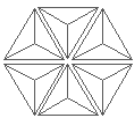

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FDA Advisory Briefing Book for Avapro® (irbesartan) Tablets NDA 20-757 (S-021)

Cardiovascular and Renal Drugs Advisory Committee

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Worldwide Clinical Research and Development
Bristol-Myers Squibb Pharmaceutical Research Institute
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EXECUTIVE SUMMARY

Introduction

Diabetic renal disease is a significant unmet medical need in a high risk population. Because of the scope of this problem, it represents a serious public health concern. In the United States approximately 42%-45% of all new cases of End Stage Renal Disease (ESRD), defined by the need for dialysis or renal transplantation, are attributed to diabetes, with the majority of patients having type 2 diabetes. Worldwide 135 million patients have diabetes with projections for the prevalence to rise to 300 million patients by 2025. Given the high costs (> $15 billion annually in the United States alone) of treatments including peritoneal dialysis, hemodialysis, and renal transplant that are associated with the development of ESRD and the high annual mortality rate in patients with diabetic ESRD, efforts must be undertaken to preserve renal function in these patients.

By the time patients are diagnosed with type 2 diabetes, hypertension is very common, especially among those with renal disease as manifested by increased urinary albumin excretion. As urinary albumin excretion increases, the prevalence of hypertension increases in these patients. The combination of type 2 diabetes, hypertension and diabetic renal disease places patients at high risk of morbidity and mortality. Once ESRD develops, average life span is dramatically reduced compared to age-matched controls without ESRD. Approximately 40% of patients with diabetic ESRD die annually; most deaths are due to cardiovascular causes.

The Continuum of Diabetic Renal Disease

The natural history of diabetic renal disease is characterized by a continuum of renal abnormalities with altered glomerular morphology and function. This continuum of abnormalities is predictable, sequential and progressive, leading to proteinuria, decreased glomerular filtration rate, and ultimately ESRD. Type 2 diabetic patients follow a similar natural history to that of type 1 diabetic patients, in whom the natural history has been extensively characterized.

One of the earliest clinical manifestations in the continuum of diabetic renal disease is the appearance of low but abnormal levels (≥ 30 mg per 24 hours) of albumin in the urine.

This is referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient diabetic renal disease. Microalbuminuria is a marker for both progressive kidney damage and cardiovascular disease. Presence of microalbuminuria in normotensive subjects with either type 1 or type 2 diabetes is associated with a three-to five-fold greater risk of cardiovascular mortality and a greater than tenfold risk of renal mortality (progression to dialysis) when compared with diabetic subjects without microalbuminuria.

In patients with incipient diabetic renal disease, the glomerular filtration rate (GFR*)* can be either normal or supernormal (i.e., hyperfiltration is occurring). The decline in GFR during this phase of the continuum is relatively slow (approximately 2.4 mL/min/yr). Without specific interventions, 20-40% of type 2 diabetic patients with sustained microalbuminuria progress to the next step in the continuum, to clinical (i.e., overt) proteinuria. Clinical (overt) proteinuria is defined as urinary albumin excretion rate (AER) ≥ 300 mg per 24 hours. Other terms have been variably used to identify patients reaching this step on the continuum. These terms include clinical albuminuria, macroalbuminuria, diabetic nephropathy and overt nephropathy.

Once overt proteinuria occurs, without specific interventions, the GFR gradually declines over several years at a rate that is highly variable from individual to individual (2-20 mL per minute per year with an average value of 10 mL per minute per year).

Also, along the continuum, glomerular morphologic changes occur which include mesangial expansion, glomerular basement membrane thickening, diffuse or nodular glomerulosclerosis, and microvascular changes, including arteriolar hyperplasia and hyalinosis. Angiotensin II (AII) is believed to be an important factor influencing these morphologic changes.

Of note, there is distinctly increasing mesangial expansion as patients progress from a normal urinary AER through microalbuminuria and overt proteinuria. Diabetic patients with incipient diabetic renal disease and microalbuminuria already have, on kidney biopsy, a larger fractional mesangial area (i.e., mesangial expansion) than diabetic patients with a normal urinary AER. Importantly, compared to those diabetic patients with microalbuminuria, patients with overt proteinuria have an even greater increased mesangial expansion which is likely due to the longer duration of disease.

Once patients develop microalbuminuria, their glomerular collagen synthesis rates become very similar to that seen in patients with overt proteinuria, both rates quite elevated from that seen in patients with a normal urinary AER. Nevertheless, patients with a normal urinary AER and microalbuminuria have very similar creatinine clearance.

Thus, increasing urinary albumin excretion, which is clinically easy to measure and monitor, reflects worsening abnormalities at the glomerular level.

Overt proteinuria is a modifiable marker that predicts progression to ESRD. The magnitude of proteinuria is directly correlated with risk for ESRD and the rate of progression to renal failure. In addition, at any given level of proteinuria, the higher the blood pressure, the more detrimental is the effect of proteinuria on progression to renal insufficiency and renal failure.

When renal insufficiency progresses, as manifested by increasing serum creatinine levels, patients are at increased risk for ESRD. Increasing serum creatinine levels correlate with loss of GFR. In particular, when a patient's serum creatinine doubles from a baseline value, that patient has lost one half of their renal function. In a clinical trial with captopril in type 1 diabetic patients with overt proteinuria, once serum creatinine levels doubled from baseline, the median time from doubling to ESRD was only 9.3 months. Thus, doubling of serum creatinine represented a very advanced worsening of renal insufficiency in these patients.

