan.* on page 15. Plasma, urine and feces were solubilized and measured for radioactivity of irbesartan and metabolites.

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

A31.5. Results

There were a total of 26 subjects screened. Two were discontinued prior to randomization. There were no dropouts after randomization. There were no significant protocol violations. Subject compliance was not given in the final study report. Several subjects were missing measurements of angiotensin II or thromboxane.

Eight subjects received anti-hypertensives prior to study. Demographics of the two treatment groups are shown in.Table 270 below

Table 270. Demographics (CV131-057).

	Placebo N=12	Irbesartan N=12		Placebo N=12	Irbesartan N=12
Age (mean±SD) Range	55±6.0	57±5.9	Weight, kg (mean±SD) Range	74.5±11.3	78.4±13.0
Male (%) Female (%)	50 50	50 50	Height, cm (mean±SD) Range	165.9±6.2	169.4±13.0
Race—White (%)	100	100			

A31.5.1. Pharmacokinetics

Mean pharmacokinetic data for day 29 is given in Table 271 below.

Table 271. Pharmacokinetic parameters for day 29 (CV131-057).

	Males N=6	Females N=6		Males N=6	Females N=6
C_{max} (ng/cc)	3720±1422	4139±951	Clearance (cc/h)	16292±5053	13395±3264
T_{max} (h)	2.25±1.89	1.25±0.27	$t_{1/2}$ (h)	8.63±3.2	8.68±5.85
AUC (ng-h/cc)	20649±9134	23397±5043			

Pharmacokinetic profiles for males and females are given in Figure 74 below.

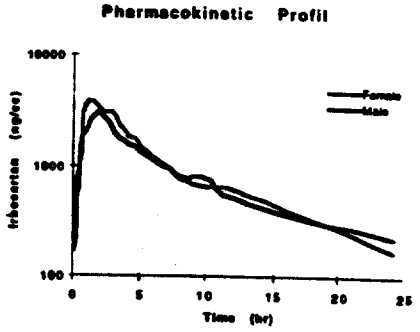

Figure 74. Pharmacokinetic profile for males and females (CV131-057).

A31.5.2. Pharmacodynamics

The 24-hour AUC for SeDBP, SeSBP, and heart rate were significantly decreased from baseline on both placebo and study drug on days 15 and 29. There was no significant difference in SeDBP between study drug and placebo on either Day 15 or 29. However, the AUC measurement of SeSBP showed a significant decrease between study drug and placebo on both days. The 24-hour AUC for heart rate for the placebo group was not significantly changed. However, there was a significant increase in heart rate with irbesartan on both study days. On study day 15, there was a significant increase in HR with irbesartan compared to placebo; however, there was no significant difference on Day 29. These data are summarized in Table 272 below.

Table 272. AUC for vital signs on days 15 and 29 (CV131-057).

	Day 15		Day 29	
	Placebo N=12	Irbesartan N=12	Placebo N=12	Irbesartan N=12
SeDBP, mmHg-h (mean±SD) Range	-146±71*	-150±58*	-127±99*	-175±94*
SeDBP, mmHg-h (mean±SD) Range	-171±175*	-296±181*†	-171±175*	-296±181*†
HR, bpm-h (mean±SD) Range	-3±87	101±73*†	-54±138	62±122*

*Significant treatment effect (p< 0.05); †Significant difference from placebo (p<0.05); ◊Significant difference from Day 15 (p<0.05)

A31.5.3. Hormones

As shown in Table 273 below, there were treatment-related increases in angiotensin II and plasma renin activity on days 15 and 29, compared with baseline and placebo controls. Urinary aldosterone excretion was decreased on both study days, compared with placebo controls, but only on the latter day when compared with baseline.

Table 273. AUC for angiotensin II and plasma renin activity (CV131-057).

	Day 15		Day 29	
	Placebo N=12	Irbesartan N=12	Placebo N=12	Irbesartan N=12
A II, pg-h/cc (mean±SD) Range	12±51	261±515*†	5±103	209±268*†
PRA, ng-h/cc (mean±SD) Range	-2±14	74±162*†	-4±13	61±104*

*Significant treatment effect (p< 0.05); †Significant difference from placebo (p<0.05).

A31.5.4. Renal pharmacodynamics

There were no statistically significant mean changes from baseline in urinary excretion of creatinine, sodium, potassium or chloride in the irbesartan treated group.Urinary excretion of the thromboxane metabolites showed no significant change from baseline in either the placebo or irbesartan group. A single significant increase in prostacyclin excretion compared to baseline and placebo was detected on day 29 in the irbesartan group.

There were no statistical differences of renal blood flow, glomerular filtration rate, plasma or urinary catecholamines compared to baseline in either the placebo or irbesartan group.

A31.5.5. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event. One subject had a mild headache for 3 hours on day 29 of the lead-in period. There were no marked laboratory abnormalities for subjects in the irbesartan group. One subject in the placebo group had proteinuria on day 29 of the double-blind period. A follow-up urinalysis 8 days after discharge was within normal limits. No significant changes in physical exam finding were noted. ECGs were either normal or consistent to those found in a hypertensive population.

A31.6. Summary.

The study was a double-blind, placebo-controlled trial of irbesartan versus placebo. There was a significant placebo effect with respect to SeDBP and SeSBP. Statistical significance between placebo and irbesartan was achieved only for SeSBP. There were study drug-related increases in angiotensin II and plasma renin activity; these changes were similar on study days 15 and 29. Pharmacokinetic measurements of irbesartan were analyzed only for day 29. AUC, C_{max}, and $T_{1/2}$ were similar in males and females. Clearance of irbesartan was greater in males than in females.

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A32. CV131-058: Effects of age on the pharmacokinetics of irbesartan following a single 150 mg oral dose in healthy male subjects.

A32.1. Source documents

Study report: NDA 20-757, vol 1.146-1.147.

A32.2. Investigators

Antonia L. Court, M.D. and Gilbert A. Schnirman, M.D., Corning Besselaar Clinical Research Units, Inc. 900 Osceola Dr., West Palm Beach, FL.

A32.3. Study dates

24 August 1995 to 22 September 1995.

A32.4. Study design

This study description was based upon the protocol dated 26 July 1995. There were no changes to the original protocol.

The objective of the study was to investigate the effects of age on the pharmacokinetics of irbesartan following a single 150-mg dose.

This study was a single center, open-label study in 12 young (18-40 years) and 12 elderly (>65 years) subjects. The subjects were taken from a healthy non-obese male Caucasian population with normal physical exam findings and laboratory values.

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

Drug supplies are shown in Table 274 below.

Table 274. Drug supplies (CV131-058).

	Batch Number
Irbesartan 75 mg	N94J126C

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

The subjects were asked to return to the center no more than 3 weeks later and were given two 75-mg capsules of irbesartan. Pharmacokinetic profiles and urine specimens were obtained according to the schedule shown in Table 275 below).

Table 275. Schedule for PK and PD sampling (CV131-058).

Time (h)	Plasma	Urine	Time (h)	Plasma	Urine
Pre-Dose	X	X	8	X	8 - 12
0.25	X	0 - 4	12	X	12 - 24
0.5	X		24	X	24 - 36
0.75	X		36	X	36 - 48
1	X		48	X	48 - 60
1.5	X		60	X	60 - 72
2	X		72	X	
4	X	4 - 8			

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

The following parameters were to be determined and compared within each group: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0-\infty}$, renal clearance [CL_R], % urinary excretion [%UR], tolerability, and safety.

Statistical analysis of safety, C_{max}, AUC, T_{max}, $T_{1/2}$, %UR, and clearance were compared using analysis of variance. Values of C_{max} and AUC were log transformed and T_{max} was rank transformed.

Physical exams, vital signs, ECGs and safety laboratory tests were to be performed during screening, during administration, and at study end.

A32.5. Results

Twelve elderly and young subjects participated in the study. There were no dropouts.

Demographics of the three treatment groups are shown in Table 276 below.

Table 276. Demographic (CV131-058).

	Young N=12	Elderly N=12		Young N=12	Elderly N=12
Age (mean±SD)	29±8	69±4	Race (%)		
Weight, kg (mean±SE)	77±7	83±9	White	75	92
Height, cm (mean±SE)	178±7	176±6	Black	8	8
			Hispanic	16	0

There were no major deviations from the protocol. The 8-hour blood sample for subjects #17, 21 and 24 and the 12-hour blood sample for subject #17 were drawn later than the specified times. No urine sample was collected at the 0 to 4 hour interval for subjects #13 and 16. These subjects were excluded from the analysis.

A32.5.1. Pharmacokinetics

The mean pharmacokinetic profiles for young and elderly subjects is given in Figure 75 below.

Mean pharmacokinetic data of irbesartan measured on study days is given in Table 277 below. Plasma clearance and the volume of distribution were based upon elimination-limited kinetics. The volume of distribution was based on the terminal half-life.

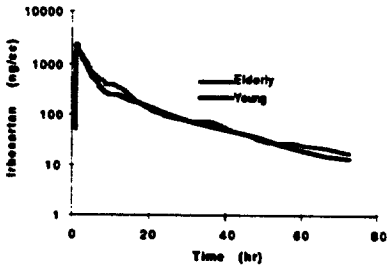

Figure 75. Mean plasma levels by time (CV131-058).

Table 277. Single- and multiple-dose pharmacokinetic parameters (mean±SE; CV131-058).

	Young N=12	Elderly N=12		Young N=12	Elderly N=12
C_{max}, ng/cc	2053±160	2575±207	Urinary excretion (%)	95±16	63±11
AUC, ng-hr/cc	12845±840	15960±1503	Renal CL, ml/min	1.95±0.32	1.27±0.23
T_{max}, h	1.31±0.14	1.15±0.13	$t_{1/2}$, h	16±2	18±3
Plasma CL, ml/min	205±15	173±16	V_d, l	265±38	254±47

A32.5.2. Safety

There were no deaths or dropouts in this study. There were a total of 5 adverse events in a total of 4 subjects. All were mild as judged by the investigator. Complaints included abdominal pain, diarrhea, hyperhidrosis, weakness and headache.

The subjects had normal ECGs at screening and at discharge. There were no significant changes in laboratory findings. No significant changes in physical exam were observed.

A32.6. Summary.

This is an open-label study of the pharmacokinetics of irbesartan. There was a ~20% difference between young and elderly subjects in C_{max}, AUC and clearance. None of the differences reached statistical significance, and estimated effect size was too small to warrant a dose adjustment by age.

A33. CV131-062: A bioequivalence study comparing the intended 300 mg commercial tablet formulation of irbesartan to the reference 100 mg BMS capsule formulation.

A33.1. Source documents

Study report: NDA 20-757, vol 1.105-1.107.

A33.2. Investigators

Randall B. Smith, Ph.D., Novum, Inc., 5900 Penn Avenue, Pittsburgh, PA 15206.

A33.3. Study design

The objective of the study was to compare the bioavailability of the intended 300 mg commercial tablet formulation of irbesartan to that of the clinically used 100 mg capsule formulation.

This was a single center, open label, single-dose, balanced, 2-period crossover study in 36 healthy male subjects. Each subject received a single oral 300 mg dose of irbesartan as either a 300 mg tablet or 3x100 mg capsules on two separate occasions. There was at least a 7-day washout period between treatment periods. Blood samples were taken at pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose.

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

ANOVA was used to compare the C_{max}, T_{max}, $T_{1/2}$, and ACU_{∞} of the 2 treatments.

A33.4. Results

The pharmacokinetic results for i.v. and oral irbesartan are summarized in Table 278 below.

Table 278. Pharmacokinetic parameters (CV131-062).

	Tablet	Capsule	Ratio (90% CI)
C_{max} (ng/mL)	3592±1189	3187±926	1.11 (1.03-1.19)
AUF_{∞} (ng.h/mL)	20463±9143	18981±5707	1.02 (0.94-1.10)
T_{max} (h)[a]	1.0 (0.3-4.0)	1.0 (0.3-4.0)	NS

a. Median (minimum, maximum)

Plasma profiles for irbesartan after oral administration of tablets or reference capsules are shown in Figure 76 below.

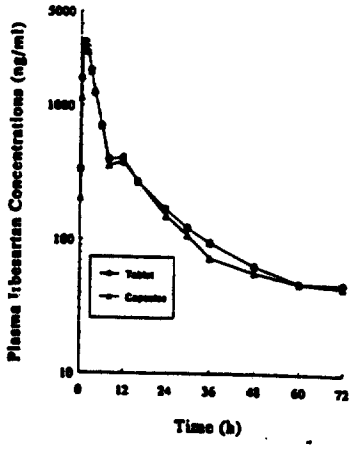

Figure 76. Plasma irbesartan after dosing by tablet or capsule (CV131-062).

A33.4.1. Safety

Not reviewed.

A33.5. Summary. The 300-mg to-be-marketed irbesartan tablet is bioequivalent to 3x100-mg irbesartan capsules used in the clinical trials.

A34. 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.

A34.1. Source documents

Study report: NDA 20-758, vol 1.29-1.34.

A34.2. Investigators

Randall Stoltz, M.D., GFI Pharmaceutical Services Inc., 800 St. Mary's Dr., Evansville, IN.

A34.3. Study design

This study description was based upon the final study report of 8 July 1996.

The objective of the study was to assess the bioequivalence of a combination tablet formulation of irbesartan and hydrochlorothiazide (75/12.5 mg) relative to the individual irbesartan capsule (75 mg) and HCTZ tablet (12.5 mg) taken in combination.

This was a single center, open-label, single-dose, balanced, 2-period crossover study in 36 healthy males subjects. Each subject received a single 75 mg dose of irbesartan and 12.5 mg dose of HCTZ as either a combination tablet or a combination of each monotherapy on two separate study days separated by at least a 7 day washout period. Blood samples were collected at pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours after dosing.

Drug supplies are shown in Table 279 below.

Table 279. Drug supplies (CV131-067).

	Lot number	Lot size
Irbesartan 75 mg capsule	N95067	—
HCTZ 12.5 mg tablet[a]	N94F086C	—
Irbesartan/HCTZ 75/12.5 mg tablet	8MLJ143	300,000

a. Manufactured by BMS; not a marketed product.

Assays are described in Table 280 below. Both assays were satisfactory.

Table 280. Assays (CV131-067).

Assay	Sample	Technique	Linearity	Specificity	Sensitivity LOQ	Accuracy %RSD interday	Precision %RSD intraday
Irbesartan	Plasma		Satisfactory	Satisfactory	3.0 ng/ml	≤1.0	≤7.0
HCTZ	Plasma		Satisfactory	Satisfactory	3.0 ng/ml	≤2.5	≤4.5

AUC_{∞}, C_{max}, T_{max}, and $T_{1/2}$ were analyzed using ANOVA. Bioequivalence was assessed using the 90% CI for AUC and C_{max}.

A34.4. Results

The 90% confidence intervals for the 75/12.5 mg combination tablet compared to individual irbesartan and HCTZ are described in Table 281 below. AUC and C_{max} were within the 80-125% CI for bioequivalence.

The mean plasma concentration time profiles for the combination tablet and the individual monotherapies, shown in Figure 77 below, were superimposable.

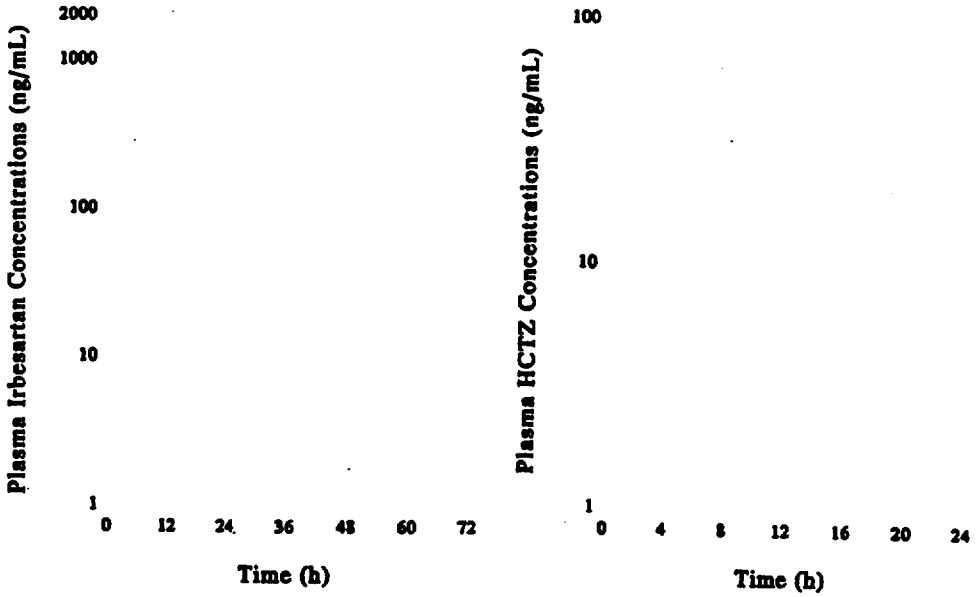

Figure 77. Plasma profiles for irbesartan and HCTZ (CV131-067).

