

CLINICAL REVIEW

NDA No.: 20-757/S-021

DRUG NAME: Avapro® (Irbesartan) Tablets

SPONSOR: Bristol-Myers Squibb Company

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INTRODUCTION AND BACKGROUND¹

The prevalence of end-stage renal disease continues to increase in the United States; currently it is approximately twice what it was a decade ago. This increase spans all racial and ethnic groups, however Hispanics, Native Americans, and Blacks carry a risk that range from two to more than four times those of whites. Diabetic nephropathy is the leading cause of end-stage renal disease in the United States and is a significant health problem because of the resultant morbidity and mortality. Of note, renal disease due to type 2 diabetes appears to account for almost all of the increasing number of patients with kidney failure. In only 10% to 15% of patients with type 2 diabetes mellitus does end-stage renal disease develop, however type 2 diabetes accounts for approximately 50% of end-stage renal disease cases with diabetic nephropathy since 85% of all patients with diabetes have type 2. Hence, the discovery of therapeutic interventions aim to prevent/attenuate the progression of diabetic nephropathy due to type 2 diabetes to end-stage renal disease is a public health priority. Patients with type 2 diabetes mellitus have a high prevalence of hypertension. In this regard, epidemiological data and results from clinical trials suggest that glycemic and blood pressure control blunt its renal complications.

Hitherto, there is not a drug approved by the FDA for the treatment of renal disease due to type 2 diabetes mellitus. Captopril, an angiotensin converting enzyme inhibitor, is the only drug to gain FDA's approval for the treatment of diabetic nephropathy but only for those patients with renal disease due to type 1 diabetes mellitus.

The sponsor reasoned that Irbesartan, through blockade of the renin-angiotensin system in addition to the antihypertensive action, could effect a treatment benefit to hypertensive patients with type 2 diabetes similar to that observed with captopril in patients with renal disease due to type 1 diabetes mellitus. To that end Bristol-Myers Squibb and Sanofi-Synthelabo jointly sponsored the clinical development of Avapro® (Irbesartan) in hypertensive patients with diabetic renal disease due to type 2 diabetes mellitus. In essence, this clinical development program consisted of two clinical trials² in hypertensive patients with renal disease (early and advanced) due to type 2 diabetes mellitus. The results from those trials were published in the *New England Journal of Medicine* and submitted to the FDA by the sponsor as an efficacy supplement (S-021) for NDA 20-757.

1. Lewis, EJ, *et al.* Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. *N Engl J Med* 2001;345:851-60.
2. Parving, HH, *et al.* The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes. *N Engl J Med* 2001;345:870-8.

GENERAL INFORMATION

Drug name: Avapro® (Irbesartan) Tablets. Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4] non-1-en-4-one.

Drug Class: Avapro® is a specific long-acting angiotensin II receptor antagonist with a much greater affinity (more than 8500-fold) for the AT₁ receptor than for the AT₂ receptor and no agonist activity.

Sponsor's Proposed Indication(s): Avapro® (Irbesartan) is approved "for the treatment of hypertension" regardless etiology. "It may be used alone or in combination with other antihypertensive agents."³

¹ U.S. Renal Data System. USRDS 2001 Annual Data Report: atlas of end-stage renal disease in the United States. Bethesda, Md.: National Institute of Diabetes and Digestive and Kidney Diseases, 2001. Hostetter TH. Prevention of end-stage renal disease due to type 2 diabetes. *N Engl J Med* 2001;345:910-912. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999;341:1127-33.

² Protocols CV131-048 (IDNT, Irbesartan Diabetic Nephropathy Trial) and EFC2481 (IRMA 2, Irbesartan MicroAlbuminuria in Type 2 Diabetes).

³ As per the current label for Avapro® (Irbesartan) Tablets.

The sponsor is seeking a new indication: "Avapro® (Irbesartan) is indicated for the treatment of type 2 diabetic renal disease."

Dose, and Regimens: Avapro® is available for oral administration in unscored tablets containing 75 mg, 150 mg or 300 mg of Irbesartan. The current recommended initial dose of Avapro® in hypertensive patients is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

Based on the results of studies IDNT and IRMA2 the sponsor recommends that "in hypertensive patients with type 2 diabetic renal disease, 300 mg once daily dose is the preferred maintenance dose."

Avapro® in Pediatric Population: The studies in support of this supplemental NDA did not evaluate patients within the pediatric age groups. Actually, the sponsor is requesting a waiver for pediatric studies because "major challenges exist in the design and conduct of such a clinical trial: 1) identifying a cohort of children with type 2 diabetes and established diabetic nephropathy; 2) ensuring linear rates of recruitment; and 3) choosing a clinically relevant measure of treatment efficacy."

Post-Marketing Experience: Avapro® (Irbesartan) was approved in United States of America on September 30, 1997, since then several countries have approved it worldwide for the treatment of hypertension.

CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

The medical reviewer relied on the results of the statistical analyses by Dr. John Lawrence (FDA, HFD-710) for the evaluation of the clinical data.

HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

DESCRIPTION OF CLINICAL DATA AND SOURCES

The clinical development program of Irbesartan in hypertensive patients with diabetic renal disease due to type 2 diabetes mainly consists of two international, multicenter, randomized, double-blind, active- and /or placebo-controlled safety and efficacy studies: Protocols EFC2481, IRMA 2 (IRbesartan MicroAlbuminuria in type 2 diabetes) and CV131-048, IDNT (Irbesartan Diabetic Nephropathy Trial). In addition, the sponsor submitted three small supportive clinical studies (Protocols CV131-046, -047, and -093). The aforementioned trials were conducted in accordance with accepted Ethical Standards. The design of the IRMA 2 and IDNT trials is presented in Table 1 and that of the three supportive studies in Table 2.

Table 1: Study Design of IRMA 2 and IDNT

Protocol	Pre-Treatment	Double-Blind Treatment	Titration Week 0→Week 2→Week 4	Treatment Duration	Total Randomized
EFC2481 (IRMA 2)	3 wks single blind placebo lead-in	placebo N = 207 irbe 150 N = 203 irbe 300 N = 201	Placebo 75→150→150 mg 75→150→300 mg	24 months	N = 611
CV 131-048 (IDNT)	7-14 days screening/enrollment	placebo N = 569 irbesartan N = 579 amlodipine N = 567	Placebo 75→150→300 mg 2.5→5→10 mg	Up to 57 months	N = 1715

[Sponsor's analysis. Source: NDA 20-757/S-021, Application Summary, Table 4.1A.]

Table 2: Study Design of Supportive Studies

Protocol	Pre-Treatment	Short-term (ST)/ Long-term (LT)	Assigned dose or Titration	Treatment Duration	Total Treated
CV 131-047	2 weeks screening and 2-3 weeks enrollment	ST Double-blind (DB)	Wk 0→Wk 4→Wk 8 irbe 75→150→300 mg aml 2.5→5→10 mg	ST: 14 weeks	N = 47
		LT Open label (OL)	Wk 0→Wk 2→Wk 4 irbe 75→150→300 mg	LT: 3 years	N = 37
CV 131-046	(up to 3 months)	ST Part I OL	Day 1→4Day 3→ Day 5	5 days	N=8
		ST Part II OL	irbe 75→150→300 mg		N = 12
		ST Part III OL	irbe 150 mg on Day 1	single dose	N = 12
		LT OL	irbe 150→300 (Wk 2) or remain on 300 mg	1 year	N=5
CV131-093	Screening (up to 3 months)	ST OL	irbe single dose 150 mg	1 day	N= 18

[Sponsor's analysis. Source: NDA 20-757/S-021, Application Summary, Table 4.1B.]

The clinical trials IDNT and IRMA 2, because are the pivotal studies, were selected for “in-depth” review and the findings are presented in the Integrated Summary of Efficacy and Safety as well as separately (see Appendix, Individual Study Reviews). The supportive clinical studies (Protocols CV131-046, -047, and -093) were evaluated by the medical reviewer but they are not presented in this review because it was concluded that the results do not contribute to the overall understanding of the efficacy or safety of Avapro® (Irbesartan).

The following materials were used for the medical review: hard desk copies, electronically submitted materials (electronic archive including SAS data files), and sponsor's responses to specific FDA's requests for further information and/or clarification of data.

INTEGRATED REVIEW OF EFFICACY

The effectiveness of Irbesartan in modifying the “natural history” of renal disease, and thus morbidity and mortality, in hypertensive patients with type 2 diabetes was evaluated in two clinical trials, IRMA 2 and IDNT; these studies randomized subjects at an early and more advanced stages of renal disease, respectively. Accordingly, any regulatory action on Avapro® (Irbesartan) for the new sought indication “treatment of type 2 diabetic renal disease” hinges on the interpretation of the results from those studies.

The IDNT study is the largest trial and examined the effect of Irbesartan on morbidity and mortality in hypertensive subjects with type 2 diabetes and diabetic nephropathy.⁴ The long-term effect of 300 mg Irbesartan on the progression of renal disease was compared to Placebo or the calcium channel blocker Amlodipine. The clinical trial had a multinational, multicenter, randomized, double blind, placebo- and active-controlled and force-titration design. The study drug was administered once daily at the following dosage Irbesartan 75 mg (titrated up to 300 mg) or Amlodipine 2.5 mg (titrated up to 10 mg) or Placebo. The primary endpoint was a composite outcome measure defined as time to doubling of baseline serum creatinine, end-stage renal disease (i.e., need for renal transplantation or dialysis or serum creatinine ≥6.0 mg/dl) or death (all-cause mortality). A total of 1715 subjects were randomized, 563 in the Placebo group, 577 in the Irbesartan group and 559 in the Amlodipine group (sixteen subjects albeit randomized into the trial did not receive study drug). The study was expected to have a two year enrollment period and a two year follow up after the last subject

enrolled, for an average follow up of three years. The mean duration of treatment was 793 days for Placebo, 815 days for Irbesartan and 773 days for Amlodipine.

The study population was predominantly white (72.4%) males (66.5%) under the age of 65 years (72.9%) with a mean body mass index (BMI) of 30.8%. The mean duration of diabetes was 14.8 years; 57.8% of the subjects had used insulin prior to entering the study. The mean baseline seated systolic and diastolic blood pressures were 159.1 mmHg and 86.9 mmHg, respectively. The mean serum creatinine and creatinine clearance were 1.6 mg/dl and 57.7 mL/min/1.73m², respectively. Mean urinary albumin and protein excretion rates were 2700 and 4144 mg/24 hr, respectively. A history of cardiovascular disease was present in 45.4% of the randomized subjects.

Irbesartan significantly increased the time to the primary composite endpoint of doubling of serum creatinine, ESRD, or death, as compared with Placebo (Table 3). Treatment with Irbesartan resulted in a relative risk reduction of 20% vs. Placebo (p=0.0234). Of interest, the difference in the median time to a primary event between the Irbesartan group and the Placebo group was approximately four months (116 days).⁵

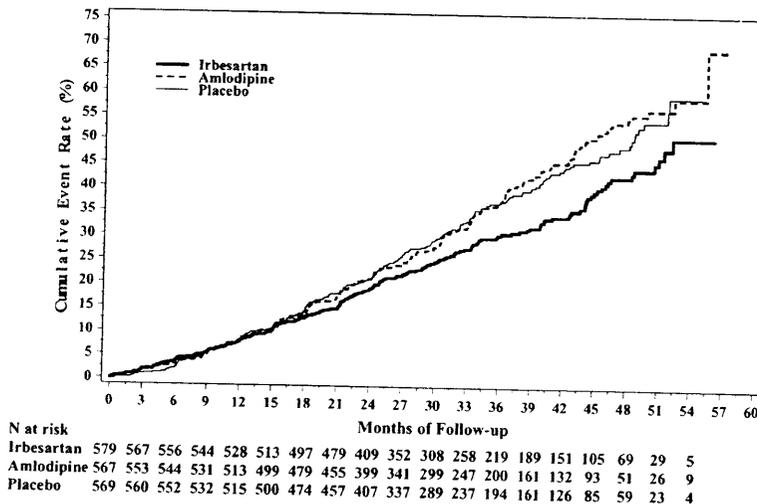
Table 3. Primary Endpoint Comparison: Irbesartan vs. Placebo

Event	Placebo N=569 n(%)	Irbesartan N=579 n(%)	Relative Risk		
			Estimate	95% Confidence Interval	p-Value
Primary Composite Endpoint	222 (39.0)	189 (32.6)	0.80	0.66-0.97	0.0234

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.1.1A, and FDA's analysis by Dr. John Lawrence, HFD-710.]

Figure 1 depicts the Kaplan-Meier curves of the cumulative event rate for the primary composite endpoint over the course of the trial for all the groups evaluated. The curve representing the Irbesartan group indicates that subjects in this group had significantly fewer events than the subjects in either the Placebo or Amlodipine curves (p=0.0234 and p=0.0064, respectively).⁶ This effect appears to become apparent approximately after 18 months of treatment with Irbesartan and to continue over the length of the study.

Figure 1. Kaplan-Meier Estimates of Primary Composite Endpoint for All Randomized Subjects.



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.1.1A.]

⁵ FDA's analysis by Dr. John Lawrence, HFD-710.

⁶ Sponsor's analyses.

The number of subjects reaching, i.e., first occurrence, any of the components of the composite primary endpoint is as follows (Table 4): a total of 111 (50.0%)⁷ and 82 (43.4%) subjects reached the doubling of serum creatinine in the Placebo and Irbesartan groups, respectively. Forty-seven (21.2%) placebo-treated subjects and 43 (22.7%) subjects receiving Irbesartan reached ESRD.⁸ The Placebo and Irbesartan groups each had 64 subjects who die during the study (28.8% and 33.9%, respectively). The accumulative number of events over time is as follows (Placebo group vs. Irbesartan group): 135 vs. 98 doubling of serum creatinine, 101 vs. 82 ESRD, and 93 vs. 87 death.

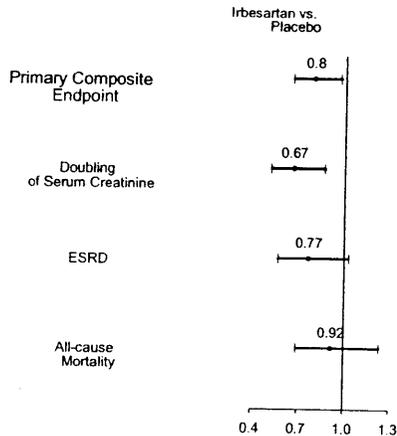
Table 4. Individual Components of Primary Composite Endpoint

EVENT		Placebo		Irbesartan	
		n		n	
Death		64		64	
ESRD	Transplant	47	0	43	0
	Dialysis		22		24
	Serum creatinine ≥6 mg/dL		25		19
Doubling Serum Creatinine		111		82	
Total		222		189	

[FDA's analysis by Dr. John Lawrence, HFD-710.]

The relative risk with 95% confidence intervals for the primary efficacy measure and its components, for the Irbesartan vs. Placebo comparison, is shown in Figure 2. The relative risk for Irbesartan vs. Placebo was 0.67 (95% CI: 0.52-0.87) for doubling of serum creatinine, 0.77 (95% CI: 0.57-1.03) for ESRD, and 0.92 (95% CI: 0.69-1.23) for all-cause mortality. Irbesartan treatment had a significant relative risk reduction of 33% in doubling of serum creatinine compared with placebo (p=0.0027).⁹ Thus the treatment benefit provided by Irbesartan was entirely due to its effect on delaying the time to doubling of serum creatinine.

Figure 2. Primary Efficacy Endpoint and Its Components: Relative Risk with 95% Confidence Intervals.



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.1.1B.]

The sponsor also conducted subgroup analyses of the primary efficacy endpoint for gender (male, female), race (white, non-white), age (<65 years, ≥65 years), and regions (Europe, North America, Latin America, and South East Asia/Australia/New Zealand). The interpretation of these results is hindered by the lack of statistical power due to the small number of subjects in each subgroup, a homogenous study population, i.e., mainly white, males under the age of 65 years, as well as regional demographics differences, i.e., in the North American region

⁷ Percent of the total number of events.

⁸ Of note, 24 (10.8%) and 16 (8.5%) reached ESRD and doubling of serum creatinine the same day in the Placebo and Irbesartan groups, respectively.

⁹ Sponsor's analyses.

47.3% of the randomized subjects were non-white vs. 6.3% of the randomized subjects in Europe (see Appendix, Individual Study Reviews).

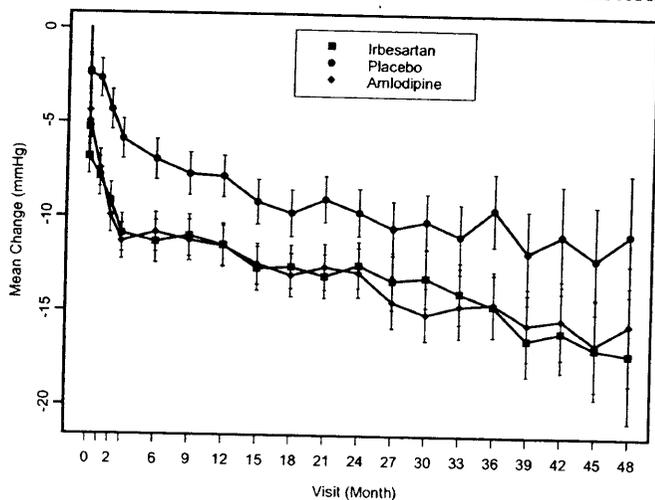
The secondary analysis for the primary endpoint was the comparison of Irbesartan vs. Amlodipine. Irbesartan treatment resulted in a relative risk reduction of 23% vs. Amlodipine (estimate 0.77, 95% CI: 0.63-0.93, $p=0.0064$). This treatment effect in favor of Irbesartan was primarily driven by a significant relative risk reduction of 37% in doubling of serum creatinine compared with Amlodipine (estimate 0.63, 95% CI: 0.49-0.81, $p=0.0003$).

Treatment with Irbesartan failed to effect a benefit on the secondary and tertiary cardiovascular outcomes as compared with Placebo or Amlodipine (see Appendix, Individual Study Reviews).

A progressive decline from baseline in the urinary excretion rates for albumin and protein occurred in all groups, however the decline observed for the Irbesartan group, at most times (except for months 42 and 48), was significantly greater ($p<0.001$) than either for Placebo or Amlodipine.

Noteworthy, “the trial was designed to attain equal degrees of blood pressure control within all three treatment groups by use of target blood pressure goals.” Blood pressure control (SeSBP or SeDBP or MAP) in Irbesartan-treated subjects was similar to that achieved in the Amlodipine group but significantly greater than that attained in the Placebo group (see Appendix, Individual Study Reviews) (Figure 3).

Figure 3. Mean Change (\pm SD) from Baseline in Mean Arterial Blood Pressure



The IRMA 2, a non-IND study, examined the effect of Irbesartan in reducing the progression from albuminuria to overt nephropathy in hypertensive subjects with type 2 diabetes and microalbuminuria.¹⁰ This study had a multinational, multicenter, randomized, double blind, placebo-controlled, and force-titration design. The subjects were randomized to regimens of Irbesartan 150 mg (75 mg titrated to 150 mg) or 300 mg (75 mg titrated to 150 mg and to a final dose of 300 mg) or Placebo, and received study drug for 24 months. A cohort of subjects (GFR Sub-Study) was selected from the main study to have GFR measurements at randomization, and at months 3 and 24 during the double-blind treatment period, and at the last visit of the 4-week extension after all study medication and concomitant antihypertensive medications were discontinued at Month 24.

Six hundred and eleven subjects were randomized into the clinical trial, 207 subjects in the Placebo group, 203 in the 150 mg Irbesartan group, and 201 in the 300 mg Irbesartan group. Two-hundred and six subjects received Placebo for an average of 561 days, 202 subjects received Irbesartan 150 mg for an average of 598 days and 200 subjects received Irbesartan 300 mg for an average of 641 days. The study population was mainly

¹⁰ Overnight urinary albumin excretion rate between 20 and 200 μ g/minute.

white (98%) males (74%) under the age of 65 years (77%) with a mean BMI of 30%. The mean duration of diabetes was 9.9 years, with 35% of the subjects having a history of insulin use prior to study entry. The mean baseline seated systolic and diastolic blood pressures were 153.2 mmHg and 90.1 mmHg, respectively. The mean serum creatinine, creatinine clearance and urinary albumin excretion was 1.06 mg/dL, 108.6 ml/min/1.73m² and 55.9 µg/min, respectively.

The primary endpoint was defined as time to the first confirmed occurrence of clinical proteinuria (defined as urinary albumin excretion rate exceeding 200 µg/minute and an increased of at least 30% from baseline at two successive evaluations).¹¹ Albeit the comparison of Irbesartan 150 mg vs. Placebo did not reach statistical significance (p=0.085) (Table 5), treatment with 300 mg of Irbesartan daily significantly reduced by 70% (p=0.004) the risk of developing “clinical proteinuria” as compared with Placebo (Table 6).

Table 5. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 150 mg vs. Placebo Comparison): Intent-to-Treat Population

Placebo N=201 n (%)	Irbesartan 150 mg N=195 n (%)	Relative Risk		p-Value
		Estimate	95% CI	
30 (14.9)	19 (9.7)	0.607	0.341, 1.079	0.085

[Sponsor’s analysis, NDA 20-757/S-021, Protocol EFC2481, Table 10.1.1.2A.]

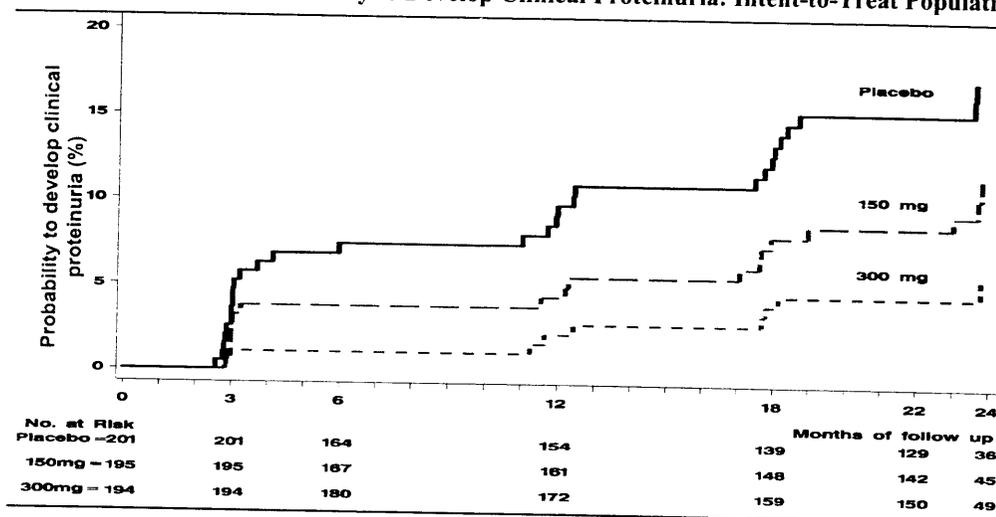
Table 6. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 300 mg vs. Placebo Comparison): Intent-to-Treat Population

Placebo N=201 n (%)	Irbesartan 300 mg N=195 n (%)	Relative Risk		p-Value
		Estimate	95% CI	
30 (14.9)	10 (5.2)	0.295	0.144, 0.606	0.0004

[Sponsor’s analysis, NDA 20-757/S-021, Protocol EFC2481, Table 10.1.1.2B.]