The median time to the development of ESRD after the onset of overt proteinuria in type 2 diabetic patients appears to be generally consistent with the above data in type 1 diabetic patients. Registry data from Minnesota in predominantly Caucasians with type 2 diabetes showed the median duration from onset of proteinuria to the development of ESRD to be 7 years. In the PIMA Indians the cumulative incidence of chronic renal failure in type 2 diabetic patients who developed persistent proteinuria was 40% at 10 years and 61% at 15 years after the diagnosis of proteinuria. The incidence of ESRD was significantly related to the duration of diabetes, duration of proteinuria, extent of hyperglycemia, type of diabetes treatment, and presence of retinopathy.

Once ESRD develops, average life span is dramatically reduced. The average survival time for patients with ESRD is 4-5 years. Furthermore, mortality among diabetics with

ESRD is approximately 1.5 to 2.5 times greater than that among nondiabetics with ESRD. Less than 20% of diabetics with ESRD survive 5 years after initiation of dialysis.

Thus, diabetic renal disease is characterized by a predictable, sequential and progressive spectrum of abnormalities, ultimately ending in ESRD. One major goal of treatment is to prevent or slow the progression to ESRD.

Strategies to Prevent Progressive Diabetic Renal Disease

Current treatment options to slow the progression of diabetic renal disease include strict blood glucose and blood pressure (BP) control and interventions to control increases in urinary albumin and protein excretion.

Effective BP control decreases the fall of GFR and lowers AER in hypertensive patients with diabetes. The combination of reduced urinary AER and lowered BP has been shown to delay the progression of diabetic renal disease. To date, lowering BP with any antihypertensive medication is generally thought to protect kidneys from functional decline. In a landmark trial with captopril in type 1 diabetic patients with overt nephropathy, this concept was challenged.

Since angiotensin II (AII) is believed to be an important factor influencing pathologic glomerular morphologic changes, drugs which lower BP by inhibiting the action of AII were hypothesized to provide renal protection above and beyond that from BP reduction alone. Specifically, drugs such as captopril which lower BP by inhibiting the renin-angiotensin-aldosterone (RAS) system were prime candidates to study.

A randomized, controlled trial was conducted to compare the antihypertensive drug captopril, an angiotensin converting enzyme inhibitor (ACE-I) with placebo in 409 patients with type 1 diabetes, diabetic retinopathy, proteinuria $\geq$ 500 mg per day, and serum creatinine concentrations $\leq$ 2.5 mg/dL. For BP control those patients randomized to placebo were given a variety of adjunctive antihypertensive medications excluding ACE inhibitors.

Captopril reduced the rate of progression of diabetic nephropathy in type 1 diabetic patients to a greater degree than would be expected from BP reduction alone. Median follow-up was 3 years. The primary endpoint was a doubling of the baseline serum

creatinine concentration. Captopril slowed the progression of diabetic nephropathy, reducing the risk of a doubling of serum creatinine by 48% ($p = 0.007$). Captopril was also associated with a 50% risk reduction of the composite endpoint of death, need for dialysis, or transplantation.

By demonstrating the additional renoprotective benefit of captopril above and beyond that achieved from BP control alone, this landmark trial changed the treatment practices of physicians, especially in type 1 diabetic patients. However, until now, in type 2 diabetic patients with diabetic renal disease there have been no adequately-sized, prospective, randomized clinical trial data demonstrating greater renal protection from one drug class over another on clinically relevant renal outcomes. These outcomes include doubling of serum creatinine or ESRD when BP was controlled to the same level by drugs from different antihypertensive drug classes.

Rationale for Use of Irbesartan in Diabetic Renal Disease

Irbesartan is a long-acting, insurmountable angiotensin II receptor blocker (ARB) that demonstrates highly selective blockade of the AT_1 receptor subtype. Like an ACE-I, irbesartan inhibits the effects of an activated RAS; however, unlike an ACE-I, which potentially allows the generation of AII through alternative pathways, irbesartan more completely blocks the effects of AII by selectively binding to the AT_1 angiotensin II receptor. Irbesartan was hypothesized to provide benefits similar to or better than those observed with ACE inhibitors in nondiabetic and diabetic renal disease.

Irbesartan safely and effectively controls BP and reduces urinary albumin and protein excretion in both experimental and clinical models of type 2 diabetes.

Understanding the relative renoprotective benefit from BP reduction itself *vs.* unique benefits of a specific antihypertensive drug class to lower BP was the objective for undertaking a clinical program with irbesartan in hypertensive patients with type 2 diabetic renal disease. A comparison of RAS blockade with an ARB, such as irbesartan, *vs.* non-RAS blockade with the calcium channel blocker (CCB) amlodipine was chosen for study. Non-RAS blockers such as CCBs were known to consistently lower BP in hypertensive diabetic patients; however, the known effects of CCBs on AER in these patients were inconsistent.

Overview of the Clinical Development Program

A comprehensive development program in hypertensive type 2 diabetic patients with diabetic renal disease was designed to test the hypothesis that RAS inhibition by irbesartan (i.e., AT_1 blockade) provides definitive renoprotection across the continuum of diabetic renal disease. The clinical development program consisted of two randomized, comparative, adequate and well-controlled studies and three supportive studies. The two large studies provide the important information regarding the effectiveness and safety of irbesartan in diabetic renal disease. These two trials were CV131-048, hereafter referred to as **IDNT (I**rbesartan **D**iabetic **N**ephropathy **T**rial) and Protocol EFC2481, hereafter referred to as **IRMA 2** (**IR**besartan **M**icro**A**lbuminuria in type **2** Diabetes). The program evaluated the ability of irbesartan to prevent overt nephropathy (IRMA 2) and to protect from further progression to advanced diabetic renal disease (IDNT). The intent was to show that the renal benefits of irbesartan exist above and beyond its ability to reduce BP. IRMA 2 and IDNT compare the clinical benefits of irbesartan to those of usual antihypertensive regimens with or without CCBs.