Table 281. Pharmacokinetic parameters (±SD; CV131-067).

	Irbesartan			HCTZ		
	Reference capsule	Combination tablet	Ratio* (90% CI)	Reference tablet	Combination tablet	Ratio* (90% CI)
C_{max} (ng/mL)	1502 (582)	1560 (531)	1.05 (0.97-1.14)	68 (20)	59 (13)	0.89 (0.82-0.96)
AUC_{∞} (ng.mL/h)	6415 (2282)	6134 (2088)	0.96 (0.92-1.01)	397 (95)	374 (81)	0.95 (0.88-1.02)
T_{max}* (h)	1.0 (0.7-3.0)	1.0 (0.3-3.0)	NS	1.5 (0.7-6.0)	2.0 (1.0-4.0)	Test>ref

*Ratio of test to formulation. Confidence limits obtained from analysis of variance of log-transformed data after correction of potency. For T_{max}, the values are the median and the minimum and maximum values are shown parenthetically.

A34.4.1. Safety Not reviewed.

A34.5. Summary. The combination tablet (75/12.5 mg) irbesartan/HCTZ is bioequivalent to irbesartan 75 mg capsules with HCTZ 12.5 mg tablets.

A35. CV131-069: Effect of a high-fat meal on the oral bioavailability of irbesartan/hydrochlorothiazide combination tablets in healthy male subjects.

A35.1. Source documents

Study report: NDA 20-758, vol 1.33-1.34.

A35.2. Investigators

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

A35.3. Study design

This study description was based upon the final study report of 18 July 1996.

The objective of the study was to investigate the effects of a high-fat meal on the oral bioavailability of irbesartan/HCTZ (150/12.5 mg) combination tablet in healthy male subjects.

This was a single-center, open label, single-dose, crossover study in 16 healthy male subjects. Subjects remained at the clinical site for four nights and 3 days during each treatment period. Each subject received a single irbesartan/HCTZ (150/12.5 mg) combination tablet under fasted or fed conditions. Following an overnight fast, fed subjects received the drug 5 min following the meal. Fasted subjects received the drug and continued fasting for 4 hours after dosing. There was at least a 7 day washout period between the two treatment periods. Blood samples were taken at pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours after dosing. The meal was an FDA standard meal.

Drug supplies are shown in Table 282 below.

Table 282. Drug supplies (CV131-069).

	Lot number	Lot size
Irbesartan/HCTZ 150/12.5 mg tablet	8MLJ142	300,000

Assays are described in Table 283 below. Both assays were satisfactory.

Table 283. Assays (CV131-069).

Assay	Sample	Technique	Linearity	Specificity	Sensitivity LOQ	Accuracy %RSD interday	Precision %RSD intraday
Irbesartan	Plasma		Satisfactory	Satisfactory	3.0 ng/ml	≤1.0	≤7.0
HCTZ	Plasma		Satisfactory	—*	3.0 ng/ml	≤2.5	≤4.5

*Chromatograms not submitted.

AUC_{∞}, C_{max}, T_{max}, and $T_{1/2}$ were analyzed using ANOVA. Bioequivalence was assessed using the 90% CI for AUC and C_{max}.

A35.4. Results

The C_{max} and AUC for irbesartan were not significantly different under fed versus fasted conditions. The C_{max} for HCTZ was statistically less (21%) under fed versus fasted conditions. The T_{max} was delayed for both irbesartan and HCTZ. The data are summarized in Table 284 below. The plasma concentration-time plot are illustrated in Figure 78 below.

Table 284. Pharmacokinetic parameters (±SD; CV131-069).

	Irbesartan			HCTZ		
	Fasted	Fed	Ratio* (90% CI)	Fasted	Fed	Ratio* (90% CI)
C_{max} (ng/mL)	2083 (502)	2033 (604)	0.97 (0.87-1.07)	64 (11)	51 (12)	0.79 (0.71-0.88)
AUC_{∞} (ng.mL/h)	11900 (4868)	11810 (3899)	1.01 (0.90-1.15)	436 (115)	399 (94)	0.92 (85-0.99)
T_{max}* (h)	1.0 (0.7-4.0)	2.0 (1.0-4.0)	1.25 (0.50-1.67)	1.5 (1.0-4.0)	3.5 (1.5-6.0)	1.50 (0.75-2.25)
$T_{1/2}$ (h)	15 (4.9)	15 (7.6)	1.00 (0.80-1.24)	7.8 (3.5)	7.4 (2.7)	0.94 (0.74-1.19)

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

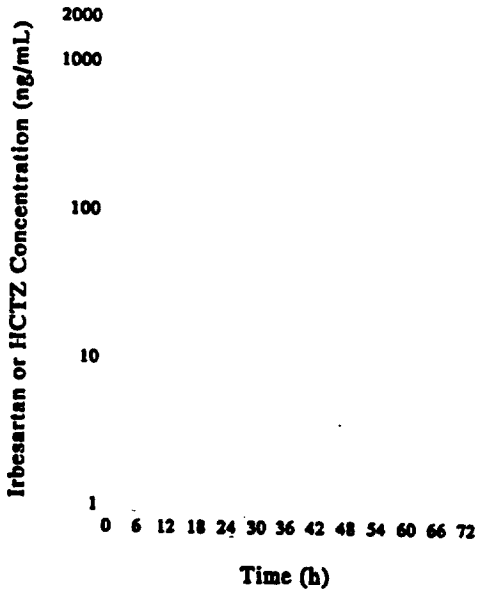

Figure 78. Plasma profiles for irbesartan and HCTZ (CV131-069).

A35.4.1. Safety Not reviewed.

A35.5. Summary. Irbesartan/HCTZ (150/12.5 mg) combination tablets have no clinically significant food effect. The C_{max} of HCTZ is 21% less when this dosage form is administered with a high fat meal.

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A36. PDY 1692: Assessment of the inhibition of pressor response to exogenous angiotensin II by irbesartan in normotensive human subjects.

A36.1. Source documents

Study report: NDA 20-757, vol. 1.174-1.181.

A36.2. Investigator

Prof. Albert Miriam, Service de Medicine Interne, Hopital Lapeyronie, Montpelier, France.

A36.3. Study dates

19 February 1993 to 15 May 1993.

A36.4. Study design

The primary objective was to assess in healthy volunteers the antagonistic properties of irbesartan on angiotensin II (AII) receptors in the presence of exogenous AII. The secondary objectives were to assess the optimal dose for this antagonism and to look for an agonist effect of irbesartan on AII receptors.

This study was a single-centered, randomized, double-blind, parallel, placebo-controlled study of irbesartan 5, 25, 50, and 100 mg in 4 groups of 6 healthy volunteers and in 2 consecutive periods. In each dose group, the subjects received a single dose of the drug or placebo in a randomized cross-over design separated by one-week washout period, as shown in Figure 79 below, with follow-up for 36 hours. The subjects were given sodium chloride supplementation (6 g/day) the day before and the day of dosing. There were 2 amendments to the approved protocol dated 12 September 1992 and 2 March 1993. Neither of these affected the overall objectives of the study.

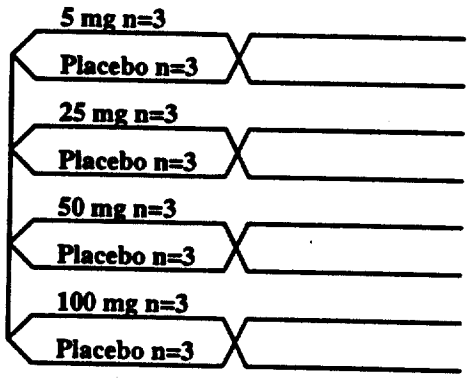

Figure 79. Study design (PDY 1692).

Table 285 below shows drug supplies.

Table 285. Drug supplies (PDY 1692).

	Product number	Lot		Product number	Lot
Placebo	186295-R000-	L94F014C	Irbesartan5 mg	186295-R050-	L94J022C
			Irbesartan 25 mg	186295-R100-	L94G017C

A total of 24 healthy, Caucasian, male volunteers age 18 to 35 years were to be enrolled. Subjects were excluded from the study if they had an inadequate pressor response to angiotensin II 100 ng/kg. Other inclusion criteria were body weight 60 to 85 kg, supine SBP <130 mmHg, normal 12-lead ECG, normal physical examination and laboratory profiles, non- smoker, alcohol consumption <20 g/day, and negative urine screen for cocaine, opiates and cannabinoids.

The schedule of events is presented in Table 286 below.

Table 286. Schedule of procedures (PDY 1692).

	Screen	Hours after dosing														
		-0.25	0	0.25	0.5	1	2	3	4	5	6	7	8	12	24	36
Study drug admin			x													
AII test-dose		x				x	x		x				x	x	x	x
Serology	x															
Urinary sodium	x															
AII dose-response curve	x															
Laboratory		x													*x	
Physical examination	x	x			x	x	x	x	x		x		x	x	x	x
12-lead ECG	x	x					x				x				x	x
BP and HR	x		x			x	x	x	x	x	x	x	x	x	x	x
Blood sampling for RAS		x				x	x		x				x	x	x	*x
PK blood sampling		x				x	x		x				x	x	x	x
Adverse events																x

*Sample added with amendment dated 2 March 1993.

Irbesartan assay was by

Safety was assessed by adverse events, electrocardiography, and laboratory tests including hematology, biochemical profiles, and quantitative urinalysis.

A36.5. Results

Twenty-four subjects enrolled and completed study. Some baseline screening procedures were not performed.

A36.5.1. Pharmacokinetics

The time-course of mean plasma concentrations of irbesartan obtained after single oral administration of 5, 25, 50, and 100 mg is shown in Figure 80 below. C_{max} increased less than linearly with dose, and mean plasma irbesartan concentrations peaked for all 4 dose levels between 1 and 4 hours post dosing.

A36.5.2. Pharmacodynamics

There were no significant dose-related effects on supine blood pressure or heart rate.

Exogenous angiotensin II produced a pressor response in all subjects, typically an increase of about 30 mmHg in diastolic pressure following placebo administration. Smaller pressor responses were obtained after administration of irbesartan. The double difference (from baseline and placebo) in diastolic pressure is shown as a function of time after dose in Figure 81 below. AII receptor antagonism was approximately 100% only in the 100-mg dose group and only 2 to 4 hours after administration. Doses above 5 mg had some residual AII receptor antagonism 24 hours after dosing. No agonist effect of irbesartan was observed.

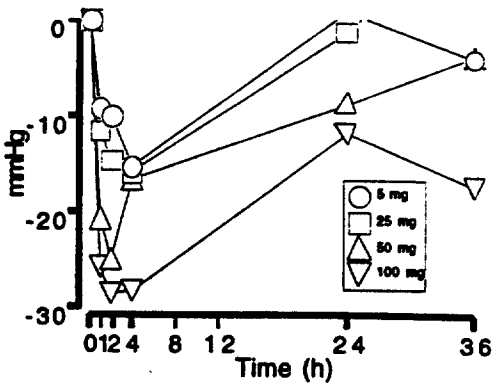

Figure 81. AII antagonism (PDY 1692).

A36.5.3. Hormones

Endogenous AII levels and renin activity rose after dosing on active treatment compared with placebo, but effects did not order by dose.

A36.5.4. Safety

There were no deaths and no withdrawals.

Twelve subjects out of 24 experienced adverse events after treatment intake. A total of 13 and 12 adverse events were reported in the irbesartan and placebo groups respectively. No orthostatic hypotension was observed. The predominant adverse events were in the gastrointestinal tract. These included nausea (5) and postprandial vomiting (5). Similar adverse events were reported in the placebo group. Other adverse events included headache (3), chest pain (1), dizziness (1), and 3 subjects had fever before the drug intake but persisted in one subject.

No clinically significant changes were seen on physical examination or ECG. Abnormal laboratory tests included leukocytosis, in one subject, eosinophilia in one subject, slight increase in AST and ALT transaminase levels following irbesartan 25 mg in one subject, and increased triglycerides and uric acid levels were observed in 2 subjects.

A36.6. Summary

This was a small, randomized, double-blind, placebo-controlled, dose-ranging study of antagonism of exogenous angiotensin II in normotensive white male volunteers. Dose-related effects on the magnitude and duration of AII antagonism were observed with irbesartan 5, 25, 50, and 100 mg. The peak inhibitory effect was observed between 2 and 4 hours post dosing, and the effects lasted up to 36 hours. No agonist activity was observed.

There were no safety concerns.

A37. 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.

A37.1. Source documents Study report: NDA 20-757, vols 1.186-1.189.

A37.2. Investigator Prof. Jean-Pierre Grunfeld, Hopital Necker, Department of Nephrology, Paris, France.

A37.3. Study dates 22 April 1993 to 8 July 1995.

A37.4. Study design This study description was based on the approved protocol dated 12 January 1993 with one amendment dated 3 March 1993.

This study was a single-center, double-blind, placebo-controlled, 10-day study in which the subjects were to receive a single dose of placebo or irbesartan 50 mg in randomized order according to a crossover design. Two study periods were separated by a 9-day interval. During each period, renal function was to be assessed after treatment under baseline conditions and during an infusion of AII 2.5 ng/kg/min over 90 minutes. Inulin, PAH, and dextran clearances were to be carried out using standard procedures. The schedule of procedures is shown in Table 287 below.

Table 287. Schedule of events (PDY 2201).

	Screen	Hours after dosing										
		0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5
Dosing		x										
Vital signs	x	x										
12 lead ECG	x	x										
Adverse events	x	x										
Serology	x											
Dinamap		Every 10 minutes										
Clinical Laboratory	x	x										
Inulin and PAH assays				x	x	x	x	x	x	x	x	x
Dextran assay (plasma)					x	x		x	x			
Sampling for AII, renin, aldosterone and ANF				x		x			x		x	
Hematocrit				x		x		x		x		
Standard urine tests	x	x										x
AII infusion (2.5 ng/kg/min)							←	—	—	→		
Urine sampling for inulin, PAH.			U1	U2	U3	U4	U5	U6	U7	U8	U9	
Dextran and electrolyte assay					x				x			

A total of 12 healthy male subjects, aged between 20 and 30, were to be enrolled. Subjects were to be included if their natriuresis was between 70 and 130 mmol/day with a normal diet. Exclusions were congenital single kidney and past history of renal or urologic disease.

Drug supplies are shown in Table 288 below.

Table 288. Drug supplies (PDY 2201).

	Product number		Product number
Placebo	J885N-Ref.1A2	Irbesartan 25 mg	J 855S-Ref.1P1X

Study objectives were (1) to demonstrate and assess the effectiveness of a single oral dose of irbesartan in antagonizing the effects of AII on glomerular filtration rate (GFR) measured by inulin clearance, effective renal plasma flow (ERPF) measured by PAH clearance, and permselectivity measured by clearance of dextrans, (2) to demonstrate a lack of agonist effects of irbesartan, and (3) to show AII antagonist activity on systemic blood pressure. The effect of irbesartan on the RAS components was to be assessed through the variations in plasma AII, active renin (AR) and aldosterone related to the AII receptor blockade. These variations were to be studied under baseline conditions and during AII infusion. Plasma atrial natriuretic factor (ANF) was also to be monitored.

Safety was to be assessed clinically and by standard laboratory blood and urine tests.

A37.5. Results

Thirteen subjects enrolled and all but one completed study. The demographic and baseline characteristics are presented in Table 289 below.

Table 289. Demographics (PDY 2201).

	Mean±SE	Min	Max		Mean±SE	Min	Max
Age (years)	24.8±0.9	20	30	Weight (kg)	67.6±1.8	58	80
Supine				Standing			
HR	64.0±3.1	45	85	HR	71.4±2.7	56	90
SBP	116.7±1.8	100	125	SBP	119.7±2.8	104	136
DBP	66.4±1.7	59	80	DBP	74.0±1.7	63	87
ECG				ECG			
HR	60.5±2.7	46	85	QT	382.3±5.6	360	420
PR	154.6±5.7	120	190	QTc	382.0±6.5	350	430
QRS	84.6±2.2	80	100				

A37.5.1. Renal pharmacodynamics

Treatment effects are summarized in Table 290 below. The effects of AII infusion in the placebo group were to increase MBP, FF, and RVR and to decrease GFR, ERPF, $U_{Na}V$, and $U_{UA}V$. These effects of AII were substantially less in the irbesartan group.

Table 290. Treatment effects (mean±SE; PDY 2201).

