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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-757/S-021

Medical Review(s)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Secondary Clinical Review

NDA: 20-757

Sponsor: SmithKline Beecham

Submission: S-021 (August 3, 2001): a request to approve irbesartan for the treatment of diabetic nephropathy.

Review date: January 24, 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 20-757

HFD-110/Project Manager

HFD-710/Lawrence

HFD-110/Pelayo

With this efficacy supplement, there are no new pharmacology or toxicology studies, no new biopharmaceutics studies, and no proposed changes to the formulation.

The sponsor has sought a waiver of pediatric studies. Such a waiver should be granted in full; diabetic nephropathy is not a disease of children.

Financial disclosure information was provided for all 5 clinical studies that were submitted with the supplemental application. The sponsor categorically denies inappropriate financial arrangements as defined by 21CFR54.2(a), (b), or (f). Several investigators in the IDNT study reported equity interests exceeding \$50,000, but they collectively enrolled a small fraction of subjects in the study.

The supplemental application consisted of reports of 5 clinical studies. Three of these studies involved a total of about 100 subjects in studies lasting 1 day to 14 weeks; these studies were not reviewed in detail. Clinical (Dr. Pelayo) and statistical (Dr. Lawrence) reviews focussed on the IDNT and IRMA-2 studies. The primary reviews identified no issues pertaining to safety of use of irbesartan in this population.

IDNT was a double-blind study in which 1715 subjects with type 2 diabetes, hypertension, proteinuria >900 mg/d, and creatinine between 1¹ and 3 mg/dL were randomized to placebo, amlodipine 10 mg, or irbesartan 300 mg (titrated in two steps over 4 weeks), and followed for up to 57 months for the first occurrence of doubling serum creatinine, end stage renal disease, or death.

In comparison with placebo, irbesartan was associated with a 20% reduction in end point events (p=0.023). The effect of treatment appeared after about 18 months and diverged over at least the following 2 years. The amlodipine arm tracked the placebo

¹ 1.1 mg/dL in women.

group, despite having as good blood pressure control as did the irbesartan group; in comparison with amlodipine, the effect of irbesartan on end point events was quite statistically different ($p=0.006$).

The following are issues to be considered in interpreting the results of IDNT.

With a nominal p-value of 0.023 for the primary end point, the binary decision about whether this was a positive study is sensitive to a small number of events. Dr. Lawrence's informal analyses suggest that if 6 subjects were switched from lost to follow-up to having end point events at that time (irbesartan), or from events to lost (placebo), the p-value would have been >0.05 . Of course, missed events will have a greater effect the earlier in the study subjects are lost.

The Medical Review suggests other possible sources for affecting the p-value by the manner in which a small number of events are handled. These opportunities included subjects who were enrolled but never received study drug, subjects who discontinued before experiencing an end point event, subjects lost to follow-up for all or some of the primary end point components, end point events captured through unsystematic examination of non-study clinical records, and creatinine elevations that were "close" to doubling.

A large number of subjects were lost to follow-up for creatinine, but had mortal status determined to some later time. The sponsor used the last date of any follow-up as the censoring date for the subject. Since most of the treatment effect is on serum creatinine, this partial follow-up contributes noise. As part of this review, an analysis of primary end point events was performed with more appropriate censoring². The corresponding Kaplan-Meier plots and p-values, as computed by Dr. Lawrence, are shown in Figure 1.

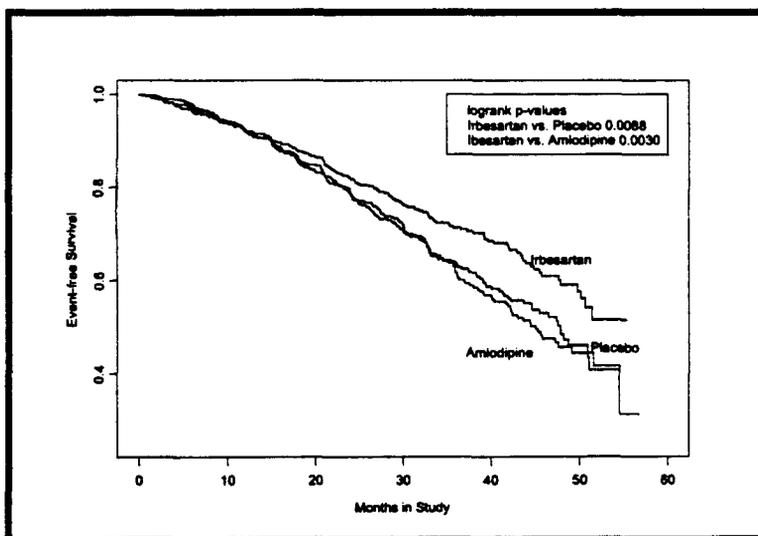


Figure 1. Kaplan-Meier analyses of primary end point (IDNT)

The figure is similar to the analyses in the primary medical and statistical reviews, but it censors subjects at the last creatinine assessment if they went more than 95 days from the last assessment without experiencing an end point event. The effect was to reduce the mean follow-up by about 6%.

² Creatinine assessments were supposed to be every 3 months (after the first few visits), so a subject who went more than 95 days without a recorded end point or a creatinine assessment was considered censored at the time of the last creatinine assessment.

Despite the large size of IDNT, there were potentially important imbalances in treatment groups with respect to 3 factors that the Advisory Committee believed to be important predictors of clinical outcome. The percentage of males, Blacks, and subjects over age 65 were all somewhat larger on placebo than on irbesartan³. The effect of these imbalances has not been formally assessed.

Because the US contributed the largest number of subjects, an unplanned analysis of the primary end point was performed by country, as shown in Figure 2. There was no regional heterogeneity.