The design strategy was to isolate the incremental effects of AT_1 blockade with irbesartan, above and beyond the beneficial effects of BP lowering with other methods of BP control. The attempt was to bring all treatment groups to the same BP goal in both IDNT and IRMA 2. In this way the treatment differences on progression of type 2 diabetic renal disease, attributable only to the additional effects of AT_1 blockade, could be observed.

IDNT Design

IDNT was designed to evaluate the benefits of irbesartan on the progression from overt proteinuria to a clinical primary composite endpoint of doubling of serum creatinine, development of ESRD (defined by serum creatinine ≥ 6 mg/dL or the need for dialysis or renal transplantation) and all-cause mortality, analyzed as the time from randomization to whichever event occurred first. All-cause mortality was considered an independent competing endpoint. Extensive discussion between the sponsors and nephrologists from academic medical centers suggested that this composite renal endpoint was a valid one. Doubling of serum creatinine was considered a failure of therapy. Therefore, subjects enrolled in IDNT were required to stop study drug once they reached doubling of serum

creatinine, rather than continuing to receive study drug until they reached ESRD. A creatinine of 6 mg/dL was chosen to represent ESRD in keeping with the Health Care Financing Administration (HCFA) registration guidelines. MEDICARE and HCFA use serum creatinine levels as the clinical criterion for determining a patient's need for renal replacement therapy.

ESRD is a clinically obvious renal outcome especially when patients begin dialysis or undergo renal transplantation. Doubling of serum creatinine while not as obvious is a direct, highly reproducible measure of failing renal function representing halving of the glomerular filtration rate. It is considered to be a clinically meaningful measure of renal morbidity. Once doubling of serum creatinine occurs, ongoing strict monitoring of patient well-being becomes critical.

When IDNT was designed, stopping study drug once creatinine doubled was considered the most ethical approach to study conduct. In this way all patients could receive additional therapy of the physicians' choice prior to complete kidney failure. It was believed that ACE inhibitors would be frequently added in these patients, despite lack of proven benefit in type 2 diabetes. Any intervention in the RAS cascade, as with an ACE-I, after doubling of serum creatinine would likely alter the intra-renal angiotensin levels, leading to an alteration of the natural course of the disease. This might reduce the rate of progression in the placebo-treated subjects, thus lessening the treatment effect on ESRD between the groups. Thus, in an intent-to-treat analysis, once study drug was stopped, this potentially reduced the ability to observe treatment differences on ESRD among the three randomized cohorts (i.e., irbesartan *vs.* 2 different non-RAS blocker arms) as patients received similar therapies from that point onward.

Subjects in IDNT were scheduled for clinic visits every 3 months at a minimum. Given this trial design, in some cases the actual date of doubled creatinine could not be ascertained exactly. Therefore, if a subject reached ESRD at a three monthly visit, that subject was assumed to have doubled his serum creatinine within the three month period prior to this time.

The patient population evaluated had hypertension (SeSBP > 135 mmHg and/or SeDBP > 85 mmHg for untreated patients or receiving antihypertensive medication), type 2 diabetes, proteinuria (24-hour urine protein excretion ≥ 900 mg) and a serum creatinine between 1.0 and 3.0 mg/dL in women and 1.2 and 3.0 mg/dL in men. Subjects were

randomized in a double-blind manner to placebo, irbesartan 300 mg or amlodipine 10 mg, each once daily. Subjects were titrated to their final dose at two-week intervals (75 mg to 150 mg to 300 mg for irbesartan and 2.5 mg to 5 mg to 10 mg for amlodipine) and remained on their randomized dose for 24 months. Use of other antihypertensive medication was permitted to maintain BP control with the exception of RAS inhibitors (ACE-I and ARB) and calcium channel blockers.

The efficacy of irbesartan was evaluated using the following outcomes measures:

Primary Outcome Measure: Time from randomization until the first 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 (530 μmol/L),] or death [all-cause mortality].

Secondary Outcome Measure: 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 (nonfatal or fatal cardiovascular events).

IRMA 2 Design

IRMA 2 was designed to evaluate benefits of irbesartan on the progression from microalbuminuria to overt proteinuria. The patient population evaluated had hypertension (SeSBP > 135 mmHg and/or SeDBP > 85 mmHg, or if receiving antihypertensive medication SeSBP ≤ 160 mHg and/or SeDBP ≤ 90 mmHg), type 2 diabetes, microalbuminuria (AER of 20-200 μg/min [30-300 mg/24 hours]) and normal serum creatinine levels. Subjects were randomized in a double-blind manner to placebo or one of two doses of irbesartan (150 mg or 300 mg), each once daily. Subjects were titrated to their final dose at two-week intervals (75 mg to 150 mg to 300 mg) and remained on their randomized dose for 24 months. Use of other antihypertensive medication was permitted to maintain BP control with the exception of RAS inhibitors (ACE-I and ARB) and dihydropyridine calcium channel blockers. The primary endpoint was occurrence of clinical (overt) proteinuria; secondary endpoints included incidence of overt proteinuria and estimated creatinine clearance after one and two years of treatment.