	Placebo			Irbesartan		
	Baseline	AII	Control	Baseline	AII	Control
MBP (mmHg)	83.1± 1.2	90.4±2.1	92.8±2.3	82.6±0.8	80.5±1.0	87.5±1.1
GFR (ml/min/1.73m^2)	112.1±3.8	95.6±2.6	99.6±3.6	106.6±4.2	104.2±4.1	98.7±4.4
ERPF (ml/min/1.73m^2)	674.9±42.3	427.5±24.9	534.0±26.6	745.1±32.6	662.3±29.1	629.2±32.4
ERBF (ml/min/1.73m^2)	1089.8±68.9	683.9±39.5	867.7±43.1	1214.4±57.1	1081.2±51.0	1034.5±59.1
FF (%)	17.1±1.0	23.0±1.3	18.9±0.7	10.34.4±	15.8±0.4	15.8±0.6
RVR (dyne.s.cm^{-5})	6313±366	11018±736	8709±399	5517224±	6109±281	6970±417
$U_{Na}V$ (µmol/min)	299.2±27.4	157.9±20.8	268.4±26.4	380.4±35.7	387.8±35.1	450.7±37.5
U_KV (µmol/min)	69.4±8.6	63.4±9.3	64.0±11.0	80.8±9.2	98.5±10	95.3±8.4
$U_{UA}V$ (µmol/min)	2878±350	1779±186	1961±290	3289±280	2924±222	2964±218
$U_{Creat}V$ (µmol/min)	12341±460	10882±404	11056±428	11776±408	11233±420	11017±439

Dextran clearance was similar between groups prior to AII challenge. Treatment group effects on parameters derived from dextran clearance were not statistically significant.

Aldosterone rose upon AII challenge in the placebo group; this rise was substantially attenuated in the irbesartan group. Endogenous AII levels and renin activity were

higher in the irbesartan group. There was no statistically significant difference between groups in ANF.

A37.5.2. Safety

One subject did not complete the study because of orthostatic hypotension with syncope; otherwise clinical safety was unremarkable.

A37.6. Summary

This was a small, randomized, double-blind, placebo-controlled study in healthy male volunteers, comparing the effects of irbesartan 50 mg to placebo on GFR, ERPF, ERBF, FF, and RVR, under baseline conditions and after stimulation with exogenous angiotensin II. Angiotensin II alone increased mean blood pressure, renal vascular resistance, and filtration fraction, and decreased GFR and ERPF. Study design did not permit assessment of effects of irbesartan alone, but irbesartan did antagonize the effects of angiotensin II. Irbesartan was well tolerated, and with the exception of one subject with orthostatic hypotension and syncope, there were no safety issues.

A38. 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.

A38.1. Source documents

Study report: NDA 20-757, vol 1.190-1.198.

A38.2. Investigators

Prof. Hans Brunner, Division d'hypertension; CHU Vaudois, CH 1011- LAUSANNE, Switzerland.

A38.3. Study dates

April 1993 to June 1993.

A38.4. Study design

This study description was based upon the protocol dated 7 January 1993. There were no protocol amendments filed with the study.

The objective of the study was to evaluate the reno-tubular effects of irbesartan.

This study was a double-blind, parallel-group study. The subjects were to be taken from a healthy non-obese Caucasian population with normal physical exam findings and laboratory values. Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, renal (other than age related decreases in creatinine clearance), pulmonary, endocrinologic, neurologic, or psychiatric disease were excluded.

Drug supplies are shown in Table 291 below.

Table 291. Drug supplies (PDY 2202).

	Batch number		Batch number
Placebo	J855S - Ref 1PIX	Irbesartan 5 mg	J 797M - Ref. 1A2
		Irbesartan 25 mg	J 885N - Ref 1A2

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

The subjects received study meals on an outpatient basis 8 days prior to dosing. Each subject's diet was controlled to 3500 cal/day with a daily sodium and potassium intake of 100 mmol and 80 mmol respectively. 24-hour urine sodium were measured for the 3 days prior to first dose. If natriuresis ranged between 80 and 120 mmol/day, the subject was to be entered into the study.

The subject was randomized to taking placebo or irbesartan 10 or 50 mg qd for 8 days.

Pharmacokinetic profiles, renin, angiotensin II (AII), and urine specimens were obtained on day 1 and day 8 according to the schedule shown in Table 292 below. In addition, inulin and PAH (para-aminohippurate) were infused to determine GFR and renal plasma flow respectively.

Physical exams, ECGs and safety laboratory tests were performed during screening and at study end (day 9).

The following parameters were to be determined and compared within each group on days 1 and 8: (1) blood pressure and heart rate variations up to 8 hours post-dose, (2) parameters of electrolytic reno-tubular excretion, (3) AII, PRA, and aldosterone levels, and (4) pharmacokinetic parameters.

Table 292. Schedule for PK and PD Procedures at Day 1 and 8 (PDY 2202)

Time (h)	PK	Pharmacodynamic procedures		Time (h)	PK	Pharmacodynamic procedures	
		Renin/AII	Urine*			Renin/AII	Urine*
Pre-dose	X	X	24-hour pre-dose	5			X
1			X	6	X	X	X
2	X	X	X	7			X
3			X	8	X	X	X
4	X	X	X				

* Urine sampled qhr for inulin, PAH, electrolytes volume, pH; 24 hour collection for pH, volume, electrolytes and uric acid.

Statistical analysis of pre- and post-study measurements, pharmacokinetic and renin/AII determinations were to be compared using analysis of variance.

A38.5. Results

A total of 25 subjects were included in the study. There were no dropouts during the study. One subject had insufficient natriuresis at baseline and was randomized but not dosed.

Demographics of the three treatment groups are shown in Table 293 below. Subjects in the placebo group at screening had a StDBP that was statistically different from the other groups. A comparison of the two groups just prior to dosing showed no statistical significance of StDBP.

Table 293. Demographics (PDY 2202).

	Placebo N=8	Irbesartan 10 mg N=8	Irbesartan 50 mg N=9		Placebo N=8	Irbesartan 10 mg N=8	Irbesartan 50 mg N=9
Age (mean±SE)	25±1	26±2	26±1	Male (%)	100	100	100
White (%)	100	100	100	Weight, kg (mean±SE)	72±2	70±4	69±3
Sit; (mean±SE)				Stand; (mean±SE)			
HR (bpm)	66±4	63±5	62±2	HR (bpm)	76±4	71±4	71±3
SBP (mmHg)	117±4	110±5	115±2	SBP (mmHg)	114±4	114±4	114±4
DBP (mmHg)	75±4	67±3	74±2	DBP (mmHg)*	83±1	74±3	74±3
ECG; (mean±SE)				ECG; (mean±SE)			
HR (bpm)	59±4	59±4	59±3	QT (ms)	381±11	390±21	387±13
PR (ms)	159±8	158±8	166±8	QTc (ms)	367±12	373±10	377±10
QRS (ms)	80±0	80±0	80±0				

*P<0.05 for difference among groups

Ten subjects had 24-hour natriuresis that fell outside the specified range (80 to 120 mmol/day). Six subjects were below 80. The investigator stated that the low values were secondary to incomplete urine collection. Four subjects had natriuresis above the protocol limit (>120 mmol/day).

A38.5.1. Pharmacodynamics

Analysis of blood pressure data showed no consistently significant dose effect of 10 or 50 mg irbesartan against placebo on either study day.

A38.5.2. Renal pharmacodynamics

There were no significant mean differences at baseline among groups with respect to GFR, ERPF, FF, or RVR.

A significant dose effect was observed for filtration fraction (AUC over 4 and 8 hours) compared to placebo. On Day 1, irbesartan tended to decrease the filtration fraction 5 hours post-dose from 22% at baseline to 18% at 10 mg and from 21% to 16% at

50 mg. Similar decreases were seen on day 8. However, there was no consistent significant treatment effect for GFR or ERPF (AUC over 4 or 8 hours), and there was no significant variation in renal vascular resistance at any dose versus placebo.

There were no significant changes in urine flow rate between the treatment groups either at baseline or during study days at any dose. There was an increased urine volume on both study days compared to screening among all dose groups.

There was a dose-related increase in sodium excretion (peak 2 hours post-dose and 4-hour AUC). However, baseline-subtracted cumulative 8-hour sodium excretion showed no significant dose effect. The naturetic effect on day 8 was similar but attenuated.

There was no significant variation in the fractional excretion of lithium at any dose. On the basis of the lithium data, there was no significant difference in the proximal reabsorption of sodium in any dosage group. There was a decrease in distal sodium reabsorption, but this occurred with both drug and placebo.

There was no significant change in urinary uric acid, calcium, phosphate, magnesium, or potassium.

A38.5.3. Hormones

Angiotensin II and PRA increased in a dose-dependent manner on both study days. Decreases in aldosterone were observed on both study days in all groups including placebo, and no dose dependent relationship was observed.

Pharmacokinetics were similar to that of previous reports.

A38.5.4. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event. A total of 5 adverse events were observed.

No case of orthostatic hypotension was reported.

No significant changes between screening and end-of-trial ECGs were noted with any dose group.

There were no obvious dose-related laboratory abnormalities observed.

No significant changes in physical exam were observed.

A38.6. Summary

This was a double-blind trial to determine the renal pharmacodynamics of irbesartan in normal male Caucasians. There is no major protocol deviations which would effect the results of this trial. The doses used (10 and 50 mg) were below the range where effects on blood pressure have been observed. This study demonstrated dose-dependent increases in PRA and angiotensin II on both study days, consistent with an angiotensin II receptor antagonist. The observed reduction in filtration fraction is also consistent with an angiotensin II receptor antagonist. However, filtration fraction is equal to GFR/ERPF, but there was no consistent dose-dependent effects on GFR or ERPF. Renal vascular resistance was not affected, possibly because of autoregulatory mechanisms. Observed increases in sodium excretion could be the result of blockade of AII, but since subjects were fed a heavy sodium load, pathways other than angiotensin II could be important determinants of increased sodium excretion. The decrease in aldosterone levels in all groups was likely a response to the increased sodium load.

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

A39. 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)

A39.1. Source documents

Study report: NDA 20-757, vol 1.199-1.207.

A39.2. Investigators

Professor JL Reid, Clinical Pharmacology Research Unit, Gardiner Institute, Glasgow Western Infirmary, Glasgow G11 6NT, UK.

A39.3. Study dates

July 1993 to November 1993.

A39.4. Study design

This study description was based upon the protocol dated 27 May 1993. There were no protocol amendments filed with the study.

The objective of the study was to provide preliminary dose ranging information on safety and acute blood pressure response in salt depleted male subjects.

This study was a double-blind, ascending dose crossover study using 3 groups of 4 subjects each. The subjects were taken from a healthy non-obese Caucasian population with normal physical exam findings and laboratory values. Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, renal, pulmonary, endocrinologic, neurologic, or psychiatric disease were excluded.

Drug supplies are shown in Table 294 below.

Table 294. Drug supplies (PDY 2203).

	Batch number		Batch number
Placebo	K910J - Ref 1PIX	Irbesartan 1 mg	K936M -Ref.1A1
		Irbesartan 5 mg	J 797M - Ref. 1A2
		Irbesartan 25 mg	J 885N - Ref 1A2

At the screening visit, each subject was to undergo a complete medical history and physical examination. A complete laboratory evaluation (SMA20, CBC, urinalysis, hepatitis B and HIV ELISA), ECG and chest X-ray was done for potential candidates meeting initial screening medical histories and age requirements (18 to 40 years). If eligible, the subject received, in a cross-over design, 3 increasing single doses of irbesartan and placebo during 4 periods of treatment conducted 7 days apart. For 3 days prior to each dose, subjects were on a sodium-restricted diet (40 mmol/day) and oral diuretic treatment with furosemide 80 mg/day. The salt-restricted diet was continued throughout each dosing day. Diuretic therapy was administered 20 hours before study drug administration. The dose schedule for the subjects at each level shown in Table 295 below.

Table 295. Dosing schedule (PDY 2203).

Level	Doses (mg)
1	1, 5, 10, placebo
2	10, 25, 50, placebo
3	10, 50, 100, placebo

Pharmacokinetic profiles, renin, angiotensin II (AII) and urine specimens were obtained on study days according to the schedule shown in Table 296 below.

Blood pressure monitoring, physical exams, ECGs and safety laboratory tests were performed prior to administration of study drug and 24 hours post-dose on all study days. Follow-up blood work was done one week after study end.

Table 296. Schedule for PK and PD procedures at days 1 and 8 (PDY 2203).

Time (h)	PK	Pharmacodynamic procedures	
		Renin/AII	Urine*
Pre-Dose	X	X	24-hour pre-dose
1	X	X	24-hour collection
2	X	X	
4	X	X	
6	X	X	
24	X	X	

*Urine for volume, uric acid, sodium, potassium, chloride, urea, and creatinine

The primary objective was to determine, during acute administration of irbesartan, the dose response relationship for (1) supine blood pressure, and (2) renin and AII. Pharmacokinetic data and safety information were also to be obtained.

Statistical analysis of pre- and post-study measurements, pharmacokinetic and renin/AII determinations were to be compared using analysis of variance.

A39.5. Results

A total of 12 subjects were included in the study. There were no dropouts.

Demographics of the 3 treatment groups are shown in Table 297 below.

Table 297. Demographics (PDY 2203).

	Panel 1 N=4	Panel 2 N=4	Panel 3 N=4		Panel 1 N=4	Panel 2 N=4	Panel 3 N=4
Age (mean±SE)	24±3	27±3	24±3	Male (%)	100	100	100
White (%)	100	100	100	Weight, kg (mean±SE)	79±14	92±10	75±9
Supine (mean±SE)				Stand (mean±SE)			
HR (bpm)	59±6	69±10	61±5	HR (bpm)	71±3	83±11	74±10
SBP (mmHg)	129±6	123±7	125±16	SBP (mmHg)	133±6	126±5	118±13
DBP (mmHg)	65±7	65±7	62±7	DBP (mmHg)	68±8	73±4	63±5

There were no major protocol deviations. The minor deviations did not affect subject evaluability for safety or activity of irbesartan. The first subject of Panel 1 received 25 mg dose instead of 10 mg due to a packaging error. Samples for PRA, AII, and irbesartan not specified in the protocol were taken at 8 and 10 hours post-dose. These values were included in all analysis. Subjects had their follow-up visit 11 to 34 days after the last administration rather than 7 days.

A39.5.1. Pharmacodynamics

The effects of pre-treatment salt depletion showed statistically significant reductions from baseline in body weight, serum sodium and potassium, urinary Na concentration, and urinary Na per day. Plasma urea and renin activity increased.

A decrease in supine blood pressure was observed for irbesartan greater than 10 mg. Maximal fall of blood pressure occurred 2 to 6 hours post-dose. Statistical differences were observed in either peak effect or AUC with doses 25 mg and higher. No statistical correlation was observed with standing blood pressure.

A39.5.2. Hormones

PRA showed an increase for all doses compared to placebo. At doses >1 mg, the increase in PRA was statistically significant.

A rise in plasma AII was observed at greater doses than 10 mg. The 25- and 50-mg doses were statistically significantly different from placebo.

A39.5.3. Pharmacokinetics

AUC and C_{max} for irbesartan increased less than linearly with dose from 1 to 100 mg.

A39.5.4. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event. Two subjects had a total of two adverse events. These were lab abnormalities (elevated transaminase levels and low ferritin) observed during the post-study visit.

No case of orthostatic hypotension was reported.

No dose dependent changes in serum chemistry or hematology were noted.

No significant changes between screening and end-of-trial ECGs were noted with any dose group.

No significant changes in physical examination were observed.

A39.6. Summary.

This was a double-blind trial to assist in dose-ranging and obtain information on acute administration of irbesartan. There is no major protocol deviations which would effect the results of this trial. The subjects were all normal Caucasian males. There were dose-related increases in PRA and angiotensin II, consistent with the effects of an angiotensin II receptor antagonist. Acute reduction in supine blood pressure was also observed. AUC and C_{max} for irbesartan increased less than linearly with dose.

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

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A40. PDY 2204: Hormonal profile and hemodynamic effects of irbesartan in healthy volunteers.

A40.1. Source documents

Study report: NDA 20-757, vol 1.208-1.212.

A40.2. Investigators

Professor J.F. Giudicelli; Dept. of Pharmacology; Faculté de Médecine Paris-sud; Hopital du Kremlin-Bicetre; 78, rue du General Leclerc; 94270 Le Kremlin-Bicetre, France.

A40.3. Study dates

October 1993 to April 1994.

A40.4. Study design

This study description was based upon the protocol dated 27 May 1993. There was one administrative protocol amendment filed with the study.

The objective of the study was to study the hormonal profile and the hemodynamic effects of irbesartan in healthy volunteers.

This study was a double-blind crossover study with 3 single dose treatment periods spaced 7 days apart. The subjects were taken from a healthy non-obese Caucasian population with normal physical exam findings and laboratory values. Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, renal, pulmonary, endocrinologic, neurologic, or psychiatric disease were excluded.

Drug supplies are shown in Table 298 below.

Table 298. Drug supplies (PDY 2204).