Figure 4 depicts the Kaplan-Meier estimates of probability to develop clinical proteinuria in all treatment groups, for the intent-to-treat population. By month 3 of treatment, i.e., time by which the first measurement of urinary albumin excretion rate after randomization was obtained, the curves had already separated.

Figure 4. Estimates of Probability to Develop Clinical Proteinuria: Intent-to-Treat Population



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Figure 10.1.1.2.]

¹¹ Changed by Amendment No. 6.

In comparison to Placebo, treatment with Irbesartan either at a dosage of 150 mg or 300 mg didn't have a beneficial effect on the progression of renal disease as assessed by either the annual rate of change in serum creatinine from the main study or GFR from the GFR Sub-Study (see Appendix, Individual Study Reviews).¹²

As was the case in the IDNT study, the IRMA 2 study was designed to attain similar degrees of blood pressure control within all treatment groups. At visits on month 3 and 6 both Irbesartan groups had MAP values significantly lower than the Placebo group did, a similar pattern was also observed at visit month 12 only for the Irbesartan 300 mg group (see Appendix, Individual Study Reviews). A similar pattern was observed for systolic and diastolic blood pressures.¹³ After two years of treatment, SeDBP and SeSBP mean values were comparable among the groups: 143.5/82.2, 143.5/82.4, and 141.6/83.4 mmHg in the Placebo, Irbesartan 150 and 300 mg groups, respectively.

The secondary endpoints were overnight urinary albumin excretion rate, von Willebrand Factor, Fibrinogen, Factor VII and Plasminogen Activator Inhibitor-1, and Lipid Profile (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and apolipoprotein). The reduction in urinary albumin excretion rate was significantly greater in the Irbesartan groups than in the placebo group at any time-point during the study (see Appendix, Individual Study Reviews). Analysis of the remaining secondary endpoints failed to demonstrate statistically significant differences between groups.

In the cohort of subjects enrolled in the GFR Sub-Study, glomerular filtration rate (ml/min/1.73m², mean±SD) at baseline was similar among the treatment groups: 104.3±4.2 in the Placebo group (n=37), 113.3±3.4 in the Irbesartan 150 mg group (n=38), and 109.9±3.8 in the Irbesartan 300 mg group (n=37). GFR measurements at visits 3 and 24 months were lower than those values obtained at baseline in all groups. The decrease in GFR was numerically larger, though not statistically significant, in the Irbesartan groups than in the Placebo group (Table 7).

Table 7. Mean (±SEM) Percentage Change in Glomerular Filtration Rate (mL/min/1.73 m²) (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Group	Visit Month	N	GMPC ±SEM	Difference with Placebo		
				Estimate	95% CI	p-Value
Placebo	3	37	-2.6±2.1			
	24	32	-8.9±2.0			
Irbesartan 150 mg	3	38	-3.2±2.1	-0.67	(-6.70, 5.76)	0.83
	24	31	-10.0±2.5	-1.10	(-7.85, 6.14)	0.76
Irbesartan 300 mg	3	37	-2.3±2.3	0.27	(-5.86, 6.80)	0.93
	24	33	-12.1±2.2	-3.41	(-9.91, 3.55)	0.32

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 13.4.1A. GMPC=Geometric Mean Percent Change]

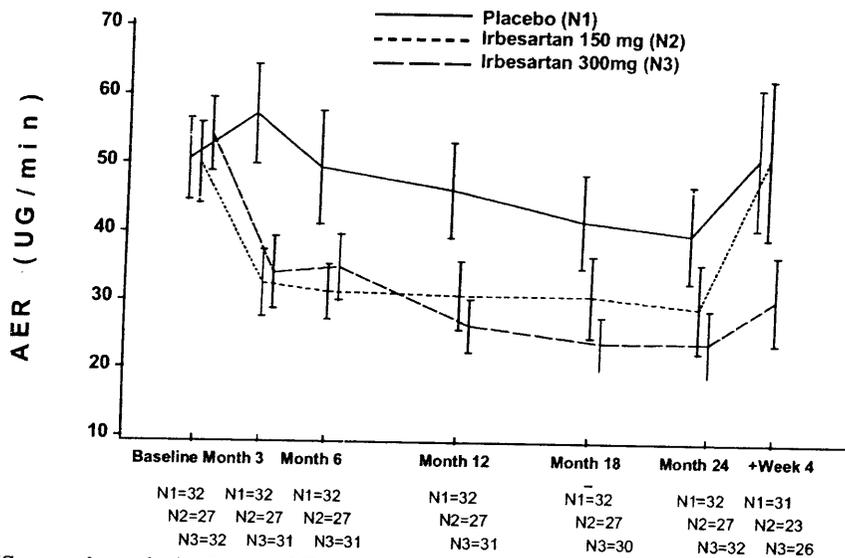
Four weeks after study drug and concomitant antihypertensive medications were discontinued at month 24, GFR increased slightly in all groups but the mean values remained below baseline values and were not statistically different from each other (see Appendix, Individual Study Reviews). The urinary albumin excretion rate increased in all three groups to the following mean (±SD) values: 51.1 (±10.2), 51.0 (±11.6) and 30.4 (±6.4) (µg/min) in Placebo, Irbesartan 150 mg and Irbesartan 300 mg groups, respectively (Figure 5). Values that did not differ significantly from each other (F statistic (2,77)= 1.97; p=0.1).¹⁴ At +week 4, MAP was not significantly different between groups.

¹² Similar results were obtained when examining mean changes in estimated creatinine clearance NDA 20-757, Protocol EFC2481, Table 10.2.2.1.

¹³ For SeSBP and SeDBP the reader is referred to NDA 20-757, Clinical Study Report Protocol EFC2481, Tables 10.2.1.1B and 10.2.1.1C.

¹⁴ Sponsor's analysis, see Appendix, Individual Study Reviews.

Figure 5. Mean (\pm SD) Change in AER (μ g/min) Over Time: GFR Sub-Study and its Extension



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Figure 13.4.2.]

INTEGRATED REVIEW OF SAFETY

This Integrated Review of Safety delineates the safety profile of Irbesartan in hypertensive subjects with type 2 diabetic renal disease who received doses up to 300 mg daily. Safety data obtained from the two placebo- and active-controlled studies, IRMA 2 and IDNT, provided the basis for this characterization.

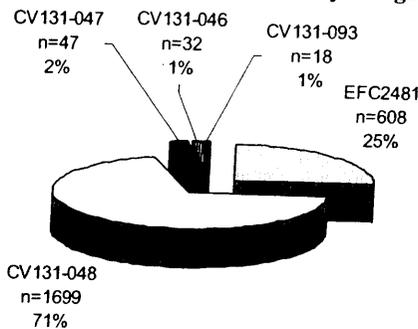
In the evaluation of the safety of Irbesartan, the Medical Reviewer primarily used the electronic archive supplied by the sponsor with the submission of NDA 20-757/S-021. In addition to reviewing the data contained in the Integrated Summary of Safety, the Medical Reviewer evaluated the results provided for the individual studies as needed. The approach used to characterize the safety profile of Irbesartan in this population consisted of examination of the entire clinical database for deaths, discontinuations, and serious adverse events, as well as an analysis of the routinely collected safety data (i.e., treatment emergent adverse events, laboratory findings, vital signs, and ECG data).

Two thousand four hundred and four hypertensive patients with type 2 diabetic nephropathy¹⁵, were exposed to study drugs in five completed clinical studies: 2307 were exposed to study drugs in the two main efficacy/safety studies IRMA 2 and IDNT, the remaining 97 subjects were exposed to study drugs in the supportive studies CV131-047 (IDNT pilot study), and CV131-046 and CV131-093 (renal hemodynamic studies) (Figure 6).

Of the 2404 subjects participating in the clinical development program for Irbesartan, 1071 subjects were exposed to Irbesartan. Seventy seven percent (n=825) of the subjects received Irbesartan for one year and 42.2% (n=452) were treated with Irbesartan for 2 years or longer, at doses of 75, 150, or 300 mg. In the two main efficacy/safety studies EFC2481 (IRMA 2) and CV131-048 (IDNT) a total of 979 subjects were exposed to Irbesartan with a mean duration of exposure of 620 and 815 days, respectively.

¹⁵ Except for 8 normal healthy subjects who participated in Protocol CV131-046.

Figure 6. Number and Percentage of Subjects Exposed to Study Drugs in All Completed Studies



[Sponsor's analysis. Source: NDA 20-757/S-021, Integrated Summary of Safety, Figure 1.1.]

The baseline demographic characteristics and baseline measures for all exposed subjects in studies IRMA 2 and IDNT are summarized in the Integrated Summary of Efficacy and in detail in the individual study reviews. In essence, the studies differ demographically from each other mainly in the duration of diabetes. Subjects randomized to the IDNT study had a longer history of disease and thus more advanced diabetic nephropathy, i.e., overt nephropathy (serum creatinine ≥ 1.5 mg/dL and urine protein excretion ≥ 900 mg/24 hours), than those subjects enrolled in IRMA 2.

Deaths: There were 255 reported deaths in the IDNT study, 90 (16.0%) in the Placebo group, 86 (14.9%) in the Irbesartan group, and 79 (14.1%) in the Amlodipine group.¹⁶ Overall, the incidence for the different causes of deaths is comparable among the treatment groups. Death occurred at a low frequency and similarly between Irbesartan-exposed subjects and placebo-exposed subjects in IRMA 2. A total of 17 deaths were reported, however one subject died during the placebo lead-in period and never received study drug. Five subjects died in the Placebo group, and 11 subjects died in the Irbesartan groups, 3 subjects were treated with Irbesartan 150 mg and 8 subjects received Irbesartan 300 mg.

Serious Adverse Events: In the IDNT study, 1082 subjects experienced at least one serious adverse event. The overall incidence of serious adverse events by treatment group was as follows: 64.5% in the Placebo group, 62.0% in the Irbesartan group, and 64.6% in the Amlodipine group. Subjects in the Irbesartan group had less events of increased serum creatinine in comparison to those subjects receiving Placebo or Amlodipine. One hundred and nine subjects experienced serious adverse events during double-blind treatment in the IRMA 2 study; the frequency of occurrence was slightly higher in placebo-treated subjects (22.8%) compared to subjects treated with Irbesartan 150 mg (15.8%) and Irbesartan 300 mg (15.0%). There were no major differences among the groups in the rate of serious adverse events when evaluated by adjudicated term.

Discontinuations Due to Adverse Events: In both studies few adverse events leading to drug withdrawal were reported in each category, thus it is not feasible to draw conclusions with any degree of certainty. It is worth to mention however that subjects receiving Amlodipine in the IDNT study had a numerically higher rate of edema and heart failure as compared to subjects in the Placebo or Irbesartan groups.

Clinical Adverse Events: In the IDNT study Irbesartan-treated subjects, in comparison to subjects receiving placebo had a higher incidence of dizziness (24.8% vs. 19.7%), orthostatic dizziness (12.8% vs. 9.4%), and hypotension (11.3% vs. 9.1%), as well as dyspepsia/heartburn (12.7% vs. 10.5%), and diarrhea (17.7% vs. 14.7%). Anemia was also more often reported by subjects treated with Irbesartan than by those subjects in the Placebo group (9.1% vs. 7.1%). However, decreased hemoglobin was reported with less frequency by Irbesartan-treated subjects than by subjects in the placebo group (1.7% vs. 3.8%). In the IRMA 2 study the fact that few adverse events were reported significantly curtails interpretation of the data on incidence rates.

¹⁶ There is a discrepancy for the total number of death reported by the sponsor in the Integrated Summary of Safety and the IDNT study.

Notwithstanding, in comparison to placebo-treated subjects, subjects receiving Irbesartan had a higher incidence of dizziness and diarrhea.

Laboratory Adverse Events: In the IDNT study, the most common treatment-emergent laboratory adverse event associated with treatment with Irbesartan was increased serum potassium, 134 (23.2%) subjects in the Irbesartan group vs. 53 (9.4%) placebo-treated subjects. Of note, “there were 16 subjects adjudicated by the Clinical Management Committee who discontinued due to persistent hyperkalemia, 11 were in the Irbesartan group, three were in the Amlodipine group, and two were in the Placebo group.” Slightly more Irbesartan-treated subjects had serum glucose decreased than subjects receiving Placebo did (14.2% vs. 11.5%). Decreased hemoglobin was reported with less frequency by Irbesartan-treated subjects than by subjects in the placebo group (1.7% vs. 3.6%). Increased serum creatinine was detected slightly more often in Irbesartan-treated subjects than in subjects receiving Placebo. A low incidence of treatment-emergent laboratory adverse events, during and up to 14 days post double-blind therapy, observed in all treatment groups in the IRMA 2 study precludes a valid conclusion. Nevertheless, review of the data failed to uncover major differences in the rates of laboratory adverse events among the groups.

ECG and Vital Signs: Alterations in ECG’s parameters, in the IRMA 2 study, occurred with similar frequency across all treatment groups with the exception of PR and QRS, which occurred with greater frequency in the Irbesartan 300 mg group. QT changes were reported with similar frequency in the Irbesartan and placebo groups. There were not significant differences in vital signs and/or ECG’s reported by in patients randomized to the IDNT study.

Drug abuse with Irbesartan: To date, there has been no evidence from clinical studies or from post-marketing surveillance that Irbesartan has a potential for drug abuse.

Drug-Drug Interactions: The sponsor also evaluated drug-drug interaction safety data for selected therapeutic classes including: antihyperglycemics, antihypertensive agents, aspirin/antiplatelet, and NSAIDs/analgesics. Review of the data on drug-drug interactions failed to discern any specific safety concern other than what is already known about the safety profile of Irbesartan.

DOSING, REGIMEN, AND ADMINISTRATION ISSUES

IRMA 2 is the only dose-response trial submitted by the sponsor where the effect of two different doses of Irbesartan (150 and 300 mg) on the progression of albuminuria to “clinical proteinuria” was evaluated. While daily administration of 150 mg of Irbesartan had no effect, treatment of hypertensive subjects with type 2 diabetes and microalbuminuria with Irbesartan 300 mg once a day significantly delayed the occurrence of clinical proteinuria, no beneficial effect was observed on GFR. The IDNT study tested only the high dose, Irbesartan 300 mg given daily significantly increased the time to doubling of serum creatinine, as compared with Placebo or Amlodipine. Based on the above results, if Avapro® (Irbesartan) is approved for the treatment of hypertensive subjects with diabetic nephropathy due to type 2 diabetes, 300 mg daily should be the recommended dosage regimen. There are no new issues concerning the administration of Irbesartan.

USE IN SPECIAL POPULATIONS

Over three-fourth of the subjects evaluated in the IRMA 2 and IDNT trials were white males under 65 years of age. Females, subjects >65 years of age, as well as Hispanics, Native Americans, and Blacks were significantly underrepresented in both trials and subjects within pediatric age groups were not randomized to the studies. The aforementioned facts preclude a tenable analysis or comment on the use of Irbesartan in special populations.

CONCLUSIONS AND RECOMMENDATIONS

A. CONCLUSIONS

Efficacy: The IDNT study demonstrated a treatment benefit for Irbesartan in hypertensive patients with advanced diabetic nephropathy due to type 2 diabetes (a relative risk reduction of 20%, $p=0.0234$ vs. Placebo and a relative risk reduction of 23%, $p=0.0064$ vs. Amlodipine). This treatment benefit is explained solely by a delay in the time to doubling of serum creatinine, since Irbesartan failed to affect ESRD or mortality. Urinary excretion rates for albumin and protein declined to a greater extent in the Irbesartan group ($p<0.001$, except for months 42 and 48) than in either the Placebo or Amlodipine groups. Noteworthy, the Irbesartan group had significantly lower blood pressures than the Placebo group did. Adjustment for differences in blood pressure control is not feasible at present because quantification of the relationship between blood pressure and progression of renal disease due to diabetes is unknown. It is important to underscore that even though the Amlodipine group had blood pressures similar to the Irbesartan group throughout the trial, Amlodipine provided no treatment benefit to this patient population.

The results from the IRMA 2 trial, a non-IND study, indicated that treatment of hypertensive subjects with type 2 diabetes and microalbuminuria with Irbesartan 300 mg significantly delayed the occurrence of clinical proteinuria (a relative risk reduction of 70%, $p=0.004$ vs. Placebo). A discrepancy between the groups in the control of blood pressure, similar to that noted in the IDNT study was observed in this trial. The GFR-Sub-Study was significantly underpowered and point assessments took place too soon after study drug and concomitant antihypertensive medications were discontinued. These deficiencies in study design rendered the results uninterpretable.

Safety: The safety profile of Irbesartan that emerged from the IDNT and IRMA 2 studies in hypertensive subjects with early or advanced diabetic renal disease due to type 2 diabetes mellitus is analogous to the safety delineated already for subjects with hypertension. Irbesartan was well tolerated and was in general safe; there are no new safety concerns.

In conclusion, in both trials a treatment effect was demonstrated for Irbesartan. The studies were not well-controlled in that dissimilar degrees of blood pressure control were achieved.¹⁷ The evidence of effectiveness is based on surrogate measures of clinical benefit, i.e., doubling of baseline serum creatinine and a pre-specified change in urinary albumin excretion rate. The FDA currently does not regard “proteinuria” as a validated surrogate endpoint. From a regulatory point of view, therefore, the IRMA 2 trial cannot be considered as a confirmatory study but rather as a “supportive” trial. Thus, although the observed changes in urinary albumin/protein excretion rate might help to understand, in part, the mechanism of action of Irbesartan treatment, they should not weigh in the regulatory decision. A risk-benefit analysis indicates that Irbesartan is associated with a treatment benefit without significant safety risks. Hence, the regulatory issue to resolve is whether and why a single study using a surrogate endpoint (the magnitude of the effect is small) with a marginal p-value ($p=0.0234$)¹⁸ and without “confirmatory evidence,” is sufficient for approval.

B. RECOMMENDATIONS

It is the Medical Reviewer’s judgment that the evidence of effectiveness provided in this efficacy supplement is not overwhelming but is sufficient to support approval. The IDNT trial even though was designed as a single study, actually tested two hypotheses, not only whether Irbesartan will be better than Placebo but also whether it will be better than Amlodipine. To reiterate, the IDNT study demonstrated a treatment benefit for Irbesartan in hypertensive patients with advanced diabetic nephropathy due to type 2 diabetes (a relative risk reduction of 20%, $p=0.0234$ vs. Placebo and a relative risk reduction of 23%, $p=0.0064$ vs. Amlodipine).

¹⁷ Dissimilar degrees of blood pressure control were also observed in the pivotal study that constituted the basis for the approval of captopril for the treatment of patients with renal disease due to type 1 diabetes mellitus.

¹⁸ Currently, the Division of Cardio-Renal Drug Products requires for approval two trials with the primary endpoint tested at a p-value = 0.05 or one trial with in patients with a p-value = 0.00125.

The recommendation is that Avapro® (Irbesartan) be approved for the treatment of hypertensive subjects with renal disease due to type 2 diabetes.

APPENDIX

C. Other Relevant Material

Not applicable.

D. Individual Study Reviews

1. PROTOCOL CV131-048 (IDNT, Irbesartan Diabetic Nephropathy Trial)¹⁹

INVESTIGATIONAL PLAN

This study examined the effect of Irbesartan on morbidity and mortality in hypertensive subjects with type 2 diabetes²⁰ and diabetic nephropathy. The long-term effect of 300 mg Irbesartan on the progression of renal disease was compared to placebo or the calcium channel blocker Amlodipine.

Study Design: This clinical trial had a multinational, multicenter, randomized, double blind, placebo- and active-controlled, and force-titration design. The study consisted of the following periods: Screening (up to 3 weeks), Enrollment (7 to 14 days), Titration (8 weeks), and Maintenance (21-57 months). Subjects were randomized (1:1:1) to regimens of Irbesartan or Amlodipine or placebo.

The study drug was administered once daily initially at the following dosage Irbesartan 75 mg or Amlodipine 2.5 mg or placebo (Level I). At the end of Week 2, the dose of study drug was increased to Irbesartan 150 mg or Amlodipine 5 mg or placebo once daily in all subjects as tolerated (Level II) and further increased to Irbesartan 300 mg or Amlodipine 10 mg or placebo at the end of Week 4 in all subjects as tolerated (Levels III).²¹

With the exception of ACE inhibitors, angiotensin II receptor antagonists and calcium channel blockers use of adjunctive antihypertensive agents was permitted throughout the trial in order to maintain blood pressure within the pre-specified target.²² Management of type 2 diabetes included dietary recommendations and oral hypoglycemic or insulin therapy.

Compliance was defined as ingestion of at least 80% of prescribed study drug and was verified each time study drug was dispensed "by capsule count and reviewing treatment intake at each study visit with the subject".

The reason for study drug discontinuation was adjudicated by the Clinical Coordinating Center.

Routine clinical and laboratory evaluations, during the maintenance period, were carried out every three months.

¹⁹ For a complete description of this study's protocol the reader is referred to NDA 20-757, Clinical Study Report CV131-048.

²⁰ Subjects with type 2 diabetes by clinical history who qualify under either A) not requiring insulin and at least one of the following: hyperglycemia requiring treatment with an oral hypoglycemic agent or history of fasting plasma glucose \geq 140 mg/dl on two occasions or fasting C-peptide level \geq the normal level of the local laboratory, or B) requiring insulin and at least one of the following: time between diagnosis of type2 diabetes and insulin use $>$ one year or fasting C-peptide level \geq the normal level of the local laboratory.

²¹ To allow for titration to the highest-tolerated dose, discontinuation of antihypertensive medications was advised between randomization and Week 4.

²² SeSBP \leq 135 mmHg and SeDBP \leq 85 mmHg, or for subjects with SeSBP $>$ 145 mmHg at the Screening visit, the target decrease in SeSBP was a least 10 mmHg; the maximum allowable SeSBP was 160 mmHg.

Study Population: Men and women between 30 and 70 years of age²³ with hypertension²⁴ (SeSBP >135 mmHg and/or SeDBP >85 mmHg) and type 2 diabetes and diabetic nephropathy (24-hour urine protein excretion \geq 900 mg and serum creatinine between 1.0 and 3.0 mg/dl in women and 1.2 and 3.0 mg/dl in men) were evaluated.²⁵

Efficacy Variables²⁶: The primary outcome measure was defined as time from randomization until the first confirmed occurrence of a doubling of a baseline serum creatinine, end-stage renal disease (ESRD; defined as renal transplantation or need for dialysis or serum creatinine equal to or greater than 6.0 mg/dl) or death (all-cause mortality).

