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 LTFU[34] 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

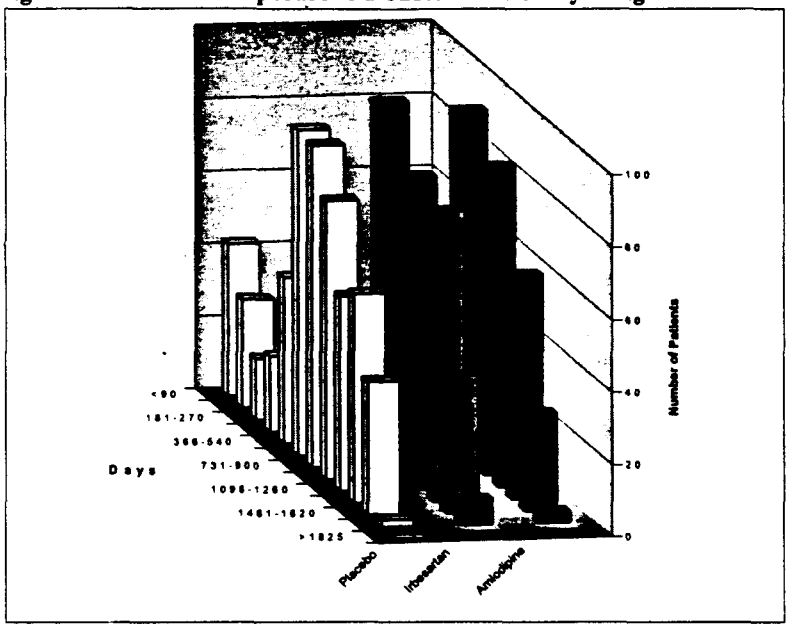
[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Sponsor's response to FDA request dated November 13, 2001, Table 1. Pb = Placebo. Irb = Irbesartan. Am = Amlodipine. *mg/dl. Unk = unknown is recorded on the Vital Status Form. ND = 0 data is recorded on the Vital Status Form. [a]Calculated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

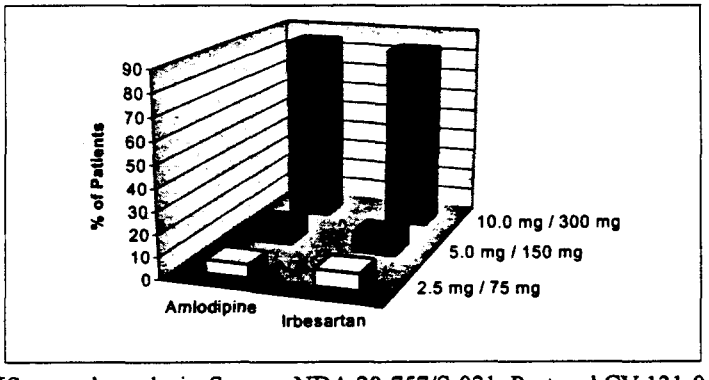


[Sponsor's analysis. Source: NDA 20-757/S-021, Protocol CV 131-048, Table 9.1A. Note: total treatment days included from the first to the last of the double-blind treatment. Days during study drug interruptions (see below) were not subtracted from the exposure calculations.]

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
AII Recep. 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/Antidepresants	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.