IRMA 2 evaluated one of the largest cohorts ever studied of subjects at the early stage of the diabetic renal disease continuum from microalbuminuria to clinical (overt) proteinuria, and IDNT evaluated subjects with clinical (overt) proteinuria at an advanced stage of diabetic renal disease. Together these two clinical studies evaluated the renoprotective effects of irbesartan in two phases of the same disease process.

IDNT and IRMA 2 taken together were intended to demonstrate a beneficial effect of irbesartan on different, but related, clinically relevant endpoints representing two different stages of the disease continuum (namely, the development of overt proteinuria in patients with early disease manifested by microalbuminuria and the development of the related renal outcomes of serum creatinine doubling and ESRD in patients with advanced disease). The demonstrated benefit of irbesartan in these two clinical trials would support a claim for irbesartan effectiveness across the continuum of diabetic renal disease.

IDNT Efficacy Results

The majority of subjects required two to four concomitant antihypertensive drugs during the double-blind period to control BP. As expected patients in the placebo group required more adjunctive therapy than patients in the irbesartan or amlodipine groups. Beta-blockers were the most commonly used adjunctive agents and were used by 52%, 43.5% and 40.6% of the placebo, irbesartan and amlodipine groups, respectively. Alpha/beta adrenergic blockers were used by 48.1%, 43.2% and 41.5% of patients in these groups, respectively.

BP was reduced in all three treatment groups to 145.2/79.3 mmHg, 141.8/77.0 mmHg, and 141.9/76.4 mmHg in the placebo, irbesartan, and amlodipine groups, respectively at the last visit. Table A displays the change from baseline to last observation in seated BP.

Table A: IDNT: Change from Baseline to Last Observation in Seated Blood Pressures

Treatment Group Number Randomized		Placebo N = 569	Irbesartan N = 579	Amlodipine N = 567
Seated Systolic BP (mmHg)	n	565	576	562
	Baseline Mean (SD)	158.2 (20.5)	160.4 (19.5)	158.5 (19.1)
	Last Observation Mean (SD)	145.2 (20.6)	141.8 (20.9)	141.9 (19.1)
	Adjusted[a] Mean Change (SE)	-13.6 (0.8)	-17.7 (0.8)	-17.0 (0.8)
	p value: Comparison vs. Irbesartan	< 0.001		0.566
Seated Diastolic BP (mmHg)	n	565	576	562
	Baseline Mean (SD)	86.9 (11.0)	86.8 (11.3)	87.0 (10.8)
	Last Observation Mean (SD)	79.3 (11.9)	77.0 (10.6)	76.4 (10.8)
	Adjusted[a] Mean Change (SE)	-7.6 (0.4)	-9.8 (0.4)	-10.5 (0.4)
	p value: Comparison vs. Irbesartan	< 0.001		0.249
Seated MAP[b] (mmHg)	n	565	576	562
	Baseline Mean (SD)	110.7 (12.0)	111.3 (11.9)	110.8 (11.4)
	Last Observation Mean (SD)	101.3 (12.9)	98.6 (12.2)	98.2 (11.7)
	Adjusted[a] Mean Change (SE)	-9.6 (0.5)	-12.4 (0.5)	-12.7 (0.5)
	p value: Comparison vs. Irbesartan	< 0.001		0.714

[a] Adjusted via analysis of covariance

[b] MAP - Mean Arterial Pressure

Clinically meaningful reductions in BP were achieved during the course of IDNT. The adjusted mean change to last visit in SeSBP was -13.6, -17.7, and -17.0 mmHg for the placebo, irbesartan and amlodipine groups, respectively; the adjusted mean change in SeDBP was -7.6, -9.8, and -10.5, respectively; and the adjusted mean change in MAP was -9.6, -12.4, and -12.7, respectively. For each of the seated BP parameters, the decrease from baseline was statistically significantly greater for irbesartan than for placebo ($p < 0.001$) even though the placebo group was actively treated by adjunctive antihypertensive medications. However, the differences between irbesartan and amlodipine in mean change in BP were not statistically significant. In addition, repeated

measures mixed model ANOVAs were performed to assess whether the treatment groups were similar in attained BP over the course of the study.

Irbesartan significantly increased the time to the primary renal composite endpoint (consisting of doubling of serum creatinine, ESRD, or all-cause mortality). Irbesartan demonstrated a 20% risk reduction (p = 0.0234) relative to placebo and a 23% risk reduction (p = 0.0064) relative to amlodipine (Table B). The significantly better renal outcome in the irbesartan-treated group was not explained by differences in BP control. The BP control in the irbesartan and amlodipine groups was similar. The treatment benefit with irbesartan remained statistically significant *vs.* both placebo and amlodipine after adjustment for the mean arterial pressures achieved in the three treatment groups.

Table B: IDNT: Comparison (Irbesartan vs. Placebo and vs. Amlodipine) of Primary Composite Endpoint - ITT Analysis

Event	Number (%) of Subjects[a]			Irbesartan *vs.* Placebo		Irbesartan *vs.* Amlodipine	
	Placebo N = 569	Irbesartan N = 579	Amlodipine N = 567	RR (95% CI)[b]	p[c]	RR (95% CI)[b]	p[c]
Primary Composite Endpoint[d]	222 (39.0)	189 (32.6)	233 (41.1)	0.80 (0.66-0.97)	0.0234	0.77 (0.63-0.93)	0.0064

a One subject in the placebo group and 2 subjects in the amlodipine group with unknown event date for ESRD were included in the event counts, but excluded from the time-to-event analyses.

b Determined from Cox proportional hazards model.

c From log-rank test

d Counts and treatment comparisons are based on the first occurrence of the composite event. Each subject is counted no more than once.