The secondary outcome measure was defined as time from randomization until the first occurrence of cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurologic deficit attributed to stroke, or above-the-ankle amputation.

The tertiary outcome measure was defined as time from randomization until the first occurrence of cardiovascular death, nonfatal myocardial infarction, unplanned coronary artery revascularization procedure, heart failure requiring hospitalization or therapy with an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, permanent neurologic deficit attributed to stroke, above-the-ankle or below-the-ankle amputation, or unplanned peripheral artery revascularization procedure.

Safety: Evaluation of the safety of Irbesartan was based upon the assessment of adverse events, and “clinically important” changes in ECG and routine safety laboratory parameters. A Data Safety Monitoring Committee (DSMC) periodically reviewed unblinded efficacy and safety results.²⁷

Statistical Methods: The sponsor calculated the sample size based on “the primary efficacy comparison of Irbesartan vs. placebo. To achieve 90% power for detecting a reduction of 26% in total incidence rate for the primary composite endpoint, using the log-rank test at the two-sided alpha level of 0.05, it was determined to be necessary to randomize 520 subjects per group, which would project a total of 316 first events in the Irbesartan and placebo groups combined.” Furthermore, the sponsor anticipated “that there would be a negligible 1% rate of loss to follow up.” Analyses of efficacy variables would be carried out using the “All Randomized Subjects” data set.

According to the sponsor, “the study was expected to have a two year enrollment period and a two year follow up after the last subject enrolled, for an average follow up of three years.”

RESULTS

Interim monitoring and Analysis: The Data Safety Monitoring Committee reviewed unblinded safety and efficacy results periodically throughout the trial.

Amendments²⁸: The original protocol, dated 3 November 1995, was amended three times.

²³ <30 years of age in subjects with biopsy-proven diabetic nephropathy.

²⁴ In either an untreated subject or one receiving antihypertensive medication.

²⁵ For a complete description of this study’s inclusion and exclusion criteria the reader is referred to NDA 20-757, Clinical Study Report CV131-048 pages 062-064.

²⁶ All efficacy events, including hospitalizations, were adjudicated by an Outcome Confirmation and Classification Committee, an independent, non-BMS entity.

²⁷ According to the sponsor, “because these interim analyses were planned in advance, the protocol specified that the final comparison of Irbesartan vs. placebo in the primary composite endpoint would use an alpha adjusted for multiple comparisons. Such adjustment reduces the alpha for the primary comparison to 0.0477 (two sided).”

²⁸ NDA 20-757, Protocol CV 131-048, Appendix 5.1A.

Amendment 1, introduced on 14 February 1997, described “an optional sub-study of timed overnight urinary albumin measurement in European sites.”

Amendment 2 (dated ?) introduced the following modifications to the protocol:

- Calcium channel blockers were not to be started once a subject was enrolled in the trial. However, the use of calcium channel blockers was permitted during the Screening and Enrollments periods, if the Investigator believed the drug was essential to maintain adequate blood pressure control.
- A more rapid titration schedule was permitted in subjects with uncontrolled hypertension.
- Subjects were eligible for enrollment if creatinine clearances fell below the lower prescribed limits (≤ 80 mL/min in women and ≤ 90 mL/min in men). The qualifying 24-hour urine protein excretion was reduced from 1000 to 900 mg.
- Clarification of the statistical analysis and methodology.

Amendment 3, dated 24 February 2000, modified the protocol as follows:

- Clarifications of the treatment of hyperkalemia and the administration of antihypertensive medications in the morning of the 12-month visits.
- The definition of a SAE had been clarified in compliance with internal BMS standards of Operating Procedures.
- Additional codes for hospitalization were added to Protocol Appendix E at the request of the Outcome Committee to improve classification, and the definition of baseline serum creatinine in Appendix H. The DSMC recommended the projected time frame for subject recruitment be extended by approximately one year to achieve the required number of randomized subjects.
- The DSMC recommended to the Executive Committee that the administrative close of the trial occur on 31 Dec 2000 (making the maintenance period between 21 and 57 months). Subjects were asked to return for a final close out visit between 01 Nov 2000 and 31 Dec 2000. Study endpoints were to be collected until the administrative close, 31 Dec 2000.

Protocol Violations: Important protocol violations²⁹ were documented pre- and post randomization in a large number of patients.³⁰ However, “all randomized subjects were included in the intent to treat efficacy analysis dataset, whether or not a subject had a significant protocol violation.”

Unblinding: Three subjects on Irbesartan 75 mg daily were unblinded during the double-blind portion of the trial.³¹

- Subject 167/005 experienced supraventricular tachycardia (149 bpm), worsening CHF, and postural hypotension, causing concern about the possibility of reoccurrence of decompensation. The treating physicians felt they could not proceed with appropriate IV therapy until they knew which study drug the subject had been taking, thus avoiding over-treatment.
- Subject 253/001 discontinued double-blind therapy after experiencing a CVA, followed by hypertensive crisis (BP 233/112 mmHg), at which time the Investigator felt the need to know what she had been taking in order to treat her current condition.
- Subject 480/003 was unblinded because the Investigator felt the need to know if other antihypertensive medications should be substituted after the subject experienced a mild TIA.

Study Population: A total of 1715 subjects were randomized into the clinical trial. The study population was predominantly composed of white (72.4%) males (66.5%) under the age of 65 years (72.9%) with a mean BMI of 30.8%. The mean duration of diabetes was 14.8 years and 57.8% of the subjects had used insulin prior to entering the study. The mean baseline seated systolic and diastolic blood pressures were 159.1 mmHg and 86.9 mmHg, respectively.

²⁹ NDA 20-757, Protocol CV 131-048, Table S.7.3A.

³⁰ NDA 20-757, Protocol CV 131-048, Table S.7.3B.

³¹ NDA 20-757, Protocol CV 131-048, Tables S.12.3C and S.12.4B.

A history of cardiovascular disease was present in 45.4% of the randomized subjects, and 44.1% received ACE inhibitors prior to randomization. Besides a history of hypertension and nephropathy which were the study entry criteria, edema (30.1%), NYHA Class II (20.8%), and symptoms of claudication (leg pain walking 20.5%) were among the most common cardiovascular conditions reported at randomization. Sixty-seven percent and 47.7% of the subjects had a history of retinopathy and neuropathy, respectively, at randomization.

Fifteen percent of the subjects had a history of albuminuria while 86.7% of the subjects had a history of proteinuria at randomization. The mean serum creatinine and creatinine clearance were 1.6 mg/dl and 57.7 mL/min/1.73m², respectively. Mean urinary albumin and protein excretion rates were 2700 and 4144 mg/24 hr, respectively. Urinary albumin excretion rate ranged from 0.027 to 22.9 g/24 hr in the Placebo group, from 0.042 to 30.2 g/24 hr in the Irbesartan group, and from 0.13 to 15.1 g/24 hr in the Amlodipine group. And the urinary protein excretion rate ranged from 0.39 to 54.9 g/24 hr in the Placebo group, from 0.47 to 47.3 g/24 hr in the Irbesartan group, and from 0.31 to 20.2 g/24 hr in the Amlodipine group.

Overall, based on a comparison of the means, there were no large imbalances among the treatment groups in the main baseline demographic characteristics, and blood pressure and laboratory measures (Table 1A).

Table 1A. Summary of Baseline Demographic Characteristics, Blood Pressure and Laboratory Measures for All Randomized Subjects.

Subject Characteristics	Placebo N=569 (%)	Irbesartan N=579 (%)	Amlodipine N=567 (%)
Gender Male	70.8	65.3	63.3
Female	29.2	34.7	36.7
Race White	72.9	75.6	68.6
Black	13.7	10.9	15.3
Hispanic	4.6	4.8	5.1
Asian/Pacific Islander	4.7	4.1	6.0
Other	4.0	4.5	4.9
Age (Mean±SD; years)	58.3±8.2	59.3±7.1	59.1±7.9
<65	72.8	74.4	71.4
≥65	27.2	25.6	28.6
SeSBP (Mean±SD; mmHg)	158±20	160±19	158±19
SeDBP (Mean±SD; mmHg)	86±10	86±11	87±10
Body Mass Index (Mean±SD)	30.5±5.8	31.0±5.5	30.9±5.9
Duration of Diabetes (Mean±SD; years)	15.0±7.8	15.4±8.5	13.8±7.7
Insulin Use Prior to Study	58.9	56.8	57.7
HbA _{1c} (Mean±SD; %)	8.1±1.7	8.1±1.7	8.1±1.7
History of CV Disease	43.8	47.7	44.8
Prior ACE inhibitors Use	45.7	43.7	42.9
Serum Creatinine (Mean±SD; mg/dl)	1.7±0.5	1.6±0.5	1.6±0.5
Creatinine Clearance (Mean±SD; mL/min/1.73m ²)	57.7±28.9	56.2±24.8	59.3±29.8
*Urinary Albumin Excretion rate (Mean±SD; mg/24 hr)	1937±1691	1941±1673	1820±1550
*Urinary Protein Excretion rate (Mean±SD; mg/24 hr)	3087±2496	3051±2383	2878±2251
Total Cholesterol (Mean±SD; mg/dl)	227±64	229±54	227±55
LDL Cholesterol (Mean±SD; mg/dl)	141±48	144±47	141±43

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Tables 8.3B and 8.3C. *Geometric mean.]

Disposition of Subjects: A total of 1715 subjects were randomized at 209 study sites,³² from 27 countries including the United States, and Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland,

³² No subjects were randomized at 37 sites, and site 129 was an administrative site. NDA 20-757, Protocol CV 131-048, Table S.4.

France, Germany, Hong Kong, Hungary, Israel, Italy, Malaysia, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Singapore, Spain, Sweden, Taiwan and the United Kingdom. The sponsor grouped these countries into four regions: Europe, North America, Latin America, and South East Asia/Australia/New Zealand. The distribution of patients by region is presented in Table 2A below. Of the 1715 randomized subjects, sixteen subjects who were randomized never received study drug, 563 received Placebo, 577 received Irbesartan and 559 received Amlodipine.

Table 2A. Distribution of Patients by Region

Region	Total N=1715 n(%)	Amlodipine N=559 n(%)	Irbesartan N=577 n(%)	Placebo N=563 n(%)	Non-Rand N=16 n(%)
Europe	810 (47.2)	264 (47.2)	274 (47.5)	264 (46.9)	8 (50.0)
North America	592 (34.5)	188 (33.6)	204 (35.3)	196 (34.8)	4 (25.0)
Latin America	147 (8.6)	49 (8.8)	49 (8.5)	46 (8.2)	3 (18.7)
Aust./N.Z./S.E. Asia	166 (9.7)	58 (10.4)	50 (8.6)	57 (10.1)	1 (6.2)

[FDA's analysis. Source: NDA 20-757/S-021, Protocol CV131-048 dataset, file demog.xpt.]

Of the 1715 subjects randomized, sixteen subjects randomized into the trial did not receive study drug. There were 408 subjects who discontinued the study, and eight subjects were lost to follow-up (Table 3A).

Table 3A. Disposition of Subjects

Subject Disposition	N (%)
Randomized	1715 (100)
Did not receive drug	16 (0.9)
Treated	1699 (99.1)
Discontinued from study drug ^a	408 (23.8)
Complete double-blind ^b	1291 (75.3)
Lost to follow-up	8 (0.5)
Completed final follow-up at study	1283 (74.8)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV131-048, Figure 8.1. ^aAll discontinued subjects were under follow-up until the end of the trial, except the eight subjects who were lost to follow-up. ^bNumber of subjects completing double-blind study drug including subjects who reached the primary composite endpoint.]

The sixteen subjects who were randomized but never received study drug and the reasons for not starting study drug are summarized in Table 4A. Eight subjects were randomized to Amlodipine, 2 were randomized to Irbesartan and the remaining 6 subjects were randomized to Placebo.

Table 4A: Subjects Who Were Randomized But Never Received Study Drug

PID	Study Drug	Reason For Not Starting Study Drug
105/006	Amlodipine	Subject refused study drug.
137/008	Amlodipine	Subject withdrew consent.
144/005	Placebo	Subject never returned for visit.
175/009	Amlodipine	Subject died shortly after randomization. Never took study drug.
187/006	Irbesartan	Subject died shortly after randomization. Never took study drug.
188/013	Amlodipine	Subject died shortly after randomization. Never took study drug.
236/005	Irbesartan	Subject withdrew consent.
404/004	Placebo	Subject refused study drug.
415/007	Amlodipine	Subject withdrew consent.
426/002	Placebo	Subject refused study drug.
441/008	Amlodipine	Subject died prior to randomization visit. Never took study drug.
442/003	Amlodipine	Subject refused study drug. Subject later died.
456/025	Placebo	Subject had an SAE shortly after randomization. Started on an ACEI and could not start study drug. Subject later died.
493/004	Placebo	Subject too ill to start study drug. Died shortly after randomization.
505/003	Placebo	GP advised subject not to begin study drug due to dyspnea. Subject later died.

520/009	Amlodipine	Subject withdrew consent.
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[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 8.1A and Sponsor’s response to FDA request dated October 10, 2001.]

Eight subjects were lost to follow-up, four subjects were receiving Irbesartan 75 mg, an two subjects each were treated with Amlodipine 2.5 mg or Placebo (Table 5A).

Table 5A. Subjects Who Were Lost to Follow Up

PID CV131048-	Study Drug	Age (years)	Sex	Race	Duration of Diabetes (years)
430-9	Placebo	62	Female	White	27
430-12	Placebo	58	Female	White	17
400-3	Irbesartan 75 mg	70	Male	White	15
422-6	Irbesartan 75 mg	67	Male	White	7
422-10	Irbesartan 75 mg	64	Male	White	9
497-17	Irbesartan 75 mg	50	Female	White	6
430-10	Amlodipine 2.5 mg	63	Male	White	7
437-11	Amlodipine 2.5 mg	54	Male	White	20

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV131-048 dataset, file demog.xpt.]

Four hundred and eight (23.8%) subjects withdrew from the study. The number of patients who discontinued the clinical trial was similar among the groups, Placebo 140 subjects (24.63%), Irbesartan 135 subjects (23.3%), and Amlodipine 133 subjects (23.4%). Table 6A describes the reason for discontinuation by treatment group. As compared with Placebo twice as many patients receiving Irbesartan or Amlodipine “discontinued regularly scheduled visits”. More patients in the Placebo group were discontinued because of inability to control blood pressure than in the Irbesartan or Amlodipine groups. Persistent hyperkalemia caused a greater number of patients receiving Irbesartan (8.1%) to withdraw from the study than subjects treated with Placebo (1.4%) or Amlodipine (2.2%).

Table 6A. Subjects who Discontinued Study Drug for Any Reason but Reaching Primary Composite Endpoints During Double-Blind Therapy

Reason for Discontinuation	Placebo N=140 n(%)	Irbesartan N=135 n(%)	Amlodipine N=133 n(%)
Discontinued regularly scheduled visits	11 (7.8)	19 (14.0)	19 (14.2)
Early creatinine rise	1 (0.7)	0 (0.0)	0 (0.0)
Inability to control BP	17 (12.1)	9 (6.6)	3 (2.2)
Other	4 (2.8)	1 (0.7)	0 (0.0)
Other adverse event	38 (27.1)	45 (33.3)	50 (37.5)
Persistent hyperkalemia	2 (1.4)	11 (8.1)	3 (2.2)
Poor compliance	3 (2.1)	1 (0.7)	0 (0.0)
Protocol violation	3 (2.1)	1 (0.7)	1 (0.7)
Required therapy with prohibited medications	40 (28.6)	34 (25.1)	45 (33.8)
Withdrawal of written consent/pt request	21 (15.0)	14 (10.3)	12 (9.0)

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 8.1B.]

The term “Discontinued regularly scheduled visits” was adjudicated by the Clinical Management Committee as a reason for discontinuation in forty-nine subjects. Adjudication of the reason for discontinuation by this Committee superseded the investigator’s reason for study drug discontinuation. Table 7A provides the investigator’s reasons for study drug withdrawal for these 49 subjects as recorded on the CRF pages 300/301. According to the sponsor, “of the 14 subjects [listed below] who were considered Lost To Follow Up (LTFU) by the investigators, 3 of the subjects (422/006, 422/010 and 437/011) were true LTFU and are included in

[Table 7A. Subjects Who Were Lost to Follow Up]. The other 11 LTFU subjects were contacted by the site prior to the end of the study and not really considered to be LTFU.”³³

Table 7A. Reasons for Study Drug Discontinuation (“Discontinued Regularly Scheduled Visits”) by Investigator’s Term by Treatment Group

Site/Subject	Treatment Group	Investigator's comments*
133/002	Placebo	Subject request to discontinue.
141/004	Placebo	Subject decided study was "inconvenient".
160/004	Placebo	Transportation issue.
172/006	Placebo	Lost to follow-up; unable to contact.
202/002	Placebo	Subject requested d/c; Clinic is too far and they do not want to transfer.
206/001	Placebo	Subject in nursing home; unable to keep appointments or take medications.
221/001	Placebo	Subject request.
235/006	Placebo	Subject lost to follow up.
235/008	Placebo	Subject refused to continue after CABG.
424/001	Placebo	Unable to attend clinic visits.
429/008	Placebo	Subject lost to follow up.
102/004	Irbesartan	Subject lost to follow up, certified letter sent and returned unclaimed.
105/007	Irbesartan	Subject moved to Puerto Rico; was supposed to be followed up there but never went to clinic in Puerto Rico.
133/003	Irbesartan	Transportation issues; presumed lost to follow up has not returned phone calls or responded to certified letter.
141/009	Irbesartan	Subject request.
153/001	Irbesartan	Subject refused to come in for scheduled visits.
153/016	Irbesartan	Subject moved; refused to return for follow-up visits; unable to contact by phone or mail.
158/010	Irbesartan	Subject moved to Mexico to care for ill family member.
160/005	Irbesartan	Subject moved to California.
174/009	Irbesartan	Lost to follow up.
202/008	Irbesartan	Lost to follow up.
207/004	Irbesartan	Subject moved.
422/006	Irbesartan	Lost to follow-up.
422/010	Irbesartan	Lost to follow up.
456/019	Irbesartan	Subject failed to attend clinic appointments.
463/005	Irbesartan	Lost to follow up; not able to contact patient.
482/004	Irbesartan	Subject began taking an ACE-I.
494/003	Irbesartan	Subject non-compliant with study medication and procedures.
501/001	Irbesartan	Subject wanted to be treated at home.
519/004	Irbesartan	Subject cannot attend clinic visits.
102/011	Amlodipine	Withdrew Consent.
107/007	Amlodipine	Subject move o another state.
108/003	Amlodipine	Subject discontinued due to family and job related stresses.
123/007	Amlodipine	Lost to follow up.
133/001	Amlodipine	Transportation problems and constipation.
140/010	Amlodipine	Does not have time to come in for study visits.
141/001	Amlodipine	Lost to follow up.
173/015	Amlodipine	Primary care physician decided to stop drug.
222/002	Amlodipine	Serious Adverse Event.
224/007	Amlodipine	Primary care physician advised subject against study.
235/005	Amlodipine	Subject refuses to come in for appointments.
410/003	Amlodipine	Based on a query response for the site - Subject did not want to come in every 3 months to hospital. He lives 20km away.
419/002	Amlodipine	Difficulties in attending clinic visits.
422/001	Amlodipine	Subject lost to follow up.
429/013	Amlodipine	Subject cannot attend clinic visits.
431/004	Amlodipine	Subject denies being sick enough to be eventually dialyzed. Left France and moved to Italy.

³³ Source: NDA 20-757, Protocol CV 131-048, Sponsor’s response to FDA request dated October 17, 2001.

437/011	Amlodipine	Subject lost to follow up.
457/006	Amlodipine	Discontinued Regularly Scheduled Visit.
457/011	Amlodipine	Subject lost to follow up.

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Sponsor's response to FDA request dated October 17, 2001, Table 1. *From CRF pages 300/301.]

The discrepancy between investigators and the Clinical Management Committee in the adjudication of LTFU³⁴ for the aforementioned 19 subjects is further clarified by the sponsor in Table 8A, i.e., the 8 subjects who were LTFU and the remaining 11 subjects who were "contacted or found prior to the end of the study by the site or private investigator". According to the sponsor, for these eleven subjects "a vital status CRF page was completed. The vital status CRF page captured the endpoint of death or ESRD, but did not capture the endpoint of doubling of serum creatinine which would have required a study visit to obtain laboratory values. Subjects 202/008 and 457/011 reached the primary endpoint, death and ESRD, respectively, and were included by the sponsor in the efficacy dataset.