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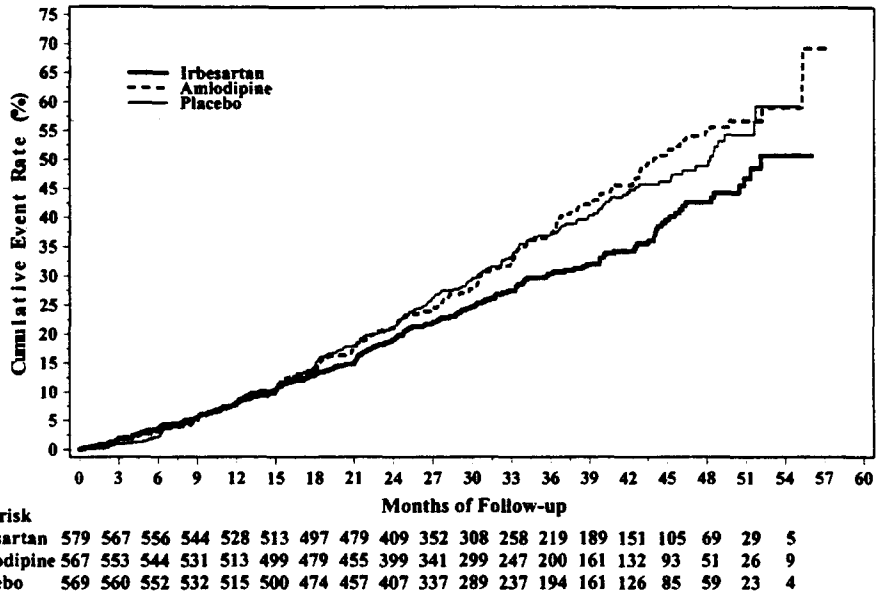
[36] FDA's analysis by Dr. John Lawrence, HFD-710.
[37] Sponsor's analyses.

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 n		Irbesartan 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]

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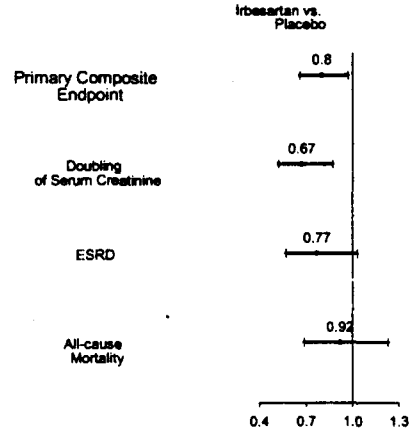
[40] Sponsor's analyses.

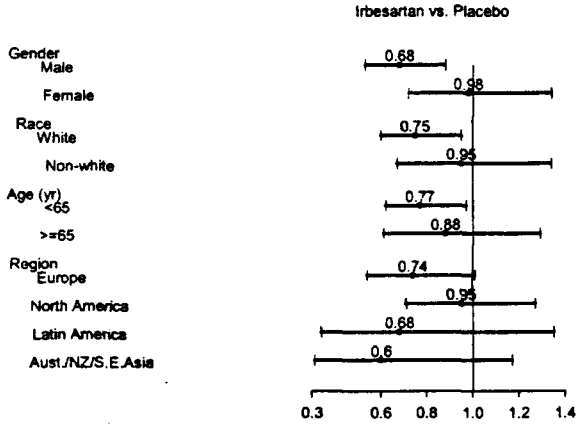
Figure 3A. Primary Efficacy Endpoint and Its Components: Relative Risk with 95% Confidence Intervals.



[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 LOCF[41], 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.]

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[41] LOCF: Last observation carry forward.

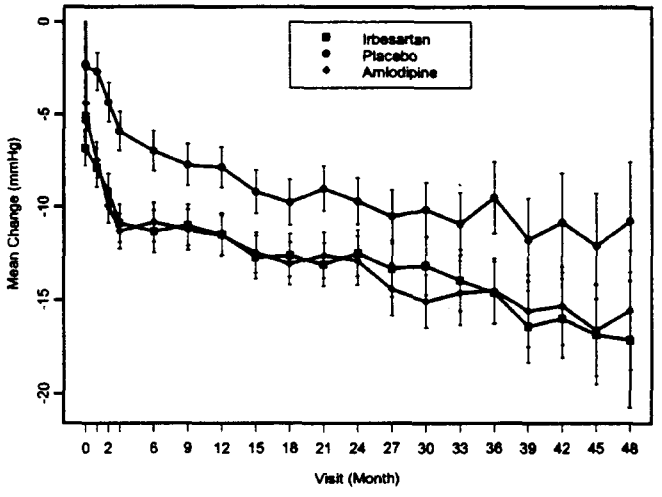
Table 15A. Treatment Comparisons at LOCF: Seated Mean Blood Pressure All Randomized Subjects

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 (±SD) change from baseline in MAP over the course of the trial for all treatment groups.