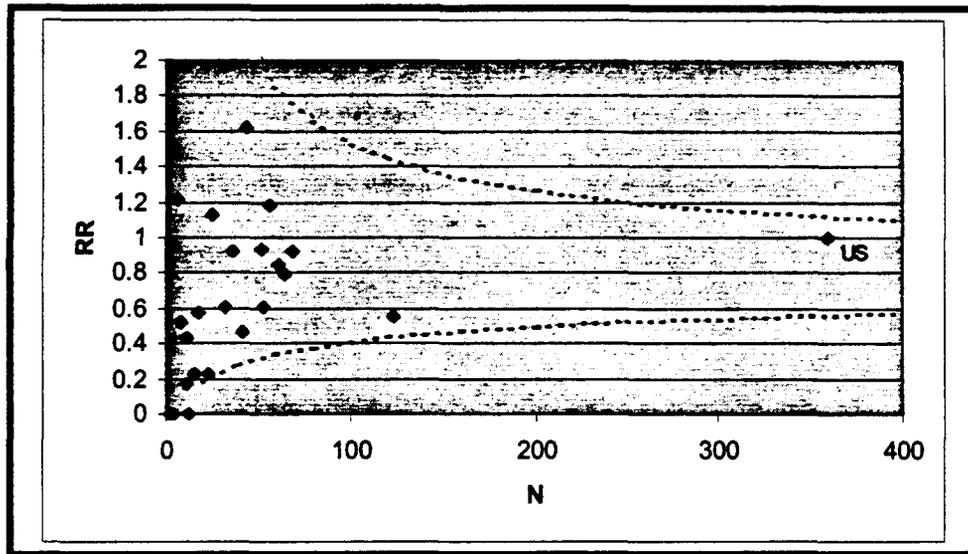


Figure 2. Relative risk of end point events by country (IDNT).

Relative risk of primary end point events was calculated by Dr. Lawrence. The plot shows relative risk (irbesartan over placebo) by number of subjects enrolled in the given country. The right-most data point represents the US. The bounding curves show the overall 95% confidence limits log-transformed and scaled by the square root of N.

In IDNT, the primary treatment effect was largely an effect on serum creatinine. There was little or no effect on death on end-stage renal disease (after exclusion of the serum creatinine component of sponsor-defined ESRD), as shown in Table 1.

Table 1. End point events (IDNT)⁴

	First event			Any event		
	Placebo N=569	Irbesartan N=579	RR (95% CI)	Placebo N=569	Irbesartan N=579	RR (95% CI)
Death	64	64	0.94 (0.67-1.33)	93	87	0.92 (0.69-1.23)
ESRD	47	43	0.88 (0.58-1.33)	101	82	0.77 (0.57-1.03)
Transplant	0	0	—	6	4	0.64 (0.18-2.26)
Dialysis	22	24	ND	86	73	0.80 (0.59-1.10)
SC>6	25	19	ND	57	36	0.60 (0.39-0.91)
SCx2 ⁵	135	98	0.67 (0.52-0.87)	135	98	0.67 (0.52-0.87)

³ See page 19 of the Medical Officer's Review dated 17 December 2001.

⁴ Largely adapted from page 3 of Statistical Review dated 7 November 2001.

⁵ Some subjects met doubling of creatinine and ESRD end points on the same date.

A comparison of primary end point events in all treatment groups is shown in Table 2.

Table 2. End point events at any time for all treatment groups (IDNT).

Events			Placebo N=569	Amlodipine N=567	Irbesartan N=579
Clin	ESRD				
		SCx2	135	144	98
	✓	SC>6	57	47	36
✓	✓	Dialysis	87	96	73
✓	✓	Transplant	6	7	4
✓		Death	93	83	87
	→	ESRD	101	104	82
→		Clinical events	157	153	145

There was a secondary end point in IDNT of time to first cardiovascular death, MI, hospitalization for CHF, disabling stroke, or above-the-ankle amputation. About 25% of subjects had such events, so there was reasonable power, but there was no evidence of a treatment benefit for irbesartan vs. placebo or irbesartan vs. amlodipine⁶.

There was a similar pre-defined end point of time to cardiovascular death, MI, unplanned coronary revascularization, or heart failure requiring hospitalization or open-label ACE inhibitor or angiotensin receptor blocker, disabling stroke, lower limb amputation, or unplanned peripheral revascularization. About 1/3 of subjects had such events, but there was no significant treatment benefit for irbesartan vs. placebo or irbesartan vs. amlodipine⁷.

Serum creatinine tended to increase over time in all treatment groups, but the average rate of rise was statistically significantly lower on irbesartan than on placebo (p=0.004) or amlodipine (p=0.01)⁸. The time course for this effect is shown in Figure 3.

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⁶ See page 31 of Medical Review dated 17 December 2001.

⁷ See page 31 of Medical Review dated 17 December 2001.

⁸ See page 32 of Medical Review dated 17 December 2001.