Table 8A. Status of all 19 LTFU Subjects by Investigator Term and/or by BMS Algorithm

Subject	Treatment group	Number of Days on Treatment	Last Dose of Study Drug	Last Date of Contact	Contacted by:	Date of Draw of Baseline Serum Creatinine	*Serum Creatinine	Date of Draw of Last Serum Creatinine	*Serum Creatinine	Doubling of Serum Creatinine	ESRD	Death
235/006	Pb	Unk	Unk	9-Mar-01	Private Inv.	7-Jul-98	1.5	14-Sep-99	1.5	ND	Unk	Alive
429/008	Pb	172	10-Aug-98	30-Nov-00	Phone	20-Feb-98	1.5	25-May-98	1.5	ND	No	Alive
430/009	Pb	541	12-Nov-98	12-Dec-98	LTFU	21-May-97	2.2	04-Aug-98	2.5	ND	Unk	Unk
430/012	Pb	368	16-Nov-98	16-Nov-98	LTFU	14-Nov-97	1.0	16-Nov-98	1.0	ND	Unk	Unk
102/004	Irb	727	21-Sep-98	9-Mar-01	Private Inv.	25-Sep-96	1.5	26-Oct-98	1.6	ND	Unk	Alive
174/009	Irb	Unk	?-Dec-98	15-Nov-00	Phone	28-Jan-98	1.4	12-Nov-98	1.8	ND	No	Alive
202/008	Irb	663	3-Mar-00	3-Nov-00	Death Certif.	11-Mar-98	1.1	22-Oct-99	1.2	ND	No	Dead
463/005	Irb	201	23-Feb-98	16-Nov-00	Phone Call	7-Au -97	0.8	23-Feb-98	0.8	ND	No	Alive
172/006	Pb	10	29-Oct-98	9-Mar-01	Other	20-Oct-98	1.3	29-Oct-98	1.0	ND	Unk	Alive
422/006	Irb	483	25-Oct-98	26-Oct-98	LTFU	30-Jul-97	2.0	26-Oct-98	3.5	ND	Unk	Unk
422/010	Irb	253	20-Jul-98	21-Jul-98	LTFU	10-Nov-97	2.0	21-Jul-98	3.2	ND	Unk	Unk
400/003	Irb	195	7-Jun-97	25-Feb-98	LTFU	25-Nov-96	2.8	01-Sep-97	4.1	ND	Unk	Unk
497/017	Irb	266	1-Dec-98	21-Dec-98	LTFU	11-Mar-98	1.1	21-Dec-98	1.4	ND	Unk	Unk
123/007	Am	Unk	?-May-97	13-Dec-00	Phone	1-Nov-96	1.4	12-Feb-97	1.3	ND	No	Alive
141/001	Am	57	17-Sep-96	9-Mar-01	Phone	23-Jul-96	1.6	17-Sep-96	1.5	ND	Unk	Alive
422/001	Am	945	28-Sep-99	2-Nov-00	Phone	26-Feb-97	1.6	28-Sep-99	2.5	ND	No	Alive
457/011	Am	32	23-Jan-98	2-Dec-00	Outpatient	23-Dec-97	2.0 ^a	23-Jan-98	2.0	ND	ESRD	Alive
437/011	Am	358	20-Apr-99	20-Apr-99	LTFU	28-Apr-98	1.2	20-Apr-99	1.3	ND	Unk	Unk
430/010	Am	2	29-May-97	4-Jul-97	LTFU	28-May-97	1.8	28-May-97	1.8	ND	Unk	Unk

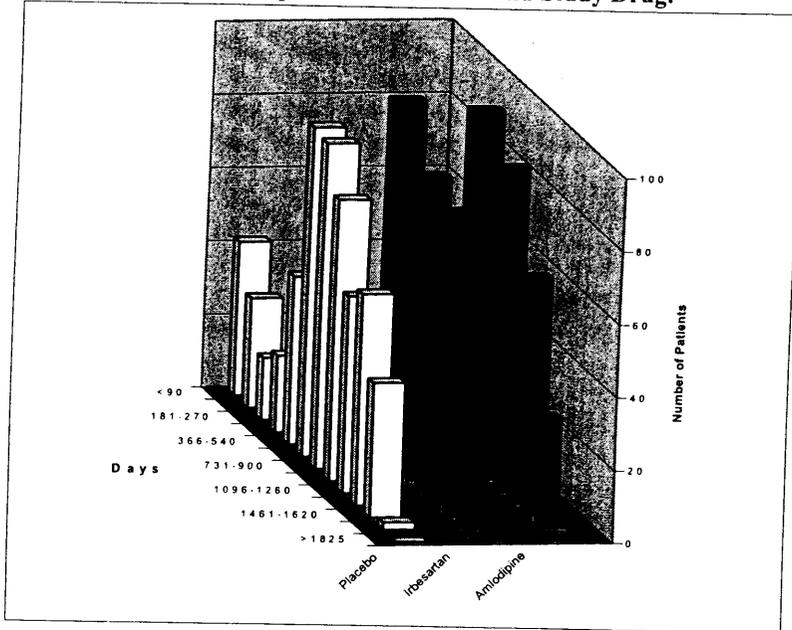
[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Sponsor's response to FDA request dated November 13, 2001, Table 1. Pb = Placebo. Irb = Irbesartan. Am = Amlodipine. *mg/dl. Unk = unknown is recorded on the Vital Status Form. ND = 0 data is recorded on the Vital Status Form. ^aCalculated by BMS in the serum creatinine database sent to FDA.]

Extent of Exposure: The sponsor defined the extent of exposure to study drug "as the number of days that a subject took study medication during the double-blind period." The mean duration of treatment was 793 days for placebo, 815 days for Irbesartan and 773 days for Amlodipine.

The extent of exposure to study drug was similar among the treatment groups. Three hundred seventeen (55.7%) patients in the Placebo group, 325 (56.1%) patients receiving Irbesartan and 302 (53.3%) patients on Amlodipine were exposed to study drug for at least 731 days (Figure 1A).

³⁴ Definition of LTFU: Investigator determination of "lost to follow up" was left to the discretion of the investigator. The algorithm used by BMS and thus the CMC "was not predefined in the protocol" (NDA 20-757, Sponsor's response to FDA request dated November 13, 2001).

Figure 1A. Extent of Exposure to Double-Blind Study Drug.

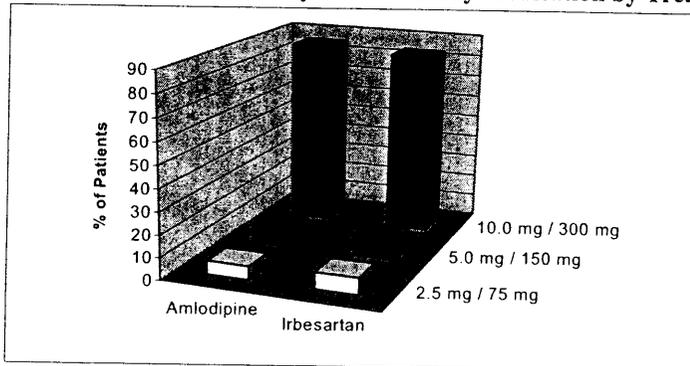


[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 9.1A. Note: total treatment days included from the first to the last of the double-blind treatment. Days during study drug interruptions (see below) were not subtracted from the exposure calculations.]

Seven subjects (Placebo n=1, Irbesartan n=3 and Amlodipine n=3) had prolonged interruption (≥ 5 months) of study treatment due to treatment emergent adverse events (n=4), treatment with prohibited medication (n=2) or out of the country (n=1).³⁵

Final total daily dose of study drug: Figure 2A depicts percentage of patients and the final total daily dose of study drug by treatment group. Over eighty percent of the patients receiving either Irbesartan or Amlodipine were receiving the maximum proposed dose as the final total daily dose, i.e., 300 mg and 10 mg daily, respectively. The mean total daily dose was 269.32 mg and 9.11 mg for Amlodipine and Irbesartan, respectively.

Figure 2A. Final Total Daily Dose on Study Medication by Treatment Group



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 9.1C.]

³⁵ NDA 20-757, Protocol CV 131-048, Table 9.3.

Treatment Compliance: According to the sponsor, compliance was defined as ingestion of at least 80% of prescribed study drug. That level of compliance was achieved in 77% of placebo-treated subjects, in 81% of subjects receiving Irbesartan, and in 79% of subjects in the Amlodipine group. Thus, drug compliance was adequate and similar among the groups.

Concomitant Medications: The most common and relevant concomitant medications at screening-enrollment and during double-blind treatment are summarized in Table 9A.

Loop diuretics, β - and α,β -blockers, and peripheral and central adrenergic blockers were the most common antihypertensive drugs used throughout the study. The use of antihypertensive medications rose significantly from the screening-enrollment period to the double-blind period. Insulin treatment was needed by over two-third of the subjects during the double blind period. Lipid lowering medications (i.e., HMG CoA reductase inhibitors), and aspirin and antiplatelet agents were also commonly used therapies.

Table 9A. Concomitant Medications at Screening and During Double-Blind Treatment

Drug Class	Placebo N=563		Irbesartan N=577		Amlodipine N=559	
	Screen. %	Double- Blind %	Screen. %	Double- Blind %	Screen. %	Double- Blind %
AntiHTN:						
β -Blockers	28.1	52.0	27.2	43.5	25.4	40.6
Perip. Vasodilators	9.1	23.4	8.7	19.6	10.7	19.1
Perip. Adren. Blockers	18.3	31.3	17.3	26.7	15.4	23.1
Cent. Adren. Blockers	19.7	40.0	21.3	35.5	17.7	29.9
α,β -Blockers	24.9	48.1	25.8	43.2	28.3	41.5
Ca Inhibitors	22.2	8.3	24.6	7.1	19.7	8.6
ACE Inhibitors	11.9	6.7	11.1	6.2	9.5	8.6
Angiotensin II Recept. Antag.	0.4	1.6	2.1	2.3	0.9	2.5
Loop Diuretics	41.2	71.9	43.3	67.2	38.8	73.5
Thiazides	14.7	35.2	16.5	31.4	16.5	34.3
Cardiac Meds.:						
Digitalis	4.6	6.9	5.2	6.8	4.8	7.3
Nitrates	11.0	19.2	11.8	18.7	12.7	21.8
Insulin & Antiglycemics:						
Insulin	58.6	70.0	56.0	67.1	56.4	67.8
Metformin/pheformin	20.4	26.1	21.5	26.0	21.6	27.7
Sulfonylureas	34.5	39.8	38.1	42.8	36.7	41.5
Lipid Lowering Meds.:						
Fibric Acid Deriv.	8.9	13.3	8.8	13.3	10.7	14.3
HMG CoA Reductase Inh.	25.9	42.6	29.8	47.7	24.7	42.8
Other Meds:						
Anticoagulants	3.0	8.9	4.0	9.0	2.7	8.4
Aspirin/antiplatelets	30.0	45.6	33.4	46.8	30.2	42.0
NSAIDs/Analgesics	12.3	35.9	11.1	36.7	13.2	34.5
Anti-ulcer	11.2	24.7	9.2	23.1	11.8	22.2
Antiinfectives	7.8	48.8	7.3	43.8	8.1	46.9
Anxiolytics/Antidepressants	11.2	22.4	10.7	46.9	11.3	22.9

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Tables S9.4A and S9.4B.]

Efficacy Results: The primary outcome measure was a composite endpoint consisting of time to the first confirmed occurrence of a doubling of a baseline serum creatinine, end-stage renal disease (ESRD; defined as renal transplantation or need for dialysis or serum creatinine equal to or greater than 6.0 mg/dl) or death (all-cause mortality). The primary analysis for the renal composite endpoint consisted of Irbesartan vs. Placebo (Table 10A) and the secondary analysis was the comparison of Irbesartan vs. Amlodipine (Table 12A). In the Irbesartan group 189 (32.6%) subjects reached the primary endpoint vs. 222 (39.0%) subjects in the Placebo group.

A statistically significant treatment benefit for Irbesartan, i.e., Irbesartan significantly increased the time to the primary composite endpoint of doubling of creatinine, ESRD, or all cause mortality, as compared with Placebo was demonstrated (Table 10A). Treatment with Irbesartan resulted in a relative risk reduction of 20% vs. Placebo (p=0.0234). Of interest, the difference in the median time to a primary event between the Irbesartan group and the Placebo group is 116 days, i.e., four months.³⁶

Table 10A. Primary Endpoint Comparison: Irbesartan vs. Placebo

Event	Placebo N=569 n(%)	Irbesartan N=579 n(%)	Relative Risk		
			Estimate	95% Confidence Interval	p-Value
Primary Composite Endpoint	222 (39.0)	189 (32.6)	0.80	0.66-0.97	0.0234

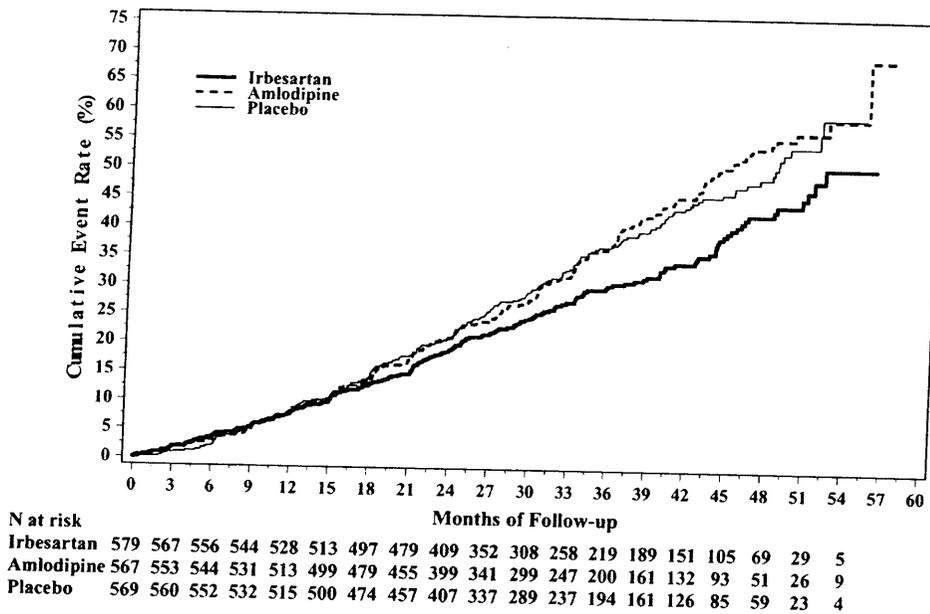
[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.1.1A, and FDA's analysis by Dr. John Lawrence, HFD-710.]

Figure 2A depicts the Kaplan-Meier curves of the cumulative event rate for the primary composite endpoint over the course of the trial for all the groups evaluated. The curve representing the Irbesartan group indicates that subjects in this group had significantly fewer events than the subjects in either the Placebo or Amlodipine curves (p=0.0234 and p=0.0064, respectively).³⁷ This effect appears to become discernible approximately after 18 months of treatment with Irbesartan and to continue over the length of the study.

³⁶ FDA's analysis by Dr. John Lawrence, HFD-710.

³⁷ Sponsor's analyses.

Figure 2A. Kaplan-Meier Estimates of Primary Composite Endpoint for All Randomized Subjects.



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.1.1A.]

The number of subjects reaching, i.e., first occurrence, any of the components of the composite primary endpoint is as follows: a total of 111 (50.0%)³⁸ and 82 (43.4%) subjects reached the doubling of serum creatinine in the Placebo and Irbesartan groups, respectively (Table 11A). Forty-seven (21.2%) placebo-treated subjects and 43 (22.7%) subjects receiving Irbesartan reached ESRD.³⁹ The Placebo and Irbesartan groups each had 64 subjects who die during the study (28.8% and 33.9%, respectively).

Table 11A. Individual Components of Primary Composite Endpoint

EVENT		Placebo		Irbesartan	
		n		n	
Death		64		64	
ESRD*	Transplant	47	0	43	0
	Dialysis		22		24
	SC ≥ 6 mg/dL no dialysis/transplantation		25		19
Doubling Serum Creatinine (not ESRD)		111		82	
Total		222		189	

[Sponsor's analysis and FDA's analysis by Dr. John Lawrence, HFD-710. *There were 55 subjects (24 Placebo-treated, 16 Irbesartan-treated and 15 Amlodipine-treated subjects) who had ESRD and doubling of the baseline serum creatinine occurring on the same day. These subjects are included in ESRD category and are not counted towards doubling of serum creatinine.]

Information was requested from the sponsor by the FDA on four subjects for whom, according to the event data set EVENT_A, the following serum creatinine events were recorded (times are post randomization): 00158 00010 reached 6.0 after 789 days, 00166 00002 reached double baseline after 1482 days, 00179 00007 reached double baseline after 933 days, and 00422 00008 reached double baseline after 1179 days, but Dr. Lawrence (FDA, HFD-710) was unable to verify these creatinine events from the electronic laboratory data file SC. What

³⁸ Percent of the total number of events.

³⁹ Of note, 24 (10.8%) and 16 (8.5%) reached ESRD and doubling of serum creatinine the same day in the Placebo and Irbesartan groups, respectively.

follows is a detailed description of the endpoint data in each case identified by Dr. Lawrence as provided by the sponsor:

Subject 158-10 (Irbesartan group): This subject ceased to take study drug after only a short time, and ceased coming in for visits as well. In following up on all subjects during the study close out procedures, it was ascertained that the subject received dialysis on 1/14/00. From the subject's medical records, it was determined that the subject had previously attained a serum creatinine (SCr) of 6.0 mg/dL on 9/7/99 (789 days). Based on medical records and the vital status page the OC adjudicated an ESRD (due to reaching a serum creatinine of 6.0 mg/dl) at 9/7/99. The SCr value giving rise to this event is not included in the electronic lab data file because it came from the records of subject's personal physician.

Subject 166-2 (Placebo group): This subject's average baseline for SCr was 1.6, obtained from the unscheduled visit preceding C00 (1.8) and the C00 visit itself (1.4). The subject had a SCr of 2.8 at 1482 days, which was not a doubling in comparison to the baseline of 1.6. It appears, however, that the site believed the baseline to be 1.4, possibly because of confusion with the value of the sole reading at C00, and initiated the protocol-defined process. The Rush lab confirmed the doubling using their values (3.1 over 1.5), and the Outcomes Committee adjudicated it as a doubling event.

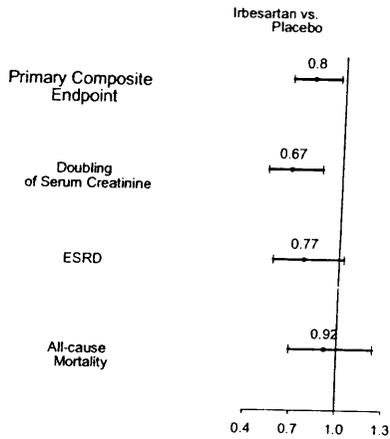
Subject 179-7 (Amlodipine group): This subject's average baseline for SCr was 2.5, obtained from the unscheduled visit preceding C00 (2.5) and the C00 visit itself (2.5). The subject discontinued early in the course of therapy and received study medication from 10/25/96 to 12/22/96. According to a letter of 2/15/01 from the investigator to BMS, the last dose of study medication was 12/22/96 and his last clinic visit was 1/10/97. However his medical course was monitored by way of medical records during the study. His renal function gradually worsened over time and on 5/13/99 a routine lab test (outside laboratory) revealed a creatinine of 6.0 mg/dL and on a follow up lab, done on 6/10/99, the creatinine was 5.1 mg/dL. Over the next six months, this subject's renal function continued to deteriorate. By 12/7/99 the subject was started on hemodialysis. At the end of the study, the vital status page of CRF (p.125.01) revealed that the subject was alive and still on dialysis. There is no SCr data in the electronic lab file except for a short time after randomization. Based on medical records and the vital status page the OC adjudicated a doubling of serum creatinine at 5/13/99 (933 days) and ESRD at 12/7/99. While 5/13/99 could have been considered the date of ESRD as well (because of reaching 6.0), the Committee chose to assign the date of dialysis, 12/7/99, to ESRD instead. The SCr value giving rise to the doubling is not included in the electronic lab data file because it came from the records of the subject's personal physician.

Subject 422-8 (Placebo group): This subject had a baseline average for SCr of 2.4, obtained from readings of 2.4 at B00 and 2.4 again at C00. On 10/25/00, the subject had a SCr reading of 4.7. Though this was not quite twice baseline, it nonetheless appears the site regarded it as a doubling. (Note: expressed in pmol/L these readings were 210 and 419, still not a doubling.) The Rush lab confirmed and the Outcomes Committee adjudicated a doubling on 10/25/00 (1179 days; 5.3 over 2.6 - Rush values).

The relative risk with 95% confidence intervals for the primary efficacy measure and its components, for the Irbesartan vs. Placebo comparison, is shown in Figure 3A. The relative risk for Irbesartan vs. Placebo was 0.67 (95% CI: 0.52-0.87) for doubling of serum creatinine, 0.77 (95% CI: 0.57-1.03) for ESRD, and 0.92 (95% CI: 0.69-1.23) for all-cause mortality. Irbesartan treatment had a significant relative risk reduction of 33% in doubling of serum creatinine compared with placebo ($p=0.0027$).⁴⁰

⁴⁰ Sponsor's analyses.

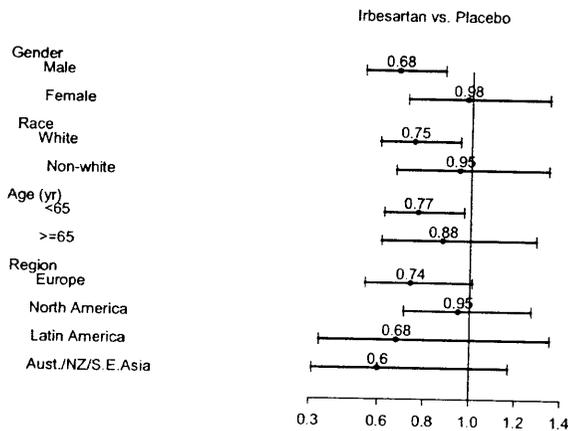
Figure 3A. Primary Efficacy Endpoint and Its Components: Relative Risk with 95% Confidence Intervals.



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.1.1B.]

Figure 4A illustrates the primary efficacy endpoint results of the subgroup analyses for gender (male, female), race (white, non-white), age (<65 years, ≥65 years), and regions (Europe, North America, Latin America, and South East Asia/Australia/New Zealand). The interpretation of these results is hindered by the lack of statistical power, study population demographics, i.e., white (72.4%) males (66.5%) under the age of 65 years (72.9%), as well as regional demographics differences, i.e., in the North American region 47.3% of the randomized subjects were non-white vs. 6.3% of the randomized subjects in Europe.

Figure 4A. Primary Efficacy Endpoint: Relative Risk with 95% Confidence Intervals within Subgroups.



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.1.2A.]

The secondary analysis for the renal composite endpoint was the comparison of Irbesartan vs. Amlodipine (Table 12A). Irbesartan treatment resulted in a relative risk reduction of 23% vs. Amlodipine (estimate 0.77, 95% CI: 0.63-0.93, p=0.0064). This treatment effect in favor of Irbesartan was primarily driven by a significant relative risk reduction of 37% in doubling of serum creatinine compared with Amlodipine (estimate 0.63, 95% CI: 0.49-0.81, p=0.0003).

Table 12A. Primary Endpoint Comparison: Irbesartan vs. Amlodipine

Event	Amlodipine N=567 n(%)	Irbesartan N=579 n(%)	Relative Risk		
			Estimate	95% Confidence Interval	p-Value
Primary Composite Endpoint	233 (41.1)	189 (32.6)	0.77	0.63-0.93	0.0064
Components*:					
Doubling of Serum Creatinine	144 (61.8)	98 (51.8)			
ESRD	35 (15.0)	27 (14.2)			
All-Cause Mortality	54 (23.2)	64 (33.8)			

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.1.1B. FDA's analysis by Dr. John Lawrence. Percent of total number of events.]

Of note, "the trial was designed to attain equal degrees of blood pressure control within all three treatment groups by use of target blood pressure goals", i.e., SeSBP ≤135 mmHg and SeDBP ≤85 mmHg. Blood pressure decreased from baseline in all groups. However, review of the data for mean change from baseline over time or LOCF⁴¹, on seated systolic, diastolic and mean arterial blood pressure reveals that blood pressure control was markedly dissimilar between the groups (Tables 13A, 14A and 15A, and Figure 5A). In particular, the control (i.e., reduction) of blood pressure in Irbesartan-treated subjects was significantly better than that achieved in the Placebo group.

Table 13A. Treatment Comparisons at LOCF: Seated Systolic Blood Pressure All Randomized Subjects

Group (N)	Baseline Mean	On-Therapy Mean	Change from Baseline Mean	Treatment Comparisons Irbesartan vs. Comparator		
				Estimated Difference	95% CI	p-Value
Placebo (N=565)	158.2	145.2	-13.1	-4.0	-6.3 -1.8	<0.001
Irbesartan (N=576)	160.4	141.8	-18.6			
Amlodipine (N=562)	158.5	141.9	-16.7	-0.7	-2.9 1.6	0.566

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table S.10.4.4A2.]