Figure 6A. Mean Change (±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)

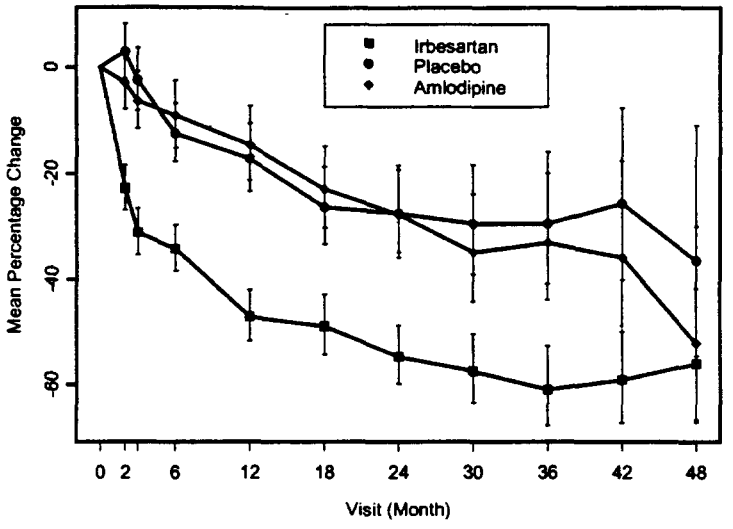
Group (N)	Estimate (95% CI)	Irbesartan *vs.* Placebo Estimate (95% CI)	p	Irbesartan *vs.* Amlodipine Estimate (95% CI)	p
Placebo (N=568)	0.55 (0.49, 0.62)	-0.13 (-0.22, -0.04)	0.004		
Irbesartan (N=578)	0.42 (0.35, 0.48)				
Amlodipine (N=565)	0.53 (0.47, 0.60)			-0.12 (-0.21, -0.02)	0.013

[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 (±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]

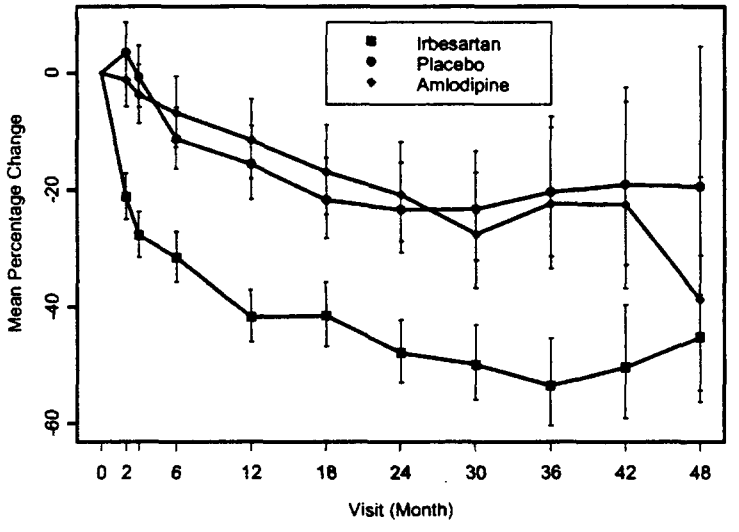
[42] NDA 20-757, Protocol CV 131-048, Tables S.10.4.3C2 and S.10.4.3D2.

Figure 7A. Geometric Mean (±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 (±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 (≥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 (≥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 (≥ 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 (≥ 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 (≥ 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, an non-IND study, examined the effect of Irbesartan in reducing the progression from albuminuria to overt nephropathy in hypertensive subjects with type 2 diabetes[48] and microalbuminuria[49]. The long-term effect (2 years) of 150 and 300 mg Irbesartan on the progression to clinical (overt) proteinuria[50] 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 agents[51] 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 hypertension[53] (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]

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[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 rate[57], 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.

Amendments[61]: The study protocol was amended nine times. The inclusion and exclusion criteria[62] as well as the primary endpoint[63] of the main study were amended.

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[55] Changed by Amendment No. 6.
[56] Changed by Amendment No. 3.
[57] GFR determination was performed by the total plasma clearance of ^{51}Cr-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)	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.