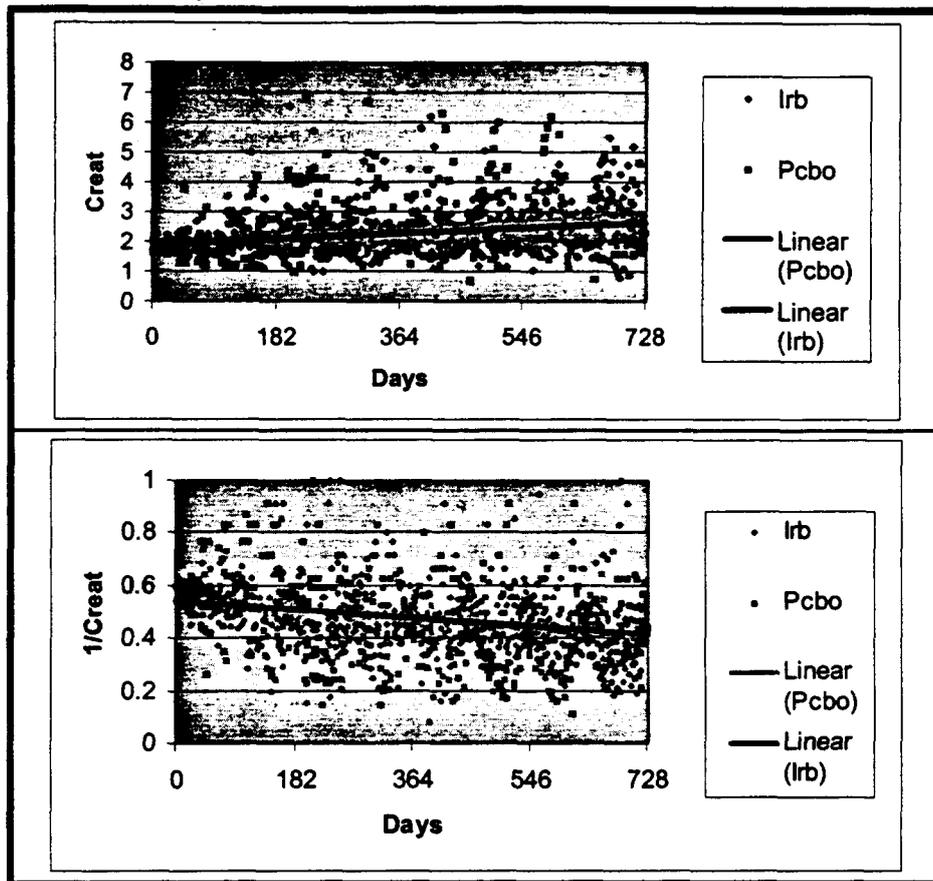


Figure 3. Serum creatinine measurements (IDNT)

The figure shows the mean serum creatinine values for subjects on placebo or irbesartan who had measurements on that day. The linear trend lines were probably not computed the same way by the sponsor.

Albumin and total protein excretion were lower on irbesartan than on placebo or amlodipine⁹. These differences developed early and parallel effects on blood pressure¹⁰.

The Advisory Committee expressed interest in BUN as a function of time. These data are shown in Figure 4.

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⁹ See page 33 of Medical Review dated 17 December 2001.

¹⁰ See page 31 of Medical Review dated 17 December 2001.

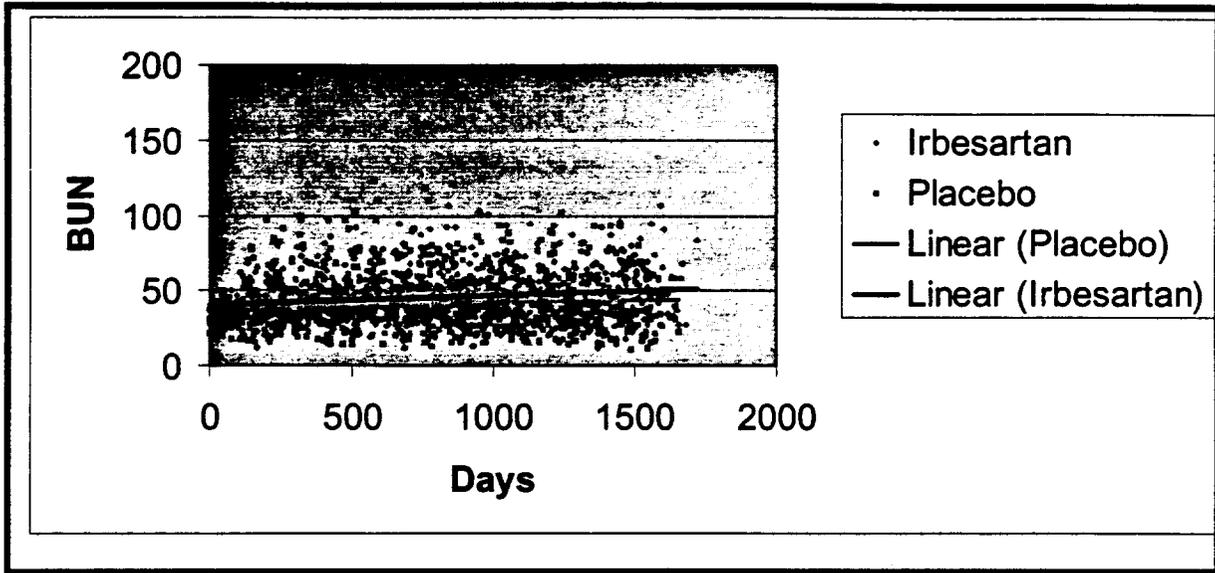


Figure 4. BUN values by time in study (IDNT).

Points show mean values of BUN by day for however many subjects happened to have measurements for that day. Lines were fit without any weighting for the numbers of subjects contributing to the average.

The Advisory Committee expressed interest in the time course of progression to death, dialysis, or transplant among the 377 subjects who experienced a doubling of serum creatinine. Survival curves for these data are shown in Figure 5.

