

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-757/S-021

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA #:	20-757
Applicant:	Sanofi-Synthelabo
Name of Drug:	Irbesartan
Indication:	Treatment of renal disease
Document reviewed:	Electronic submission
Date of submission:	August 3, 2001
Statistical Reviewer:	John Lawrence, Ph.D. (HFD-710)
Medical Reviewer:	Juan-Carlos Pelayo, M.D. (HFD-110)

1 Introduction

This is a review of Studies CV131-048 (The Collaborative Study Group Trial: the Effects of Irbesartan on Morbidity and Mortality in Hypertensive Patients with Type II Diabetes and Diabetic Nephropathy) and EFC2481 (IRbesartan MicroAlbuminuria in type 2 diabetes). These were the main studies conducted in support of this application.

2.1 Study Design

1715 hypertensive patients (SeSBP > 135 mmHg and/or SeDBP > 85 mmHg in an untreated patient, or receiving antihypertensive medication) with type 2 diabetes mellitus and overt nephropathy (urine protein excretion > 900 mg/24 hours) were randomized into one of three treatment groups- once daily administration of placebo, irbesartan, or the active control amlodipine. Patients in the irbesartan group were initially given 75 mg, and were force-titrated up to 150 mg at week 2, and up to the final dose of 300 mg at week 4. Patients in the amlodipine group were initially given 2.5 mg, and were force-titrated up to 5 mg at week 2, and up to the final dose of 10 mg at week 4. Additional antihypertensive agents were encouraged to attain equal degrees of blood pressure reduction within all treatment groups. Downward titration was permitted per protocol at the discretion of the Investigator. The demographic characteristics of the patients in each group appear in Table 2.1.1. There do not appear to be any major differences in the baseline characteristics of the three groups. There was expected to be an enrollment period of approximately 2 years and the study was expected to end 2 years after the last patient was recruited.

Table 2.1.1 Characteristics of the patients in the two groups at baseline. For continuous variables, this table shows the group mean $\pm$ standard deviation. [Reviewer's analysis]

Characteristic	Irbesartan	Amlodipine	Placebo
N	577	559	563
Age (years)	59 $\pm$ 7	58 $\pm$ 8	59 $\pm$ 8
Gender (Male/Female)	376/ 201	356/ 203	401/ 162
Race (Caucasian/Black/Other)	436/ 63/ 78	384/ 84/ 91	411/ 77/ 75
Baseline SeDBP	87 $\pm$ 11	87 $\pm$ 11	87 $\pm$ 11
Baseline SeSBP	160 $\pm$ 20	159 $\pm$ 19	158 $\pm$ 21
Log of baseline urinary protein excretion rate	8.0 $\pm$ 0.8	8.0 $\pm$ 0.8	8.0 $\pm$ 0.8

2.2 Planned Statistical Analysis

The primary endpoint was the time to the first occurrence of doubling of serum creatinine, end-stage renal disease (ESRD), or all cause mortality. ESRD was defined by renal transplantation, need for dialysis, or serum creatinine $\geq$ 6 mg/dL. The primary analysis used the logrank test to compare the distribution of the time to the composite event in the irbesartan group versus the placebo group. The comparison of the irbesartan group to the active control amlodipine was a secondary analysis and therefore, no adjustment for multiplicity was used for these two comparisons.

There were four interim analyses. The actual number and timing of these interim analyses were not specified in advance. The stopping boundaries were defined using the Lan-DeMets alpha-spending function of the O'Brien-Fleming type. The information times of the interim analyses and the nominal critical values appear in Table 2.2.1. This reviewer used the Lan-DeMets software from the University of Wisconsin and found close agreement between the limits that were used by the sponsor and the limits that were found by this reviewer.

Table 2.2.1 Nominal critical values and information times of interim analyses. [Source: Appendix 6 of Study Report and confirmed by reviewer]

Interim Analysis	Information Time	Nominal critical value	Nominal alpha
1	6.76%	7.5326	< 0.0001
2	15.37%	5.0071	< 0.0001
3	33.81%	3.4047	0.0007
4	50.97%	2.775	0.0055
Final	100%	1.98	0.0477

There was one pre-specified secondary cardiovascular composite endpoint (cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurological deficit attributed to stroke, or above-the-ankle amputation). The three pre-specified secondary analyses were: comparison of irbesartan to placebo on this secondary endpoint and the comparison of irbesartan to amlodipine on both the primary and secondary endpoints.

2.3 Results

A total of eight patients were lost to follow-up out of the 1715 patients enrolled. Sixteen patients in the study were not randomized but were included as part of the treatment group corresponding to the treatment they actually were given (2 in the irbesartan group, 8 in the amlodipine group, and 6 in the placebo group). 19 patients in the irbesartan group and 11 patients in the placebo group discontinued treatment and/or regularly scheduled office visits. However, many of these patients (6 in irbesartan, 2 in placebo) were counted in the analysis as having a primary event. Since these are relatively small numbers, these issues are not likely to cause as much concern in this study as they would in other studies. Table 2.3.1 shows the number of events in each of the three arms for the composite endpoint and each of its components. The Kaplan-Meier curves appear in Figure 2.3.1.