	Batch number		Batch number
Placebo	K962A - Ref 1PIX	Irbesartan 5 mg	K938M- Ref. 1A2
		Irbesartan 25 mg	K965A - Ref 1A2

At the screening visit, each subject was to undergo a complete medical history and physical examination. A complete laboratory evaluation (SMA20, CBC, urinalysis, hepatitis B and HIV ELISA), ECG and chest X-ray were done for potential candidates meeting initial screening medical histories and age requirements (18 to 30 years). If eligible, the subject received in a cross-over design, 2 doses of irbesartan (10 and 50 mg) and placebo during 3 periods of treatment spaced 7 days apart.

Systemic and peripheral hemodynamics, renin, angiotensin II (AII) and urine specimens were obtained on study days according to the schedule shown in Table 299 below.

Evaluation of systemic hemodynamics comprised of vital signs and cardiac output. Cardiac output was calculated from pulsed doppler ultrasound measurement of flow velocity and diameter at the aortic valve leaflets. Total vascular resistance was calculated from the cardiac output. Peripheral hemodynamics of humeral, carotid and femoral arteries were similarly determined by pulsed doppler ultrasongraphy. However, since ultrasonography of the MCA is technically difficult, volume flow rates and resistance were not calculated.

Physical exams, ECGs, and safety laboratory tests were performed prior to administration of study drug and 24 hours post-dose on all study days. Follow-up blood work was done one week after study end.

The primary objective was to determine during acute administration the dose response relationship of irbesartan for (1) systemic hemodynamics (BP, CO, TVR), (2) peripheral hemodynamics (volume flow rates of humeral, femoral, and carotid

Table 299. Schedule for PK and PD procedures on days 1 and 8 (PDY 2204).

Time (h)	HD	Pharmacodynamic procedures		Time (h)	HD	Pharmacodynamic procedures	
		Renin/AII	Urine*			Renin/AII	Urine*
Pre-dose	SPC	X	24-hour pre-dose	1	C	X	24-hour collection
				2	SPC	X	
				3	C		
				4	SPC	X	
				6	C	X	
				8	SPC		
				24	SPC	X	

*Urine for volume, uric acid, sodium, potassium, chloride, urea and creatinine
HD= hemodynamics; S=systemic, P=Peripheral; C=Cerebral

arteries), (3) middle cerebral artery velocity, and (4) renin, AII, angiotensin converting enzyme (ACE), and atrial naturetic factor (ANF).

Statistical analysis of pre and post study measurements, pharmacokinetic and renin/AII determinations were to be compared using analysis of variance.

A40.5. Results

A total of 9 subjects were included in the study. There were no dropouts during the study.

There were no major protocol deviations. The minor deviations did not affect subject evaluability for safety or activity of irbesartan.

A40.5.1. Pharmacodynamics

There was no statistically significant effect of irbesartan 10 or 50 mg on peak or AUC for supine blood pressure.

There was a qualitative increase in cardiac output and a concomitant decrease in TVR with the 50-mg dose, but neither dose was statistically significantly different from placebo with respect to either peak effect or AUC.

There was no statistical evidence of treatment effect on humeral, femoral, or carotid volume flow. However, transient increases in femoral, carotid, and humeral flow were observed for the 50-mg dose 4 to 8 hours after ingestion. There was no change in middle cerebral velocity either statistically or qualitatively.

A40.5.2. Hormones

There was a statistically significant increase in active renin (peak and AUC) at 50 mg and, for each active dose, an increase in angiotensin II.

There was no evident effect of treatment on aldosterone, angiotensin converting enzyme, atrial naturetic factor, or antidiuretic hormone levels.

A40.5.3. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event. One subject experienced a headache 8 hours after treatment with irbesartan 10 mg.

No case of orthostatic hypotension was reported.

No dose-dependent changes in serum chemistry or hematology were noted.

No significant changes between screening and end-of-trial ECGs were noted with any dose group.

No significant changes in physical exam were observed.

A40.6. Summary.

This was a double-blind trial of normal Caucasian males to determine whether there were significant changes in systemic, peripheral, and cerebral hemodynamics with irbesartan. There were no major protocol deviations which would effect the results of this trial. No statistically significant dose-dependent effects were found for any hemodynamic parameter. However, notable qualitative differences were observed in the direction that would be expected for the proposed mechanism of action. Statistically significant increases in renin activity and angiotensin II were observed.

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

A41. PDY 2278: Assessment of acute and chronic renal hemodynamics following treatment with an AII antagonist (irbesartan) or an ACEI (enalapril) in essential hypertensive patients.

A41.1. Source documents

Study report: NDA 20-757, vol 1.233-238.

A41.2. Investigator

Prof. Hans Brunner, Department of Hypertension, CHU Vaudois, Lausanne, Switzerland.

A41.3. Study dates

10 January 1995 to 13 November 1995.

A41.4. Study design

There was one protocol amendment to permit enrollment of non-pregnant, premenopausal women.

Study objectives were (1) to compare the acute and long-term renal effects of irbesartan to those of enalapril in subjects with essential hypertension and normal renal function, (2) to compare the anti-hypertensive effects of the 2 drugs given in a morning or evening sequence, and (3) to assess changes in the renin-angiotensin system parameters during chronic treatment with both drugs.

This study was a single-center, randomized, double-blind, 12-week study in which 2 parallel groups of subjects received daily doses of either irbesartan 100 mg or enalapril 20 mg in the morning for 6 weeks and in the evening for 6 weeks in randomized order according to a cross-over design, as shown in Figure 82 below. There was no washout interval between the 2 successive 6-week treatment periods.

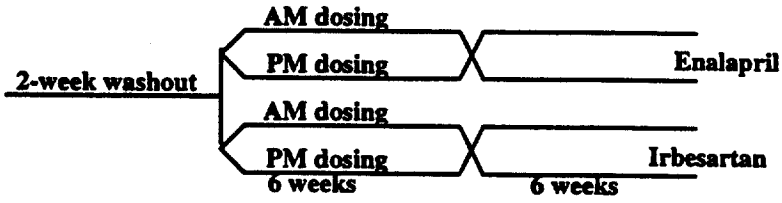

Figure 82. Study design (PDY 2278).

Subjects were males and females of non-childbearing potential with mild to moderate hypertension (DBP between 95 and 115 mmHg). Exclusions were recent stroke, renal insufficiency, heart failure, type I diabetes or poorly controlled type II diabetes, and unstable angina or recent MI.

At the end of a single-blind, 2-week washout period, subjects were randomized to either irbesartan 100 mg or enalapril 20 mg. On the morning of the first day, all subjects received an active dose. Thereafter, subjects were to receive active treatment in the morning or evening for 6 weeks and then cross over to the other treatment period. The 2 cross-over periods were placebo-controlled.

Table 300 below shows drug supplies.

Table 300. Drug supplies (PDY 2278).

	Product number	Lot		Product number	Lot
Placebo		K005T	Enalapril 20 mg		L121E
			Irbesartan 100 mg		L081F

Irbesartan assay was by

The pharmacokinetic parameters evaluated included plasma concentrations of irbesartan, 4, 12, and 24 hours after dosing at baseline, and after 6 and 12 weeks of

treatment. The pharmacodynamic studies carried out after 6 or 12 weeks of treatment included renal parameters (GFR, RPF, FF, RVR), blood pressure, heart rate, and RAS components (AII, PRA, and aldosterone).

A41.5. Results

Twenty-one subjects were enrolled. One subject withdrew for lack of efficacy. The remainder completed study.

A41.5.1. Pharmacokinetics

The single measurements of irbesartan 4 hours after morning dosing provide some assurance that study drug was taken according to the protocol.

A41.5.2. Hormones

Four hours after a single dose of irbesartan on day 1, angiotensin II levels were increased, whereas enalapril was associated with a decrease in angiotensin II. Plasma renin activity increased in both groups. Aldosterone levels were not significantly changed in either group after 6 or 12 weeks of treatment.

A41.5.3. Renal pharmacodynamics

The acute effects of irbesartan and enalapril were similar on GFR, RPF, and RVR assessed 4 hours after the first dose. A small decrease was seen in filtration fraction (FF) following enalapril treatment compared to irbesartan. The long-term effects showed no statistically significant differences between treatments. No significant differences were observed in the excretion fractions of different electrolytes or of uric acid.

A41.5.4. Pharmacodynamics

Table 301 below shows changes from baseline to the end of the 6- or 12-week double-blind period in vital signs. There were no statistically significant differences between groups with respect to effects on blood pressure, regardless of the time of drug intake (morning or evening).

Table 301. Change from baseline in vital signs (PDY 2278).

	Enalapril N=10		Irbesartan N=10	
	Morning	Evening	Morning	Evening
SBP	-10.9±5.0	-9.6±5.0	-7.4±3.6	-7.6±3.3*
DBP	-6.3±2.8	-8.0±2.6*	-5.4±1.9*	-5.1±2.8
HR	-1.9±1.7	-4.0±1.8*	0.1±1.5	-3.3±1.8

*P<0.05 by sponsor's analysis (Student's t-test).

A41.5.5. Safety

There were no deaths, and 1 subject discontinued after enrollment. The only serious drug-related adverse event was a life-threatening vagal syncope that occurred in a subject during removal of an iv catheter. In 4 subjects randomized to enalapril, 6 adverse events were reported in 4 subjects. These included cough, dizziness, edema of the tongue and bronchitis. The latter 2 were not considered drug-related.

No clinically significant changes were seen in laboratory tests or ECGs.

A41.6. Summary

This was a small, randomized, double-blind study in subjects with mild-to-moderate essential hypertension comparing blood pressure and renal hemodynamics with irbesartan 100 mg versus enalapril 20 mg and morning versus evening dosing. Irbesartan and enalapril had similar effects on blood pressure, glomerular filtration rate, renal plasma flow, renal vascular resistance, and filtration fraction. Plasma angiotensin II and renin were significantly elevated 24 hours after irbesartan 100 mg, whereas plasma angiotensin decreased from baseline after enalapril 20 mg. Plasma aldosterone was not significantly different in subjects randomized to irbesartan or enalapril.

A42. 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.

A42.1. Source documents

Study report: NDA 20-757, vols 1.182 - 1.185.

A42.2. Investigator

Prof. Albert Miriam, Service de Medicine Interne, Hopital Lapeyronie, Montpelier, France.

A42.3. Study dates

19 September 1995 to 15 November 1995.

A42.4. Study design

The primary objective was to assess the duration and the amplitude of the AII receptor antagonist activity of irbesartan over 24 hours. The secondary objectives were to assess the overall dose-response for AII receptor antagonist activity, complementing Study PDY 1692's doses of 5, 25, 50, and 100 mg, and to look for any agonist effect of irbesartan.

This study, diagrammed in Figure 83 below, was a single-centered, randomized, double-blind, placebo-controlled study of irbesartan 75, 150, and 300 mg in healthy volunteers. Subjects received a single dose of drug or placebo in a randomized order separated by a one-week washout period. The subjects were given sodium chloride supplementation (6 g/day) the day before and the day of dosing.

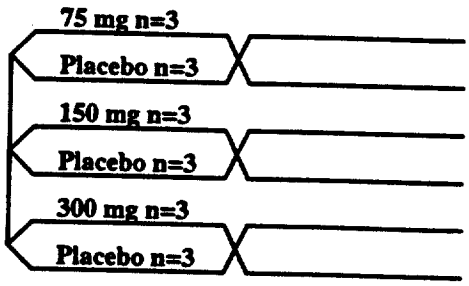

Figure 83. Study design (PDY 2801).

A total of 18 eligible healthy volunteers were to be enrolled (6 per group). Subjects were to be male Caucasians aged 18 to 35 years, with body weights 60 to 85 kg, supine SBP <130 mmHg, normal 12-lead ECG, normal physical examination and laboratory profiles, non-smoker, alcohol consumption <20 g/day, and negative urine screen for cocaine, opiates and cannabinoids.

Table 302 below shows drug supplies.

Table 302. Drug supplies (PDY 2801).

	Product number	Lot		Product number	Lot
Placebo	186295-R000-	L94F014C	Irbesartan75 mg	186295-R050-	L94J022C
			Irbesartan 100 mg	186295-R100-	L94G017C

The schedule of events is presented in Table 3.

Irbesartan levels were assayed by [redacted]

The pharmacokinetic parameters evaluated included plasma irbesartan concentration and AUC_{0-24}.

Safety was assessed by physical exams, vital signs, adverse events, ECG, and laboratory tests including hematology, biochemistry, and quantitative urinalysis.

Table 303. Schedule of procedures (PDY 2801).

	Screen	Time from dosing (h)													Post
		-0.25	0	0.25	0.5	1	2	3	4	5	6	7	8	12	24	
Administration /Irb/placebo			x													
AII test-dose injection		x				x	x		x				x	x	x	
Serology	x															
Urinary sodium	x															
Angiotensin II dose-response	x															
Laboratory		x													x	
Physical examination	x	x			x	x	x	x	x		x		x	x	x	x
12-lead ECG	x	x					x				x				x	x
BP and HR	x		x			x	x	x	x	x	x	x	x	x	x	x
Blood sampling for RAS		x				x	x		x				x	x	x	
PK blood sampling		x				x	x		x				x	x	x	
Adverse events																x

A42.5. Results

Eighteen subjects were enrolled and completed study.

A42.5.1. Pharmacokinetics

Plasma levels of irbesartan following a single dose are shown in Figure 84 below. C_{max} increased less than dose-proportionally, but AUC_{0-24h} was dose-proportional.

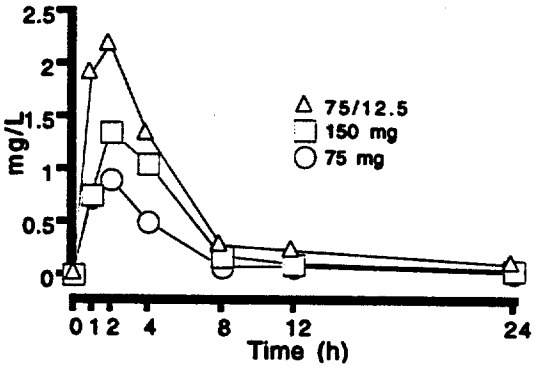

Figure 84. Pharmacokinetics (PDY 2801).

A42.5.2. Pharmacodynamics

There were dose-related changes in SuSBP and SuDBP. These effects reached a maximum between 2 and 4 hours post dose. There were significant increases in plasma levels of angiotensin II and active renin on active doses compared to placebo. Aldosterone plasma levels were significantly decreased at 75 and 300 mg.

There was a dose-related pressor response to angiotensin administered 2 hours after placebo as shown in Figure 85 below. This pressor effect was antagonized to a similar extent by all doses of irbesartan at peak. The 300 mg dose was associated with

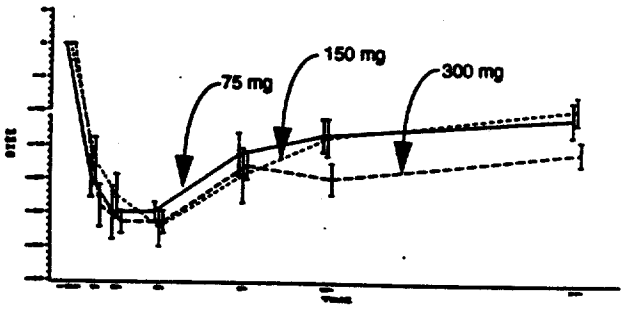

Figure 85. AII antagonism (DBP; PDY 2801).

greater preservation of inhibition at 24 hours.

A42.5.3. Safety

There were no deaths. Two subjects on irbesartan 150 mg had headache and syncope, and 3 subjects had application site disorders. One subject on placebo had headache, and 4 subjects had application site disorders. The frequencies of drug-related adverse events were not different in the active treatment groups compared to placebo. No clinically significant changes were seen on physical examination, ECG, or in any of the laboratory tests.

A42.6. Summary

This was a small, randomized, parallel, placebo-controlled, cross-over study in which normotensive white male volunteers were given single doses of irbesartan 75, 150, and 300 mg followed by angiotensin II. There was a significant increase in plasma angiotensin and active renin in subjects given irbesartan consistent with AII receptor blockade and a feedback mechanism. The pressor response to exogenous angiotensin was attenuated or abolished by irbesartan. There was no clear effect on plasma aldosterone levels.

A43. PPK 1690: Pharmacokinetic study in a single dose assessment of the food effect on the SR47436 pharmacokinetics in healthy volunteers.

A43.1. Source documents

Study report: NDA 20-757, vol 1.152-1.159.

A43.2. Investigators

Dr. Thierry Denolle, Biotrial Center, 20 rue du Pr Jean Pecker, 35000 Rennes, France.

A43.3. Study design

The objective of the study was to assess the effect of food on the pharmacokinetics and pharmacodynamics of irbesartan (5- 100 mg) and the dose proportionality.

This was a single center, open-label, randomized, 4-period crossover study in 12 healthy male volunteers. The four periods were: (a) irbesartan 5 mg capsule, fasting, (b) irbesartan 25 mg capsule, fasting, (c) irbesartan 4x25 mg capsules, fasting, and (d) Irbesartan 25 mg capsule, fed (FDA standard meal).