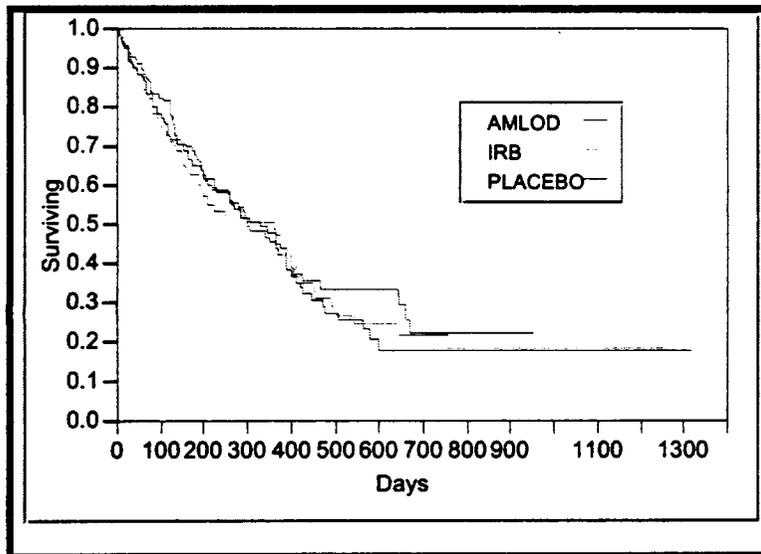


Figure 5. Event-free survival after creatinine doubling (IDNT).

Subjects whose serum creatinine doubled contributed to the analysis. Events of interest were death, need for dialysis, or renal transplant (not serum creatinine > 6)¹¹.

The results do not suggest a treatment effect among subjects whose creatinine doubled.

¹¹ SELECT EVENT_A.RANDGRP, If{[dial],[daysdial]},If{[tran],[daystran],[daysdth]})-[daysdbl] AS d, 1+([dial] Or [tran] Or [death]) AS cens FROM EVENT_A WHERE (((EVENT_A.DBL)<>0));

IRMA-2 was a double-blind study in which 611 subjects with type 2 diabetes, hypertension, albuminuria <0.29 g/d, and serum creatinine <1.5 mg/dL¹² were randomized to placebo or irbesartan 150 or 300 mg, and followed for 24 months for the appearance of "clinical proteinuria", defined as >0.29 g/d and >30% increase from baseline.

In comparison with placebo, the group on irbesartan 300 mg had a 70% reduction in the risk of developing clinical proteinuria (p=0.0004), and the irbesartan 150 mg group had an effect that fell in between (p=0.085)¹³.

The following are issues to be considered in interpreting the results of IRMA-2.

Serum creatinine rose in all treatment groups of IRMA-2. The slope of this rise was not significantly different among groups, but creatinine levels tended to increase more quickly in the irbesartan arms¹⁴. Perhaps this effect, if it is real, is a result of volume contraction, but it is certainly not indicative of beneficial effects on renal function.

One hundred thirty-three subjects participated in a GFR sub-study of IRMA-2. GFR tended to decrease over time in all treatment groups. The GFR decrease at 24 months was not statistically different among groups, but the decreases trended larger on irbesartan¹⁵. This is certainly not indicative of a beneficial effect on renal function.

Subjects in the GFR sub-study of IRMA-2 also had a final assessment of albumin excretion rate 4 weeks after the last dose of study drug. Compared with the month 24 data, albumin excretion increased in all treatment arms 4 weeks after the last dose. The sponsor's statistical analysis indicates no treatment effect. This is not indicative of a sustained, anatomically mediated effect on renal function. At the low dose, the entire treatment effect disappeared by 4 weeks after the last dose.

Safety in this development program for hypertensives with type 2 diabetes looked much like the safety experience in overall program for hypertension, with the following noteworthy exceptions. Orthostatic hypotension, orthostatic dizziness, and dizziness in general were quite common, regardless of treatment group, but all were most common on irbesartan. In addition, elevations in serum potassium were much more common on irbesartan; this was a more frequent cause for discontinuation from the irbesartan treatment arm than from placebo. The sponsor's proposed description of these findings in the label seems adequate.

The development program for irbesartan should be considered in the context of two other programs for diabetic nephropathy, those for captopril and losartan.

Captopril is the only drug approved for the treatment of diabetic nephropathy. Its approval was based largely on an IDNT-like study in which 409 subjects with type I diabetes, proteinuria >500 mg/d, retinopathy or biopsy-proven nephropathy, and serum creatinine <2.5 mg/dL were randomized to placebo or to captopril 25 mg t.i.d. and followed for up to 4 years (mean of 2 years) for development of doubling of serum creatinine to >2 mg/dL, end-stage renal disease¹⁶, or death.

The captopril treatment group had 50% fewer end point events (p=0.004), and although the end point was driven by doubling of serum creatinine, 96% of doubling events were followed by death or end stage renal disease. The risk reduction was in the

¹² <1.1 mg/dL in women

¹³ See page 44 of Medical Review dated 17 December 2001.

¹⁴ See page 46 of Medical Review dated 17 December 2001.

¹⁵ See page 50 of Medical Review dated 17 December 2001.

¹⁶ Transplant or dialysis only.

neighborhood of 50% for all components—creatinine doubling, ESRD, and death—of the primary end point. This study also demonstrated better preservation of creatinine clearance (statistically significant).

Does the captopril experience establish a relevant prior expectation for interpreting the irbesartan data? Captopril is an ACE inhibitor, and irbesartan is an angiotensin receptor antagonist, so the underlying presumed mechanisms of action are related, but they are not the same. The captopril program was in type 1 diabetes, while irbesartan was studied in type 2's, but the pathophysiology and clinical course of diabetic nephropathy is thought to be similar¹⁷.

If the captopril data are relevant to irbesartan, do they support irbesartan? The irbesartan data rule out, with >95% confidence, an effect on the composite end point as large as the estimated effect of captopril. Effects of captopril on doubling of creatinine were visible within the first few months of study and the between-group difference grew over time, while the effects of irbesartan appeared only after about 18 months and diminished towards the end of study. What effect there was with irbesartan was little manifest in end stage renal disease or mortality, but in both cases excluding, with >95% confidence, effects as large as were seen with captopril, and this was not simply a problem of power. Again, effects of captopril on end stage renal disease or death appeared in the first few months of study and the difference increased throughout the study.