Table 2.3.1 Number of events in each arm, point estimates of relative risk, 95% confidence interval for relative risk of event in irbesartan group relative to placebo. [Source: Tables 10.1.1.A and B of Study Report and confirmed by reviewer]. The components are tabulated in two ways: first by the definition of the primary endpoint (i.e. counting only the first event for each patient) and second by the number of patients that had the event at any time during the study.

	Amlodipine	Placebo	Irbesartan	RR / 95%CI/ p-value Irb vs. Pbo
N	567	569	579	
Primary Endpoint (death, ESRD, 2× SC)	233	222	189	0.80/(0.66, 0.97)/ 0.0234
Decomposition of Events in Definition of Primary Endpoint (counting only first occurrence of primary event)				
Death	54	64	64	0.94/(0.67, 1.33)/0.744
ESRD	50 [†]	47 [†]	43 [†]	0.88/(0.58, 1.33)/0.542
2× SC	144 [†]	135 [†]	98 [†]	0.67/(0.52, 0.87)/0.003
Summary of All Events Occurring at Any Time in Study				
Death	83	93	87	0.92/(0.69, 1.23)/0.568
ESRD	104	101	82	0.77/(0.57, 1.03)/0.073
2× SC	144	135	98	0.67/(0.52, 0.87)/0.003

[†]24 patients in placebo, 16 patients in irbesartan, and 15 patients in the amlodipine group reached ESRD and doubling of serum creatinine on the same date and appear in both rows.

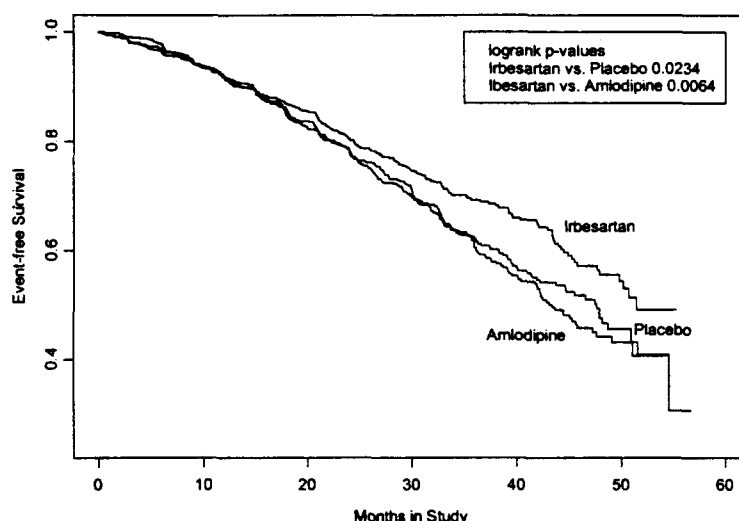


Figure 2.3.1 Kaplan-Meier curves for estimated event-free survival in three arms.

From the curves in Figure 2.3.1 and the counts of number of events in Table 2.3.1, it is apparent that the patients in the irbesartan group had fewer events than the patients in either the placebo arm or the amlodipine arm. The p-value for the primary analysis (irbesartan versus placebo on time to the composite endpoint using the logrank test) is 0.0234 [Source: *Tables 10.1.1.A of Study Report and confirmed by reviewer*]. Most of the apparent reduction in relative risk is from the creatinine component. Note that serum creatinine ≥ 6 mg/dL is included in the definition of ESRD. If one excludes those patients who met the definition of ESRD because of high serum creatinine, then there are numerically fewer patients in the placebo group who reached the primary endpoint due to ESRD (23 patients in the placebo group and 27 patients in the irbesartan group). Moreover, when the components are analyzed individually, a significant difference only appears in the serum creatinine component. Although this composite endpoint was pre-specified as the primary endpoint, one can argue that the benefit was only shown on a surrogate endpoint (SC). One patient in the placebo group progressed to ESRD and was alive at the end of the study, but the date of the event was unknown. In the sponsor's analysis, this patient was included in the counts of events, but not included in the logrank analysis. Since the patient was in the placebo group, this is a conservative way of handling the missing value and this reviewer would prefer to use a less conservative approach that adheres to the intention-to-treat principle, viz. performing an analysis that counts this patient as having an event at a time that is interval censored. As a way of checking the robustness of the primary analysis, this reviewer tried imputing 0, 700, or 1400 days as the time of the event for this patient. In all three cases, the p-value was even more significant than the analysis that ignores this patient. Likewise, there were two patients in the amlodipine group that had a missing date for the time to ESRD and were not included in the secondary analysis comparing irbesartan to amlodipine. For those

patients had missing serum creatinine measurements, it is possible to use interval censoring techniques or a worst case analysis (i.e. assume all patients in the treatment group had an event and those in the placebo group did not). However, since there were so few patients (19 in the irbesartan group and 11 in the placebo group) and many of them had events, it is unlikely that these alternative analyses will be useful. Moreover, a mixed effects model showed that the mean rate of change of serum creatinine was significantly smaller in patients in the irbesartan group relative to either placebo or amlodipine ($p=0.004$ and $p=0.013$ respectively from Section 10.4.1 of the Study Report). Hence, it is possible that the missing serum creatinine levels, if missing at random, would bias the results against the irbesartan treatment.