Table 14A. Treatment Comparisons at LOCF: Seated Diastolic Blood Pressure All Randomized Subjects

Group (N)	Baseline Mean	On-Therapy Mean	Change from Baseline Mean	Treatment Comparisons Irbesartan vs. Comparator		
				Estimated Difference	95% CI	p-Value
Placebo (N=565)	86.9	79.3	-7.6	-2.2	-3.4 -1.0	<0.001
Irbesartan (N=576)	86.8	77.0	-9.7			
Amlodipine (N=562)	87.0	76.4	-10.6	0.7	-0.5 1.9	0.249

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table S.10.4.4B2.]

⁴¹ LOCF: Last observation carry forward.

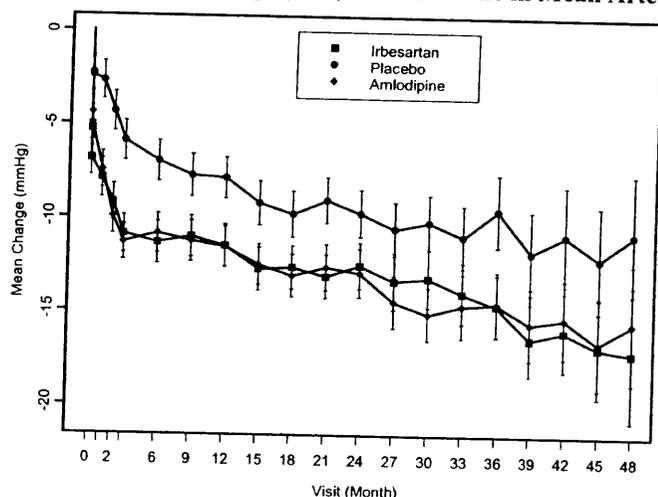
Table 15A. Treatment Comparisons at LOCF: Seated Mean Blood Pressure All Randomized Subjects

Group (N)	Baseline Mean	On-Therapy Mean	Change from Baseline Mean	Treatment Comparisons Irbesartan vs. Comparator		
				Estimated Difference	95% CI	p-Value
Placebo (N=565)	110.7	101.3	-9.4	-2.8	-4.2 -1.4	<0.001
Irbesartan (N=576)	111.3	98.6	-12.7			
Amlodipine (N=562)	110.8	98.2	-12.6	0.3	-1.1 1.6	0.714

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table S.10.4.4B2.]

Figure 6A illustrates mean (\pm SD) change from baseline in MAP over the course of the trial for all treatment groups.

Figure 6A. Mean Change (\pm SD) from Baseline in Mean Arterial Blood Pressure



The secondary outcome measure was a cardiovascular composite endpoint defined as time to first occurrence of cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurologic deficit attributed to stroke, or above-the-ankle amputation. Statistical analyses of the data failed to demonstrate significant differences among the groups (Table 16A).

Table 16A. Secondary Cardiovascular Composite Endpoint Comparison

Event	Placebo N=569 n(%)	Irbesartan N=579 n(%)	Amlodipine N=567 n(%)	Relative Risk† Estimate (95% Confidence Interval) p-Value‡	
				Irbesartan vs. Placebo	Irbesartan vs. Amlodipine
Secondary Cardiovascular Composite	146 (25.7)	141 (24.4)	129 (22.8)	0.92 (0.73-1.15) p = 0.4537	1.05 (0.83-1.33) p = 0.6935

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.2.1A. †Determined using the Cox proportional hazards model. ‡From the long-rank test.]

The tertiary outcome measure was defined as time to first occurrence of cardiovascular death, nonfatal myocardial infarction, unplanned coronary artery revascularization procedure, heart failure requiring hospitalization or therapy with an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, permanent neurologic deficit attributed to stroke, above-the-ankle or below-the-ankle amputation, or unplanned peripheral artery revascularization procedure. The relative risk estimates and 95% confidence

intervals for the tertiary cardiovascular composite endpoint for Irbesartan vs. Placebo or Amlodipine are summarized in Table 17A.

Table 17A. Tertiary Cardiovascular Composite Endpoint Comparison

Event	Placebo N=569 n(%)	Irbesartan N=579 n(%)	Amlodipine N=567 n(%)	Relative Risk† Estimate (95% Confidence Interval) p-Value‡	
				Irbesartan vs. Placebo	Irbesartan vs. Amlodipine
Tertiary Cardiovascular Composite	185 (32.5)	172 (29.7)	161 (28.4)	0.88 (0.72-1.08) p = 0.2306	1.03 (0.83-1.27) p = 0.8026

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.2.2A. †Determined using the Cox proportional hazards model. ‡From the long-rank test.]

Other Efficacy Measures: The sponsor also investigated the effect of Irbesartan on, among others, the annual rate of change in serum creatinine, the percentage change from baseline in albumin and protein excretion rate, and HbA_{1c} levels. Table 18A summarizes the results of the mixed model analysis on the annual rate of change in serum creatinine.

Table 18A. Annual Rate of Change in Serum Creatinine-Slope (mg/dL/yr)

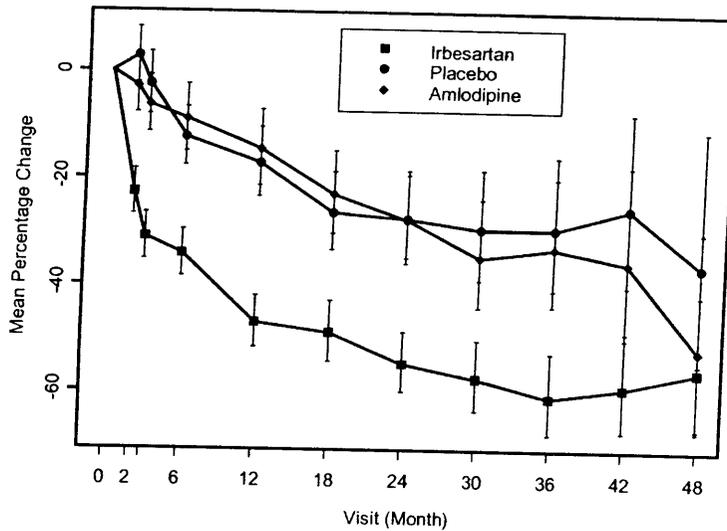
Group (N)	Estimate (95% CI)	Irbesartan vs. Placebo Estimate (95% CI) p		Irbesartan vs. Amlodipine Estimate (95% CI) p	
Placebo (N=568)	0.55 (0.49, 0.62)	-0.13 (-0.22, -0.04)	0.004	-0.12 (-0.21, -0.02)	0.013
Irbesartan (N=578)	0.42 (0.35, 0.48)				
Amlodipine (N=565)	0.53 (0.47, 0.60)				

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 10.4.1.]

Figures 7A and 8A depict the geometric mean (\pm SE) percentage change from baseline in albumin and protein excretion rate, respectively, for the length of the study. Albeit a progressive decline from baseline in the urinary excretion rates for albumin and protein occurred in all groups, the decline observed for the Irbesartan group, at most times (except for months 42 and 48), was significantly greater ($p < 0.001$) than either for Placebo or Amlodipine.⁴²

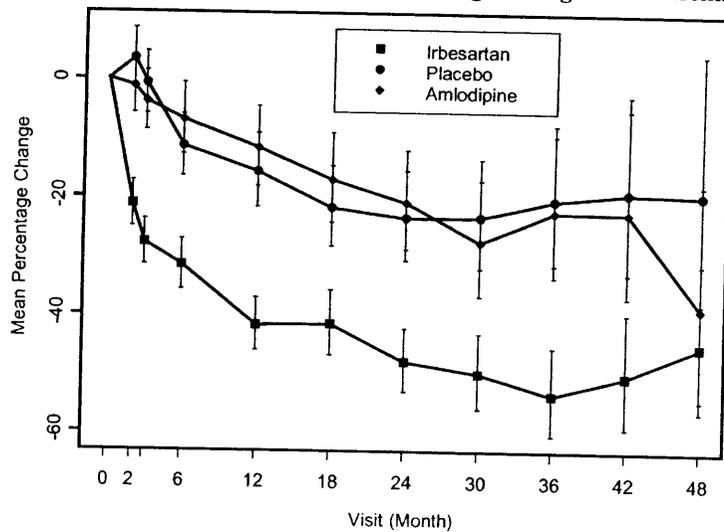
⁴² NDA 20-757, Protocol CV 131-048, Tables S.10.4.3C2 and S.10.4.3D2.

Figure 7A. Geometric Mean (\pm SE) Percentage Change from Baseline in Albumin Excretion Rate



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.4.3.C.]

Figure 8A. Geometric Mean (\pm SE) Percentage Change from Baseline in Protein Excretion Rate



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Figure 10.4.3.D.]

Diabetic control, as assessed by HbA_{1c} levels, was similar among the groups. Furthermore, the levels of HbA_{1c} did not change significantly over time in any of the treatment groups.⁴³

Pharmacokinetic/Pharmacodynamic Results: not applicable.

Safety Results: According to the sponsor, "the evaluation of safety includes all 1699 treated subjects who received at least one dose of trial medication." Table 19A summarizes the number and overall incidence of adjudicated serious adverse events, discontinuations due to adverse events and deaths for all three groups from study CV131-048. Similar incidence rates for these adjudicated outcomes were observed in all treatment groups.

⁴³ NDA 20-757, Protocol CV 131-048, Table S.10.4.3E.

Table 19A. Summary of Serious Clinical Adverse Events (as Adjudicated Outcome) During and Up to 14 Days Post Double-Blind Therapy by Treatment Group

Event	Placebo N=563 n(%)	Irbesartan N=577 n(%)	Amlodipine N=559 n(%)
Serious Adverse Event*	363 (64.5)	358 (62.0)	361 (64.6)
Discontinuations due to AE†	36 (6.4)	43 (7.5)	44 (7.9)
Death‡	90 (16.0)	86 (14.9)	79 (14.1)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV131-048, Table 12.0B. *As adjudicated outcome from the Outcome Confirmation and Classification Committee. †As adjudicated outcome from the Clinical Management Committee. ‡During and post double-blind therapy up to trial closure as adjudicated by the Mortality Committee.]

The number (%) of subjects who died during and post double-blind therapy up to study closure (adjudicated terms by the Mortality Committee) by treatment group is presented in Table 20A. There were 255 reported deaths, 90 (16.0%) in the Placebo group, 86 (14.9%) in the Irbesartan group, and 79 (14.1%) in the Amlodipine group. Overall, the incidence of the different causes of deaths is comparable among the treatment groups.

Table 20A. Number (%) of Subjects Who Died During and Post Double-Blind Therapy up to Study Closure (Adjudicated Terms) by Treatment Group

Body Systems*	Placebo N=563 n (%)	Irbesartan N=577 n (%)	Amlodipine N=559 n (%)
Cardiovascular	41 (7.3)	49 (8.5)	40 (7.2)
General	26 (4.6)	24 (4.2)	26 (4.7)
Nervous system	7 (1.2)	6 (1.0)	4 (0.7)
Renal/Genitourinary	6 (1.1)	4 (0.7)	3 (0.5)
Respiratory	3 (0.5)	2 (0.3)	3 (0.5)
Drug interaction	0	1 (0.2)	0
Endocrine/Metabolic/Electrolyte imbalance	4 (0.7)	0	0
Gastrointestinal	1 (0.2)	0	2 (0.4)
Hepatic/Biliary	1 (0.2)	0	1 (0.2)
Hematopoietic	1 (0.2)	0	0
Overall Total Subjects	90 (16.0)	86 (14.9)	79 (14.1)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 12.2. *Cause of death is reported in primary terms as adjudicated by the Mortality Committee.]

The incidence of most common adverse events (≥ 2 events) leading to discontinuation is summarized in Table 21A. Because of the few events reported in each category is difficult to draw conclusions with any degree of certainty. It is worth to mention however that subjects receiving Amlodipine had a numerically higher rate of edema and heart failure as compared to subjects in the Placebo or Irbesartan groups.

Table 21A. Most Common Discontinuations (≥ 2 Events) by Adjudicated Terms Due to Clinical Adverse Events During Double-Blind Therapy by Treatment Group

Adverse Events by Primary Term	Placebo N = 563 n (%)	Irbesartan N = 577 n (%)	Amlodipine N = 559 n (%)
Edema	7 (1.2)	4 (0.7)	14 (2.5)
Cerebrovascular accident	2 (0.4)	4 (0.7)	1 (0.2)
Increased serum creatinine	3 (0.5)	3 (0.5)	1 (0.2)
Myocardial infarction	0	3 (0.5)	1 (0.2)
Headaches	4 (0.7)	2 (0.3)	3 (0.5)
Nausea/Vomiting	3 (0.5)	2 (0.3)	2 (0.4)
Dizziness	3 (0.5)	2 (0.3)	0

Malignant neoplasm Hepatic Biliary	1 (0.2)	2 (0.3)	0
Renal failure	1 (0.2)	2 (0.3)	0
TIA	0	2 (0.3)	1 (0.2)
Angina pectoris	0	2 (0.3)	0
Cardiac rhythm disturbance	0	2 (0.3)	0
Hct/Hgb decreased	0	2 (0.3)	0
Angina Pectoris	0	2 (0.3)	0
Heart failure	1 (0.2)	1 (0.2)	5 (0.9)
Hypertension	2 (0.4)	1 (0.2)	1 (0.2)
Musculoskeletal pain	2 (0.4)	1 (0.2)	1 (0.2)
Rash	2 (0.4)	1 (0.2)	1 (0.2)
Abdominal pain	2 (0.4)	1 (0.2)	0
Orthostatic dizziness	0	1 (0.2)	2 (0.4)
Intracranial hemorrhage	2 (0.4)	1 (0.2)	0
Pulmonary Edema	2 (0.4)	1 (0.2)	0
Fatigue	6 (1.1)	0	0
Pruritus	0	0	2 (0.4)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV131-048, Table 12.4.]

The frequencies of the most serious adverse events ($\geq 1\%$) reported are shown by treatment group in Table 22A.⁴⁴ Subjects in the Irbesartan group had less events of increased serum creatinine in comparison to those subjects receiving Placebo or Amlodipine. Otherwise, no major differences among the groups seem apparent this may be the result of the small number of serious adverse events reported in each category.

Table 22A. Most Common ($\geq 1\%$) Serious Adverse Events and Cardiovascular Events by Adjudicated Terms, by Body System, During and Up to 14 Days Post Double-Blind Therapy by Treatment Group

Body System Primary Term	Number (%) of Subjects		
	Placebo N = 563	Irbesartan N = 577	Amlodipine N = 559
Cardiovascular			
Heart failure	65 (11.5)	60 (10.4)	89 (15.9)
Myocardial infarction	41 (7.3)	47 (8.1)	29 (5.2)
Hypertensive crisis	30 (5.3)	27 (4.7)	12 (2.1)
Angina pectoris	31 (5.5)	26 (4.5)	27 (4.8)
Invasive cardiac procedure	32 (5.7)	21 (3.6)	18 (3.2)
Invasive peripheral vascular procedure	22 (3.9)	21 (3.6)	22 (3.9)
Peripheral vascular disease artery	14 (2.5)	18 (3.1)	12 (2.1)
Coronary artery disease	19 (3.4)	13 (2.3)	16 (2.9)
Sudden death	16 (2.8)	12 (2.1)	8 (1.4)
Cardiac disturb rhythm	9 (1.6)	10 (1.7)	9 (1.6)
Atrial rhythm disturbance	16 (2.8)	9 (1.6)	11 (2.0)
Abnormality vascular	10 (1.8)	8 (1.4)	2 (0.4)
Conduction disorder	1 (0.2)	7 (1.2)	1 (0.2)
Edema	5 (0.9)	2 (0.3)	8 (1.4)
Endocrine/Metabolic/Electrolyte Imbalance			
Diabetes	34 (6.0)	41 (7.1)	29 (5.2)
Diabetic coma	14 (2.5)	8 (1.4)	11 (2.0)
Electrolyte abnormality	5 (0.9)	7 (1.2)	5 (0.9)
Hypoglycemic coma	6 (1.1)	6 (1.0)	8 (1.4)
Endocrine disorder	3 (0.5)	4 (0.7)	10 (1.8)
Gastrointestinal			
Abnormality GI	21 (3.7)	18 (3.1)	19 (3.4)
Gastroenteritis	8 (1.4)	5 (0.9)	6 (1.1)

⁴⁴ Of note, before the implementation of amendment 3 on February 16, 2000, both hypotension and hypertension were adjudicated under the primary term "hypertensive crisis", thus the incidence rates reported under this category did not faithfully capture the occurrence of the event.

Upper GI bleeding	2 (0.4)	5 (0.9)	8 (1.4)
Peptic ulcer	7 (1.2)	4 (0.7)	2 (0.4)
General			
Infection	40 (7.1)	46 (8.0)	49 (8.8)
Clinical Event-Other	32 (5.7)	38 (6.6)	41 (7.3)
Death	26 (4.6)	30 (5.2)	22 (3.9)
Neoplasm malignant unspecified	10 (1.8)	12 (2.1)	16 (2.9)
Trauma	6 (1.1)	6 (1.0)	10 (1.8)
Septicemia	7 (1.2)	3 (0.5)	9 (1.6)
Surgical complications	1 (0.2)	1 (0.2)	6 (1.1)
Hematopoietic			
Anemia	17 (3.0)	19 (3.3)	13 (2.3)
Hemorrhage	5 (0.9)	2 (0.3)	6 (1.1)
Hepatic/Biliary			
Gallbladder disorder	2 (0.4)	6 (1.0)	5 (0.9)
Musculoskeletal/Connective Tissue			
Orthopedic surgery	14 (2.5)	17 (2.9)	17 (3.0)
Musculoskeletal abnormality	19 (3.4)	13 (2.3)	13 (2.3)
Fracture bone	9 (1.6)	10 (1.7)	10 (1.8)
Nervous System			
Neurologic abnormality	25 (4.4)	24 (4.2)	15 (2.7)
Cerebrovascular accident	19 (3.4)	19 (3.3)	10 (1.8)
Cerebrovascular disease	6 (1.1)	12 (2.1)	4 (0.7)
TIA	17 (3.0)	12 (2.1)	9 (1.6)
Intracranial hemorrhage	4 (0.7)	6 (1.0)	0
Renal/Genitourinary			
Increased serum creatinine	107 (19.0)	73 (12.7)	120 (21.5)
Renal disease	34 (6.0)	33 (5.7)	45 (8.1)
Renal failure	17 (3.0)	17 (2.9)	20 (3.6)
Renal dialysis	6 (1.1)	9 (1.6)	12 (2.1)
UTI	5 (0.9)	4 (0.7)	6 (1.1)
Respiratory			
Pulmonary edema	12 (2.1)	14 (2.4)	18 (3.2)
Pulmonary infection	21 (3.7)	13 (2.3)	21 (3.8)
COPD	16 (2.8)	12 (2.1)	14 (2.5)
Asthma	2 (0.4)	2 (0.3)	6 (1.1)
Special Senses			
Eye surgery	17 (3.0)	12 (2.1)	10 (1.8)
Lens opacity	7 (1.2)	10 (1.7)	8 (1.4)
Abnormality retina	6 (1.1)	4 (0.7)	8 (1.4)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV131-048, Table 12.3.]

Table 23A summarizes the most common clinical adverse events ($\geq 5\%$ of subjects in any treatment group) reported during and up to 14 days post double-blind therapy.⁴⁵ In comparison to placebo-treated subjects, subjects receiving Irbesartan had a higher incidence of dizziness (24.8% vs. 19.7%), orthostatic dizziness (12.8% vs. 9.4%), and hypotension (11.3% vs. 9.1%), as well as dyspepsia/heartburn (12.7% vs. 10.5%), and diarrhea (17.7% vs. 14.7%). Anemia was also more often reported by subjects treated with Irbesartan than by those subjects in the Placebo group (9.1% vs. 7.1%). However, decreased hemoglobin was reported with less frequency by Irbesartan-treated subjects than by subjects in the placebo group (1.7% vs. 3.8%).

Table 23A. Most Common Clinical Adverse Events ($\geq 5\%$ of Subjects in any Treatment Group) Reported During and Up to 14 Days Post Double-Blind Therapy

Adverse Events	Placebo N=563 n (%)	Irbesartan N=577 n (%)	Amlodipine N=559 n (%)

⁴⁵ The incidences for all adverse events reported could be found in NDA 20-757, Integrated Summary of Safety, Table S.4.1.2.2.

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)
Orthostatic dizziness	53 (9.4)	74 (12.8)	39 (7.0)
Dyspepsia/Heartburn	59 (10.5)	73 (12.7)	53 (9.5)
Vision disturbance	71 (12.6)	67 (11.6)	69 (12.3)
Orthostatic hypotension	51 (9.1)	65 (11.3)	50 (8.9)
Dyspnea	81 (14.4)	62 (10.7)	93 (16.6)
Influenza	66 (11.7)	62 (10.7)	61 (10.9)
Abdominal pain	67 (11.9)	61 (10.6)	64 (11.4)
Periph vascular disease artery	55 (9.8)	61 (10.6)	51 (9.1)
Rash	55 (9.8)	61 (10.6)	65 (11.6)
UTI	58 (10.3)	60 (10.4)	64 (11.4)
Angina pectoris	66 (11.7)	58 (10.1)	60 (10.7)
Heart failure	60 (10.7)	57 (9.9)	77 (13.8)
Ulcer skin	52 (9.2)	56 (9.7)	52 (9.3)
Hypertension	60 (10.7)	55 (9.5)	37 (6.6)
Anemia	40 (7.1)	53 (9.2)	41 (7.3)
Constipation	55 (9.8)	52 (9.0)	45 (8.1)
Paresthesia	48 (8.5)	50 (8.7)	55 (9.8)
Pruritis	39 (6.9)	45 (7.8)	55 (9.8)
Myocardial infarction	41 (7.3)	43 (7.5)	22 (3.9)
Pharyngitis	36 (6.4)	40 (6.9)	38 (6.8)
Abnormal urination	37 (6.6)	38 (6.6)	52 (9.3)
Infection	31 (5.5)	38 (6.6)	32 (5.7)
Sleep disturbance	34 (6.0)	36 (6.2)	27 (4.8)
Disturbance eye other	39 (6.9)	35 (6.1)	31 (5.5)
Eye surgery	33 (5.9)	35 (6.1)	35 (6.3)
Depression	28 (5.0)	34 (5.9)	32 (5.7)
Muscle cramp	41 (7.3)	34 (5.9)	36 (6.4)
Tachycardia	34 (6.0)	33 (5.7)	44 (7.9)
Chest pain	43 (7.6)	32 (5.5)	28 (5.0)
Decreased appetite	29 (5.2)	29 (5.0)	21 (3.8)
Dry mouth	35 (6.2)	27 (4.7)	19 (3.4)
Pulmonary infection	38 (6.7)	27 (4.7)	28 (5.0)
Somnolence	36 (6.4)	26 (4.5)	26 (4.7)
Renal failure	16 (2.8)	22 (3.8)	30 (5.4)
Pulmonary congestion	24 (4.3)	19 (3.3)	33 (5.9)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 12.1.2A.]