Are the differences between the effects of captopril on type 1 diabetes and irbesartan on type 2 diabetes attributable to differences in baseline disease severity? This can best be addressed by comparing the two placebo groups, as shown in Table 3.

Table 3. Comparison of captopril and irbesartan placebo groups.

	Captopril Study 257	Irbesartan IDNT
N	202	569
Duration of diabetes	21 y	15 y
Baseline creatinine mg/dL	1.3	1.7
Baseline urinary protein g/d	3.0	3.1
HbA1c %	11.6	8.2
Duration of follow-up		
Max	54 mo	57 mo
Median	2 y+	2 y+
Mortality	7%	16%
ESRD ¹⁸	15%	16%

Compared with the pivotal study with captopril, IDNT enrolled subjects with a similar degree of protein excretion and somewhat higher baseline serum creatinine. With similar degrees of follow-up, the placebo group in IDNT had a similar amount of end-stage renal disease and a higher mortality rate than the captopril study's placebo group. Despite a high placebo group event rate, IDNT, with almost 3 times as large a sample size, showed little effect of treatment on mortality and end stage renal disease.

Either the captopril data are really irrelevant to irbesartan—perhaps because of population differences—or there is a problem reconciling these datasets, especially with respect to treatment effects on ESRD and mortality.

¹⁷ At least type of diabetes per se does not seem to be a recognized risk factor for progression of diabetic nephropathy.

¹⁸ Transplant or dialysis only.

Are differences between clinical outcome with captopril and irbesartan attributable to differences in effects on protein excretion? In both studies, the placebo group experienced about 20% reduction in proteinuria¹⁹, while the reduction on captopril was about 30% and the reduction on irbesartan was about 45%. Clearly, the magnitude of reduction in proteinuria is an unsatisfactory indicator of effects on clinical events.

Losartan has been the subject of a similar development program, but it has not been reviewed by the Agency. In a parallel, double-blind study²⁰ (RENAAL), 1513 subjects with type 2 diabetes, hypertension, albuminuria >500 mg/d, and creatinine 1.3-3 mg/dL, and without recent history of MI, CABG, CVA, TIA, or heart failure, were randomized to placebo or losartan 100 mg and followed for an average of 3.4 years.

There was a 16% reduction (p=0.02) in the primary composite end point of doubling of creatine, ESRD, and death. While there was no effect on death, there was a 25% reduction in doubling of serum creatinine and a 28% reduction in ESRD²¹. Between-group differences developed after 1 year of treatment.

There was no effect on a secondary end point of cardiovascular morbidity and mortality (although the publication claims an effect on some components of the combined end point). Protein excretion was reduced by about 30% at 24 months and the rate of decline in renal function, as assessed by 1/creatinine and GFR, was less on losartan than on placebo, but, the authors note, these effects were much smaller than was reported with captopril.

Summary. In a population of type 2 diabetes mellitus manifesting gross proteinuria, IDNT demonstrated irbesartan to have an effect compared with placebo, on serum creatinine, marginal by the sponsor's analysis, but relatively robust but the analysis described herein. This effect received some corroboration in comparison with amlodipine, but (a) this is not the evidentiary equivalent of a second study, and (b) the result is as strong as it is because amlodipine is somewhat worse than placebo.

Serum creatinine rises in diabetic nephropathy presumably as a result of reduced creatinine clearance, a marker of renal function. IDNT had no independent measure of renal function.

Urinary protein excretion was reduced in IDNT and in IRMA-2, in the earlier stage population of type 2 diabetics. The nature of the link between proteinuria and reduced renal function is unclear. Some non-diabetic nephropathies are associated with larger protein excretion rates and slower loss of renal function. In IDNT, there was a year's delay or more between the emergence of effects on protein excretion and effects on creatinine, and little effect of clinical outcomes with years of follow-up. IRMA-2, with shorter follow-up and a population more distant from clinical events, had little chance of showing effects on renal function or clinical outcomes. At best, the link between reduction in proteinuria and clinical benefit is unproven in general or as effected by irbesartan.

IRMA-2 suggests that treatment effects on proteinuria are not preserved for long after discontinuation of study drugs. This result is suggestive that irbesartan affects renal hemodynamics rather than producing structural changes.

The Advisory Committee exhibited a remarkable interest in non-irbesartan trials to make a decision about irbesartan. They voted 10:1 against approval based on the

¹⁹ Geometric means compared, arbitrarily, at 24 months. Data for irbesartan from Medical Review dated 17 December 2001. Data for captopril from Joint Medical and Statistical Review dated 10 November 1993.

²⁰ *New England Journal of Medicine* (2001) 345:861-869.

²¹ *Transplant or dialysis only.*

results of the irbesartan development program alone²², but 4 members voted in favor of approval because of prior expectations generated by studies of captopril and losartan.

In comparison to captopril's pivotal study, irbesartan's IDNT study demonstrated smaller effects on serum creatinine, end stage renal disease, and mortality, despite a high event rate in the placebo group and a larger study. Whether differences between these development programs are attributable to treatments or populations cannot be ascertained from available data. At best, the captopril experience in diabetic nephropathy is not well recapitulated with irbesartan. The more relevant one considers the captopril data to be, the more troubling are the discrepancies in outcomes.²³

As far as one can judge from the RENAAL publication, losartan looks superficially much like irbesartan, but losartan has a better apparent claim for beneficial effects on end stage renal disease. The sponsor's pre-NDA presentation of the RENAAL data gives reason to be cautious in their interpretation.