For the secondary analyses, there was an estimated 23% reduction in risk on the primary endpoint relative to amlodipine ($p=0.0064$). Again, this apparent effect is explained mainly by changes in SC. There was no significant difference observed on the secondary cardiovascular endpoint relative to either placebo or amlodipine ($p=0.45$ and $p=0.69$ respectively).

2.4 Safety

The ten most common adverse events are listed in Table 2.4.1. There appears to be a difference in the reports of edema in the amlodipine group relative to the other two groups. There does not appear to be a difference between irbesartan and placebo in the number of any specific adverse event.

Table 2.4.1 Most common clinical adverse events; number and % of subjects.

Adverse Event	Placebo N = 563	Irbesartan N = 577	Amlodipine N = 559
Edema	211 (37.5)	222 (38.5)	337 (60.3)
Musculoskeletal Pain	215 (38.2)	218 (37.8)	193 (34.5)
Upper Respiratory Infection	143 (25.4)	144 (25.0)	136 (24.3)
Dizziness	111 (19.7)	143 (24.8)	97 (17.4)
Fatigue	147 (26.1)	134 (23.2)	129 (23.1)
Nausea/Vomiting	111 (19.7)	112 (19.4)	108 (19.3)
Diarrhea	83 (14.7)	102 (17.7)	73 (13.1)
Headache	110 (19.5)	94 (16.3)	72 (12.9)
Cough	84 (14.9)	84 (14.6)	96 (17.2)
Abnormality Retina	68 (12.1)	75 (13.0)	52 (9.3)

2.5 Results by subgroup

The confidence intervals for the relative risk for the primary endpoint appear in Figure 2.5.1. Although the study was not powered to show a treatment effect in each subgroup, these confidence intervals appear to show that the possible benefit of irbesartan over placebo is greater in males than in females and is also greater among the White race than it is among Non-whites. Moreover, the point estimate for the relative risk among North American patients in the study is 0.95. This appears to be larger than the relative risk in other regions. There were 204 North American patients in the irbesartan group and 197 North American patients randomized to the placebo group.

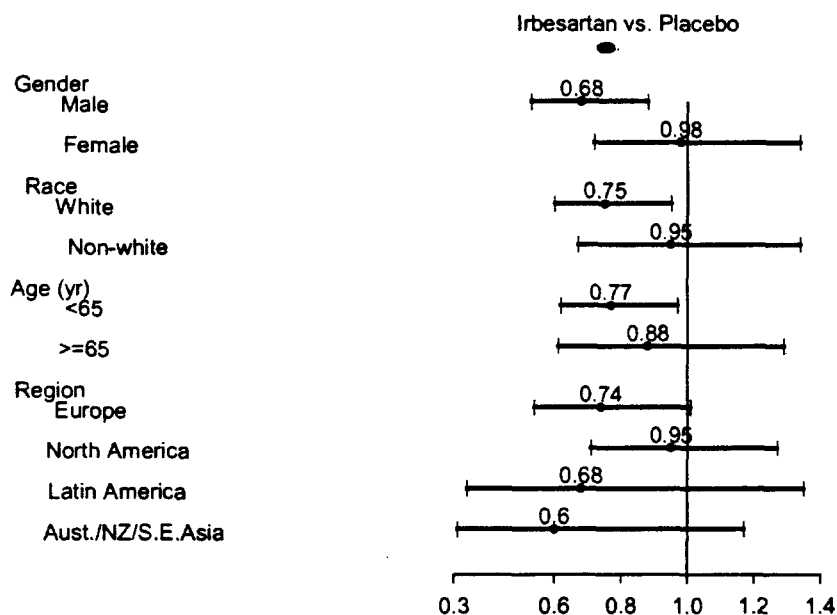


Figure 2.5.1 Relative risk by subgroups [Source: Figure 10.1.2A of Study Report]

3.1 Study Design

Study EFC2481 was a multinational double-blind study comparing two doses of irbesartan with placebo. 611 patients with Type 2 diabetes mellitus and SeSBP>135 mmHg or SeDBP>85 mmHg or being treated for hypertension and evidence of microalbuminuria were randomized. After a 3-week placebo run-in period, patients randomized to one of the irbesartan groups were given 75 mg for the first two weeks of the double-blind treatment period and were titrated up to 150 mg for the next two weeks. Those patients randomized to the 300 mg dose were then titrated up to the final dose at week 4. Subjects remained on this dosing regimen until month 24. Table 3.1.1 shows the patient demographics.