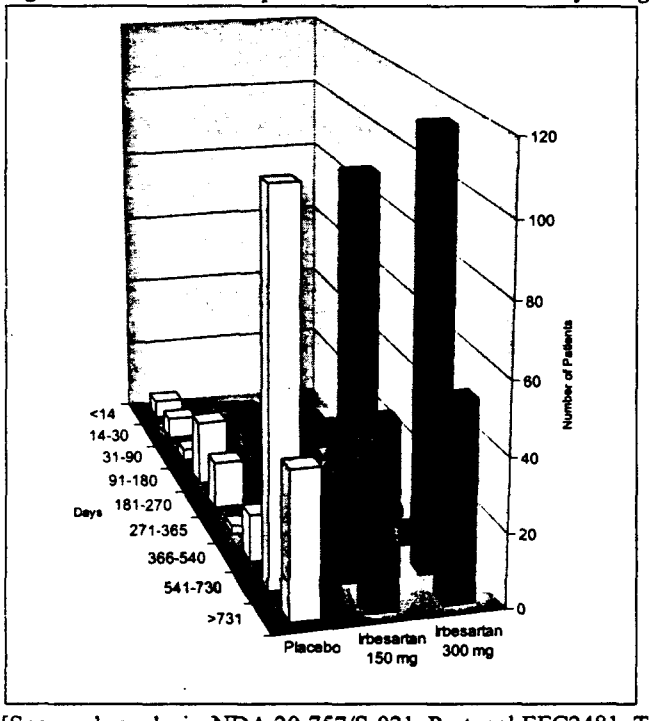
Table 3B. Reasons for Discontinuation During Double-Blind Therapy*

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 Compliance[67]***:*** 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 Medications[68]: "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 hydrazinophthalazone 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 μg/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 μg/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.

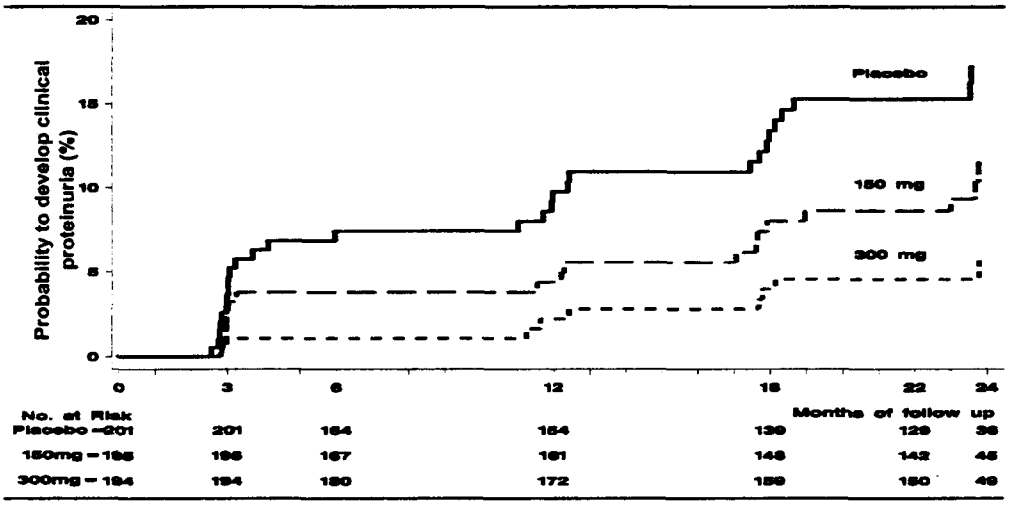
Table 5B. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 300 mg *vs.* Placebo Comparison): Intent-to-Treat Population

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]

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[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:							
vVVF, %	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 rate[74], 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/1.73m^2, 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 m^2) (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 ^{51}Cr-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.