There was a 2 week washout period between each treatment period. Blood samples were collected at pre-dose, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours after dosing. Urine samples were collected at the following intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, and 96-120 hours post-dose.

Drug supplies are shown in Table 304 below.

Table 304. Drug supplies (PPK 1690).

	Lot number
Irbesartan 5 mg capsules	J797M
Irbesartan 25 mg capsules	J798M

Assay of plasma and urinary irbesartan was performed according to methods 1 and 6, respectively, in Table 7. *Assay validation for irbesartan.* on page 15.

ANOVA was used to analyze C_{max}, $AUC_{0\text{-}obs}$, AUC_{∞}, $T_{1/2}$, Cl/F, V_d/F, Ae and Fe. The 90% CI were constructed for C_{max}, $AUC_{0\text{-}obs}$, $AUC_{0\text{-}\infty}$ and Fe. Wilcoxon's (food effect) and Friedman's (dose effect) non-parametric tests were applied to T_{max}.

A43.4. Results

The mean time of dose administration was 0.62±0.14 hours after the start of breakfast.

The mean plasma concentration-time profiles are shown in Figure 86 below, for each dose (5, 25, 100 mg) of irbesartan fasting (left panel) and irbesartan 25 mg fed vs fasted (right panel).

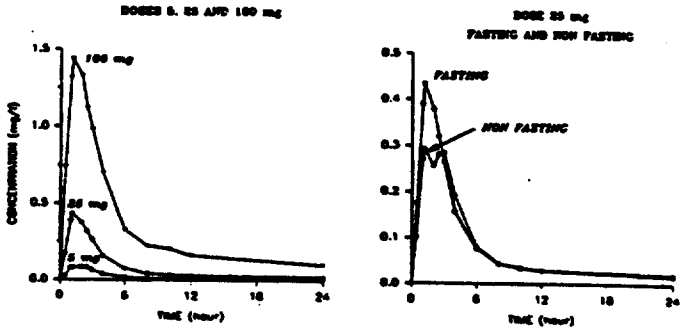

Figure 86. Plasma irbesartan by dose and under fasted and fed conditions (PPK 1690).

Pharmacokinetic parameters are compared in Table 305 below. Analysis of normalized log-transformed C_{max} data revealed a statistically significant dose-effect (p=0.006) and a significant subject effect (p=0.003).

Table 305. Irbesartan pharmacokinetics under fasted and fed conditions (PPK 1690).

	Fasted—non-normalized			Fasted—normalized to 25 mg			Fed
	5 mg	25 mg	100 mg	5 mg	25 mg	100 mg	25 mg
C_{max} (ng/mL)	0.12±0.06	0.50±0.13	1.60±0.73	0.57±0.27	0.50±0.13	0.40±0.18	0.52±0.26
$AUC_{0\text{-}obs}$ (ng.h/mL)	0.56±0.23	2.29±0.61	9.88±7.11	2.28±1.13	2.29±0.61	2.47±1.78	2.05±0.30
$AUC_{0\text{-}\infty}$ (ng.h/mL)	0.54±0.12	2.31±0.60	9.92±7.12	—	2.31±0.60	—	2.07±0.30
$T_{1/2}$ (h)	15.8±7.7	15.0±7.7	13.2±4.9	—	15.0±7.7	—	16.3±8.4
T_{max} (h)	1.88±0.77	1.37±0.55	1.64±0.60	—	1.37±0.55	—	2.21±1.17[a]
Ae (mg)	0.04±0.01	0.23±0.06	0.88±0.28	—	0.23±0.06	—	0.30±0.11
Fe (%)	0.84±0.24	0.90±0.24	0.88±0.28	—	0.90±0.24	—	1.22±0.44

a. Food effect (P=0.019 by Wilcoxon non-parametric test).

The Spearman rank correlation, $0.60<r<0.70$ between the RAS and irbesartan (fasting doses) was not compelling. There was no correlation found for aldosterone.

A43.4.1. Safety

Not reviewed.

A43.5. Summary.

The T_{max} of irbesartan 25 mg was delayed by 30 minutes in the presence of food. C_{max} and AUC were unchanged. C_{max} for irbesartan 5, 25, and 100 mg capsules was less than dose proportional at the 100-mg dose. AUC was dose proportional.

A44. PPK 2198: Comparative pharmacokinetics of irbesartan in healthy young and elderly volunteers: single and repeated oral administration of 25 mg during 8 days.

A44.1. Source documents

Study report: Vol 1.133-1.140.

A44.2. Investigators

Professor O.G. Nilsen, Dept. of Pharmacology and Toxicology; University of Trondheim-Medisinsk Teknisk Senter 7005, Trondheim, Norway.

A44.3. Study dates

June 1993 to February 1994.

A44.4. Study design

This study description was based upon the protocol dated 10 February 1993. There were 5 changes to the protocol which were made after subjects were enrolled but before pharmacokinetic measurements were taken. None of these amendments would affect the basic pharmacokinetic measurements or bias the study.

The objective of the study was to compare the pharmacokinetics of irbesartan 25 mg qd in healthy young and elderly subjects with mild-moderate renal insufficiency.

This study was a open-label, parallel-group study. The subjects were taken from a healthy non-obese Caucasian population with normal physical exam findings and laboratory values. The subjects were placed in one of 3 groups based on age and creatinine clearance (calculated by the Cockroft formula) as follows: Group 1—age 65 to 85 with creatinine clearance 45 to 60 ml/min, Group 2—age 65 to 85 with clearance >60 ml/min, and Group 3—age 18 to 35 with clearance >90 ml/min. Subjects with evidence of clinically relevant cardiovascular, hematologic, hepatic, gastrointestinal, renal (other than age related decreases in creatinine clearance), pulmonary, endocrinologic, neurologic or psychiatric disease were excluded.

Drug supplies are shown in Table 306 below.

Table 306. Drug supplies (PPK 2198).

Unit	Batch Number
Irbesartan 25 mg	J 885N - Ref 1A2

At the screening visit, each subject was to undergo a complete medical history, physical examination and calculation of renal clearance based on the Cockroft formula:

$$CrCl = \frac{(140 - Age) \times Weight \times F}{PlasmaCr}$$

where CrCl is in ml/min, Age in years, Weight in kg, and Plasma Cr in μmol/l. F is a multiplicative constant which is 1.23 for males and 1.04 for females. A complete laboratory evaluation (SMA20, CBC, urinalysis, hepatitis B, and HIV ELISA), ECG and chest X-ray was to be done for potential candidates meeting initial screening medical histories, age, and creatinine clearances.

The subjects were asked to return to the center 2 weeks later and were given irbesartan 25 mg on days 1 and 11. Pharmacokinetic profiles, renin, angiotensin II (AII) and urine specimens were obtained on days 1 and 11 according to the schedule shown in Table 307 below.

After the last blood sample on day 4, the subjects took irbesartan 25 mg qd for 8 days (to day 10). Trough levels of irbesartan were to be obtained and vital signs and adverse events were recorded on days 7, 9, and 10.

Table 307. PK and PD sampling on days 1 and 11 (PPK 2198).

Time (h)	PK	Pharmacodynamic sampling		Time (h)	PK	Pharmacodynamic sampling	
		Renin/AII	Urine			Renin/AII	Urine
Pre-Dose	X	X	(night collection)*	12	X		12- 24
0.5	X		0-12	24	X		
1.0	X			48	X		
1.5	X			72	X		
2	X	X					
3	X						
4	X	X					
6	X						
8	X						
10	X						

*Day 1 only

Assay of plasma and urinary irbesartan was performed according to methods 1 and 7, respectively, in Table 7. *Assay validation for irbesartan.* on page 15.

The following pharmacokinetic parameters were to be determined and compared within each group on day 1: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0-\tau}$, $AUC_{0-\infty}$, Cl/F (apparent clearance), and V_d/F (apparent volume of distribution). On day 11, the following parameters were to be determined and compared: C_{max}, T_{max}, C_{min}, $AUC_{0-\tau}$, R_{ac} (accumulation ratio), Cl_{ss}/F, and V_{dss}/F.

Statistical analysis of pre- and post-study measurements, pharmacokinetics, and renin/AII determinations were to be compared using analysis of variance.

Physical exams, vital signs, ECGs and safety laboratory tests were to be performed during screening, during administration, and at study end.

A44.5. Results

A total of 35 subjects were screened. There were 3 subjects who did not meet entry criteria. Two subjects left prematurely on day 3. One subject (young) had increased liver enzymes at screening and on day 1 and was wrongly included. The other subject who had hypothyroidism withdrew due to patient request. Overall a total of 30 subjects (10 per group) were included in the analysis.

Hematocrit was not determined during the study because of an error in the design of the case report forms. One subject on day 11 did not have vital signs measured prior to drug intake.

Demographics of the 3 treatment groups are shown in Table 308 below. Male and female subjects were not matched among the groups.

Table 308. Demographics (PPK 2198).

	Age 65 to 85		Age 18 to 35		Age 65 to 85		Age 18 to 35
	45<CrCl<60 N=10	CrCl>60 N=10	Crcl>90 N=10		45<CrCl<60 N=10	CrCl>60 N=10	Crcl>90 N=10
Age (mean±SE)	74±1.6	70±1.1	23±1.8	Weight, kg (mean±SE)	65.6±3.1	77.3±2.1	77.5±2
Race (%)	100	100	100	Height, cm (mean±SE)	164.8±2.7	174.1±2.6	172.8±1.7
Male (%)	20	73	100	CrCl, ml/min (mean±SE)	51±2	69±2.5	113±3
Female (%)	80	27	0				
Sitting (mean±SE)				Standing (mean±SE)			
HR (bpm)	66±2	61±2	60±3	HR (bpm)	72±3	67±2	64±2
SBP (mmHg)*	143±7	145±5	122±2	SBP (mm Hg)*	146±7	145±6	121±2
DBP (mmHg)	82±4	89±2	84±2	DBP (mm Hg)	87±3	93±3	86±2
ECG (mean±SE)				ECG (mean±SE)			
HR (bpm)	63±3	58±3	59±2	QT (ms)	404±5	419±9	410±5
PR (ms)*	149±9	182±6	165±5	QTc (ms)	409±5	412±6	406±3
QRS (ms)*	84±3	95±3	95±2				

*Significant (p<0.02) difference among groups.

A44.5.1. Pharmacokinetics

The single- and multiple-dose pharmacokinetic profiles of the 3 groups are shown in Figure 87 below.

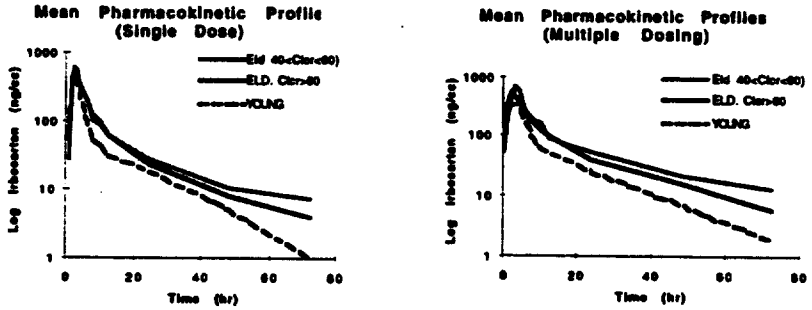

Figure 87. Mean plasma levels of irbesartan (PPK 2198).

Pharmacokinetic parameters for irbesartan are shown in Table 309 below. There was a statistically significant negative correlation between creatinine clearance and $AUC_{0-\tau}$ or $AUC_{0-\infty}$. There was a statistically significant correlation between irbesartan clearance on days 1 and 11 and creatinine clearance.

Mean urinary pharmacokinetic parameters is given in Table 310 below.

Table 309. Pharmacokinetic parameters (mean±SD; PPK 2198).

	Single dose			Multiple dose		
	Age 65 to 85		Age 18 to 35 CrCl>90 N=10	Age 65 to 85		Age 18 to 35 CrCl>90 N=10
	45<CrCl<60 N=10	CrCl>60 N=10		45<CrCl<60 N=10	CrCl>60 N=10	
C_{max}, mg/l	0.722±0.191	0.634±0.224	0.534±0.139	0.733±0.344	0.683±0.304	0.552±0.144
T_{max}, h	2.36±0.57	2.10±0.97	2.20±0.92	2.80±0.63	2.64±1.46	2.50±1.15
AUC, mg-hr/l 0-τ 0-∞ 0-24 h	4.143±1.482 4.597±1.887	3.706±1.157 3.957±1.195	2.468±0.607 2.434±0.759	4.885±1.603	3.887±1.143	2.662±0.786
Cl/F, ml/min-kg	1.66±0.95	1.47±0.44	2.37±0.78	1.59±0.53	1.47±0.36	2.22±0.69
$t_{1/2}$, h	24±11.1	16.8±4.7	11.6±3.5	25.5±12.0	17.8±5.9	11.9±2.7
V_d/F, l/kg	3.29±1.67	2.22±1.13	2.29±0.83	3.5±1.84	2.31±0.95	2.19±0.66
Accumulation Ratio				1.32	1.25	1.26

Table 310. Urinary pharmacokinetic parameters (mean±SD; PPK 2198).

	Single dose			Multiple dose		
	Age 65 to 85		Age 18 to 35 CrCl>90 N=10	Age 65 to 85		Age 18 to 35 CrCl>90 N=10
	45<CrCl<60 N=10	CrCl>60 N=10		45<CrCl<60 N=10	CrCl>60 N=10	
Irb, mg/24-h	0.123±0.097	0.191±0.127	0.174±0.130	0.123±0.097	0.209±0.84	0.157±0.091
Unchanged Irb (%)	0.49±0.39	0.76±0.51	0.69±0.52	0.49±0.33	0.83±0.34	0.63±0.36
Renal Cl, ml/min	0.617±0.437	1.099±0.841	1.437±1.125	0.483±0.362	0.970±0.475	1.120±0.804

A44.5.2. Hormones

Plasma renin and angiotensin II at 0, 2, and 4 hours on days 1 and 11 are shown in Figure 88 below. Values of renin and angiotensin II below the detection limit were given concentrations of 4.0 and 1.5 ng/l respectively.

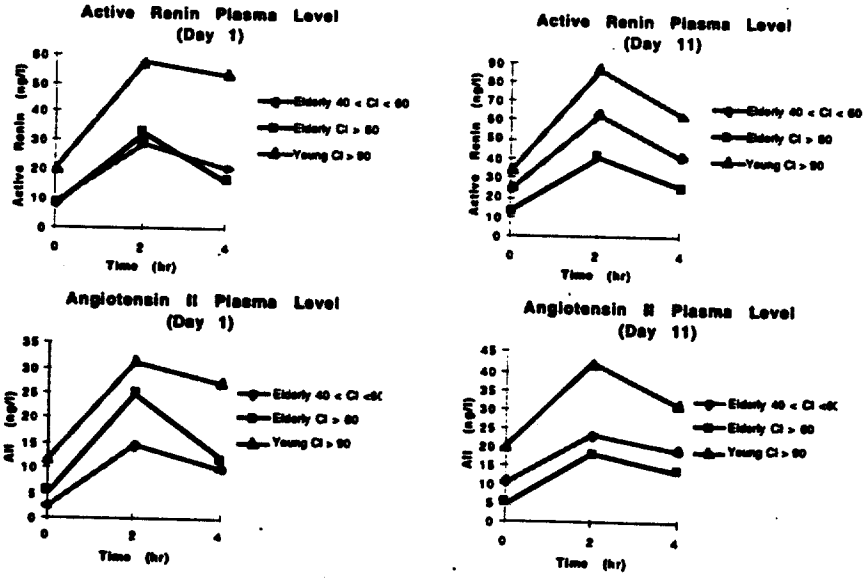

Figure 88. Active renin and angiotensin II levels (PPK 2198)

A44.5.3. Pharmacodynamics

No significant between-group differences were seen with respect to hemodynamic parameters (SBP, DBP, or HR).

A44.5.4. Safety

There were no deaths or serious adverse events during the study. No subjects were withdrawn as a result of an adverse event. A total of 7 adverse events were observed. There was one case of orthostatic hypotension at home.

According to the sponsor, no significant overall variation between screening and end-of-trial ECGs were noted. There were two subjects (both elderly, CrCl>60) with elevated and marked increases (120% of baseline) in PR interval. One young subject had marked increases in HR (41 to 75) associated with elevations and marked increases in QRS duration and QTc.

A number of hematology samples were considered erroneous due to equipment error. No significant change was observed for all groups except for a mild decrease in RBCs and hemoglobin. There was a mild thrombocytosis in both elderly populations.

There were 3 subjects with transient increases of K^+ (>5.0 mM) on day 7. A mild decrease in bilirubin in all 3 groups was observed. There was a decrease in magnesium in young subjects.