Table 3.1.1 Characteristics of the patients in the two groups at baseline. For continuous variables, this table shows the group mean $\pm$ standard deviation. [Source: Table 8.3 of Study Report]

Characteristic	Irbesartan 150 mg	Irbesartan 300 mg	Placebo
N	203	201	207
Age (years)	58 ± 8	57 ± 8	58 ± 9
Gender (Male/Female)	134/ 69	140/ 61	142/ 65
Race (Caucasian/Black/Other)	198/ 2/ 3	194/ 0/ 7	203/ 0/ 4
Baseline SeDBP	90 ± 9	91 ± 10	90 ± 9
Baseline SeSBP	153 ± 14	153 ± 14	153 ± 15

3.2 Planned Statistical Analysis

The primary endpoint was the time to occurrence of clinical proteinuria (defined as albuminuria excretion rate greater than 200 µg/min and an increase of 30% from baseline at two consecutive evaluations). Each active treatment group was compared to placebo using the two-sided logrank test with a Bonferroni adjustment so that each comparison was done with a nominal alpha of 0.025. The primary analysis was on the per-protocol population. Only patients who met all inclusion criteria and who stayed on double-blind therapy for at least 3 months were included in the per-protocol population. Also, all patients from site 1004 were removed from the per-protocol population due to significant lack of compliance. No efficacy interim analyses were planned.

The pre-specified secondary objectives were to evaluate the changes from baseline in overnight urinary albumin excretion rate, estimated creatinine clearance, von Willebrand factor, fibrogen, factor VII, plasminogen activator inhibitor-I, and lipid profile.

3.3 Results

The number of events in each subgroup, as well as the p-value from the logrank test appears in Table 3.3.1. There is a statistically significant difference between the 300 mg group and placebo ($p=0.0013$) and the 150 mg group showed a numerical trend toward longer proteinuria-free survival, but did not reach statistical significance ($p=0.096$). The analysis on the intent-to-treat population gives similar results ($p=0.0004$ for the high dose vs. placebo and $p=0.085$ for the low-dose vs. placebo). The Kaplan-Meier curves for the estimated probability of remaining proteinuria-free appear in Figure 3.3.1.

Table 3.3.1 Number of events in each arm. [Source: Tables 10.1.1.1 of Study Report and confirmed by reviewer]

Placebo	Irbesartan 150 mg	Irbesartan 300 mg
---------	-------------------	-------------------

N (per-protocol population)	172	160	162
Primary Endpoint (Proteinuria)	27	16	10
Nominal p-value vs. placebo		0.096	0.0013*
Relative risk vs. placebo 95% CI for RR		.595 (0.321, 1.105)	0.311 (0.146, 0.662)

*Significant at level 0.025 using Bonferroni adjustment.

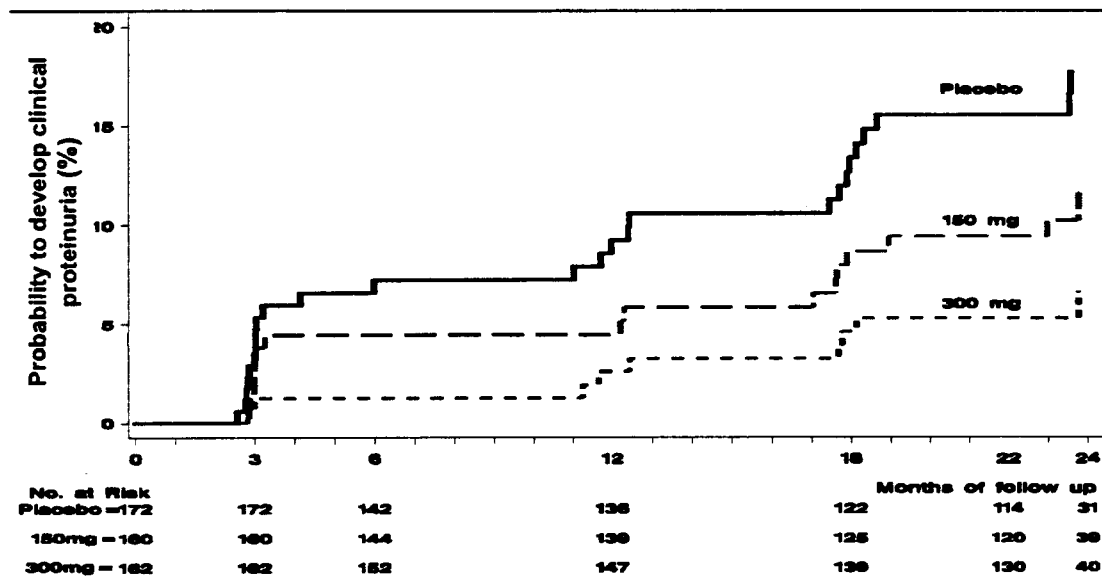


Figure 3.3.1 Kaplan-Meier curves for estimated event-free survival in three arms
[Source: Figure 10.1.1.1 of Study Report].