The number (%) of subjects ($\geq 1\%$) with treatment-emergent laboratory adverse events during and up to 14 days post double-blind therapy by body system, primary term, and treatment regimen is presented in Table 24A. The most common treatment-emergent laboratory adverse event associated with treatment with Irbesartan was increased serum potassium, 134 (23.2%) subjects in the Irbesartan group vs. 53 (9.4%) placebo-treated subjects. Of note, "there were 16 subjects adjudicated by the Clinical Management Committee who discontinued due to persistent hyperkalemia,⁴⁶ 11 were in the Irbesartan group, three were in the Amlodipine group, and two were in the Placebo group." Slightly more Irbesartan-treated subjects had serum glucose

⁴⁶ Serum potassium ≥ 6.0 mEq/L.

decreased than subjects receiving Placebo did (14.2% vs. 11.5%). Decreased hemoglobin was reported with less frequency by Irbesartan-treated subjects than by subjects in the placebo group (1.7% vs. 3.6%). Increased serum creatinine was detected slightly more often in Irbesartan-treated subjects than in subjects receiving Placebo.

Table 24A. Number (%) of Subjects (≥ 1%) With Treatment-Emergent Laboratory AEs During and Up To 14 Days Post Double-Blind Therapy By Body System, Primary Term, and Treatment Regimen

Body System/Primary Term	Placebo N=563 n(%)	Irbesartan N= 577 n(%)	Amlodipine N=559 n(%)
Endocrine/Metabolic/ Electrolyte Imbalance			
Serum Potassium Increased	53 (9.4)	134 (23.2)	45 (8.1)
Serum Glucose Decreased	65 (11.5)	82 (14.2)	73 (13.1)
Serum Glucose Increased	73 (13.0)	62 (10.7)	81 (14.5)
Increased Uric Acid	20 (3.6)	20 (3.5)	23 (4.1)
Increased Cholesterol	24 (4.3)	16 (2.8)	21 (3.8)
Increased Triglycerides	5 (0.9)	12 (2.1)	6 (1.1)
Serum Sodium Decreased	4 (0.7)	6 (1.0)	3 (0.5)
Serum Potassium Decreased	19 (3.4)	5 (0.9)	24 (4.3)
Decreased Calcium	7 (1.2)	3 (0.5)	2 (0.4)
Increased Lipids	7 (1.2)	2 (0.3)	8 (1.4)
Hematopoietic			
Decreased Hemoglobin	20 (3.6)	10 (1.7)	14 (2.5)
Glyco Hemoglob Increased	17 (3.0)	6 (1.0)	21 (3.8)
Decreased Hematocrit	6 (1.1)	5 (0.9)	6 (1.1)
Decreased Platelets	5 (0.9)	5 (0.9)	8 (1.4)
Hepatic/Biliary			
Liver Func Test Increased	17 (3.0)	22 (3.8)	23 (4.1)
Musculoskeletal/Connective Tissue			
Increased CPK	1 (0.2)	6 (1.0)	3 (0.5)
Renal/Genitourinary			
Increased Serum Creatinine	111 (19.7)	127 (22.0)	124 (22.2)
Urine RBC Increased	15 (2.7)	13 (2.3)	19 (3.4)
Increased BUN	11 (2.0)	12 (2.1)	10 (1.8)
Urine Protein Increased	7 (1.2)	4 (0.7)	7 (1.3)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 12.6.]

2. PROTOCOL EFC2481 (IRMA 2, Irbesartan MicroAlbuminuria in Type 2 Diabetes)⁴⁷

INVESTIGATIONAL PLAN

This clinical trial, a non-IND study, examined the effect of Irbesartan in reducing the progression from albuminuria to overt nephropathy in hypertensive subjects with type 2 diabetes⁴⁸ and microalbuminuria⁴⁹. The long-term effect (2 years) of 150 and 300 mg Irbesartan on the progression to clinical (overt) proteinuria⁵⁰ was compared to placebo. In a sub-study, “the effects of withdrawing the study drug and adjunctive antihypertensive medication on BP, microalbuminuria, and GFR were evaluated at the end of 2 years.”

Study Design: This study had a multinational, multicenter, randomized, double blind, placebo-controlled, and force-titration design. The study consisted of the following periods: following a 3-week single-blind placebo period (washout phase) the subjects were randomized (1:1:1) to regimens of Irbesartan 150 mg or 300 mg or placebo. For the first 2 weeks study drug was administered once daily initially at the following dosage Irbesartan 75 mg or placebo. At the end of Week 2, the dose of study drug was increased to Irbesartan 150 mg or placebo. At Week 4 subjects randomized to Irbesartan 150 mg remained on the same daily dose and those subjects allocated to 300 mg Irbesartan had their daily dose increased to 300 mg, until Month 24 in the double-blind maintenance period.

With the exception of ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium antagonists use of adjunctive antihypertensive agents⁵¹ was permitted throughout the trial in those subjects the SeBP had not responded.⁵² In addition, prohibited concomitant medications included chronic treatment with NSAIDs and oral anticoagulants. Management of type 2 diabetes included dietary recommendations and oral hypoglycemic or insulin therapy. The target diabetic control was HbA_{1c} <9.5%.

Compliance was defined as ingestion of at least 80% of prescribed study drug and was verified each time study drug was dispensed by capsule count and reviewing treatment intake at each study visit with the subject.

Of note, in the GFR sub-study, a cohort of subjects was selected from the main clinical trial to have GFR measurements at randomization, and at months 3 and 24 during the double-blind treatment period, and at the last visit of the 4-week extension after all study medication and concomitant antihypertensive medications were discontinued at visit 9 (Month 24).

Study Population: Men and women between 30 and 70 years of age with hypertension⁵³ (SeSBP >135 mmHg and/or SeDBP >85 mmHg) and type 2 diabetes and evidence of microalbuminuria (an urinary albumin excretion rate below 200 µg/minute and serum creatinine ≤1.1 mg/dl in women and ≤1.5 mg/dl in men) were studied.⁵⁴

⁴⁷ For a complete description of this study’s protocol the reader is referred to NDA 20-757, Clinical Study Report EFC2481.

⁴⁸ Subjects with type 2 diabetes by clinical history who qualify under either A) not requiring insulin and at least one of the following: hyperglycemia requiring treatment with an oral hypoglycemic agent or history of fasting plasma glucose ≥ 140 mg/dl on two occasions or fasting C-peptide level ≥ the normal level of the local laboratory, or B) requiring insulin and at least one of the following: time between diagnosis of type2 diabetes and insulin use > one year or fasting C-peptide level ≥ the normal level of the local laboratory.

⁴⁹ Overnight urinary albumin excretion rate between 20 and 200 µg/minute.

⁵⁰ Urinary albumin excretion rate >300 mg/day.

⁵¹ Recommended agents were: Loop diuretics, β-adrenergic receptor antagonists, Non-dihydropyridine Ca antagonists, central α-adrenergic receptor agonists.

⁵² SeSBP >160 mmHg and SeDBP >90 mmHg.

⁵³ In either an untreated subject or one receiving antihypertensive medication SeSBP ≤160 mmHg and/or SeDBP ≤90 mmHg.

⁵⁴ For a complete description of this study’s inclusion and exclusion criteria the reader is referred to NDA 20-757, Clinical Study Report EFC2481, pages 074-076.

Efficacy Variables-Main Study: The primary outcome measure was defined as time from randomization until the first confirmed occurrence of clinical proteinuria (defined as urinary albumin excretion rate exceeding 200 µg/minute and an increased of at least 30% from baseline at two successive evaluations).⁵⁵

The secondary endpoints were overnight urinary albumin excretion rate, von Willebrand Factor, Fibrinogen, Factor VII and Plasminogen Activator Inhibitor-1, and Lipid Profile (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and apolipoprotein).⁵⁶

Efficacy Variables-GFR Sub-Study and Its Extension: In this subset of subjects efficacy was assessed by the following variables: glomerular filtration rate⁵⁷, extracellular fluid volume, pro-renin, active renin, and angiotensin II.

Safety: Evaluation of the safety of Irbesartan was based upon the assessment of adverse events, and changes in ECG and vital signs, and routine safety laboratory parameters. The Data Safety Monitoring Committee monitored safety in the study.

Statistical Methods: Because the sponsor proposed two comparisons, Irbesartan 150 mg and 300 mg vs. placebo, on the primary endpoint (time-to-occurrence of clinical proteinuria) the sample size was calculated with an alpha level of 2.5% in place of 5%.⁵⁸ Sample size was calculated based on a 21% rate of clinical proteinuria on placebo after 2 years, a 7% rate of clinical proteinuria on one dose of Irbesartan after 2 years, a drop-out rate of 20%, a (two-tailed) type I error rate of 0.025 and equal proportions of subjects in each group. A log-rank test of equality of survival curves has a power level of 90% to detect a difference between one dose of Irbesartan and placebo when the sample size is 522 (174 subjects in each group).⁵⁹ The intent-to-treat population was used as a basis for all efficacy analyses.

The study was expected to have one-year enrollment period and a two-year follow up.

Committees: Four independent committees were established: Scientific Committee, Data Safety Monitoring Committee, Independent Statistical Center, and an Adjudication Event Committee.⁶⁰

RESULTS

Interim Monitoring and Analysis: The DSMC reviewed unblinded safety results periodically throughout the study. However, there were no interim statistical analyses of efficacy performed for this study.

Amendments⁶¹: The study protocol was amended nine times. The inclusion and exclusion criteria⁶² as well as the primary endpoint⁶³ of the main study were amended.

⁵⁵ Changed by Amendment No. 6.

⁵⁶ Changed by Amendment No. 3.

⁵⁷ GFR determination was performed by the total plasma clearance of ⁵¹Cr-EDTA using a simplified single injection method. For more information on the subject the reader is referred to NDA 20-757, Protocol EFC2481, Appendix 5.1.

⁵⁸ Bonferroni's correction.

⁵⁹ The initial planned number of randomized subjects was increased on two occasions: In June 1998, 28 selection criteria violations were highlighted (violation of inclusion/exclusion criteria). In order to maintain the planned sample size for per-protocol analysis, the target number of randomized subjects was increased to 550. In October 1998, rate of accrual of subjects in the GFR sub-study was considered too low to obtain a sufficient number of subjects in this sub-study. It was decided to continue the recruitment of subjects in the GFR sub-study. The final number of randomized subjects was increased to 611.

⁶⁰ For the responsibilities of each Committee the reader is referred to NDA 20-757, Protocol EFC2481, Table 4.0B.

⁶¹ NDA 20-757, Protocol EFC2481, Appendix 5.1.

⁶² Amendment 3 (26 June 1997).

The primary endpoint was amended as follows: Definition of overt proteinuria was changed to urinary AER > 200 µg/minute at 2 successive 6-month evaluations (Amendment No. 3). A second measurement of microalbuminuria was permitted if the first measurement met the criteria for primary endpoint (Amendment No. 6). The definition of progression to clinical proteinuria was changed to increase in urinary AER exceeding 200 µg/minute at 2 successive evaluations, and an increase in the urinary AER of at least 30% over baseline (Amendment No. 6).

Protocol Violations: Significant protocol violations were documented in 117 randomized subjects (Placebo = 35 [16.9%], Irbesartan 150 mg = 43 [21.2%], and Irbesartan 300 mg = 39 [19.4%]) during the study.⁶⁴

The sponsor closed Site 1004 because of several serious compliance and practice issues with regard to study conduct. This center had screened 10 subjects and subsequently randomized 6 subjects. The sponsor omitted data from subjects at this site from the efficacy analyses.

Unblinding: Subject ID # 7150008 (Irbesartan 150 mg) had his treatment assignment unblinded before completion of the study. The subject received treatment for two years before discontinuing study drug because of right carotid artery stenosis.

Study Population: Six hundred eleven subjects were randomized into the clinical trial. Overall, the study population was white (98%) males (74%) under the age of 65 years (77%) with a mean BMI of 30%. The mean duration of diabetes was 9.9 years, with 35% of the subjects having a history of insulin use prior to study entry. The mean baseline seated systolic and diastolic blood pressures were 153.2 mmHg and 90.1 mmHg, respectively. Baseline demographic characteristics, blood pressure and laboratory measures for all randomized subjects are summarized by treatment in Table 1B. Baseline demographic characteristics and blood pressure and laboratory measures were similar among the groups.

Table 1B. Summary of Baseline Demographic Characteristics, Blood Pressure and Laboratory Measures for All Randomized Subjects.

Subject Characteristics		Placebo N=207 (%)	Irbesartan 150 mg N=203 (%)	Irbesartan 300 mg N=201 (%)
Gender	Male	69.0	66.0	70.0
	Female	31.0	34.0	30.0
Race	White	98.0	98.0	97.0
	Black	0.0	1.0	0.0
	Oriental	1.0	0.5	0.5
	Other	1.0	1.0	3.0
Age (Mean±SD; years)	<65	58.4±8.6	58.3±7.9	57.3±7.8
	<65	70.0	74.0	78.0
	≥65	30.0	26.0	22.2
SeSBP (Mean±SD; mmHg)		153±14	153±14	153±14
SeDBP (Mean±SD; mmHg)		89±8	89±8	90±10
Body Mass Index (Mean±SD)		30.3±4.5	29.8±3.8	30.0±4.3

⁶³ Amendments 3 (26 June 1997) and 6 (23 June 1998).

⁶⁴ NDA 20-757, Protocol EFC2481, Table 7.3A.

Duration of Diabetes (Mean±SD; years)	10.5±8.5	9.7±7.1	9.5±7.1
Insulin Use Prior to Study	40.0	33.0	31.0
HbA _{1c} (Mean±SD; %)	7.2±1.6	7.3±1.7	7.0±1.7
History of CV Disease	24.2	30.5	26.4
Prior ACE inhibitors Use	34.3	40.9	43.3
Serum Creatinine (Mean±SD; mg/dl)	1.1±0.2	1.0±0.2	1.1±0.2
*Creatinine Clearance (GMean±SD; mL/min/1.73m ²)	108.9±31.3	109.4±28.3	107.7±32.1
Urinary Albumin Excretion rate (GMean±SD; µg/min)	56.4±39.5	58.6±38.3	52.8±31.4
Total Cholesterol (Mean±SD; mg/dl)	224±42	228±55	223±47
LDL Cholesterol (Mean±SD; mg/dl)	143±37	143±47	135±37

[Sponsor's analysis. NDA 20-757/S-021, Protocol EFC2481, Tables 8.3A, 8.3B, 8.3C, S.8.4C and S.8.5.C. *Estimated.]

Disposition of Subjects: Six hundred and eleven subjects were randomized into the study at 96 study sites, from 18 countries including: Argentina, Australia, Belgium, Canada, Czech Republic, France, Greece, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Scandinavia, South Africa, Spain, Switzerland, and the United Kingdom. The sponsor grouped these countries into five regions: Europe, North America, Latin America, Southeast Asia/Australia/New Zealand, and South Africa. The distribution of patients into each region is presented in Table 2B. At least 75% of the subjects were randomized in clinical sites located in Europe. Three subjects randomized to the study were discontinued before receiving study drug.⁶⁵

Table 2B. Distribution of Patients by Region

Region	Placebo N=207 n(%)	Irbesartan 150 mg N=203 n(%)	Irbesartan 300 mg N=201 n(%)
Europe	158 (76.3)	157 (77.3)	151 (75.1)
North America	11 (5.3)	8 (3.9)	10 (4.9)
Latin America	11 (5.3)	12 (5.9)	10 (4.9)
Southeast Asia/Australia/New Zealand	19 (9.2)	17 (8.4)	20 (9.9)
South Africa	8 (3.8)	9 (4.4)	10 (4.9)

[Source: NDA 20-757/S-021, Protocol EFC2481 dataset, file demog.xpt]

One hundred sixty six subjects withdrew prematurely from the study, 71 (34.3%) placebo-treated subjects, 55 (27.1%) receiving Irbesartan 150 mg, and 40 (19.9%) subjects treated with Irbesartan 300 mg (Table 3B). Three subjects discontinued before receiving study medication.⁶⁶ Overall the rate of discontinuation was numerically higher for the placebo group than for the Irbesartan groups. In particular, 13% of the subjects in the placebo group withdrew from the study due to “lack of efficacy” compared to 6.9% and 4.0% in the Irbesartan 150 mg and 300 mg groups, respectively. In addition, inability to control blood pressure led to the discontinuation of six subjects, four subjects were receiving placebo, and one each in the Irbesartan 150 mg and 300 mg groups. Of note, the rate of discontinuation from the study due to death was higher in the Irbesartan 300 mg group (4.0%) than in Placebo group (0.5%) or in the Irbesartan 150 mg group (0.5%).

⁶⁵ Subjects PID#s 2070012, 7090012, and 29030005.

⁶⁶ Subject 2070012 discontinued because of inclusion criteria violation; Subject 7090012 discontinued because of an adverse event; Subject 29030005 withdrew because of elevated urinary albumin excretion rate values, this subject was randomized before the investigator received the results.

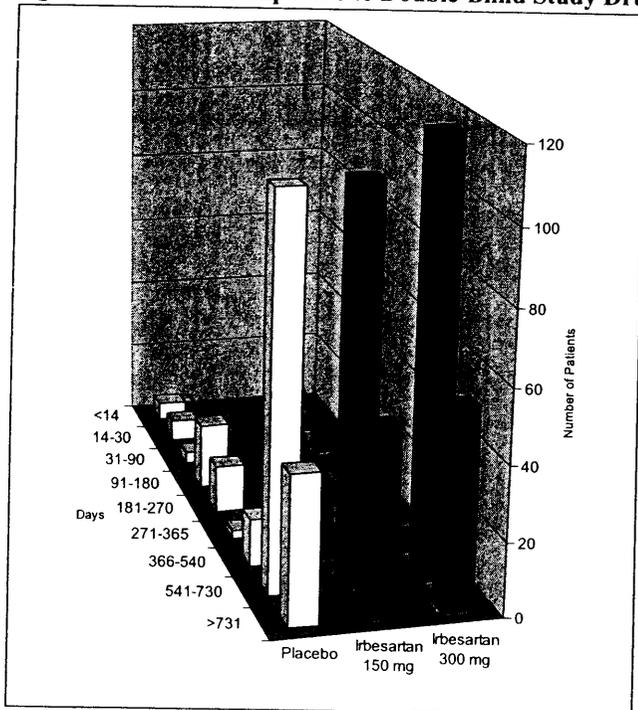
Table 3B. Reasons for Discontinuation During Double-Blind Therapy*

Reason for Discontinuation	Placebo N=207 n(%)	Irbesartan 150 mg N=203 n(%)	Irbesartan 300 mg N=201 n(%)
Adverse event	18(8.7)	19(9.4)	9(4.5)
Death	1(0.5)	1(0.5)	4(2.0)
Lack of efficacy	27(13.0)	14(6.9)	8(4.0)
Lost to follow up	0(0.0)	3(1.5)	3(1.5)
Other reason**	25(12.1)	18(8.9)	16(8.0)
Total	71(34.3)	55(27.1)	40(19.9)

[Sponsor's analysis. Source NDA 20-757/S-021, Protocol EFC2481, Table 8.1. *Main study. **Other reasons included withdrawn consent, inability to control blood pressure and center closing.]

Extent of Exposure: The extent of exposure to double-blind study drug by treatment group is depicted in Figure 1B. The percentage of patients exposed beyond 18 months to study therapy was comparable among the groups: 70.1%, 77.8% and 86% in the placebo, Irbesartan 150 mg, and Irbesartan 300 mg, respectively.

Figure 1B. Extent of Exposure to Double-Blind Study Drug by Treatment Group*



[Sponsor's analysis, NDA 20-757/S-021, Protocol EFC2481, Table 9.1A. *Exposed Subjects.]

Treatment Compliance⁶⁷: Compliance of 80% to 100% was achieved in 75.2% of placebo-treated subjects, in 82.2% of subjects receiving Irbesartan 150 mg and in 72.0% of subjects treated with Irbesartan 300 mg. Thus, overall compliance with study drug was adequate and similar among the groups. However, adverse events resulted in interruptions of study therapy in 49 subjects: 13 subjects in the placebo group, 17 subjects in the Irbesartan 150 mg group, and 19 subjects in Irbesartan 300 mg group.

⁶⁷ NDA 20-757, Protocol EFC2481, Table 9.2A.

Concomitant Medications⁶⁸: “The proportion of subjects using antihypertensive medication before the placebo run-in period was similar across all treatment groups: 120/207 (58.0%) in the Placebo group, 137/203 (67.5%) in the Irbesartan 150 mg group, and 139/201 (69.2%) in the Irbesartan 300 mg group. The most commonly used antihypertensive medications were ACE inhibitor/diuretic combinations, α -adrenoceptor blocking agents, calcium antagonists, clonidine, angiotensin II antagonist agents, and hydrazinophthalazine derivatives; these medications were used by 52.9% of all subjects across all treatment groups before the placebo run-in period. The proportion of subjects using lipid-lowering medications at study entry was similar across all treatment groups: 38/207 (18.4%) in the Placebo group, 38/203 (18.7%) in the Irbesartan 150 mg group, and 33/201 (16.4%) in the Irbesartan 300 mg group. Simvastatin was the most commonly used lipid-lowering medication, used by 5.6% of all subjects across all treatment groups at study entry. The proportion of subjects using antidiabetic medications at study entry was similar across all treatment groups: 180/207 (87.0%) in the placebo group, 171/203 (84.2%) in the Irbesartan 150 mg group, and 178/201 (88.6%) in the irbesartan 300 mg group. The most commonly used class of antidiabetic agents was oral hypoglycemic agents (biguanide, 36.2%; sulfonamide, 53.2%); insulin was used by 38.6% of placebo-treated subjects, 32.0% of Irbesartan 150 mg-treated subjects and 29.9% of Irbesartan 300 mg-treated subjects.”

“The proportion of exposed subjects who used concomitant medications during the double-blind period was similar across all treatment groups: 202/206 (98.1 %) in the Placebo group, 197/202 (97.5%) in the Irbesartan 150 mg group, and 198/200 (99.0%) in the Irbesartan 300 mg group. The most commonly used class of concomitant medications during double-blind treatment was antidiabetic therapies: 92.7% of placebo-treated subjects, 91.1% of Irbesartan 150 mg-treated subjects, and 91.5% of Irbesartan 300 mg-treated subjects. Anti-hypertensive drugs other than study medication were used in 55.3% of subjects; these concomitant medications included diuretics (24.2% of all subjects), beta-blocking agents (35% of all subjects: 19.2% cardio-selective beta-blockers and 15.8% cardio-nonselective beta-blockers) and calcium channel blockers non-dihydropyridine agents (24.2% of subjects). Other commonly used classes of concomitant medications were cholesterol-reducing agents (27.0%), antithrombic drugs (26.6%), intermittent systemic antibiotics (20.7%), and analgesics (17.3%). The use of concomitant antihypertensive agents was greater in the Placebo group than in the Irbesartan 150 mg and Irbesartan 300 mg groups (64.6%, 52.0%, and 49.0%, respectively).”