No significant changes in physical exam were observed.

A44.6. Summary

This was an open-label trial to determine the pharmacokinetics of irbesartan 25 mg, comparing young normal subjects, elderly normal subjects, and elderly subjects with mild renal impairment. The subjects studied were predominantly male and all Caucasian.

Creatinine clearance was calculated by a population equation rather than by measurement. Therefore, the true creatinine clearance of the subjects is not known. The error of this estimate is greater in the elderly population who has some renal impairment where the plasma creatinine may correlate less with GFR. This is shown by the larger standard deviation in a majority of pharmacokinetic parameters. Semi-log plots of irbesartan versus time show a rapid increase to C_{max}. Redistribution of irbesartan occurs over 10 to 15 hours. Differences in clearance between the young and elderly were larger (40% difference in AUC) than differences between the normal elderly and the renally impaired elderly. The results may warrant a more careful titration to effect in elderly patients from a pharmacokinetic standpoint (if pharmacodynamic effects as a function of dose are held constant).

A45. TDR 1691: Tolerability assessment of SR47436 administered in repeated ascending doses to healthy volunteers.

A45.1. Source documents

Study report: NDA 20-757, vol 1.113-1.119.

A45.2. Investigators

Dr. Y. Donzaaolo, OPTIMED, 2 Rue de Vignate, 38610 GIERES- France.

A45.3. Study dates

August 1992 to December 1992.

A45.4. Study design

This study description was based upon the protocol dated 17 July 1992. There was one change to the protocol made after subjects were enrolled but before pharmacokinetic measurements were taken. None of these amendments would affect the basic pharmacokinetic measurements or bias the study.

The objective of the study was to assess general tolerability of irbesartan during repeated administration and pharmacokinetic profiles of the drug.

This study was a randomized placebo-controlled repeated ascending dose study. The subjects were taken from a healthy non-obese male Caucasian population with normal physical exam findings and laboratory values. Successive cohorts received 10, 50, 100, and 200 mg.

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

Drug supplies are shown in Table 311 below.

Table 311. Drug supplies (TDR 1691).

	Batch number		Batch number
Placebo	1PX/J794M	Irbesartan 10mg	1A2/J799 M
		Irbesartan 25 mg	1A2/J798 M

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

The subjects were asked to return to the center within 3 weeks and were given irbesartan or placebo for 7 days. Pharmacokinetic profiles, renin, angiotensin II (AII), and urine specimens were obtained according to the schedule shown in Table 312 below.

Physical exams, vital signs, ECGs and safety laboratory tests were performed during screening, during administration, study end (day 7) and 3 days after the last dose (day 10).

Assay of plasma irbesartan was performed according to method 1 in Table 7. *Assay validation for irbesartan.* on page 15.

The following parameters were to be determined and compared within each group: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0-\tau}$, C_{min}, C_{av} (AUC/24 h), C_{bf} (plasma concentration before dose), peak-trough fluctuation ratio ($[C_{max}-C_{min}]/C_{av}$), AII and renin, tolerability, and safety.

Table 312. Schedule for PK and PD Procedures (TDR 1691)

Time (h)	PK	Procedures		Time (h)	PK	Procedures	
		Renin/AII	Urine			Renin/AII	Urine
Pre-Dose	X,Y,Z	X,Y,Z	X	8	Z	X,Z	Day 7 8-24 h
0.5	X, Z		Day 7 0-8 h	10	Z		
1.0	X,Z	X,Z		12	Z		
1.5	X,Z			14		X,Z	
2	X, Z	Y		24	Z		
3	X, Z						
4	X,Z						
6	Z						

X=Day 1, Y=Days 2-6, Z=Day 7

Statistical analysis of safety, C_{max}, C_{bt}, renin/AII determinations were compared using analysis of variance. Kruskal-Wallis test was used to assess a dose effect on T_{max}. Wilcoxon signed rank test was used to assess a day effect on T_{max}. Linear dose proportionality was evaluated on log-transformed data.

A45.5. Results

A total of 42 subjects were considered eligible. One subject was dropped on day 1 prior to dose because of 1st degree AV block on the ECG. A total of 41 subjects were included in the study. The study treatment on one subject was prematurely dropped on day 4 following the occurrence of right bundle branch block before dosing.

Demographics of randomized subjects are shown in Table 313 below.

Table 313. Demographics (TDR 1691).

	Placebo N=8	Irbesartan			
		10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8
Age (mean±SE)	23 ±1	22±2	26±2	26 ±1.1	23±1
Weight, kg (mean±SE)	72±2	73±1.9	73.0±2.4	73±2	71±2
Height, cm (mean±SE)	179±1	180±1.4	178 ±2.4	179 ±1.5	179±2
Sitting (mean±SE)					
HR (BPM)	63±5	55±3	56±3	56±2	63±3
SBP (mmHg)*	123±4	122±4	127±4	125±4	125±4
DBP (mmHg)*	63±3	82±2	74±3	67±2	73±2
Standing (mean±SE)					
HR (bpm)	75±4	64±5	79±4	73±3	86±5
SBP (mmHg)	127±3	119±5	119±4	128±4	130±4
DBP (mmHg)*	79±2	64±4	74±3	81±3	84±2
ECG (mean±SE)					
HR (bpm)	59±5	54±3	53±3	57±2	65±3
PR (ms)*	159±6	165±9	164±9	153±7	150±7
QRS (ms)*	89±2	89±3	86±3	85±1	92±3
QT (ms)	388±10	409±10	396±11	380±7	372±9
QTc (ms)	381±9	387±5	369±6	367±4	383±6

*Significant ($p < 0.02$) difference among groups.

There were no major deviations from the protocol. The pre-dose blood sampling for subject #5 (10 mg) was taken on days 1 and 7 at 0.17 and 0.08 h, respectively. On day

1, pharmacokinetic blood samples were drawn with a discrepancy in time of more than 10% on 3 samples and on day 7 with one sample.

A45.5.1. Pharmacokinetics

The mean pharmacokinetic profiles of the 4 doses is shown in Figure 89 below.(

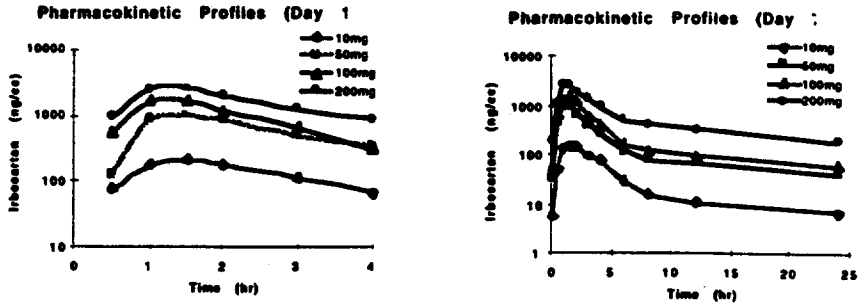

Figure 89. Pharmacokinetic profiles (TDR 1691).

$AUC_{0\text{-}24h}$ as a function of dose is shown in Figure 90 below. C_{max} as a function of dose is shown in Figure 90 below.

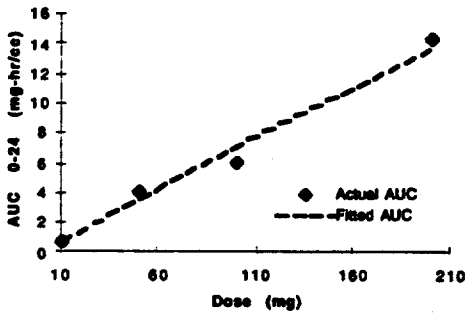

Figure 90. AUC versus dose (TDR 1691).

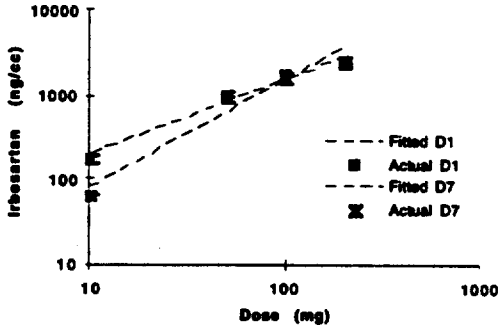

Figure 90. C_{max} versus dose (TDR 1691).

Pharmacokinetic parameters are shown in Table 314 below. There was a statistically significant negative correlation between creatinine clearance and $AUC_{0\text{-}\tau}$ or $AUC_{0\text{-}\infty}$. There was a statistically significant correlation between irbesartan clearance on days 1 and 11 and creatinine clearance.

Table 314. Pharmacokinetic parameters (mean±SD; TDR 1691).

	Single dose				Multiple dose			
	10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8	10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8
C_{max}, mg/L	0.24±0.15	1.12±0.35	1.88±0.59	2.74±1.04	0.24±0.10	1.22±0.43	1.86±0.54	3.12±1.42
T_{max}, h	1.88±0.54	1.44±0.82	1.25±0.27	1.19±0.26	1.87±1.17	1.38±0.35	1.38±0.35	1.19±0.26
Cbt, µg/L	—	—	—	—	7±4	37±24	58±24	197±119
C_{min}, µg/L	—	—	—	—	7±4	37±25	54±24	172±93
C_{max}-C_{min}, mg/L	—	—	—	—	0.23±0.09	1.18±0.41	1.80±0.53	2.95±1.35
$AUC_{0\text{-}24h}$, mg.h/L	—	—	—	—	0.88±0.37	4.16±1.76	6.13±1.79	14.43±6.62
Cl/F, ml/min-kg	—	—	—	—	1.59±0.53	1.47±0.36	2.22±0.69	—
$t_{1/2}$, h	—	—	—	—	25.5±12.0	17.8±5.9	11.9±2.7	—
V_d/F, l/kg	—	—	—	—	3.5±1.84	2.31±0.95	2.19±0.66	—

Mean urinary pharmacokinetic parameters is given in Table 315 below.

Table 315. Single-dose urinary pharmacokinetic parameters (TDR 1691).

	10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8
Irb (24 h collection; mg)	0.123±0.097	0.191±0.127	0.174±0.130	—
Fraction of unchanged Irb (%)	0.49±0.39	0.76±0.51	0.69±0.52	—
Renal Cl, ml/min (mean±SD)	0.617±0.437	1.099±0.841	1.437±1.125	—

A45.5.2. Hormones

Graphs of plasma renin and angiotensin II are shown in Figure 91. and Figure 92 below. Values angiotensin II who were lower than the detection limit were given a concentration of 1.6 ng/l.

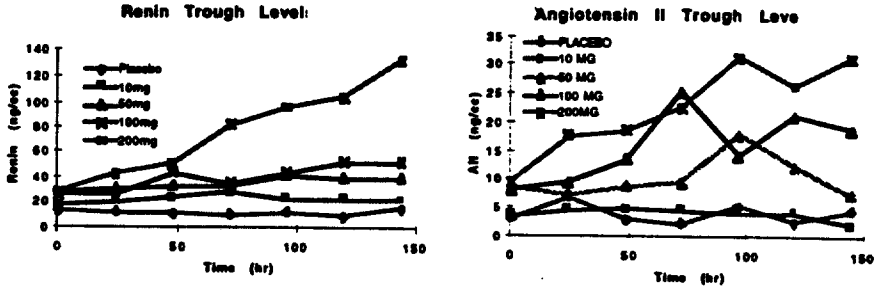

Figure 91. Trough renin and angiotensin II levels over time (TDR 1691).

Peak and trough renin as a function of dose on days 1 and 7 are given in Figure 92 below.

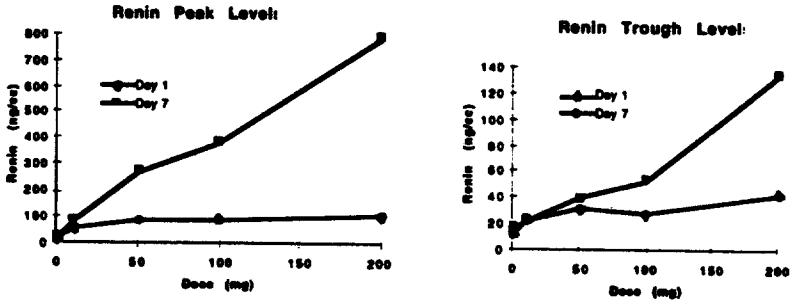

Figure 92. Peak and trough renin levels for days 1 and 7 (TDR 1691).

Peak and trough angiotensin as a function of dose on days 1 and 7 are given in Figure 93 below.

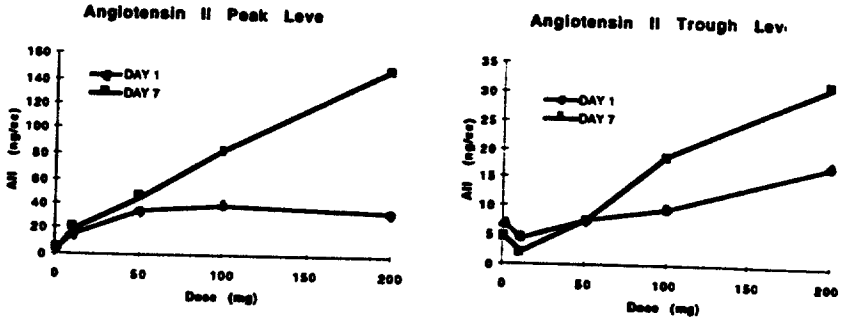

Figure 93. Peak and trough angiotensin II levels on days 1 and 7 (TDR 1691).

A45.5.3. Pharmacodynamics

Changes from baseline in peak supine and standing blood pressure on days 1 and 7 are presented in Table 316 below. There was no significant decrease in trough blood pressure for any day or for any irbesartan dose or placebo.

Table 316. Peak vital signs on days 1 and 7 (TDR 1691).

Characteristic	Supine					Standing				
	Placebo N=8	10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8	Placebo N=8	10 mg N=8	50 mg N=8	100 mg N=9	200 mg N=8
HR (bpm)										
Day 1	9±3	12±3	16±3	16±2	11±2	24±3	24±4	17±4	27±4	14±4
Day 7	10±4	10±4	17±2	24±2	17±3	24±6	33±4	29±6	43±5	28±5
SBP (mmHg)										
Day 1	-3±1	-9±4	-14±3	-13±3	-15±5	-12±3	-7±3	-11±3	-22±7	-23±3
Day 7	-7±3	-2±3	-13±3	-9±5	-14±5	-13±3	-8±6	-12±4	-16±4	-26±5
DBP (mmHg)										
Day 1	-10±3	-5±1	-12±2	-14±2	-22±4	-11±2	-4±2	-13±2	-21±6	-21±1
Day 7	-10±3	-9±2	-11±2	-12±2	-20±3	-14±2	-4±4	-11±2	-10±2	-26±3

A45.5.4. Safety

Eleven subjects experienced adverse events in the course of the trial (1/8 placebo, 10/33 receiving irbesartan.

A total of 4 subjects experienced orthostatic hypotension (1 on 50 mg, 3 on 100 mg).

Five cases of hypertriglyceridemia were observed (1 on 50 mg, 1 on 200 mg). Three had at least one elevation on either day 5 or day 7 (1.72 to 2.53 mM; ULN=1.70 mM). Two subjects had greater than one elevation during the study period (1.72 to 4.01 mM). All subjects returned to normal values within 15 days.

One subject experienced complete right bundle branch block, which led to the subject's removal from the trial on day 4. The abnormality was observed intermittently on days 7 and 8.

There were no statistically significant changes in ECG parameters.

Other adverse events were headache (3), vomiting (1), flu-like syndrome (1), and leg pain (1).

There was a moderate decrease in the mean potassium levels at 2 hours in all 5 groups. This difference did not exceed 0.8 mM. Of note, potassium excretion did increase 8 to 24 hours after the dose was given.

No significant changes in physical examination were observed.

A45.6. Summary.

This was a double-blind placebo controlled trial to determine the pharmacokinetics of irbesartan at doses from 10 to 200 mg. In addition, blood pressure, renin and angiotensin II were measured. All subjects were young, male Caucasians. Population means for C_{max} and AUC increased less than linearly with dose. Mean peak levels of irbesartan in plasma are reached in about 1 hour, and redistribution occurs over 10 to 15 hours. Cl_R and %UR appeared to change with dose, although no conclusion can be reached because of the variability in the data. Trough renin and angiotensin II levels continue to rise over 7 days, apparently reaching steady-state more slowly than does irbesartan.

A46. TDU 1693: Tolerability assessment of irbesartan administration single ascending doses to healthy volunteers

A46.1. Source documents

Study report: NDA 20-757, vol 1.108-1.112.

A46.2. Investigators

Dr. Panis-Rouzier Regine, Centre CAP, Centre Hospitalier Regional; 2, Rue Noche, 30800 NIMES, France.

A46.3. Study dates

19 May 1992 to 19 July 1992.

A46.4. Study design

This study description was based upon the protocol dated 15 April 1992. There were 4 protocol amendments. None of these amendments would affect the basic pharmacokinetic measurements or bias the study.