The results for the secondary analyses appear in Tables 3.3.2, 3.3.3, and 3.3.4. The first two variables were only analyzed at 3, 6, 12, 18 and 24 months from randomization while the remaining variables were analyzed at 1-year and 2-years from randomization. Both doses were compared to placebo and there were no adjustments for multiple testing. The only striking difference that appears among all of the secondary parameters was in urinary excretion rate. There were nominally significant differences in change in urinary excretion rate at every time point between both doses of irbesartan and placebo. There were no significant changes in serum creatinine at any time point for any dose of irbesartan. There did not appear to be any significant difference in the coagulation parameters in Table 3.3.4 although there was a nominally significant difference in plasminogen activator inhibitor-I for the high dose relative to placebo. Finally, there did not appear to be any significant difference in the mean change in lipid profile in Table 3.3.5 although there was a nominally significant difference in HDL cholesterol levels for the low dose relative to placebo.

Table 3.3.2 Results on secondary analyses on change from baseline in overnight urinary excretion rate. GM = geometric mean, PC = % change, SEM = standard error of mean.

[Source: Tables 10.2.1.1A of Study Report]

Treatment	Visit	N	Baseline		Change from Baseline		Difference with Placebo		
			GM	SEM	GMPC	SEM	Estimate	95% Confidence Interval	P-value
Placebo	Month 3	170	55.7	2.67	14.75	6.28			
	Month 6	157	53.3	2.61	13.87	7.11			
	Month 12	140	52.5	2.71	-10.46	5.83			
	Month 18	129	49.8	2.62	-10.52	7.04			
	Month 24	107	49.2	2.83	-7.55	8.95			
Irbesartan 150mg	Month 3	157	57.7	2.83	-16.59	4.62	-27.315	[-38.08,-14.68]	0.0001
	Month 6	150	57.9	2.87	-28.03	4.39	-36.800	[-46.65,-25.14]	16E-8
	Month 12	140	56.2	2.81	-30.72	4.81	-22.629	[-35.92,-6.58]	0.0078
	Month 18	134	54.8	2.79	-34.49	5.48	-26.790	[-42.13,-7.39]	0.0094
	Month 24	109	54.3	2.99	-30.48	6.80	-24.795	[-43.12,-0.56]	0.046
Irbesartan 300mg	Month 3	160	54.1	2.38	-32.56	4.27	-41.226	[-49.89,-31.06]	2E-10
	Month 6	155	53.8	2.40	-33.70	3.91	-41.774	[-50.78,-31.12]	6E-10
	Month 12	145	54.3	2.54	-39.84	4.07	-32.814	[-44.26,-19.01]	35E-6
	Month 18	144	53.1	2.41	-39.73	5.19	-32.637	[-46.53,-15.13]	0.0008
	Month 24	121	52.3	2.61	-47.15	5.27	-42.833	[-56.46,-24.94]	0.0001

Table 3.3.3 Results on secondary analyses on change from baseline in serum creatinine. GM = geometric mean, PC = % change, SEM = standard error of mean. [Source: Tables 10.2.2.1 of Study Report]

treatment	Visit	Baseline		On therapy		Change from baseline			Estimate	P value	95% Confidence Interval	
		N	GM	SEM	GM	SEM	GMPC	SE			IC	
Creatinine Clearance, Estimated (BSA), mL/min/1.73m ²												
placebo	Month 3	171	109.51	2.45	107.41	2.31	-1.92	1.03	[-3.92,0.11]			
	Month 6	157	109.76	2.59	105.87	2.35	-3.55	1.01	[-5.51,-1.55]			
	Month 12	137	110.76	2.85	104.23	2.63	-5.89	1.15	[-8.12,-3.60]			
	Month 18	129	110.52	2.93	105.40	2.78	-4.63	1.43	[-7.39,-1.79]			
	Month 24	107	109.01	3.22	104.56	3.07	-4.08	1.79	[-7.51,-0.51]			
Irbesartan 150 mg	Month 3	158	109.85	2.25	106.71	2.37	-2.85	1.10	[-4.98,-0.68]	-0.950	0.53	[-3.87,2.06]
	Month 6	149	110.66	2.30	107.04	2.43	-3.27	1.24	[-5.66,-0.82]	0.122	0.94	[-3.01,3.36]
	Month 12	139	110.61	2.41	105.93	2.48	-4.23	1.10	[-6.36,-2.04]	2.058	0.24	[-1.39,5.63]
	Month 18	134	109.73	2.43	102.76	2.39	-6.35	1.35	[-8.96,-3.67]	-1.845	0.37	[-5.80,2.28]
	Month 24	111	110.49	2.79	103.97	2.69	-5.90	1.39	[-8.59,-3.13]	-1.496	0.46	[-5.38,2.55]
Irbesartan 300 mg	Month 3	160	107.28	2.60	102.52	2.44	-4.44	1.02	[-6.41,-2.42]	-2.563	0.088	[-5.43,0.39]
	Month 6	156	107.35	2.65	102.37	2.36	-4.63	1.07	[-6.71,-2.52]	-1.162	0.47	[-4.23,2.00]
	Month 12	150	107.56	2.67	101.39	2.56	-5.74	1.22	[-8.10,-3.31]	0.541	0.75	[-2.80,4.00]
	Month 18	145	108.20	2.75	99.65	2.46	-7.91	1.34	[-10.50,-5.24]	-3.486	0.085	[-7.31,0.49]
	Month 24	127	109.15	3.07	100.76	2.71	-7.68	1.32	[-10.23,-5.06]	-3.734	0.061	[-7.50,0.18]