Each patient could potentially have more than one event from the primary composite endpoint (e.g., starting with doubling of serum creatinine, progressing to ESRD, and ultimately dying). The primary composite endpoint evaluated the time to the first occurrence of any one of these events.

After adjustment for BP control the treatment benefit of irbesartan in relative risk reduction for the primary composite endpoint compared to either placebo or amlodipine was still statistically significant.

If BP control was the sole mechanism of action responsible for the significant renoprotective effects achieved with irbesartan, the same favorable effects on kidney function should have been evident with amlodipine. The renoprotective effects of irbesartan are independent of BP reduction.

Renal Endpoints

Doubling of Baseline Serum Creatinine

Irbesartan significantly decreased the total incidence of doubling of baseline serum creatinine (SrCr). A total of 377/1715 (22%) randomized subjects reached doubling of baseline serum creatinine. The incidence rate of doubling of SrCr was 16.9% in the irbesartan group compared with 23.7% in the placebo group and 25.4% in the amlodipine group. The relative risks of SrCr doubling for irbesartan *vs.* placebo were 0.67 (95% CI 0.52-0.87) and 0.63 (95% CI 0.49-0.81) for irbesartan *vs.* amlodipine. Irbesartan demonstrated a statistically significant 33% relative risk reduction in SrCr doubling compared to placebo ($p = 0.0027$) and a 37% relative risk reduction compared to amlodipine ($p = 0.0003$). Of the 377 subjects whose SrCr doubled from baseline, 202 (53.6%) progressed to ESRD later in the trial. The median follow-up time to ESRD after doubling was 9.8 months.

End Stage Renal Disease (ESRD)

Irbesartan also decreased the total incidence of ESRD. The relative risks of ESRD for irbesartan *vs.* placebo and for irbesartan *vs.* amlodipine were both 0.77 (95% CI: 0.57 - 1.03). While these differences did not reach statistical significance, in a post hoc analysis, irbesartan demonstrated a statistically significant 23% relative risk reduction in ESRD compared to the combined placebo and amlodipine groups ($p = 0.0422$ for irbesartan *vs.* the combined placebo and amlodipine groups).

Combination of Doubling of Serum Creatinine or ESRD

Irbesartan significantly reduced the time to the combined endpoint of doubling of serum creatinine or ESRD (i.e., the first occurrence of either event). The p value *vs.* placebo was 0.0116 and *vs.* amlodipine was 0.0003. The relative risks were 0.74 (95% CI: 0.59-0.94) for irbesartan *vs.* placebo and 0.66 (95% CI: 0.53-0.83) for irbesartan *vs.* amlodipine. Irbesartan demonstrated significant relative risk reductions of 26% compared

with placebo and 34% compared with amlodipine. For irbesartan *vs.* placebo and amlodipine combined, the relative risk was 0.70 (95% CI 0.57-0.85).

All-Cause Mortality

A total of 263/1715 (15.3%) subjects died during the trial, 87/579 (15%) in the irbesartan group, 93/569 (16.3%) in the placebo group, and 83/567 (14.6%) in the amlodipine group (Tables 10.1.1A and 10.1.1B). The relative risks for all-cause mortality were 0.92 (95% CI: 0.69-1.23) for irbesartan *vs.* placebo, and 1.04 (95% CI: 0.77-1.40) for irbesartan *vs.* amlodipine. There was no significant difference in risk of all-cause mortality between irbesartan and placebo or amlodipine.

Secondary Cardiovascular Composite Endpoint

There was no statistically significant relative risk reduction in the secondary cardiovascular composite endpoint of cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurological deficit attributed to stroke or above-the-ankle amputation for irbesartan *vs.* placebo or amlodipine.

IRMA 2 Efficacy Results

The results of the primary endpoint, occurrence of clinical proteinuria, were positive. The risk to reach clinical proteinuria was significantly reduced by 70% in the irbesartan 300 mg group ($p = 0.0004$ in the ITT population). This risk was reduced by 39% in the irbesartan 150 mg group but it was not statistically significant ($p = 0.085$ in ITT population). This effect was not explained by differences in the baseline level of AER or BP lowering effect at the two doses tested, since the risk reduction was similar after adjustment of the Cox's model analysis for these two factors (Table C).

Table C: IRMA 2: Comparison (Irbesartan vs Placebo) of Primary Efficacy Outcomes (Unadjusted and Adjusted Analyses)-ITT Analysis

	Number of subjects			Irbesartan 150 mg *vs.* placebo		Irbesartan 300 mg *vs.* placebo	
	Placebo	**Irbesartan 150**	**Irbesartan 300 mg**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
Unadjusted [a]	**N= 201**	**N = 195**	**N = 194**	0.607 (0.341-1.079)	0.085	0.295 (0.144-0.606)	0.0004
Primary end point reached	30 (14.9 %)	19 (9.7 %)	10 (5.2 %)				
Adjusted [b]	**N = 201**	**N = 194**	**N = 191**	0.556 (0.311-0.993)	0.047	0.316 (0.153-0.653)	0.0018
Primary end point reached	30 (14.9 %)	19 (9.8 %)	10 (5.2%)				

[a] Mantel Haenszel Log rank test

[b] Cox model adjustment on baseline AER and MAP time dependent variables.