It is also worthwhile to note that irbesartan is an approved drug and that the IDNT and IRMA-2 studies have been published. There is, therefore, no barrier to the proposed use of irbesartan. The regulatory question is whether the data support advocating this use of irbesartan.

With small and doubtful effects on serum creatinine, and less evidence of effects on end stage renal disease or mortality—real clinical benefit—irbesartan should not be approved for use in diabetic nephropathy associated with type 2 diabetes. Existing data do not make a subsequent placebo-controlled outcome study unethical, although a non-inferiority trial with captopril would be of great interest.

Alternatively, the Agency might consider an approval under Subpart H. The basis of approval would be the adequate demonstration that irbesartan reduces time to doubling of serum creatinine. One might consider the further follow-up for clinical events of subjects from IDNT to be an adequate post-marketing study.

Among drugs to treat diabetic nephropathy, available data do not demonstrate a strong relationship between effects on proteinuria and clinical benefit. The Advisory Committee unanimously agreed with this position.

Neither the primary medical review (which recommended approval) nor this secondary review (which does not) contains marked-up labeling. How to describe the trial results and the indication depends on the basis for approval.

**APPEARS THIS WAY
ON ORIGINAL**

²² Review of the transcript will, I believe, show the lone dissenting voter was considering non-irbesartan trials in explaining his position.

²³ If one were to rely much upon the captopril data in type 1 diabetes to support the approval of irbesartan in type 2 diabetes, one should consider that the captopril data are, by themselves, much more compelling. If that experience is relevant, then perhaps captopril deserves a claim in type 2 diabetes. But then, if one were willing to have attested to the relevance of captopril before the IDNT and RENAAL studies were undertaken, then it seems they would not have been ethical.

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**MEDICAL REVIEW
ADDENDUM**

NDA No.: 20-757

DRUG NAME: Avapro® (Irbesartan) Tablets

SPONSOR: Bristol-Myers Squibb Company

P.O. Box 4000

Princeton, NJ 08543-4000

TYPE OF DOCUMENT: Amendment (dated April 4, 2002) to Supplement NDA 20-757/S-021

DATE RECEIVED: April 5, 2002

DATE REVIEW COMPLETED: May 1, 2002

MEDICAL REVIEWER: Juan Carlos Pelayo, M.D.

BACKGROUND

Bristol-Myers Squibb and Sanofi-Synthelabo jointly sponsored the clinical development of Avapro® (Irbesartan) for the treatment of renal disease in patients with type 2 diabetes mellitus. In essence, the effectiveness of Irbesartan in modifying the “natural history” of diabetic nephropathy, and thus morbidity and mortality, was evaluated in two clinical trials¹, IRMA 2 and IDNT. The results from these trials were published in the *New England Journal of Medicine*² and submitted to the FDA by the sponsor as an efficacy supplement (S-021) for NDA 20-757 on August 3, 2001. The new indication for Avapro® (Irbesartan) sought by the sponsor is for the “treatment of type 2 diabetic renal disease”.

The results of the efficacy supplement were presented and reviewed at the Cardio-Renal Advisory Committee on January 17, 2002. At the Advisory Committee meeting, the members of the panel requested additional follow-up clinical event data, specifically on dialysis, transplant or death. To that end the sponsor is now providing an amendment to the efficacy supplement to incorporate the new information requested, i.e., dialysis status, transplantation status, and vital status on those subjects who had an event of doubling of serum creatinine during the study period.

The primary purpose of this post-study data collection was to assess the impact of extended follow up on the frequency of dialysis, transplantation or death in subjects whose serum creatinine concentration had doubled. More specifically, these data were collected in an effort to further demonstrate that subjects who had a doubling of serum creatinine eventually required transplantation or dialysis; i.e., that creatinine doubling is predictive of impending renal failure in this population.

METHODS

To obtain the data for this addendum, the sponsor requested from the original sites on a post-study basis information on dialysis, transplantation, and vital status for a cohort of 246 subjects. The data was gathered via a questionnaire. The cohort was selected using the following criteria:

- a) Subjects who had a doubling of serum creatinine during the study period, but for whom there was no reported renal transplantation, dialysis, or death up to study closure on December 31, 2000 (n = 179);
- b) Subjects who both doubled and died during the study period without recording a transplantation or dialysis, since such subjects might have had an unreported transplant or dialysis (n = 21); and
- c) Subjects who did not reach a renal endpoint or die, but whose date of last known transplant/dialysis status preceded the study closure period (n = 46).

For purposes of defining this cohort, the date of the last known transplant/dialysis status for those subjects not recording transplantation or dialysis was taken as the date of the final clinical visit if that was the last contact, or as the last known alive date if there was contact (with the subject or other responsible party) after the final clinical visit. The new information requested was dialysis status, transplantation status, and vital status (alive/dead), as of the present time, together with the date of last known follow up.

RESULTS

By the questionnaire lock date of March 22, 2002, 154 (62.6%) out of 246 questionnaires sent to the sites had been returned, and 142 (57.7%) contained usable information. Dialysis, transplant and mortality status

¹ Protocols CV131-048 (IDNT, Irbesartan Diabetic Nephropathy Trial) and EFC2481 (IRMA 2, Irbesartan MicroAlbuminuria in Type 2 Diabetes).

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

remains unknown in 12 subjects.

Follow-up data from the questionnaire identified 54 newly reported events. Of the 54 newly reported events, 12 occurred in irbesartan-treated subjects, 18 in placebo-treated subjects and 24 in amlodipine-treated subjects. Overall, 231 (61.3%) of the 377 subjects who doubled creatinine are now reported to have subsequently reached dialysis or transplantation, and 265 (70.3%) subjects to have subsequently reached dialysis, transplantation, or death from any cause (Table I).