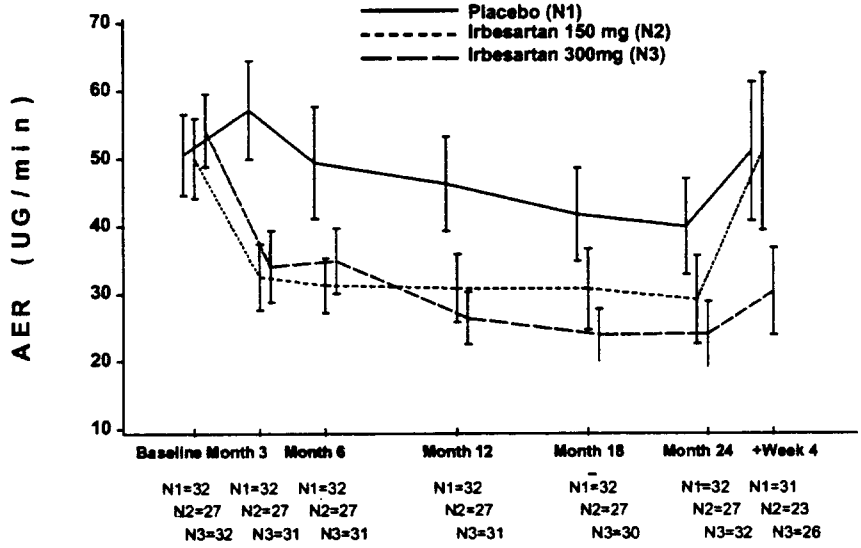
Table 13B. Mean (±SEM) Percentage Change in Glomerular Filtration Rate (mL/min/1.73 m^2) (Irbesartan vs. Placebo): GFR Sub-Study Extension (+Week 4) Subjects

Group	N	Baseline Month 24 GM±SEM	N	Change from Baseline GMPC±SEM	Difference with Placebo		
					Estimate	95% CI	p-Value
Placebo	27	96.1±4.9		5.7±2.1			
Irbesartan 150 mg	21	102.7±4.3		1.2±2.4	-4.3	(-10.4, 2.2)	0.18
Irbesartan 300 mg	26	97.8±5.3		3.7±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 (±SD) changes in urinary albumin excretion rate (µg/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 (±SD) values of urinary albumin excretion rate reached at + 4 weeks were 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 3B. Mean (±SD) Change in AER (µg/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."

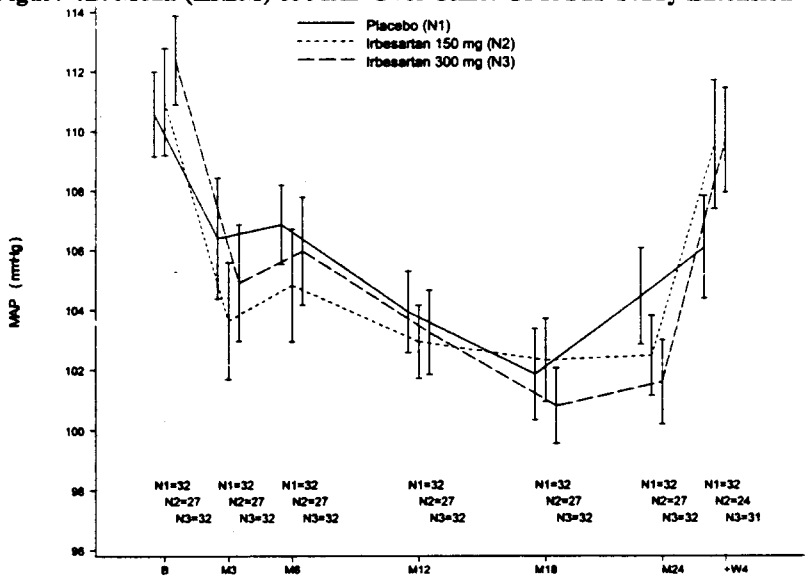
Table 15B. AER* in the GFR Sub-Study at Week 4 - Geometric Mean Percentage, Confidence Interval and p-Value for the Comparison of the Two Irbesartan Groups and Placebo

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 (±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 (±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 (±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 (±SEM) Percentage Change in Active 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	-6.0±16.3			
	24	27	40.8±19.8			
Irbesartan 150 mg	3	15	82.0±27.2	93.5	(11.8, 235.1)	0.020
	24	28	108.6±34.7	48.2	(-6.7, 135.4)	0.094
Irbesartan 300 mg	3	13	108.1±52.9	121.4	(25.4, 290.8)	0.0074
	24	26	250.4±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
HepaticBiliary	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 (≥ 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 ≥ 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."

Safety Update Review

There have been no safety updates since the original submission of August 3, 2001.