The results for the major secondary endpoints were also positive. Irbesartan, in both treatment groups, demonstrated a significant dose-dependent reduction in urinary AER compared with placebo. The geometric mean percentage reductions from baseline (± SEM) at 2 years were 12.1 (7.3) in the placebo group, 16.1 (7.8) for the irbesartan 150 mg group, and 42.7 (5.5) in the irbesartan 300 mg group.

Irbesartan did not affect kidney function as evaluated by estimated creatinine clearance. There were no statistically significant differences *vs.* placebo on the mean estimated creatinine clearance at any time point up to Month 24 in either irbesartan dose group. Creatinine clearance remained in the normal range in all three treatment groups throughout the trial. The length of follow-up was likely too short to demonstrate an effect on this parameter.

In the GFR substudy which enrolled 133 patients (where GFR was estimated by total plasma clearance of ^{51}Cr-EDTA), there were no significant differences in GFR between the three treatment groups throughout the study and up to Month 24.

At 4 weeks after discontinuation of study drugs and other adjunctive antihypertensive drugs, AER remained substantially below baseline only for subjects who had been treated with irbesartan 300 mg. Thus, irbesartan 300 mg maintained its effect on AER after drug withdrawal. These results suggest a relative residual renoprotective effect of irbesartan 300 mg.

Clinical Relevance of Overt Proteinuria

The medical literature indicates the natural course of type 2 diabetic renal disease includes the evolution from overt proteinuria to ESRD. The magnitude of proteinuria is directly correlated with risk for ESRD and decline in renal function. Results from the irbesartan clinical program in early and advanced type 2 diabetic renal disease are consistent with the literature.

The irbesartan clinical program in diabetic renal disease demonstrated that the level of urinary albuminuria at baseline was a strong and significant predictor of the risk to develop the primary endpoints in both IDNT and IRMA 2. In IRMA 2, the urinary AER was the only baseline factor statistically significant as a prognostic risk factor and thus confirmed that microalbuminuria predicts progression to overt proteinuria. In IDNT, the baseline urinary AER was also a significant predictive risk factor. It was seen that higher baseline urinary protein excretion rate values predicted an increased future risk of doubling of baseline serum creatinine and development of ESRD. Elevated levels of protein excretion also predicted cardiovascular mortality. This finding provides documentation that the level of urinary protein excretion is a useful marker to identify which subjects are at greater risk of progression to ESRD and reinforces the clinical necessity for pharmacological intervention at the microalbuminuria stage of the continuum of diabetic renal disease.

The effects of irbesartan on urinary albumin excretion were strongly consistent and comparable in both IRMA 2 and IDNT study populations representing the spectrum of the type 2 diabetic renal disease from incipient diabetic renal disease to a more advanced stage. In IRMA 2, irbesartan 300 mg reduced the risk to reach clinical proteinuria by 70% ($p = 0.0004$ in the ITT population) relative to placebo for subjects with microalbuminuria. One third of the subjects normalized their urinary AER (AER last value below 20 μg/min) after 2 years in the irbesartan 300 mg group. In IDNT, irbesartan demonstrated a consistent beneficial effect on critical renal outcomes

(i.e., doubling of serum creatinine and ESRD) compared with placebo or amlodipine. These results are accompanied by expected beneficial results on related renal outcomes of change in creatinine clearance and in urinary albumin and protein excretion.

During the first year of follow-up, the mean change from baseline of urinary protein excretion rate in IDNT was reduced on average by 41.7% in the irbesartan group compared to 11.5% in the amlodipine group and 15.6% in the placebo group. This positive effect of irbesartan on overt proteinuria was sustained over the three years of study follow up.

Furthermore, among the IDNT population with advanced diabetic renal disease, irbesartan therapy resulted in a preservation of renal function with a significant effect on the annual rate of change in serum creatinine and in creatinine clearance compared with placebo or amlodipine.