The objective of the study was to assess general tolerability of irbesartan to a range of doses.

This study was a randomized placebo-controlled single ascending dose study. The subjects were taken from a healthy non-obese male Caucasian population with normal physical exam findings and laboratory values. The subjects were placed in 12 dosage groups from 5 to 400 mg. There were 4 subjects in each group, three receiving irbesartan and one placebo.

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

Drug supplies are shown in Table 317 below.

Table 317. Drug supplies (TDU 1693).

	Batch Number		Batch Number
Placebo	1P1X/RG030	Irbesartan 5 mg	1A2/J797 M
		Irbesartan 10mg	1A2/J799 M
		Irbesartan 25 mg	1A2/J798 M

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

The subjects were asked to return to the center within 2 weeks and were given a single dose of irbesartan or placebo. The subjects stayed for 48 hours. Pharmacokinetic profiles, renin, angiotensin II (AII), and urine specimens were obtained according to the schedule shown in Table 318 below.

Physical exams, vital signs, ECGs and safety laboratory tests were to be performed during screening, during administration, study end (day 2) and 7 days post-dose. Continuous ECG monitoring was performed during the first 24 hours of the clinic stay.

The primary and secondary objectives were (1) general tolerability and safety in healthy male volunteers, (2) impact of AII receptor blockade on the RAS cascade, and (3) preliminary pharmacokinetic profile of the drug.

Statistical analysis of safety, pharmacokinetic and renin/AII determinations were compared using analysis of variance. The relationships between C_{max} and dose and between AUC and dose were to be determined.

Table 318. Schedule for PK and PD sampling (TDU 1693)

Time (h)	PK	Procedures		Time (h)	PK	Procedures	
		Renin/ AII	Urine			Renin/ AII	Urine
Pre-Dose	X	X	X	8	X	X	8 - 48 h
0.5	X	X	0 - 8 h	12	X	X	
1.0	X	X		24	X	X	
1.5	X	X		36	X		
2	X	X		48	X		
3	X	X					
4	X	X					
6	X	X					

Assay of plasma irbesartan was performed according to method1 in Table 7. *Assay validation for irbesartan.* on page 15. Plasma, urine and feces were solubilized and measured for radioactivity of irbesartan and metabolites.

A46.5. Results

A total of 48 male volunteers enrolled and completed the study.

Demographic characteristics are shown in Table 319 below.

Table 319. Demographic (TDU 1693).

	N=48			N=48
Age (mean±SE)	24±1		ECG (mean±SE)	
Weight, kg (mean±SE)	72±1		HR (bpm)	55±1
Height, cm (mean±SE)	180±1		PR (ms)	162±3
			QRS (ms)	93±1
			QT (ms)	398±4
			QT_c (ms)	377±3
Sit (mean±SE)			Stand (mean±SE)	
HR (bpm)	57±1		HR (bpm)	69±2
SBP (mmHg)	117±2		SBP (mmHg)	120±2
DBP (mmHg)	70±1		DBP (mmHg)	83±2

There were no major protocol deviations.

A46.5.1. Pharmacokinetics

The mean pharmacokinetic profiles are given in Figure 94 below.

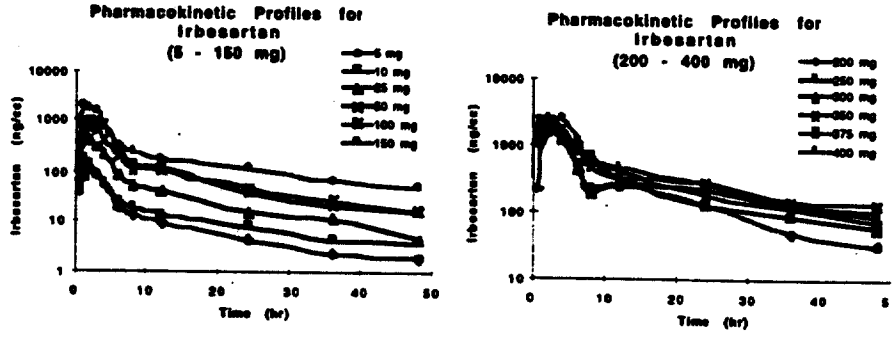

Figure 94. Mean pharmacological profiles (TDU 1693).

Pharmacokinetic parameters are shown in Table 320 below. AUC and C_{max} as a function of dose are shown in Figure 95 below.

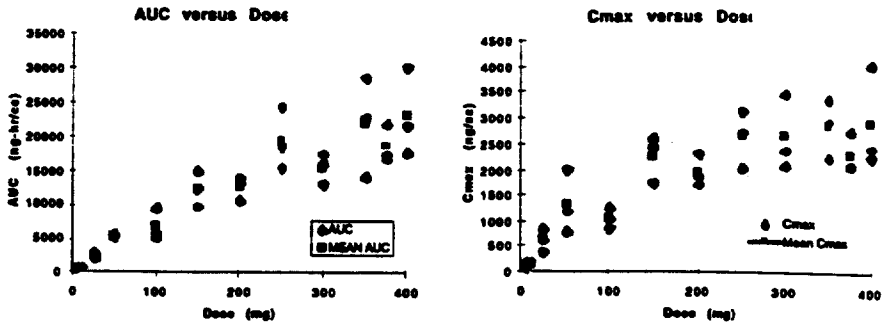

Figure 95. AUC and C_{max} versus dose (TDU 1693).

Table 320. Pharmacokinetic parameters (TDU 1693).

	Irbesartan dose (mg)											
	5	10	25	50	100	150	200	250	300	350	375	400
C_{max} ng/mL	123 ±46	186 ±12	637 ±226	1327 ±620	1057 ±208	2274 ±467	1961 ±308	2651 ±565	2650 ±743	2861 ±573	2312 ±384	2915 ±985
T_{max} h	1.5 ±0.5	1.0	1.0	1.5 ±0.5	3.3 ±1.2	1.5 ±0.5	2.7 ±0.6	1.8 ±1.9	2.0	2.3	1.8	3.3
AUC_{0-48h} ng.h/mL	625 ±207	885 ±37	2611 ±395	565 ±129	6951 ±2420	12516 ±2627	12662 ±1682	19640 ±4525	15617 ±2212	21994 ±7296	18771 ±2824	23268 ±6469

T_{max} ranged from 1.5 to 3.3 hours in the dosage range. The $t_{1/2}$ ranged from 9 to 39 hours. Neither parameter had an obvious dose-dependency.

Urine was collected for metabolism analysis. The results were not part of the reviewed material.

A46.5.2. Hormones

Relationships between angiotensin II and plasma renin activity were linear with AUC in the dose range 5 to 100 mg. Doses >100 mg did not correlate linearly with these variables.

A46.5.3. Pharmacodynamics

Following drug intake, there was no decrease in blood pressure in the supine position compared to placebo at any dose.

A46.5.4. Safety

There were no deaths or serious adverse events during the study. Seventeen orthostatic hypotension episodes occurred during the 48-hour observation period. Two occurred on placebo. Out of the remaining 15, 6 were clinically symptomatic. Six subjects reported other adverse events. The most common was headache. There was no dose-related change in ECG parameters. There were no unusual variations in either serum chemistry or hemotological lab values. No significant changes in physical exam were observed.

A46.6. Summary

This was a double-blind placebo controlled trial to determine preliminary pharmacokinetics and tolerability of irbesartan. In addition, pharmacodynamic variables were measured. All subjects were normal, male Caucasians. Both C_{max} and AUC increased linearly with dose up to 100 mg. AUC and C_{max} increased less than linearly at higher doses, possibly the result of saturable absorption.

A47. 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).

A47.1. Source documents

Study report: NDA 20-757, vol 1.340-1.348; files MONOMAST.PDF and MONOSUPP.PDF.

A47.2. Investigators

There were 154 investigators at 152 centers in Australia, Canada, France, Germany, New Zealand, Spain, United Kingdom, and United States.

A47.3. Study dates

Open-label enrollment began 9 December 1993. All studies were ongoing until 6 November 1995 for CV131-002, CV131-025, and CV131-029, 30 November 1995 for CV131-027 and CV131-028, and 15 February 1996 for CV131-031.

Subjects completing the double-blind period had the option of enrolling in the open-label study with irbesartan and adjunctive treatment for 1 (CV131-027 and CV131-028) or 2 years (CV131-002, CV131-025, CV131-029, and CV131-031).

A47.4. Study design

Open-label extensions were part of 6 double-blind, randomized, placebo- or active-controlled trials in subjects with essential hypertension (seated diastolic blood pressure 95 to 110 mmHg. To achieve the target BP, HCTZ 12.5 to 25 mg), nifedipine sustained release 20 mg daily, or atenolol 50 mg daily were added in open-label after titration to protocol-specified maximal doses of irbesartan (100 to 300 mg). All subjects initiated open-label treatment with irbesartan alone. The target BP was <140/90 mmHg in each protocol. Inclusion and exclusion criteria were similar to those applied during the double-blind period.

A47.5. Results

Of the 1829 subjects randomized to double-blind therapy in these studies, a total of 1201 (66%) entered the open-label treatment period. Enrollment by protocol is presented in Table 321 below. All protocols were ongoing as of their data lock dates with a total of 1033 subjects continuing in the open-label extension label.

Table 321. Subjects enrolled in open-label studies (Long-term monotherapy).

	Study CV131-						Total
	002	025	027	028	029	031	
Subjects randomized to double-blind	570	319	231	202	319	188	1829
Subjects completing double-blind	499	299	200	191	282	138	1557
Subjects enrolled in open-label period % of randomized subjects	304 53	234 72	133 58	171 85	262 82	97 52	1201 66
Subjects discontinued from open label	77	48	4	6	21	12	168
Subjects ongoing as of CRF data lock	227	186	129	165	241	85	1033

The demographics of the subjects and the baseline blood pressure are presented in Table 322 below.

Table 322. Demographics and baseline characteristics (Long-term monotherapy)

	N=1201		N=1201
Male (%)	64	Female (%)	36
White (%) Black (%)	90 8	Other (%)	3
Age (Mean±SD) Range	56±11	≥65 (%)	24
SeDBP (Mean±SD)	101±4.1	SeSBP (Mean±SD)	154±15.5

The treatment regimens for all subjects in open label are presented in Table 323 below.

Table 323. Treatment regimens (Long-term monotherapy).

	2 months N=1018	4 months N=870	6 months N=656	12 months N = 380
Irbesartan alone (%)	95	67	56	45
With HCTZ 12.5 mg (%)	1.7	11	10	10
With HCTZ 25 mg (%)	1.4	13	19	24
With HCTZ and other (%)	0.4	5.2	6.4	6.0
With other (%)	0.7	3.9	8.4	14

Exposure is summarized in Table 324 below. One subject was excluded from safety analysis because of an unspecified protocol violation.

Table 324. Duration of exposure (Long-term monotherapy).

	All N=1201	Any monotherapy N=1200	Only monotherapy N=783	Any adjunct N=440
≤90 days (%)	27	47	40	45
91-180 days	26	28	29	16
181-270 days	11	7.8	8.4	11
271-365 days	6.2	4.0	4.0	11
366-545 days	20	11	15	16
546-730 days	9.1	2.3	3.3	1.8
Mean exposure	234 days	152 days	174 days	179 days
Subject-years	770	500	373	216

Adverse events were cause for withdrawal of 6.4% of all subjects, 4.4% of subjects on irbesartan alone, and 5.5% of subjects on irbesartan and any adjunctive therapy.

A47.5.1. Pharmacodynamics

Efficacy outcome was defined as change from baseline in trough SeDBP and SeSBP, where baseline was the last assessment preceding randomization, and as response rate. The sponsor presented several analyses of efficacy outcomes. These data are difficult to interpret because of the open-label nature of the trials. Consistent reductions from baseline were observed in trough SeDBP and SeSBP at all time points, as shown in Table 325 below.

Responders were considered to be subjects with SeDBP <90mmHg or a reduction from baseline of 10 mmHg. Response rates at end point are shown in Table 325 below as a function of time. Both SeHR and StHR were stable throughout the open- label phase.

Table 325. Efficacy assessments (Long-term monotherapy).

	2 months N=1018	4 months N=870	6 months N=656	12 months N=380
ΔSeSBP (mean±SD)	-13.6±14.5	-17.5±14.1	-18.3±14.8	-17.2±14.3
ΔSeDBP (mean±SD)	-10.9±7.7	-13.3±6.4	-14.1±7.2	-14.7±6.8
SeDBP normalized (%)	55	73	76	78
Total responders (%)	64	82	82	85

A47.5.2. Safety

There were 2 deaths during long-term open-label exposure. One subject died of Goodpasture's syndrome[1]. The other death was from hemorrhagic shock. Neither death was considered drug-related.

Fourteen percent of subjects withdrew from open-label irbesartan, nearly half of whom came from study CV131-002, which limited dose to 100 mg. Adverse events led to withdrawal for 6.4% of subjects, and these are summarized by body system in Table 326 below.

Table 326. Counts of adverse events, by body system, leading to withdrawal (Long-term monotherapy).

	All subjects N=1201	Any monotherapy N=1200	Any adjunct N=440
Cardiovascular	23	18	6
Dermatologic	6	5	1
Endocrine/metabolic	5	5	0
Gastrointestinal	5	4	1
Hematopoietic	2	2	0
Immunologic	1	1	0
Musculoskeletal	3	2	1
Nervous	23	17	6
Renal	6	1	0
Respiratory	8	3	5
Special senses	1	1	0
General	13	10	3
Total	77	53	24

Overall, 58% of subjects on open-label irbesartan reported at least one adverse event. Table 327 below lists events by body system.

Orthostatic hypotension was reported by 2 subjects. Musculoskeletal pain was reported by 12% of subjects. Other treatment-emergent events included sexual dysfunction (1.7%), paresthesia (1.7%), swelling of extremities (1.7%), sleep disturbance (2.3%), rash (2.2%), and ocular disturbances (1.6%).

The only laboratory abnormality associated with withdrawal was decreased hematocrit (1 subject). Other laboratory findings of potential significance were eosinophilia (1.3%), leukocytosis (1.1%), lymphocytopenia (1.1%), thrombocytopenia (0.3%), leukopenia (0.3%), and neutropenia (0.3%).

[1] Glomerular basement membrane antibody disease.

Table 327. Subjects (%) with adverse events (Long-term monotherapy).

	All subjects N=1201	Any monotherapy N=1200	Monotherapy only N=783
Any	58	50	45
Any drug-related	26	21	17
Serious AE	4.3	3.2	—
Discontinuations	6.4	4.4	—
Respiratory	26	19	18
Nervous	23	17	15
Musculoskeletal	22	15	15
Gastrointestinal	17	11	11
Dermatological	9.9	6.8	5.9
Cardiovascular	9.6	6.1	5.4
Special senses	7.2	4.3	4.2
Renal/genitourinary	6.7	4.6	4.5
Endocrine/metabolic	4.6	2.8	2.4
Immunological	3.0	2.1	1.4
Hematopoietic	0.7	0.3	0.4
Hepatic/biliary	0.2	0.2	0.3
Drug interaction	0.2	0	0
General	17	11	9.7

A47.6. Summary

Despite Agency encouragement, the sponsor performed no placebo-controlled, randomized withdrawal study as part of any long-term follow-up. Consequently, the evidence of continued antihypertensive effect is not robust. Ninety-five percent of subjects were on irbesartan alone at 2 months, but only 45% remained on study drug alone at 12 months. The data best support the general safety of the use of irbesartan with other antihypertensive agents.

A48. 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).

A48.1. Source documents

Study report: NDA 20-757, vol 1.349-1.356; files COMBOMAST.PDF and COMBOSUPP.PDF.

A48.2. Investigators

There were 92 investigators at 91 centers in Argentina, Brazil, Mexico, and United States.

A48.3. Study dates

Open-label enrollment began 16 February 1995. Both studies were ongoing as of the data lock date of 30 November 1995.

A48.4. Study design

Open-label extensions were part of 2 double-blind, randomized, placebo-controlled trials in subjects with essential hypertension (seated diastolic blood pressure 95 to 110 mmHg. Study CV131-37 was a 4x4 factorial study with irbesartan 37.5 to 300 mg and HCTZ 6.25 to 25 mg. To achieve the target BP, nifedipine sustained release 320 mg daily, or atenolol 25 or 50 mg daily were added in open-label after titration to the maximal dose of irbesartan. All subjects initiated open-label treatment with irbesartan alone. The target BP was <140/90 mmHg in each protocol. Inclusion and exclusion criteria were similar to those applied during the double-blind period.

A48.5. Results

Of the 1498 subjects randomized to double-blind therapy in these studies, a total of 975 (65%) entered the open-label treatment period. Enrollment by protocol is presented in Table 328 below. Both protocols were ongoing as of their data lock dates with a total of 868 subjects continuing in the open-label extension label.