Table 3.3.4 Results on secondary analyses on change from baseline in von Willebrand factor, fibrinogen, factor VII, and plasminogen activator inhibitor-I. [Source: Tables 10.2.3.1 of Study Report]

Change	Mean Change from Baseline			Irbesartan 150 mg vs. Placebo		Irbesartan 300 mg vs. Placebo	
	Placebo	Irbesartan 150 mg	Irbesartan 300 mg				
	n Mean ^a (SD)	n Mean ^a (SD)	n Mean ^a (SD)	Estimate Difference [95% CI]	p	Estimate Difference [95% CI]	p
After 12 months in:							
vWF, %	118 7.81 (47.18)	118 7.08 (28.40)	129 3.27 (29.96)	-0.720 [-9.94, 8.50]	0.88	-4.534 [-13.56, 4.49]	0.32
Fibrinogen, µg/g/L	118 9.71 (90.75)	122 1.40 (69.35)	130 -2.78 (81.87)	-8.310 [-28.89, 12.27]	0.43	-12.489 [-32.75, 7.77]	0.23
Factor VII, %	116 0.61 (2.97)	119 0.68 (3.68)	130 2.80 (3.85)	0.065 [-9.38, 10.49]	0.99	2.179 [-7.27, 12.59]	0.66
PAI ₁ , µg/L	120 12.62 (8.89)	119 12.64 (3.08)	129 -13.38 (6.23)	0.019 [-18.80, 23.30]	1.00	-23.089 [-37.31, 5.65]	0.012
After 24 months in:							
vWF, %	104 14.48 (50.17)	104 12.63 (34.19)	117 6.11 (35.54)	-1.856 [-12.88, 9.17]	0.74	-8.370 [-19.09, 2.35]	0.13
Fibrinogen, µg/g/L	104 12.49 (111.02)	106 11.33 (82.78)	118 -6.66 (81.65)	-1.160 [-26.22, 23.90]	0.93	-19.151 [-43.58, 5.27]	0.12
Factor VII, %	100 3.11 (3.53)	101 0.10 (2.79)	115 2.76 (3.88)	-2.914 [-11.88, 6.96]	0.55	-0.338 [-9.27, 9.47]	0.94
PAI ₁ , µg/L	104 -5.90 (8.32)	100 3.08 (9.12)	118 9.82 (8.67)	9.537 [-14.06, 39.61]	0.46	16.699 [-7.55, 47.32]	0.19

^aUnadjusted raw mean change for vWF and Fibrinogen; geometric mean % change for Factor VII and PAI.

Table 3.3.5 Results on secondary analyses on mean change from baseline in lipid profile.
 [Source: Tables 10.2.4.1A of Study Report]

Change	Placebo N=172	Irbesartan 150 mg N=160	Irbesartan 300 mg N=162	Irbesartan 150 mg vs. Placebo		Irbesartan 300 mg vs. Placebo	
	n Mean* (SD)	n Mean* (SD)	n Mean* (SD)	Estimate Difference [95% CI]	p	Estimate Difference [95% CI]	p
After 1 year in:							
Total cholesterol (mg/dL)	139 -13.27 (36.92)	142 -11.31 (41.46)	150 -4.70 (36.57)	1.956 [-7.04, 10.95]	0.67	8.566 [-0.31, 17.44]	0.059
HDL cholesterol (mg/dL)	120 2.31 (7.64)	124 3.18 (6.95)	132 3.90 (8.31)	0.869 [-1.06, 2.80]	0.38	1.593 [-0.31, 3.50]	0.10
Apolipoprotein (mg/dL)	120 4.49 (18.59)	124 7.15 (24.34)	132 3.69 (20.50)	2.662 [-2.70, 8.02]	0.33	-0.802 [-6.08, 4.48]	0.77
Triglycerides (mg/dL)	139 -3.02 (3.91)	142 -1.35 (4.13)	150 4.21 (3.63)	1.722 [-8.84, 13.51]	0.76	7.458 [-3.56, 19.73]	0.19
After 2 years in:							
Total cholesterol (mg/dL)	55 -11.55 (33.21)	68 -17.51 (37.00)	68 -6.04 (45.56)	-5.969 [-20.03, 8.09]	0.40	5.501 [-8.56, 19.56]	0.44
HDL cholesterol (mg/dL)	107 3.90 (9.85)	107 6.80 (8.37)	121 5.63 (10.56)	2.907 [0.30, 5.51]	0.029	1.731 [-0.80, 4.26]	0.18
Apolipoprotein (mg/dL)	107 5.25 (17.17)	106 8.58 (24.46)	121 3.69 (24.16)	3.323 [-2.68, 9.32]	0.28	-1.558 [-7.37, 4.25]	0.60
Triglycerides (mg/dL)	55 -2.18 (7.93)	68 -5.30 (5.92)	68 7.81 (6.03)	-3.195 [-19.73, 16.75]	0.73	10.211 [-8.62, 32.92]	0.31