Table I. Number (%) of Subjects with Dialysis, Transplantation, or Death (to 22/Mar/2002) after Doubling of Serum Creatinine*

Event	Number (%) of Subjects [†]			
	Placebo N = 135	Irbesartan N = 98	Amlodipine N = 144	Total N = 377
Dialysis/Transplant	85	60	86	231 (61.3)
Dialysis/Transplant/Death	94	71	100	265 (70.3)
Breakdown of Dialysis/Transplant/Death:[‡]				
Dialysis first	83	58	86	227 (60.2)
Transplant first	2	2	0	4 (1.1)
Death (all cause) without Dial. or Trans.	9	11	14	34 (9.0)
Total Incidence of:[§]				
Dialysis	83	58	86	227 (60.2)
Transplant	6	5	5	16 (4.2)
Death (all cause)	22	20	26	68 (18.0)

[Sponsor's analysis. Source: NDA 20-757/S-021, Supplement Amendment dated April 4, 2002. *Includes cases where date of event is on or after date of doubling. [†]One subject with dialysis in the Placebo group could not be included in the event counts because the date of dialysis was not available. [‡]First component to occur in dialysis/transplant/death; first two rows give a breakdown of dialysis/transplant. [§]Individual components are not mutually exclusive and thus do not give a breakdown of composite endpoints.]

COMMENTS³

In summary, the new data is in keeping with the conclusion from the original IDNT study report, i.e. that treatment with irbesartan delays the progressive nature of the nephropathy associated with type II diabetes mellitus.

APPEARS THIS WAY
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³ When interpreting the updated results contained in this addendum, it should be noted that the design of the study was carried out according to the principles that the Collaborative Study Group established in the Type I diabetic nephropathy study with captopril. When a subject reached doubling of serum creatinine as a clinical endpoint, coded medication was stopped to allow the study investigator to treat the subject outside of the protocol. As a consequence, the interval between doubling of serum creatinine and events that occurred after December 31, 2000 is further increased.

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/s/

Juan Carlos Pelayo
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INTRODUCTION AND BACKGROUND¹

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

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

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

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

GENERAL INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

DESCRIPTION OF CLINICAL DATA AND SOURCES

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

Table 1: Study Design of IRMA 2 and IDNT

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

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

Table 2: Study Design of Supportive Studies

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

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

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

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

INTEGRATED REVIEW OF EFFICACY

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

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

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

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

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

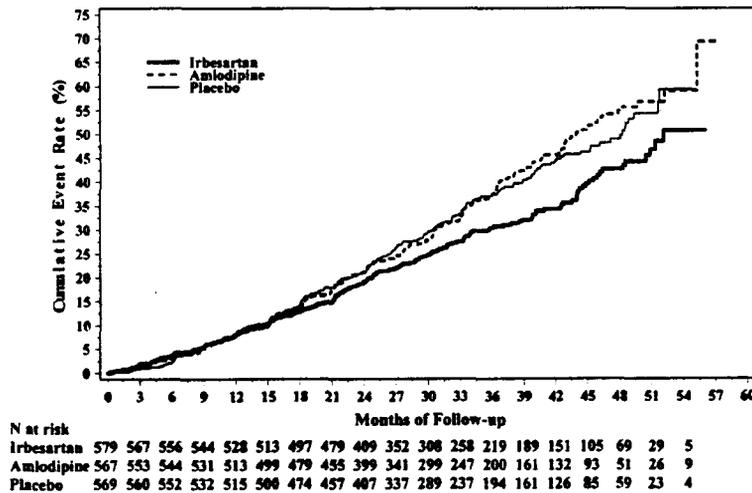
Table 3. Primary Endpoint Comparison: Irbesartan vs. Placebo

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

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

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

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



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

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

⁶ Sponsor's analyses.

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

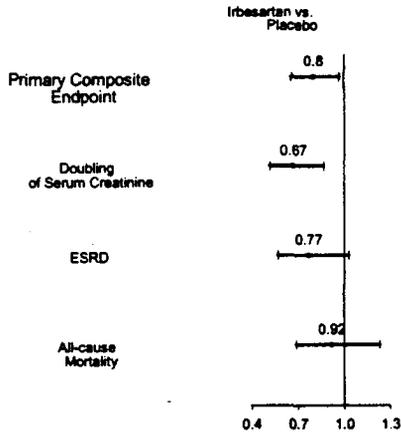
Table 4. Individual Components of Primary Composite Endpoint

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

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

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

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



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

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

⁷ Percent of the total number of events.

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

⁹ Sponsor's analyses.

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

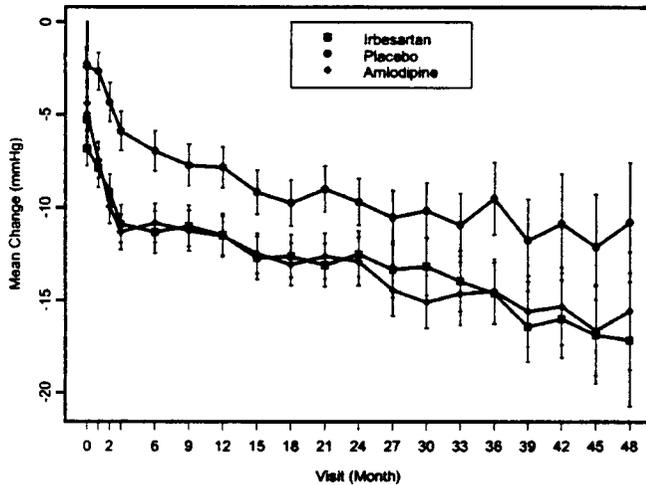
The secondary analysis for the primary endpoint was the comparison of Irbesartan vs. Amlodipine. Irbesartan treatment resulted in a relative risk reduction of 23% vs. Amlodipine (estimate 0.77, 95% CI: 0.63-0.93, $p=0.0064$). This treatment effect in favor of Irbesartan was primarily driven by a significant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