Table 328. Subjects enrolled in open-label studies (Long-term combination therapy).

	Study CV131-		Total
	037	038	
Subjects randomized to double-blind	683	815	1498
Subjects completing double-blind	631	722	1353
Subjects enrolled in open-label period % of randomized subjects	458 67	517 63	975 65
Subjects discontinued from open label	41	66	107
Treatment failures	4	5	9
Subjects ongoing as of CRF data lock	417	451	868

The demographics of the subjects and the baseline blood pressure are presented in Table 329 below.

Table 329. Demographics and baseline characteristics (Long-term combination therapy)

	N=1201		N=1201
Male (%)	60	Female (%)	40
White (%) Black (%)	76 10	Other (%)	14
Age (Mean±SD) Range	54±10	≥65 (%)	15
SeDBP (Mean±SD)	100±4.1	SeSBP (Mean±SD)	151±14.7

The treatment regimens for all subjects in open label are presented in Table 330 below.

Table 330. Treatment regimens (Long-term combination therapy).

	2 months N=729	4 months N=619	6 months N=393	8 months N=118
HCTZ ≤12.5 mg + irbesartan				
75 mg (%)	54	55	52	41
150 mg (%)	33	23	24	33
300 mg (%)	0.7	1.5	1.0	0.8
With HCTZ 25 mg (%)	8.8	11	12	11
With HCTZ ≤12.5 mg + other (%)	0.2	1.1	0.8	0.8
With HCTZ 25 mg + other (%)	1.6	7.1	7.6	12

Exposure is summarized in Table 331 below. One subject was excluded from safety analysis because of an unspecified protocol violation.

Table 331. Duration of exposure (Long-term combination therapy).

	All N=975	Any irb/HCTZ N=974	Irb/non-HCTZ N=2	Irb/HCTZ/ adjunct N=70
≤90 days (%)	36	41	100	63
91-180 days	41	40	0	37
181-270 days	22	20	0	0
271-365 days	0.2	0.2	0	0
366-545 days	0	0	0	0
Mean exposure	123 days	117 days	30 days	78 days
Subject-years	329	311	0.2	15

Adverse events were cause for withdrawal of 4.9% of all subjects, 4.5% of subjects on irbesartan plus HCTZ, and 4.3% of subjects on irbesartan, HCTZ, and any adjunctive therapy.

A48.5.1. Pharmacodynamics

Efficacy outcome was defined as change from baseline in trough SeDBP and SeSBP, where baseline was the last assessment preceding randomization, and as response rate. The sponsor presented several analyses of efficacy outcomes. These data are difficult to interpret because of the open-label nature of the trials. Consistent reductions from baseline were observed in trough SeDBP and SeSBP at all time points, as shown in Table 332 below.

Responders were considered to be subjects with SeDBP <90mmHg or a reduction from baseline of 10 mmHg. Response rates at end point are shown in Table 332 below as a function of time. Both SeHR and StHR were stable throughout the open- label phase.

Table 332. Efficacy assessments (Long-term combination therapy).

	2 months N=729	4 months N=619	6 months N=393
ΔSeSBP (mean±SD)	-18.8±14.1	-19.0±13.7	-19.0±13.9
ΔSeDBP (mean±SD)	-14.2±7.0	-15.0±6.7	-15.1±6.2
SeDBP normalized (%)	76	83	85
Total responders (%)	81	88	90

A48.5.2. Safety

There were 2 deaths during long-term open-label exposure. One subject died in a road traffic accident. The other death was a gastrointestinal hemorrhage. Neither death was considered drug-related.

Adverse events led to withdrawal for 4.9% of subjects, and these are summarized by body system in Table 333 below.

Table 333. Counts of adverse events, by body system, leading to withdrawal (Long-term combination therapy).

	All subjects N=975	Any irb/HCTZ N=974	Irb/HCTZ/ adjunct N=70
Cardiovascular	9	9	0
Dermatologic	4	3	0
Endocrine/metabolic	4	4	0
Gastrointestinal	9	9	0
Hematopoietic	2	2	0
Hepatic/biliary	4	3	1
Musculoskeletal	4	2	0
Nervous	13	13	0
Renal	6	6	0
Respiratory	2	1	0
Special senses	2	1	0
General	13	11	2
Total subjects	48	44	3

Overall, 54% of subjects on open-label irbesartan reported at least one adverse event. Table 334 below lists events by body system.

Table 334. Subjects (%) with adverse events (Long-term combination therapy).

	All subjects N=975	Any irb/HCTZ N=974	Irb/HCTZ/ adjunct N=70
Any	54	52	63
Any drug-related	18	17	—
Serious AE	2.2	1.8	4.3
Discontinuations	4.9	4.5	4.3
Respiratory	16	15	10
Nervous	15	14	20
Musculoskeletal	16	15	14
Gastrointestinal	12	11	13
Dermatological	7.1	6.4	8.6
Cardiovascular	4.7	4.4	4.3
Special senses	3.7	3.6	1.4
Renal/genitourinary	4.2	4.0	2.8
Endocrine/metabolic	2.8	2.4	5.7
Immunological	0.7	0.7	0
Hematopoietic	0.3	0.3	0
Hepatic/biliary	0.3	0.2	1.4
Drug interaction	0.1	0.1	0
General	12	11	17

Orthostatic hypotension was reported by 22 subjects, some cases of which followed changes in irbesartan and HCTZ or adjunctive therapy. Musculoskeletal pain was

reported by 6.8% of subjects, fatigue by 5.9%. headache by 5.9%, and upper respiratory infections by 5.5%.

No laboratory abnormality was associated with withdrawal.

A48.6. Summary

Despite Agency encouragement, the sponsor performed no placebo-controlled, randomized withdrawal study as part of long-term follow-up. Consequently, the evidence of continued antihypertensive effect is not robust. Ninety-five percent of subjects were on irbesartan plus HCTZ at 2 months, but only 77% remained on study drug alone at 6 months. The data best support the general safety of the use of irbesartan with other antihypertensive agents.

A49. Metabolism of irbesartan (from pharmacologist's review).

This section of the review was derived from Dr. Jagadeesh's review of pharmacology and toxicology:

> *2.3.11. Involvement of Cytochrome P4502C9 in SR 47436 Oxidation by Human Hepatic Microsomal Fractions (Report #RS0005960620/01, Study #MIV0214), Vol. 83*
>
> *This non GLP study was conducted by the Preclinical Metabolism and Pharmacokinetics department of Sanofi Recherche, Montpellier Cedex, France between January 1995 and June 1995. The aim of this study was to investigate the major cytochrome P450 isoform(s) involved in SR 47436 oxidation* in vitro *using a phenotyped human hepatic microsomal bank.*
>
> *Human hepatic microsomal fractions were prepared from large biopsies obtained following surgical operation in secondary liver cancer patients (Caucasian, 8 males and 4 females). The fractions were characterized by determining protein concentration, cytochrome P450 content and for their ability to perform specific enzyme reactions reported to be catalyzed by a single cytochrome P450 isoform.*
>
> *Biotransformation was initiated by incubating microsomal fraction with graded concentrations (10 to 100 µM) of SR 47436 (batch 93.06 and 5ARL005, solubilized in DMSO) for 30 min at 37°C. Enzymatic reaction was initiated with the addition of NADPH, the essential cofactor for cytochrome P450 monooxygenase-dependent reactions. Interacting drugs (specific P450 isoform substrates or inhibitors, see Table 2.3.11.1) were added to the incubation mixture just before NADPH addition. At the end of incubation, enzyme reaction was stopped by the addition of 1 volume of 20% TCA-acetonitrile for 1 volume of incubation mixture. SR 47436 metabolites were quantified by HPLC with UV detection.*
>
> *Additionally, the sponsor studied specific enzyme reactions of eight P450 isoforms in metabolizing SR 47436. This was investigated in microsomal fractions prepared from human β-lymphoblastoid cell lines (purchased commercially), which are engineered to stably express human cytochrome P450 cDNA. Studies were also performed with microsomal fractions prepared from non engineered cells (control conditions). The biotransformation procedure remained the same except for incubation time (1 hr) and SR 47436 concentration (50 µM). The specificity of cytochrome P450 isoforms to perform specific enzyme reactions are summarized in Table 2.3.11.1.*

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TABLE 2.3.11.1
METABOLIC CAPACITIES OF CYTOCHROME P450 ISOFORMS

CYP	Substrate	K_M (μM)	Investigated Reaction	Inhibitor	K_i (μM)
1A1	7-ethoxyresorufin	0.2 - 0.3	*O*-Deethylation	α-Naphthoflavone	0.01
1A2	Phenacetin	23 - 113	*O*-Deethylation	Furafylline	3
2A6	Coumarin	0.3 - 0.5	7-Hydroxylation	Pilocarpine	3
2B6			Not performed		
2C9	Tolbutamide	148 - 373	4-Hydroxymethylation	Sulphaphenazole	0.15
2D6	Dextromethorphan	20 - 22	*O*-Demethylation	Quinidine	0.30
2E1	Aniline	60 - 62	4-Hydroxylation	Diallyldisulfide	50
3A4	Nifedipine	34.7 - 160	Dehydrogenation	Ketoconazole	0.03

Results

In the presence of NADPH, human hepatic microsomal fractions metabolized SR 47436 to generate 4 main mono-hydroxy metabolites, « A », « B », « C » and « D ». Metabolite formation was similar irrespective of the human hepatic microsomal fraction investigated. Percentage of biotransformation varied from 30.3 to 64.6% across the subjects. Since the capacity of the different hepatic microsomal fractions to metabolize the different cytochrome P450 isoform substrates was already determined (see Table 2.3.11.1), the relationship between SR 47436 total oxidation and cy P450 isoform substrates was investigated. A positive correlation was only observed between SR 47436 total oxidation and tolbutamide 4-methylation, r2 being equal to 0.7687. No relationship at all was observed with the biotransformation of other specific substrates (Table 2.3.11.2). Thus, the data suggest that both SR 47436 oxidation and tolbutamide 4 methylhydroxylation share a common (or closely related) isoform of cy P450.

TABLE 2.3.11.2
CORRELATION COEFFICIENTS (PEARSON VALUES) FOR IRBESARTAN TOTAL OXIDATION AND OTHER ENZYME ACTIVITY CATALYZED BY SPECIFIC *CYP* ISOFORMS

Enzyme	P450	IRB	7ER	POD	COH	DOD	TOH	AOH	NDH
P450	1	0.005	0.125	ND	0.222	0.004	0.001	0.075	0.117
IRB		1	0.023	ND	0.177	0.046	0.769	0.348	0.024
7ER			1	ND	0.001	0.002	0.055	0.148	0.333
POD				1	ND	ND	ND	ND	ND
COH					1	0.029	0.138	0.139	0.210
DOD						1	0.025	0.164	0.012
TOH							1	0.168	0.115
AOH								1	0.147
NDH									1

IRB, Irbesartan oxidation; 7ER, 7-ethoxyresorufin O-deethylase (CYP1A1); POD, phenacetin O-deethylase (CYP1A2); COH, coumarin 7-hydroxylase (CYP2A6); DOD, dextromethorphan O-demethylase (CYP2D6); TOH, Tolbutamide 4-methyl-hydroxylase (CYP2C9); AOH, aniline 4-hydroxylase (CYP2E1); NDH,

nifedipine Dehydrogenase (CYP3A4).
ND = Not determined

The second experiment studied the effect of different specific cy P450 isoform-substrates on SR 47436 oxidation in human hepatic microsomal fractions. Among the different substrates investigated, only two of them exhibited a potent concentration-dependent inhibitory effect on the formation of metabolites, « A », « B », « C » and « D ». At 10-fold their Km values, tolbutamide (specific metabolic probe for CYP2C9 isozyme) decreased the formation of SR 47436 metabolites by 80-100%, while nifedipine (specific metabolic probe for CYP3A4 isozyme) decreased metabolites by 50 to 85%. In order to understand the interactions between either tolbutamide and SR 47436, or nifedipine and SR 47436, enzymatic studies were performed using a larger range of concentrations (0.5 to 50-fold their Km value). In these studies, a competitive-type inhibition was observed between tolbutamide and SR 47436, while a noncompetitive-type inhibition was observed between nifedipine and SR 47436.

A third experiment studied the effect of different specific cy P450 isoform-inhibitors on SR 47436 oxidation (see Table 2.3.11.1 for different inhibitors). Among the different inhibitors studied, both pilocarpine (inhibitor of CYP2A6) and sulfaphenazole, (inhibitor of CYP2C9) exhibited concentration-dependent inhibitory effects on the formation of SR 47436 metabolites. The inhibitory effects of pilocarpine on SR 47436 oxidation are due to its inhibition of CYP2C9 isoenzyme. The sponsor investigated the effect of an array of substrates and inhibitors on the SR 47436 metabolism and the results are summarized as follows:

- *A decrease in SR 47436 metabolism was not observed in hepatic microsomal fractions lacking CYP2D6. Neither dextromethorphan (CYP2D6-substrate) nor quinidine (CYP2D6 inhibitor) decreased SR 47436 oxidation.*

- *Both tolbutamide and warfarin, i.e. two CYP2C9-substrates, and sulfaphenazole (CYP2C9-inhibitor), inhibited SR 47436 oxidation in a concentration-dependent manner. Moreover, tolbutamide 4- methylhydroxylation was competitively inhibited by SR 47436.*

- *Nifedipine (CYP3A4-substrate) powerfully inhibited the formation of the various mono hydroxy SR 47436 metabolites. Neither verapamil nor diltiazem, two highly specific CYP3A4-substrates, nor ketoconazole and troleandomycin, two highly specific CYP3A4- inhibitors, inhibited SR 47436 biotransformation. Moreover, nifedipine oxidation was not decreased in the presence of increasing SR 47436 concentrations. It has already been reported in the literature that nifedipine inhibits CYP2C9 metabolic activity.*

Finally, metabolism of SR 47436 was also investigated following a one hour incubation of 50 µM SR 47436 and 1 mM NADPH with microsomal fractions prepared from AHH-1 TK ± human β lymphoblastoid cell lines which have been engineered to stably express human cytochrome P450 isozymes (see Table 2.3.11.1 for 8 isozymes investigated). Among cytochrome P450 isozyme subfamilies, only two of them (CYP2C9 and CYP3A4) were able to metabolize SR 47436. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1 isozymes were not able to metabolize SR 47436 to its various mono-hydroxy metabolites. CYP2C9-

engineered microsomal fractions highly metabolized SR 47436 to its four mono-hydroxy metabolites (« A », « B », « C » and « D »). CYP3A4-engineered microsomal fractions slightly metabolized SR 47436 to its mono hydroxy metabolites, « C » and « D ».

In conclusion, CYP2C9 is the main isoform involved in the oxidation of SR 47436 to its four mono-hydroxy derivatives. This cytochrome P-450 isozyme exhibits a low inter-individual variability in humans and is not subject to a genetic polymorphism.

2.3.12. Effect of SR 47436 on Cytochrome P450 Monooxygenase Regulation Using Primary Cultures of Human Hepatocytes (Report #RS00059201I7/01, Study #MIV108), Vol. 85

This non GLP study was conducted by the department of Metabolism and Pharmacokinetics of Sanofi Recherche, Montpellier Cedex, France between June and November 1990. The effect of SR 47436 on metabolic enzymes such as cytochrome P450 monooxygenase was evaluated on primary cultures of human hepatocytes.

Primary cultures of human hepatocytes were prepared from liver biopsy samples from two male (49-51 years old) and one female (31 years old) Caucasian patient undergoing hepatectomy. Cultures were incubated for 72 hr in the presence of solvent (dimethylsulfoxide); 1, 10, 25 or 50 µM SR 47436; or reference inducers (positive control), dexamethasone (P450 IIIA inducer, 50 µM) or β-naphthoflavone (P450 IA inducer, 50 µM). After a 3-day incubation (at 37°C), hepatocytes were scraped from culture flasks and microsomal fractions were prepared. Enzyme activity indicative of cytochrome P450 isozymes (7-ethoxyresorufin O-deethylase, phenacetin O deethylase, and nifedipine oxidase) was measured by enzymatic methods; cytochrome P450 isozymes were analyzed by Western blot methods.

Following a three day-treatment of primary cultures of human hepatocytes, SR 47436, at concentrations up to 25 µM, had no significant induction/inhibition effects on cytochrome P450 isozyme activities. At 50 µM, both 7-ethoxyresorufin O-deethylase (cytochrome P450 1A1) and phenacetin O-deethylase (cytochrome P450 1A2) were slightly increased (1.8 to 2.4-fold), but only in one of three hepatocyte cultures. SR 47436 had no effect on nifedipine oxidation (catalyzed by P450 3A gene subfamily) at all concentrations studied. Thus, the sponsor concludes that SR 47436 is neither an inducer nor an inhibitor of cytochrome P450 1A and 3A gene subfamilies in primary cultures of human hepatocytes.

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