*Geometric mean for triglycerides; raw means for everything else.

3.4 Safety

The ten most common adverse events are listed in Table 2.4.1. There appears to be a difference in the reports of dizziness and diarrhea in the 300 mg group relative to placebo and numerically more reports in the 150 mg group relative to placebo. There does not appear to be a difference between irbesartan and placebo in the number of any other specific adverse event.

Table 3.4.1 Most common clinical adverse events; number and % of subjects.

Primary Terms	Placebo N=206	Irbesartan 150 mg N=202	Irbesartan 300 mg N=200
Number (%) of subjects with AEs	141 (68.4%)	129 (63.9%)	149 (74.5%)
Musculo/Skeletal Pain	20 (9.7%)	21 (10.4%)	25 (12.5%)
Upper Resp Infection	14 (6.8%)	16 (7.9%)	12 (6.0%)
Headache	13 (6.3%)	10 (5.0%)	14 (7.0%)
Influenza	14 (6.8%)	10 (5.0%)	14 (7.0%)
Urinary tract infection	11 (5.3%)	9 (4.5%)	14 (7.0%)
Dizziness	6 (2.9%)	8 (4.0%)	13 (6.5%)
Diarrhea	5 (2.4%)	9 (4.5%)	11 (5.5%)
Hypertension	10 (4.9%)	11 (5.4%)	6 (3.0%)
Cough	9 (4.4%)	10 (5.0%)	5 (2.5%)
Pulmonary Infection	4 (1.9%)	5 (2.5%)	10 (5.0%)

3.5 Results by subgroup

The estimates of the relative risk in subgroups appear in Table 3.5.1. The point estimates are always less than 1 and appear to be particularly small in females, patients under 59, and patients with normal creatinine clearance (>107 ml/min/1.73 m²).

Table 3.5.1 Estimates of Relative Risk in subgroups from Cox model in per-protocol population [Source: Figure 10.1.2C of Study report]

Baseline factor	Category	— Number (%) of subjects — Risk Ratio* (95% CI)				
		Placebo		IR 300 mg		300 mg/Placebo
		N	n(%)	N	n(%)	
Age at entry (yr)	<= 59	80	17(21.3)	95	5(5.3)	0.177(0.060,0.526)
	> 59	92	10(10.9)	67	5(7.5)	0.634(0.216,1.858)
Baseline AER	<= 53	83	4(4.8)	87	2(2.3)	0.231(0.026,2.071)
	> 53	89	23(25.8)	74	8(10.8)	0.326(0.145,0.731)
Baseline fundoscopic grade	Grade II-IV	44	9(20.5)	31	2(6.5)	0.286(0.061,1.351)
	Normal to Grade I	125	15(12.0)	128	8(6.3)	0.417(0.170,1.024)
Body Mass Index (kg/m ²)	<= 29.48	82	12(14.6)	88	5(5.7)	0.260(0.084,0.806)
	> 29.48	90	15(16.7)	74	5(6.8)	0.367(0.133,1.012)
Calcium Channel Blockers use at start/end of study	No	124	17(13.7)	126	7(5.6)	0.368(0.153,0.888)
	Yes	48	10(20.8)	36	3(8.3)	0.208(0.045,0.951)
Diabetes duration (yr)	<= 8	94	14(14.9)	90	5(5.6)	0.342(0.123,0.950)
	> 8	78	13(16.7)	72	5(6.9)	0.284(0.093,0.872)
Diabetic Retinopathy	No	95	11(11.6)	102	7(6.9)	0.452(0.167,1.224)
	Yes	76	15(19.7)	56	3(5.4)	0.229(0.066,0.792)
Estimated CrCl	<= 107	84	10(11.9)	88	7(8.0)	0.601(0.229,1.580)
	> 107	87	16(18.4)	74	3(4.1)	0.125(0.029,0.542)
Gender	F	49	9(18.4)	43	2(4.7)	0.105(0.013,0.831)
	M	123	18(14.6)	119	8(6.7)	0.406(0.176,0.934)

The results by country are summarized in Figure 3.5.1. There is one point in the graph for each country where there were a sufficient number of patients recruited so that an estimate of the hazard ratio could be obtained. The y-axis represents the estimated log-hazard ratio for irbesartan relative to placebo on the primary endpoint. The x-axis represents the standard error of this estimate. Countries with more patients have more information about the hazard ratio (smaller standard error), and therefore appear on the left side of the graph. The dashed lines represent the overall pooled log-hazard ratio as well as the 95% confidence bands (pooled estimate $\pm$ 1.96 standard errors). Since all of the points lie within the confidence bands, there are no countries that have significantly different treatment effects than what one would expect given the pooled results. The only country in North America where patients were recruited in this study is Canada and there were too few events among Canadian patients to estimate the relative risk in this subgroup.