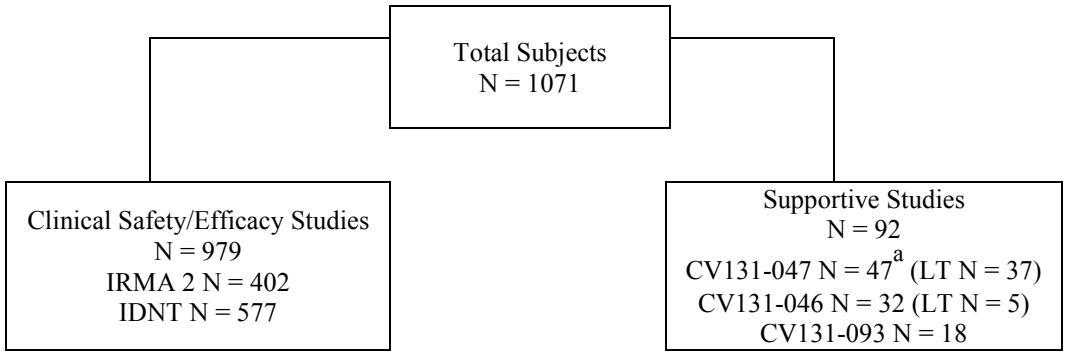
Irbesartan Safety and Tolerability

Compared with the IRMA 2 subjects, the subjects in IDNT had more advanced hypertension, diabetes, and diabetic renal disease; therefore, subjects in IDNT were more likely to have other concomitant illnesses (and/or sequelae) and medications as compared to the population of subjects recruited from an earlier phase of the disease process. Specifically, subjects in IDNT had a longer history of type 2 diabetes mellitus (14.8 years *vs.* 9.9 years) and were more likely to use insulin (i.e., more severe and refractory diabetes) as compared with subjects in IRMA 2. Baseline laboratory evaluation also revealed higher mean values for serum creatinine (1.68 *vs.* 1.06 mg/dL), glycosylated hemoglobin (8.1% *vs.* 7.2%), and urinary albumin excretion rate (1899.6 *vs.* 80.5 mg/24h [55.9 μg/min]) in IDNT as compared with IRMA 2. Based upon these differences (i.e., baseline characteristics and concomitant therapies), these subjects were sufficiently different to warrant independent safety analyses for both IDNT and IRMA 2. If the safety datasets of IRMA 2 and IDNT had been pooled, significant signals from IRMA 2 could have potentially been overshadowed by the number of anticipated adverse events in IDNT. Additionally, the IRMA 2 and IDNT studies were each of sufficient size to permit a separate assessment of safety. Presented in this section is an integrated assessment of the two separate safety analyses from IDNT and IRMA 2 to provide an understanding of the clinically important safety considerations across the continuum of diabetic renal disease.

A total of 2404 subjects were treated in the five completed studies, IRMA2 , IDNT and three supportive studies (Figure A). Of these, 1071 subjects were exposed to irbesartan (double-blind and open-label), which included 979 subjects in the clinical safety/efficacy studies (IRMA 2 and IDNT) and 92 subjects in the supportive studies.

Overall, the mean duration of exposure to irbesartan was 620 days in IRMA 2 and 815 days in IDNT. The days of exposure to irbesartan ranged from 1 day to 785 days in the three supportive studies and their long-term open-label extensions.

Figure A: Overall Number of Subjects Exposed to Irbesartan in All Studies



[a] Of the 47 subjects in CV131-047 double-blind phase, 24 received irbesartan and 23 received amlodipine. Of the amlodipine-exposed subjects, 18 entered the long-term open-label extension and were exposed to irbesartan. Therefore, there was an overall total of 42 irbesartan-exposed subjects in CV131-047.

The data from these trials show that irbesartan is generally safe and well tolerated in the treatment of patients with type 2 diabetes, hypertension and diabetic renal disease. The safety findings are consistent with the existing label for irbesartan in the treatment of hypertensive patients.

The incidence of reported clinical and laboratory adverse events was higher in IDNT than in IRMA 2 which likely represents increased comorbidities from the longer duration and the severity of diabetes mellitus and higher baseline creatinine in IDNT. Specific events that were consistently identified (e.g., dizziness, orthostatic dizziness, orthostatic hypotension) are likely to occur secondary to the known antihypertensive effects of irbesartan in subjects with diabetes mellitus and its sequelae (i.e. peripheral and autonomic neuropathy). Treatment-emergent AEs for dizziness, orthostatic dizziness, and

orthostatic hypotension occurred in all treatment groups in both IRMA 2 and IDNT. The majority of these symptoms, however, were of little clinical significance as they were mild or moderate in intensity, were considered unrelated to study drug and did not require any action to be taken with respect to study drug. Finally these symptoms were not associated with SAEs and infrequently (≤ 0.3%) associated with study drug discontinuation.

Hyperkalemia was a frequent occurrence in subjects in IDNT, but infrequently resulted in the discontinuation of study drug (Table D). The frequency of these clinical and laboratory abnormalities related to hyperkalemia in IDNT, but not in IRMA 2, underscores the difference between these two patient populations. In addition, the cause of the hyperkalemia is likely multifactorial with components of both a decline of underlying renal function and the presence of hyporeninemic hypoaldosteronism that is not uncommon in type 2 diabetic patients. Moreover, it demonstrates the importance of monitoring serum potassium, irrespective of drug therapy, in all patients with type 2 diabetes and overt proteinuria as standard of care.

Table D: Summary of Clinical Events and Laboratory Abnormalities (During and Greater Than or Equal to 14 Days Post Double-Blind Therapy) for Elevated Serum Potassium or Hyperkalemia in IDNT

	Number (%) of Subjects		
	Placebo N = 563	**Irbesartan N = 577**	**Amlodipine N = 559**
Treatment-emergent AEs	53 (9.4)	134 (23.2)	45 (8.1)
Elevated Serum Potassium ($K^+ \geq 6.0$ mEq/L)	40 (7.1)	124 (21.5)	37 (6.6)
Elevated Serum Potassium ($K^+ \geq 6.0$ mEq/L) on 2 or more consecutive occasions	9 (1.6)	26 (4.5)	2 (0.4)
Study drug discontinuations	2 (0.4)	12 (2.1)	3 (0.5)
SAEs	1 (0.2)	5 (0.9)	3 (0.5)
Any sudden death[a]	16 (2.8)	12 (2.1)	8 (1.4)

[a] Sudden death may potentially reflect undiagnosed hyperkalemia; however, serum potassium was unknown at the time of each of these specific events.

Benefit:Risk Considerations

Benefit

Irbesartan is the first drug of any class to demonstrate beneficial effects on slowing progression of renal disease above and beyond BP control in a high risk population with type 2 diabetes, hypertension and early and later stages of diabetic renal disease.

Evidence to Support Irbesartan Effectiveness

The results of IDNT and IRMA 2 complement each other and support both early and later intervention in the natural history of type 2 diabetic renal disease (see Table E). The results provide strong evidence to support the hypothesis that RAS inhibition with irbesartan has renoprotective effects above and beyond those from blood pressure reduction alone.