Efficacy Results: The primary outcome measure was defined as time from randomization until the first confirmed occurrence of clinical proteinuria (defined as urinary albumin excretion rate exceeding 200 μ g/minute and an increased of at least 30% from baseline at two successive evaluations).

Tables 4B and 5B summarizes the number of events for each treatment group as well as point estimates with 95% confidence intervals and p-values from Mantel-Haenszel log-rank test for the intent-to-treat population. Albeit the comparison of Irbesartan 150 mg vs. Placebo did not reach statistical significance (p=0.085) (Table 4B), treatment with Irbesartan 300 mg significantly reduced (p=0.004) the risk of developing “clinical proteinuria” (defined as urinary albumin excretion rate exceeding 200 μ g/minute and an increased of at least 30% from baseline at two successive evaluations) as compared with Placebo (Table 5B).

Table 4B. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 150 mg vs. Placebo Comparison): Intent-to-Treat Population

Placebo N=201 n (%)	Irbesartan 150 mg N=195 n (%)	Relative Risk		p-Value
		Estimate	95% CI	
30 (14.9)	19 (9.7)	0.607	0.341, 1.079	0.085

[Sponsor’s analysis, NDA 20-757/S-021, Protocol EFC2481, Table 10.1.1.2A.]

⁶⁸ NDA 20-757, Protocol EFC2481: Supplemental Tables S9.4A and S9.4B present summaries of antihypertensive and lipid-lowering medication use, respectively, during double-blind treatment in the randomized population. Appendices 9.4.1.1 through 9.4.4.4 present summaries of concomitant medication use by study period and population. An individual subject listing is provided in Appendix 9.4.5.

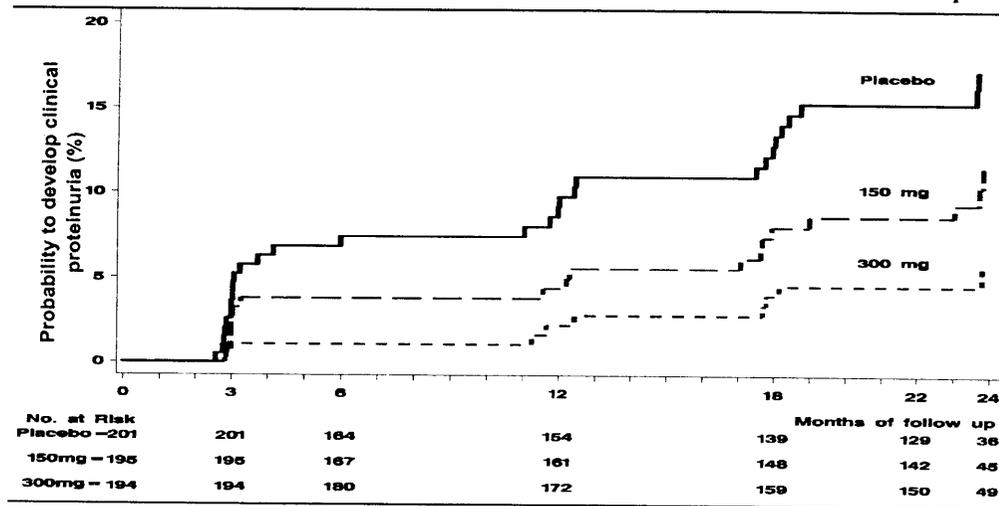
Table 5B. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 300 mg vs. Placebo Comparison): Intent-to-Treat Population

Placebo N=201 n (%)	Irbesartan 300 mg N=195 n (%)	Relative Risk		p-Value
		Estimate	95% CI	
30 (14.9)	10 (5.2)	0.295	0.144, 0.606	0.0004

[Sponsor’s analysis, NDA 20-757/S-021, Protocol EFC2481, Table 10.1.1.2B.]

Figure 2B depicts the Kaplan-Meier estimates of probability to develop clinical proteinuria in all treatment groups, for the intent-to-treat population. By month 3 (Visit 5) of treatment, i.e., time by which the first measurement of urinary albumin excretion rate after randomization was obtained, the curves had already diverged.

Figure 2B. Estimates of Probability to Develop Clinical Proteinuria: Intent-to-Treat Population



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Figure 10.1.1.2.]

Albeit, the assessment of the progression of renal disease by any direct or indirect method to determine glomerular filtration rate was not a pre-specified component of the primary endpoint it seems of interest to determine the effect of study drug on this parameter of renal function. To this end the FDA requested from the sponsor to provide the annual rate of change in serum creatinine for the intent-to-treat population (Table 6B). In comparison to Placebo, treatment with Irbesartan either 150 mg or 300 mg didn’t have a beneficial effect on the progression of renal disease as assessed by the annual rate of change in serum creatinine.⁶⁹

⁶⁹ Similar results were obtained when examining mean changes in estimated creatinine clearance NDA 20-757, Protocol EFC2481, Table 10.2.2.1.

Table 6B. Annual Rate of Change in Serum Creatinine (mg/dL) – ITT Population

Parameter in mixed model	Treatment group (N)	Parameter estimate (95% confidence interval)	Irbesartan 150 mg vs. Placebo		Irbesartan 300 mg vs. Placebo	
			Estimate (95% CI)	p	Estimate (95% CI)	p
Intercept (mg/dL)	Placebo (206)	1.06 (1.04;1.09)				
	Irbesartan 150 (202)	1.05 (1.03;1.07)	- 0.01 (-0.05;0.02)	0.435		
	Irbesartan 300 (200)	1.08 (1.06;1.11)			0.02 (-0.01;0.05)	0.256
Slope (mg/dL/year)	Placebo (206)	0.03 (0.02;0.04)				
	Irbesartan 150 (202)	0.03 (0.02;0.04)	0.01 (-0.01;0.02)	0.402		
	Irbesartan 300 (200)	0.04 (0.03;0.05)			0.01 (-0.002;0.03)	0.083

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001.]

The study was designed to attain similar degrees of blood pressure control within all treatment groups.⁷⁰ Table 7B summarizes the results on mean arterial blood pressure for the intent-to-treat population. At visits on months 3 and 6 both Irbesartan groups had MAP values significantly lower than the Placebo group did, a similar pattern was also observed at visit month 12 only for the Irbesartan 300 mg group. Similar changes were observed for systolic and diastolic blood pressures.⁷¹ After two years of treatment, SeDBP and SeSBP mean values were comparable among the groups: 143.5/82.2, 143.5/82.4, and 141.6/83.4 mmHg in the Placebo, Irbesartan 150 and 300 mg groups, respectively.

⁷⁰ “Blood pressure readings were used to make therapeutic decisions. Given variable subject responses to changes in BP medications, the physician could use his/her clinical judgment to choose intervals between adjustments of antihypertensive medication dosage in order to achieve control. If the maximally titrated dose of study medication did not result in a reduction of BP to target levels (shown below), treatment with adjunctive antihypertensive therapy was permitted, except for treatment with the ACE inhibitors, dihydropyridine calcium antagonists (changed by Amendment No. 1) and angiotensin II antagonists. Investigators were encouraged to lower SBP as much as possible in subjects with systolic hypertension. If, despite titration to the maximum doses of (tolerated) study medication and adjunctive antihypertensive agents, the SeBP had not responded (defined as a SeSBP > 160 mmHg or SeDBP > 90 mmHg), the Investigator was to consult with the Sponsor’s Trial Monitor or the Principal Investigator. In addition, the Scientific Committee reviewed these cases every 6 months to make recommendations for changes in permitted adjunctive antihypertensive medications in order to achieve BP control. Unscheduled visits were authorized for BP assessments and for adjustments of the recommended antihypertensive therapies. The recommended agents to be used for adjunctive antihypertensive were: 1) Loop diuretics. 2) Beta adrenergic receptor antagonists. 3) Non-dihydropyridine calcium antagonists (e.g., diltiazem, verapamil). 4) Central alpha adrenergic receptor agonists. Reduction of doses of adjunctive antihypertensive agents was encouraged for suspected or documented symptoms of hypotension. If the subject’s BP could not be controlled at or below the target values after utilizing maximal therapy and there was an absolute need for the use of a prohibited medication then the subject was considered to have reached a failure to control BP endpoint and the study drug was stopped. Within 1 week of discontinuing study medication, the subject was to complete the Month 24 procedures (Visit 9 and 1 week later Visit 10).”

⁷¹ For SeSBP and SeDBP the reader is referred to NDA 20-757, Clinical Study Report Protocol EFC2481, Tables 10.2.1.1B and 10.2.1.C.

Table 7B. Overall Change in MAP (Irbesartan vs. Placebo): Intent-to-Treat Population

Group	Visit Month	N	Baseline Mean±SD	Change from Baseline Mean±SD		Difference with Placebo		
						Estimate	95% CI	p-Value
Placebo	3	195	110.9±9.1	-4.89	10.23			
	6	183	110.7±9.1	-5.87	9.59			
	12	161	111.2±9.1	-9.35	10.70			
	18	150	111.4±9.2	-9.80	11.21			
	24	136	111.3±9.3	-8.43	10.59			
Irbesartan 150mg	3	189	110.9±8.9	-7.35	9.62	-2.459	[-4.47,-0.45]	0.017
	6	182	110.7±8.9	-8.65	9.31	-2.782	[-4.75,-0.82]	0.0056
	12	171	110.7±9.0	-8.74	9.63	0.607	[-1.54,2.76]	0.58
	18	159	110.7±9.1	-10.63	9.54	-0.824	[-3.09,1.44]	0.48
	24	145	111.1±9.1	-8.30	11.31	0.126	[-2.34,2.60]	0.92
Irbesartan 300mg	3	191	111.6±9.5	-8.51	10.22	-3.624	[-5.63,-1.62]	0.0004
	6	185	112.0±9.3	-9.91	9.78	-4.040	[-6.00,-2.08]	0.0001
	12	177	112.1±9.3	-11.59	9.60	-2.245	[-4.38,-0.11]	0.039
	18	171	112.3±9.4	-11.76	9.67	-1.954	[-4.18,0.27]	0.085
	24	162	112.0±9.2	-10.02	9.74	-1.591	[-4.00,0.82]	0.19

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table S.10.2.1.2B.]

The secondary endpoints were overnight urinary albumin excretion rate, von Willebrand Factor, Fibrinogen, Factor VII and Plasminogen Activator Inhibitor-1, and Lipid Profile (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and apolipoprotein).

The percent change in urinary albumin excretion rate is summarized by treatment group for per-protocol subjects in Table 8B.⁷² The reduction in urinary albumin excretion rate was significantly greater in the Irbesartan groups than in the placebo group at any time-point during the study.

Table 8B. Secondary Endpoint Comparison – Percentage Change in Urinary AER (Irbesartan vs. Placebo): Per-Protocol Subjects

Group	Visit Month	N	Baseline GM±SEM	Change from Baseline GMPC±SEM		Difference with Placebo		
						Estimate	95% CI	p-Value
Placebo	3	170	55.7±2.67	14.75±6.28				
	6	157	53.3±2.61	13.87±7.11				
	12	140	52.5±2.71	-10.46±5.83				
	18	129	49.8±2.62	-10.52±7.04				
	24	107	49.2±2.83	-7.55±8.95				
Irbesartan 150mg	3	157	57.7±2.83	-16.59±4.62	-27.3	[-38.08,-14.68]	0.0001	
	6	150	57.9±2.87	-28.03±4.39	-36.8	[-46.65, 25.14]	16E-8	
	12	140	56.2±2.81	-30.72±4.81	-22.6	[-35.92; 6.58]	0.0078	
	18	134	54.8±2.79	-34.49±5.48	-26.7	[-42.13,-7.39]	0.0094	
	24	109	54.3±2.99	-30.48±6.80	-24.7	[-43.12; 0.56]	0.046	
Irbesartan 300mg	3	160	54.1±2.38	-32.56±4.27	-41.2	[-49.89; 31.06]	2E-10	
	6	155	53.8±2.40	-33.70±3.91	-41.7	[-50.78; 31.12]	6E-10	
	12	145	54.3±2.54	-39.84±4.07	-32.8	[-44.26,-19.01]	35E-6	
	18	144	53.1±2.41	-39.73±5.19	-32.6	[-46.53; 15.13]	0.0008	
	24	121	52.3±2.61	-47.15±5.27	-42.8	[-56.46,-24.94]	0.0001	

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table S.10.2.1.2B.]

The other secondary endpoints include: von Willebrand Factor, Fibrinogen, Factor VII and Plasminogen Activator Inhibitor-1, and Lipid Profile (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and apolipoprotein) (Table 9B). Analyses of these parameters after 12 and 24 months of treatment with study

⁷² A similar analysis for the Intent-to-Treat Population was requested from the sponsor.

indicate that only at 12 months there was a statistically significant difference for plasminogen activator inhibitor between Placebo and Irbesartan 300 mg groups ($p < 0.012$).

Table 9B. Secondary Endpoint Comparison - Mean Change in Coagulation Parameters After 1 Year and 2 Years (Irbesartan vs. Placebo): Per-Protocol Subjects

Change	Mean Change from Baseline			Irbesartan 150 mg vs. Placebo		Irbesartan 300 mg vs. Placebo	
	Placebo n Mean (SD)	Irbesartan 150 mg n Mean (SD)	Irbesartan 300 mg n Mean (SD)	Estimate Difference [95% CI]	p	Estimate Difference [95% CI]	p
After 12 months in:							
vWF, %	118	118	129	-0.720	0.88	-4.534	0.32
	7.81	7.08	3.27	[-9.94, 8.50]		[-13.56, 4.49]	
	(47.18)	(28.40)	(29.96)				
Fibrinogen, µg/g/L	118	122	130	-8.310	0.43	-12.489	0.23
	9.71	1.40	-2.78	[-28.89, 12.27]		[-32.75, 7.77]	
	(90.75)	(69.35)	(81.87)				
Factor VII, %	116	119	130	0.065	0.99	2.179	0.66
	0.61	0.68	2.80	[-9.38, 10.49]		[-7.27, 12.59]	
	(2.97)	(3.68)	(3.85)				
PAI ₁ , µg/L	120	119	129	0.019	1.00	-23.089	0.012
	12.62	12.64	-13.38	[-18.80, 23.30]		[-37.31, 5.65]	
	(8.89)	(3.08)	(6.23)				
After 24 months in:							
vVWF, %	104	104	117	-1.856	0.74	-8.370	0.13
	14.48	12.63	6.11	[-12.88, 9.17]		[-19.09, 2.35]	
	(50.17)	(34.19)	(35.54)				
Fibrinogen, µg/g/L	104	106	118	-1.160	0.93	-19.151	0.12
	12.49	11.33	-6.66	[-26.22, 23.90]		[-43.58, 5.27]	
	(111.02)	(82.78)	(81.65)				
Factor VII, %	100	101	115	-2.914	0.55	-0.338	0.94
	3.11	0.10	2.76	[-11.88, 6.96]		[-9.27, 9.471]	
	(3.53)	(2.79)	(3.88)				
PAI ₁ , µg/L	104	100	118	9.537	0.46	16.699	0.19
	-5.90	3.08	9.82	[-14.06, 39.61]		[-7.55, 47.32]	
	(8.32)	(9.12)	(8.67)				

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 10.2.3.1.]

Based on the results on HbA_{1c} levels diabetic control was similar among the groups. Furthermore, the levels of HbA_{1c} did not change significantly over time in any of the treatment groups.⁷³

GFR-Sub-Study and Its Extension: In the GFR sub-study, a cohort of subjects was selected from the main clinical trial to have GFR measurements at randomization, and at months 3 and 24 during the double-blind treatment period, and at the last visit of the 4-week extension after all study medication and concomitant antihypertensive medications were discontinued at Month 24.

Study Population-GFR Sub-Study and Its Extension: One hundred and thirty three subjects were randomized into the GFR Sub-Study. Overall, the study population was white (97%) males (68%) under the age of 65 years (74%) with a mean BMI of 30%. The mean duration of diabetes was 7.6 years, with 24% of the subjects having a history of insulin use prior to study entry. The mean baseline seated systolic and diastolic blood pressures were 153.2 mmHg and 90.1 mmHg, respectively. Baseline demographic characteristics, blood pressure and

⁷³ NDA 20-757, Protocol EFC2481, Table 10.3.1.

laboratory measures for all randomized subjects by treatment are summarized in Table 10B. Overall, baseline demographic characteristics and blood pressure and laboratory measures were balanced among the groups.

Table 10B. Summary of Baseline Demographic Characteristics, Blood Pressure and Laboratory Measures for All Randomized Subjects.

Subject Characteristics		Placebo N=48 (%)	Irbesartan 150 mg N=42 (%)	Irbesartan 300 mg N=43 (%)
Gender	Male	73.0	79.0	72.0
	Female	27.0	21.0	28.0
Race	White	100	95.0	98
	Black	0.0	2.4	0.8
	Oriental	0.0	2.4	0.8
	Other	0.0	0.0	0.8
Age (Mean±SD; years)		57.2±8.8	56.9±8.7	55.2±8.6
	<65	75.0	71.0	84.0
	≥65	25.0	29.0	16.0
SeSBP (Mean±SD; mmHg)		153±15	153±13	153±14
SeDBP (Mean±SD; mmHg)		90±8	89±9	91±9
Body Mass Index (Mean±SD)		30.9±4.9	29.8±3.4	29.8±4.7
Duration of Diabetes (Mean±SD; years)		7.3±6.3	8.0±6.0	7.6±6.6
Insulin Use Prior to Study		21.0	29.0	23.0
HbA _{1c} (Mean±SD; %)		7.1±1.7	7.2±1.7	7.1±1.7
Serum Creatinine (Mean±SD; mg/dl)		1.1±0.2	1.0±0.1	1.1±0.2
*Creatinine Clearance (GMean±SD; mL/min/1.73m ²)		114.5±34.3	113.4±27.2	113.3±30.2
Urinary Albumin Excretion rate (GMean±SD; µg/min)		49.5±31.5	57.9±40.7	56.2±33.5
Total Cholesterol (Mean±SD; mg/dl)		220±43	228±41	225±41
LDL Cholesterol (Mean±SD; mg/dl)		131±40	139±40	134±35

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Tables 13.2A, 13.2B, and 13.2C. *Estimated.]

Disposition of Subjects-GFR Sub-Study and Its Extension: Of the hundred and thirty three subjects who were initially randomized to double-blind treatment and selected to participate in the GFR Sub-Study, 115 completed the 2 years of double-blind treatment, 91 subjects entered the 4-week extension period and 76 completed this extension.

Table 11B describes the reasons for discontinuation during double-blind therapy for the GFR-Sub Study subjects.

Table 11B. Reasons for Discontinuation During Double-Blind Therapy: GFR Sub-Study Subjects

Reason for Discontinuation	Placebo N=48 n (%)	Irbesartan 150 mg N=42 n (%)	Irbesartan 300 mg N=43 n (%)
Adverse event	2 (4.2)	1 (2.4)	2 (4.7)
Death	0 (0.0)	0 (0.0)	2 (4.7)
Lack of efficacy	3 (6.3)	3 (7.0)	0 (0.0)
Other reason	3 (6.3)	1 (2.4)	1 (2.3)
Total	8 (16.7)	5 (11.9)	5 (11.6)

[Sponsor's analysis, NDA 20-757/S-021, Protocol EFC2481, Table 13.1.]

Treatment Compliance-GFR Sub-Study and Its Extension: According to the sponsor, "the majority of all subjects (78.9%) were between 80 and 100% compliant with study medication during the study. The percentage of compliant subjects was similar across all treatment groups."

Efficacy Variables-GFR Sub-Study and Its Extension: Efficacy Variables-GFR Sub-Study and Its Extension: In this subset of subjects efficacy was assessed by the following variables: glomerular filtration rate⁷⁴, extracellular fluid volume, pro-renin, active renin, and angiotensin II. Of note, the number of subjects evaluated in the GFR-Sub-Study and its extension is small, and that significantly hinders the interpretation of the results.

Glomerular filtration rate (ml/min/1.73m², mean±SD) at baseline was similar among the treatment groups: 104.3±4.2 in the Placebo group, 113.3±3.4 in the Irbesartan 150 mg group, and 109.9±3.8 in the Irbesartan 300 mg group. GFR measurements at visits 3 and 24 months were lower than those values obtained at baseline in all groups. The percent change GFR from baseline at months 3 and 24 are shown in Table 12B. The decrease in GFR was numerically larger, though not statistically significant, in the Irbesartan groups than in the Placebo group.

Table 12B. Mean (±SEM) Percentage Change in Glomerular Filtration Rate (mL/min/1.73 m²) (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Group	Visit Month	N	GMPC ±SEM	Difference with Placebo		
				Estimate	95% CI	p-Value
Placebo	3	37	-2.6±2.1			
	24	32	-8.9±2.0			
Irbesartan 150 mg	3	38	-3.2±2.1	-0.67	(-6.70, 5.76)	0.83
	24	31	-10.0±2.5	-1.10	(-7.85, 6.14)	0.76
Irbesartan 300 mg	3	37	-2.3±2.3	0.27	(-5.86, 6.80)	0.93
	24	33	-12.1±2.2	-3.41	(-9.91, 3.55)	0.32

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 13.4.1A. GMPC=Geometric Mean Percent Change]

Four weeks after study drug and concomitant antihypertensive medications were discontinued at month 24, GFR increased slightly in all groups but the mean values remained below baseline values.⁷⁵ The mean (±SEM) percentage changes in GFR, at +week 4 from month 24, were not statistically different across treatment groups (Table 13B).

⁷⁴ GFR determination was performed by the total plasma clearance of ⁵¹Cr-EDTA using a simplified single injection method. For more information on the subject the reader is referred to NDA 20-757, Protocol EFC2481, Appendix 5.1.

⁷⁵ NDA 20-757, Protocol EFC2481, Clinical Study Report, page 188.