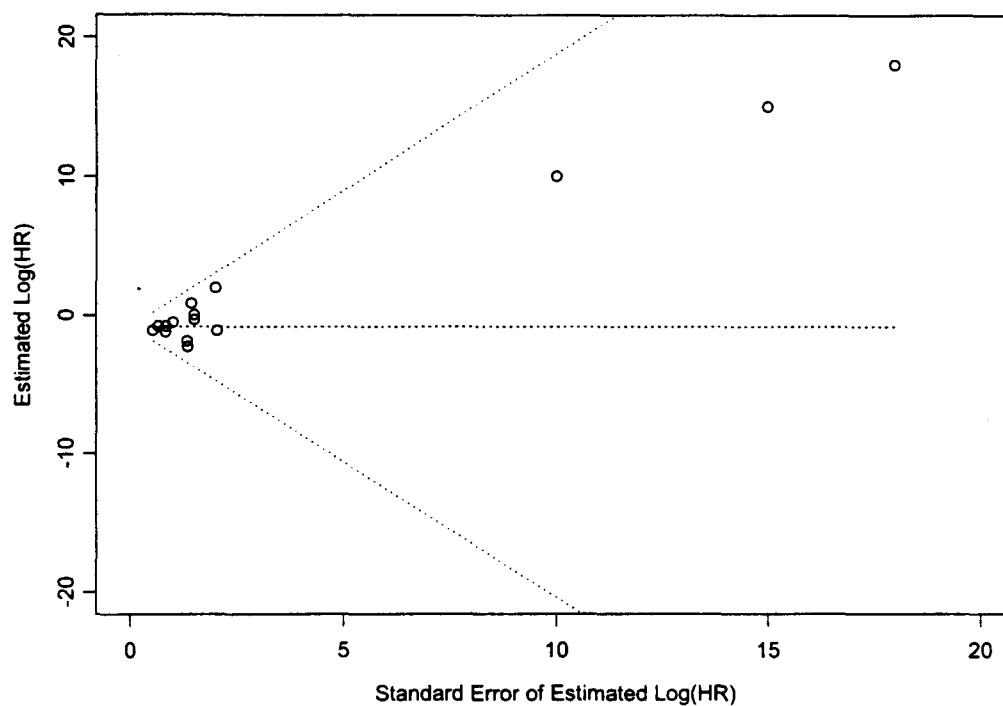


Figure 3.5.1 Plot of log-hazard ratios for primary endpoint by country.

4. Conclusions

Two placebo controlled studies appeared to show positive findings on the primary endpoints for irbesartan 300 mg in the populations studied. Study CV131-048 showed a statistically significant increase in the time to a composite endpoint (doubling of serum creatinine, ESRD, all-cause mortality) with a p-value of 0.023 and also appeared to show superior efficacy to the active control amlodipine 10 mg. Most of the apparent benefit seemed to be in delaying increases in serum creatinine. The effect of irbesartan on the primary endpoint appeared to be smaller in North America than in other regions. Study EFC2481 showed a statistically significant increase in the time to occurrence of clinical proteinuria with a p-value of 0.0013, but failed to show a statistically significant difference between a lower dose of 150 mg relative to placebo ($p=0.096$). There were positive findings on some of the secondary endpoints: a 23% reduction in relative risk in the irbesartan group relative to the active control amlodipine on the primary endpoint in Study CV131-048 and nominally significant differences in change in urinary excretion rate at every time point and in change in plasma activator inhibitor-I in Study EFC2481. Diarrhea and dizziness were reported more often in the irbesartan groups than in the

placebo groups in both trials, but there did not appear to be significantly more reports of any other adverse event in the irbesartan groups in these studies.

151

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 16 pages of text, tables, and figures.

Concur: James Hung, Ph.D.
Acting Team Leader, Biometrics I

George Chi, Ph.D.
Division Director, Biometrics I

cc: NDA # 20-757
HFD-110/Dr. Lipicky
HFD-110/Dr. Pelayo
HFD-110/Mr. Fromme
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/chron

LAWRENCEJ/594-5375/report.doc/11/07/01

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

John Lawrence
11/7/01 03:11:16 PM
BIOMETRICS

James Hung
11/7/01 04:52:01 PM
BIOMETRICS

George Chi
11/13/01 11:21:29 AM
BIOMETRICS