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

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

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

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



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

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

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

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

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

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

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

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

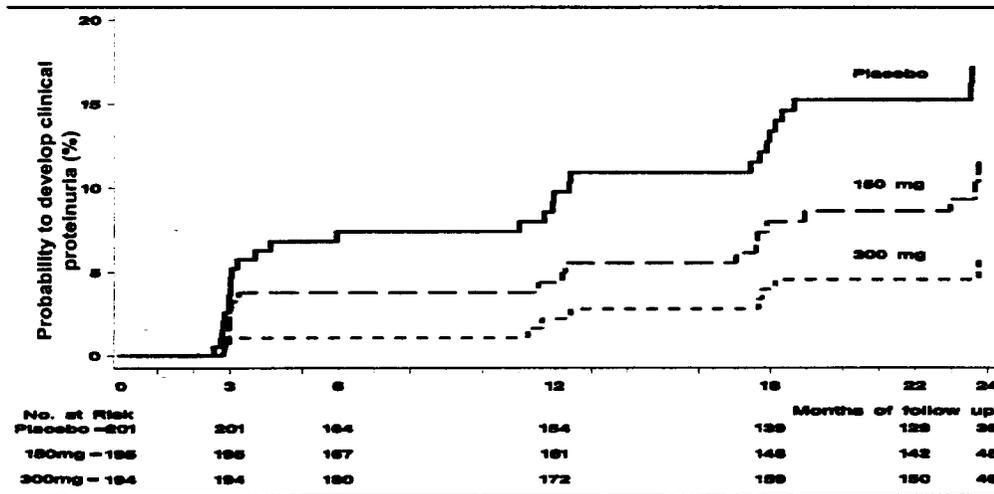
Table 6. Primary Endpoint Analysis: Time to Occurrence of Clinical Proteinuria (Irbesartan 300 mg vs. Placebo Comparison): Intent-to-Treat Population

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

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

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

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



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

¹¹ Changed by Amendment No. 6.

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

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

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

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

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

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

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

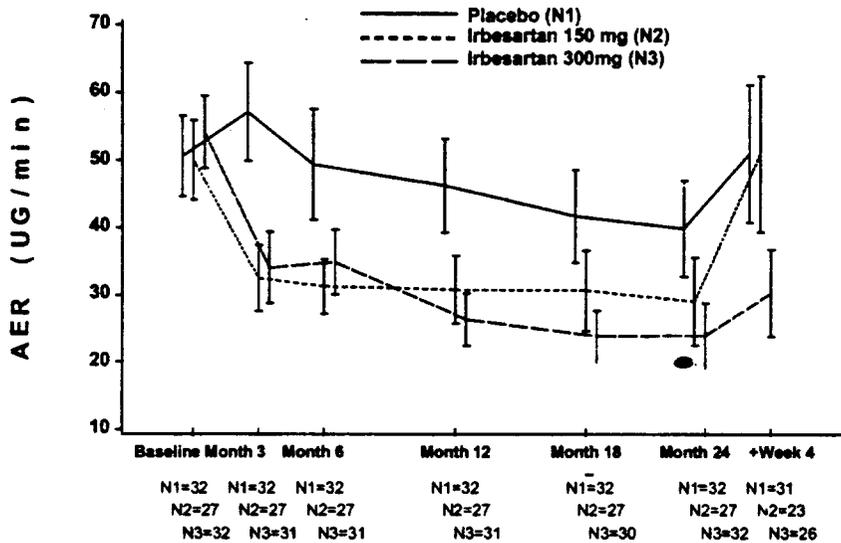
Four weeks after study drug and concomitant antihypertensive medications were discontinued at month 24, GFR increased slightly in all groups but the mean values remained below baseline values and were not statistically different from each other (see Appendix, Individual Study Reviews). The urinary albumin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

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

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

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

Figure 5. Mean (±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.]

INTEGRATED REVIEW OF SAFETY

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

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

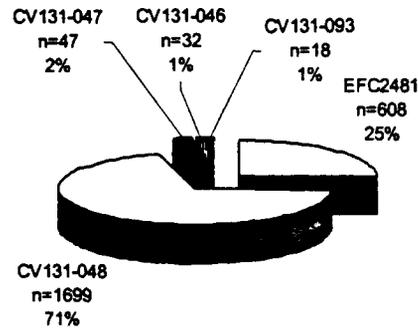
Two thousand four hundred and four hypertensive patients with type 2 diabetic nephropathy¹⁵, were exposed to study drugs in five completed clinical studies: 2307 were exposed to study drugs in the two main efficacy/safety studies IRMA 2 and IDNT, the remaining 97 subjects were exposed to study drugs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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

DOSING, REGIMEN, AND ADMINISTRATION ISSUES

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

USE IN SPECIAL POPULATIONS

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

CONCLUSIONS AND RECOMMENDATIONS

A. CONCLUSIONS

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

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

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

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

B. RECOMMENDATIONS

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

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

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

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

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX

C. Other Relevant Material

Not applicable.

D. Individual Study Reviews

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

INVESTIGATIONAL PLAN

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2A. Distribution of Patients by Region

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

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

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

Table 3A. Disposition of Subjects

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

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

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

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

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

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

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

Table 5A. Subjects Who Were Lost to Follow Up

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

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

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

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

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

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

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

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

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

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

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