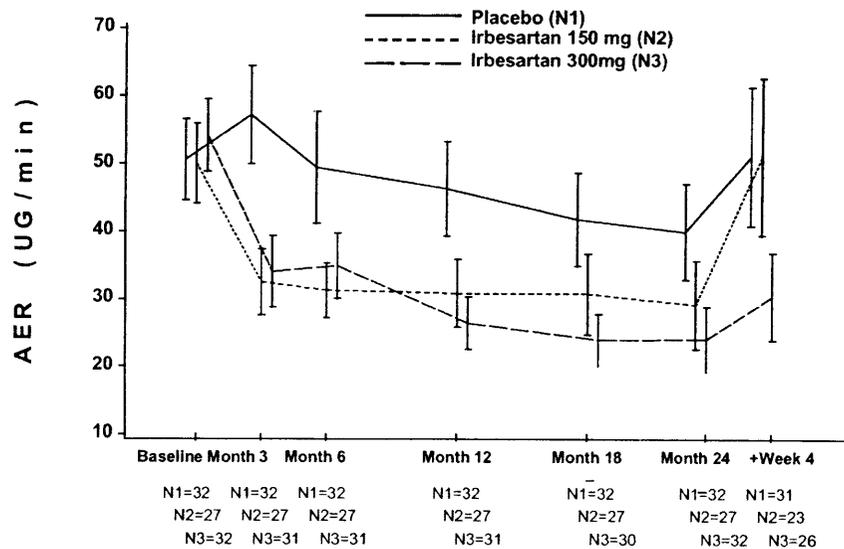
Table 13B. Mean (\pm SEM) Percentage Change in Glomerular Filtration Rate (mL/min/1.73 m²) (Irbesartan vs. Placebo): GFR Sub-Study Extension (+Week 4) Subjects

Group	N	Baseline Month 24 GM \pm SEM	N	Change from Baseline GMPC \pm SEM	Difference with Placebo		
					Estimate	95% CI	p-Value
Placebo	27	96.1 \pm 4.9		5.7 \pm 2.1			
Irbesartan 150 mg	21	102.7 \pm 4.3		1.2 \pm 2.4	-4.3	(-10.4, 2.2)	0.18
Irbesartan 300 mg	26	97.8 \pm 5.3		3.7 \pm 2.6	-1.9	(-7.8, 4.3)	0.53

[Sponsor’s analysis, NDA 20-757/S-021, Protocol EFC2481, Table 13.4.1B. GM=Geometric Mean; GMPC=Geometric Mean Percent Change.]

Figure 3B depicts the mean (\pm SD) changes in urinary albumin excretion rate (μ g/min) over time in the cohort of subjects that participated in the GFR Sub-Study and its Extension. As was the case for the main study, in the GFR-Sub-Study the Irbesartan groups had urinary albumin excretion rates lower than in the placebo group up to month 24. In response to four weeks of study drug and concomitant antihypertensive medications discontinuation the urinary albumin excretion rate increased in all three groups. However, this increase was less in the Irbesartan 300 mg group (15.9%) than in the Irbesartan 150 mg group (83.7%) or the Placebo group (27.6%). The mean (\pm SD) values of urinary albumin excretion rate reached at + 4 weeks were 51.1 (\pm 10.2), 51.0 (\pm 11.6) and 30.4 (\pm 6.4) (μ g/min) in Placebo, Irbesartan 150 mg and Irbesartan 300 mg groups, respectively.

Figure 3B. Mean (\pm SD) Change in AER (μ g/min) Over Time: GFR Sub-Study and its Extension



[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Figure 13.4.2.]

“The analysis of variance performed on the difference between +week 4 visit and month 24 visit (time period where study drug was stopped) of the log-transformed urinary albumin excretion rate aiming at comparing the 3 treatment groups (Placebo, Irbesartan 150mg and 300mg) did not show an overall significant treatment group effect (F statistic (2,77)= 2.10; p=0.1). The contrasts between placebo and each Irbesartan dose are presented in Table 14B: no significant difference was observed between each Irbesartan dose and placebo.”

Table 14B. Difference between Month 24 and Week 4 of AER* in the GFR Sub-Study - Geometric Mean Percentage Change, Confidence Interval and p-Value for the Comparison of the Two Irbesartan Groups and Placebo

Comparison	Geometric mean percentage change	95% Confidence interval for geometric mean percentage change	p-value
Irbesartan 150mg vs. placebo	43.90	-8.4 to 126.1	0.11
Irbesartan 300mg vs. placebo	-9.20	-41.3 to 40.5	0.66

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001. *Urinary albumin excretion rate.]

"Four weeks after having stopped the study drug (+week 4 visit), the mean urinary albumin excretion rate did not differ significantly between the 3 groups (F statistic (2,77)= 1.97; p=0.1). The contrasts between Placebo and each Irbesartan dose are presented in Table 15B; no significant difference was observed between each dose of Irbesartan and placebo although urinary albumin excretion rate remained lower with Irbesartan 300 mg compared to the 2 other groups."

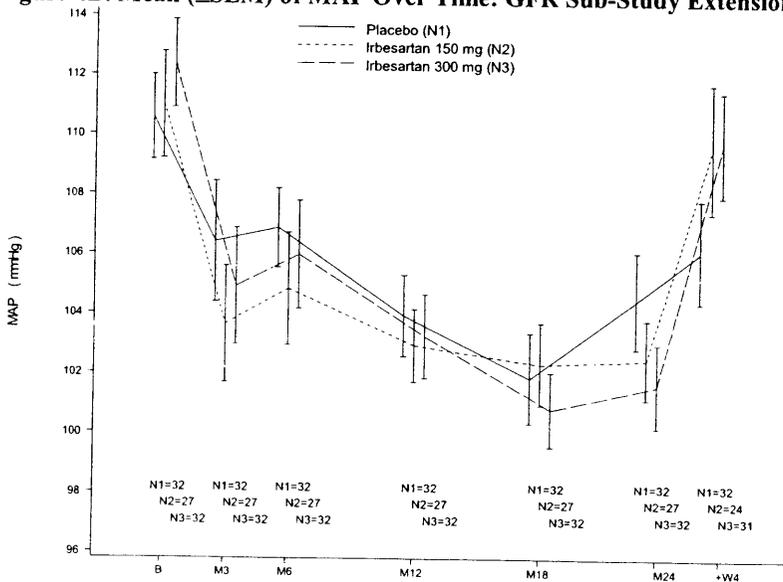
Table 15B. AER* in the GFR Sub-Study at Week 4 - Geometric Mean Percentage, Confidence Interval and p-Value for the Comparison of the Two Irbesartan Groups and Placebo

Comparison	Geometric mean percentage	95% Confidence interval for geometric mean	p-value
Irbesartan 150mg vs. placebo	-0.10	-45.2 to 82.3	1.00
Irbesartan 300mg vs. placebo	-40.60	-66.8 to 6.2	0.078

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001. *Urinary albumin excretion rate.]

Figure 4B depicts the results on mean (\pm SEM) arterial blood pressure for the intent-to-treat population for those subjects participating in the GFR-Sub-Study and its extension. Upon withdrawal of study drug and antihypertensive medications MAP increased in all treatment groups to values that were not statistically different.

Figure 4B. Mean (\pm SEM) of MAP Over Time: GFR Sub-Study Extension



[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001.]

“The analysis of variance performed on the difference between +week 4 and month 24 visits of the mean arterial pressure (MAP) aiming at comparing the 3 treatment groups (Placebo, Irbesartan 150mg and 300mg) showed an overall significant treatment group effect (F statistic (2,84)= 3.57; p=0.03). The contrasts between placebo and each Irbesartan dose are presented in Table 16B; significant difference was observed between each Irbesartan dose and placebo. MAP values increased more in the Irbesartan groups than in the placebo group during the GFR sub-study extension (after withdrawal of study medication).”

Table 16B. Difference between Month 24 and Week 4 of MAP (mmHg) in the GFR Sub-Study - Mean Change, Confidence Interval and p-Value for the Comparison of the Two Irbesartan Groups and Placebo

Comparison	Mean change (mmHg)	95% Confidence interval for mean change	p-value
Irbesartan 150mg vs. placebo	5.60	0.2 - 11.0	0.041
Irbesartan 300mg vs. placebo	6.20	1.2 - 11.2	0.017

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001.]

“At +week 4, MAP was not significantly different between groups although the MAP level was slightly higher in the Irbesartan groups compared to placebo (Table 17B).”

Table 17B. MAP (mmHg) in the GFR Sub-Study at +Week 4- Mean, Confidence Interval and p-Value for the Comparison of the Two Irbesartan Groups and Placebo

Comparison	Mean	95% Confidence interval for mean	p-value
Irbesartan 150mg vs. placebo	3.50	-1.9 - 8.8	0.20
Irbesartan 300mg vs. placebo	3.60	-1.4 - 8.6	0.16

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481. Response to FDA request dated November 27, 2001.]

The mean (\pm SEM) percentage changes in Active Renin, Pro-Renin and Angiotensin II by treatment group for the subjects randomized to the GFR-Sub-Study are summarized in Tables 18B, 19B, and 20B. In comparison to Placebo group, treatment with Irbesartan 150 mg or 300 mg groups resulted in significant increases in the aforementioned parameters at months 3 and 24.

Table 18B. Mean (\pm SEM) Percentage Change in Active Renin (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Group	Visit Month	N	GMPC \pm SEM	Difference with Placebo		
				Estimate	95% CI	p-Value
Placebo	3	13	-6.0 \pm 16.3			
	24	27	40.8 \pm 19.8			
Irbesartan 150 mg	3	15	82.0 \pm 27.2	93.5	(11.8, 235.1)	0.020
	24	28	108.6 \pm 34.7	48.2	(-6.7, 135.4)	0.094
Irbesartan 300 mg	3	13	108.1 \pm 52.9	121.4	(25.4, 290.8)	0.0074
	24	26	250.4 \pm 66.0	148.9	(55.4, 298.8)	0.0002

[Sponsor’s analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 13.4.4A. GMPC=Geometric Mean Percent Change]

Table 19B. Mean (±SEM) Percentage Change in Pro-Renin (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Group	Visit Month	N	GMPC ±SEM	Difference with Placebo		
				Estimate	95% CI	p-Value
Placebo	3	13	14.5±13.0			
	24	27	80.9±19.5			
Irbesartan 150 mg	3	15	52.1±10.2	32.8	(1.0, 74.7)	0.043
	24	28	86.6±21.7	3.1	(-23.7, 39.3)	0.84
Irbesartan 300 mg	3	13	89.8±20.8	65.8	(24.8, 120.1)	0.0009
	24	26	191.1±28.2	60.9	(18.5, 118.5)	0.0028

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 13.4.4B. GMPC=Geometric Mean Percent Change]

Table 20B. Mean (±SEM) Percentage Change in Angiotensin II (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Group	Visit Month	N	GMPC ±SEM	Difference with Placebo		
				Estimate	95% CI	p-Value
Placebo	3	12	-11.0±10.2			
	24	25	4.4±16.2			
Irbesartan 150 mg	3	14	56.9±18.7	76.4	(21.7, 155.5)	0.0037
	24	27	97.8±24.5	89.5	(29.1, 178.2)	0.0014
Irbesartan 300 mg	3	13	126.4±33.7	154.4	(74.4, 271.1)	14E-6
	24	26	157.4±33.5	146.6	(67.4, 263.3)	14E-6

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 13.4.4C. GMPC=Geometric Mean Percent Change]

Pharmacokinetic/Pharmacodynamic Results: not applicable.

Safety Results: The sponsor evaluated safety from the exposed population, i.e., all subjects who received at least 1 dose of study medication, based on the medical review of clinical adverse events, laboratory adverse events, clinical laboratory test evaluations, 12-lead ECGs, and vital sign measurements. The following tables describe all adverse events that occurred during the study and through 14 days post-study.

The number (%) of reported serious adverse events, discontinuations due to adverse events and deaths for all three groups from study EFC2481 is summarized in Table 21B. Serious adverse events were more often reported in placebo-treated subjects than in those subjects receiving either 150 mg or 300 mg of Irbesartan. The frequency of discontinuations due to adverse events was lower for the Irbesartan 300 mg group than for the placebo or Irbesartan 150 mg groups. Similar incidence rates for death were reported for all treatment groups.

Table 21B. Summary of Serious Clinical Adverse Events (as Reported) During and Up to 14 Days Post Double-Blind Therapy by Treatment Group

Event	Placebo N=206 N(%)	Irbesartan 75/150 mg N=202 n(%)	Irbesartan 150/300 mg N=200 n(%)
Serious Adverse Event	47 (22.8)	32 (15.8)	30 (15.0)
Discontinuations due to AE	19 (9.2)	18 (8.9)	11 (5.5)
Death	5 (2.4)	3 (1.5)	6 (3.0)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.0.]

The number of subjects who died during and post double-blind therapy up to study closure by treatment group is presented in Table 22B. A total of 17 deaths were reported, however one subject died during the placebo lead in period and never received study drug. Five subjects died in the Placebo group, and 11 subjects died in the Irbesartan groups, 3 subjects were treated with Irbesartan 150 mg and 8 subjects received Irbesartan 300 mg.

Table 22B. Listing of Subjects Who Died During the Double-Blind Study Period or During the Post Double-Blind Period: All Subjects who Participated in the Study

Treatment Group	Subject ID	Study Period	Days Since First Dose	Primary Reason for Death
Placebo	2070013	DB	430	Malignant Lung Cancer
Placebo	9010009	DB	101	Myocardial Infarction
Placebo	12060005	Post-Rx >14 days	327	Not listed by Investigator
Placebo	13050004	DB	90	Hematemesis
Placebo	16010035	DB	254	Postoperative sepsis
Irbesartan 75 mg*	16010004	DB	-	Malignant liver neoplasm
Irbesartan 75 mg**	2810014	DB	-	Pancreatic carcinoma
Irbesartan 150 mg	7120007	DB	77	Myocardial Infarction
Irbesartan 150 mg	28100004	DB	127	Glioma multiforme of right occipital lobe
Irbesartan 300 mg	7150004	Post-Rx >14 days	1033	Acute Myocardial Infarction
Irbesartan 300 mg	7190003	DB	-	Accident at work
Irbesartan 300 mg	19020002	DB	-	Non small cell lung cancer
Irbesartan 300 mg	22140002	DB	104	Ischemic infarct of cerebrum
Irbesartan 300 mg	28040006	Post-Rx >14 days	603	Disorientation/ confusion
Irbesartan 300 mg	29010013	DB	109	Ischemic heart disease
Irbesartan 300 mg	33060023	DB	343	Sudden death

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.2. *Randomized to Irbesartan 150 mg. **Randomized to Irbesartan 300 mg.]

The incidence of adverse events leading to discontinuation is summarized in Table 23B. The few events reported in each category preclude arriving to conclusions with any degree of confidence. It is worth to mention however that the Irbesartan 300 mg group (5.5%) had a numerically lower rate of total discontinuation due to adverse events than the Placebo (9.2%) or Irbesartan 150 mg (8.9%) groups did.

Table 23B. Number (%) of Subjects who had Adverse Events Leading to Discontinuation of Study Therapy During Double-Blind Therapy: Exposed Subjects

Primary Terms	Placebo N=206 n (%)	Irbesartan 150 mg N=202 n (%)	Irbesartan 300 mg N=200 n (%)
Nausea/Vomiting	0	4 (2.0)	0
Angina Pectoris	0	2 (1.0)	0
Coronary Artery Dis	1 (0.5)	0	2 (1.0)
Vertigo	0	0	2 (1.0)
Serum Potassium increase	0	2 (1.0)	0
Abdominal Pain	0	1 (0.5)	0
Anorectal Disorder	0	0	2 (1.0)
Atrial Rhythm Disturbance	1 (0.5)	0	1 (0.5)
Cardiomyopathy	0	1 (0.5)	0
Cough	0	1 (0.5)	0
Distention, Abdomen	0	1 (0.5)	0

Dyspnea	0	1 (0.5)	0
Edema	0	0	1 (0.5)
Fatigue	0	0	1 (0.5)
Flushing	0	0	1 (0.5)
Headache	0	0	1 (0.5)
Heart Failure	0	1 (0.5)	0
Muscle Cramp	0	1 (0.5)	0
Musculo/skeletal Pain	0	0	1 (0.5)
Myocardial Infarct	2 (1.0)	1 (0.5)	0
Neoplasm, Unspecified	0	1 (0.5)	0
Neurological			
Periph Vasc Dis Arte	0	0	1 (0.5)
Periph Vasc Dis Veno	1 (0.5)	1 (0.5)	0
Pulmonary Infection	0	1 (0.5)	0
Sexual Dysfunction	0	0	1 (0.5)
Sudden Death	0	0	1 (0.5)
Vasodilation	0	1 (0.5)	0
Ventricular rhythm disturbance	0	1 (0.5)	0
Abnormal liver function	1 (0.5)	0	0
Aortic Aneurysm	1 (0.5)	0	0
Cerebrovascular Accident	1 (0.5)	0	0
Dis Intest Ischemic	1 (0.5)	0	0
Dizziness	1 (0.5)	0	0
Gastritis	1 (0.5)	0	0
Hernia	1 (0.5)	0	0
Hypertension	2 (1.0)	0	0
Hypertensive Crisis	1 (0.5)	0	0
N-Ang Car Chst Pain	1 (0.5)	0	0
Neoplasm, Malig Pulmonary	1 (0.5)	0	0
Pruritus	1 (0.5)	0	0
Pulmonary Edema	1 (0.5)	0	0
Septicemia	1 (0.5)	0	0
Serum glucose increase	1 (0.5)	0	0
Ulcerative Colitis	1 (0.5)	0	0
Upper GI Bleeding	1 (0.5)	0	0

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.4.]

One hundred and nine subjects experienced serious adverse events during double-blind treatment; the frequency of occurrence was slightly higher in placebo-treated subjects (22.8%) compared to subjects treated with Irbesartan 150 mg (15.8%) and Irbesartan 300 mg (15.0%). The most frequently occurring serious adverse events were those associated with cardiovascular body system (8.3% in Placebo-treated subjects and 6.2% in Irbesartan-treated subjects) (Table 24B).⁷⁶

Table 24B. Number (%) of Subjects with Serious Adverse Events, by Body System, During and Up to 14 Days Post Double-Blind Therapy: Exposed Subjects

Body Systems	Placebo N=206	Irbesartan 150 mg N=202	Irbesartan 300 mg N=200
Cardiovascular	17 (8.3%)	12 (5.9%)	13 (6.5%)
Renal/Genitourinary	7 (3.4%)	7 (3.5%)	4 (2.0%)
Gastrointestinal	7 (3.4%)	5 (2.5%)	4 (2.0%)
Respiratory	3 (1.5%)	6 (3.0%)	3 (1.5%)
Nervous System	8 (3.9%)	3 (1.5%)	4 (2.0%)

⁷⁶ For the frequency of serious adverse events by investigator term the reader is referred to NDA 20-757, Clinical Study Report EFC2481, Tables S12.3A and 12.3B.

Endocrine/Metabolic/Electrolyte Imbal.	4 (1.9%)	3 (1.5%)	3 (1.5%)
Musculoskeletal/Connective Tissue	6 (2.9%)	2 (1.0%)	4 (2.0%)
General	4 (1.9%)	1 (0.5%)	3 (1.5%)
Dermatologic	3 (1.5%)	1 (0.5%)	0
Special Senses	1 (0.5%)	1 (0.5%)	0
Hematopoietic	1 (0.5%)	0	0
Hepatic/Biliary	2 (1.0%)	0	0

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.3.]

Table 25B summarizes the clinical adverse events ($\geq 3\%$ of subjects in any treatment group) reported during and up to 14 days post double-blind therapy.⁷⁷ The few number of events for each primary term significantly curtails interpretation of the data on frequency of clinical adverse events. Notwithstanding, in comparison to placebo-treated subjects, subjects receiving Irbesartan had a higher incidence of dizziness and diarrhea.

Table 25B Number (%) of Subjects with Clinical Adverse Events Occurring at a Frequency of $\geq 3\%$ in any Treatment Group, by Body System, During and Up to 14 Days Post Double-Blind Therapy: Exposed Subjects

Primary Terms	Placebo N=206 n (%)	Irbesartan 150 mg N=202 n (%)	Irbesartan 300 mg N=200 n (%)
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%)
Tracheobronchitis	7 (3.4%)	6 (3.0%)	9 (4.5%)
Edema	9 (4.4%)	4 (2.0%)	10 (5.0%)
Chest Pain	7 (3.4%)	7 (3.5%)	6 (3.0%)
Angina Pectoris	6 (2.9%)	4 (2.0%)	7 (3.5%)
Musculoskeletal Trauma	5 (2.4%)	6 (3.0%)	5 (2.5%)
Abdominal Pain	5 (2.4%)	3 (1.5%)	7 (3.5%)
Abnormal Urination	2 (1.0%)	3 (1.5%)	7 (3.5%)
Depression	4 (1.9%)	2 (1.0%)	8 (4.0%)
Dyspepsia/Heartburn	11 (5.3%)	3 (1.5%)	6 (3.0%)
Nausea/Vomiting	2 (1.0%)	7 (3.5%)	2 (1.0%)
Degenerative Arthritis	3 (1.5%)	2 (1.0%)	6 (3.0%)
Infect Skin Bacteria	1 (0.5%)	6 (3.0%)	2 (1.0%)
Vertigo	2 (1.0%)	1 (0.5%)	6 (3.0%)
Sleep Disturbance	0	0	6 (3.0%)
Skin Ulcer	9 (4.4%)	2 (1.0%)	4 (2.0%)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.1.2.]

A low incidence of treatment-emergent laboratory adverse events during and up to 14 days post double-blind therapy observed in all treatment groups precludes a valid assessment. Nevertheless, review of the data failed to uncover major differences in the rates of laboratory adverse events among the groups.⁷⁸

⁷⁷ The incidences for all adverse events reported could be found in NDA 20-757, Clinical Study Report EFC2481, Table S12.1.1.

⁷⁸ The incidences for all laboratory adverse events reported could be found in NDA 20-757, Clinical Study Report EFC2481, Table S12.5.

Table 26B presents the number (%) of subjects by treatment group with at least 1 potentially clinically significant ECG abnormality post-baseline for the exposed subjects. Alterations in ECG's parameters occurred with similar frequency across all treatment groups with the exception of PR and QRS, which occurred with greater frequency in the Irbesartan 300 mg group. QT changes were reported with similar frequency in the Irbesartan and placebo groups.

Table 26B. Number (%) of Subjects with at Least One Potentially Clinically Significant ECG Abnormality Post-Baseline: Exposed Subjects

Parameter	Placebo N=206 n (%)	Irbesartan 150 mg N=202 n (%)	Irbesartan 300 mg N=200 n (%)
HR (≤ 50 bpm + decrease ≥ 15 bpm)	0	0	1 (0.5%)
HR (≥ 120 bpm + increase ≥ 15 bpm)	0	1 (0.5%)	0
PR (≥ 200 ms + increase ≥ 20 ms)	13 (6.3%)	14 (6.9%)	27 (13.6%)
QRS (≥ 120 ms)	12 (5.8%)	18 (8.9%)	29 (14.6%)
QT (≥ 500 ms)	2 (1.0%)	3 (1.5%)	2 (1.0%)
QTc (males: ≥ 450 ms) (females: ≥ 470 ms)	34 (16.5%)	36 (17.8%)	26 (13.2%)

[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol EFC2481, Table 12.7A.]

The sponsor also evaluated the results of grade changes in fundoscopic examination by treatment group for exposed subjects. "Overall, there were no clinically relevant grade changes in any treatment group. The majority of subjects in each treatment group for whom results were available were normal-to-grade I at baseline and remained as such by the end of the double-blind period."