The pathophysiology of diabetic renal disease is well understood, and the proposed mechanism by which RAS inhibition would favorably alter the kidney is fairly well recognized. One of the proposed mechanisms for progression of renal failure in diabetic renal disease is an increase in intraglomerular capillary pressure due to AII-mediated vasoconstriction of the efferent arteriole which results in hyperfiltration in the surviving glomeruli and eventual glomerular scarring. The effects of AII may be abrogated by either reducing the generation of AII through ACEI use or by inhibition of AII binding to its receptor (AT1) through the use of an AII receptor antagonist, such as irbesartan.

In IRMA 2 in patients with microalbuminuria, irbesartan significantly reduced urinary albumin excretion and progression to clinical proteinuria, which predicts progression to ESRD. In IDNT, irbesartan reduced clinically relevant renal outcomes that occur later in the continuum of diabetic renal disease.

For IDNT, compared with placebo, irbesartan therapy was associated with a substantial treatment effect, namely a 20% reduction in the primary composite endpoint, a 33% reduction in doubling of serum creatinine, and a 23% reduction in ESRD. These overall results which are consistent within IDNT are complemented by the treatment effect observed with the 300 mg dose of irbesartan in IRMA 2, namely a 70% reduction in the incidence of overt proteinuria compared with placebo.

Taken together, IRMA 2 results on clinical proteinuria relate to the prevention of a disease with a potentially serious outcome, and IDNT results relate to protection of renal function once patients have advanced renal disease.

The chosen endpoints for IRMA 2 and IDNT were clinically appropriate to the stage of disease and could be objectively assessed (e.g., urinary albumin excretion rates and doubling of serum creatinine). The primary endpoints in the two studies, though different, are pathogenically related. A dose-response was observed in the IRMA 2 study with the 300 mg irbesartan dose showing statistically significant delay of progression from microalbuminuria to overt proteinuria.

IDNT demonstrated clinically relevant effects on irreversible morbidity, namely a permanent doubling of serum creatinine which represents halving of renal function. Furthermore, the trends in risk reduction for IDNT across all individual renal component endpoints of the primary renal outcome favor irbesartan for the comparison of irbesartan *vs.* placebo or amlodipine.

Importantly, the IDNT design included a comparison of irbesartan with another active comparator, namely amlodipine. The achieved mean arterial BPs in the irbesartan and amlodipine treatment groups were virtually identical, and lower than that achieved in the placebo treatment group. Unlike irbesartan, however, amlodipine did not have a renoprotective effect at the same level of achieved mean arterial BP. The comparable treatment benefit of irbesartan relative to placebo and amlodipine re-enforced the findings on the primary endpoint.

In IDNT the results for the critical renal outcomes (doubling of serum creatinine and ESRD) are accompanied by expected beneficial results on related outcomes of change in creatinine clearance and in urinary albumin and protein excretion.

In IRMA 2 an important new finding was observed in this patient population with early diabetic renal disease. At 4 weeks after study drug and other antihypertensive drugs were stopped, the urinary AER remained substantially below the baseline for subjects treated with irbesartan 300 mg. This new finding supports the view that irbesartan 300 mg affords a relative residual renoprotective effect once the drug is stopped. This finding is consistent with the view that RAS inhibition provides a fundamental change in the renal

millieu in addition to and distinct from the reversible renal hemodynamic effects resulting from changes in BP alone.

The results of IDNT with irbesartan are consistent with those in a recently published clinical trial with another member of the same pharmacologic class. This randomized, prospective trial comparing losartan with placebo used the identical primary composite endpoint as IDNT in type 2 diabetic patients with overt nephropathy. The magnitude of the beneficial treatment effect in the losartan trial (16%) is approximately that seen with irbesartan in IDNT (20%) with an identical p value of 0.02.

Table E: Summary of Primary Efficacy - IDNT and IRMA 2 (ITT Analysis)

	Placebo Regimen	Irbesartan 150 mg Regimen	Irbesartan 300 mg Regimen	Amlodipine Regimen
IDNT				
Primary Composite Endpoint[a]	222 (39.0)		189 (32.6)	233 (41.1)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			20% (0.0234)	
Irebesartan vs Amlodipine[b]			23% (0.0064)	
Total Incidence of Renal Endpoints				
Doubling of Serum Creatinine[a]	135 (23.7)		98 (16.9)	144 (25.4)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			33% (0.0027)	
Irbesartan vs Amlodipine[b]			37% (0.0003)	
End Stage Renal Disease[a]	101 (17.8)		82 (14.2)	104 (18.3)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			23% (0.0731)	
Irbesartan vs Amlodipine[b]			23% (0.0746)	
Total Incidence of All-Cause Mortality[a]	93 (16.3)		87 (15.0)	83 (14.6)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			8% (0.5683)	
Irbesartan vs Amlodipine[b]			-4% (0.8083)	
IRMA 2				
Progression to Clinical Proteinuria[a,c]	30 (14.9)	19 (9.7)	10 (5.2)	
Relative Risk Reduction				
Irbesartan vs Placebo[b]		39% (0.085)	70% (0.0004)	

Note: Relative risk reduction and p-values are from time-to-first event analysis.

[a] Total number of subjects with the event (percent)

[b] Relative Risk Reduction (p value)

[c] Clinical proteinuria is defined as albumin excretion rate > 200 µg/min and an increase of at least 30% from baseline

In IDNT, irbesartan significantly increased the time to the primary (renal) composite endpoint of doubling of serum creatinine, ESRD, or all-cause mortality in hypertensive subjects with type 2 diabetes and overt proteinuria, demonstrating a 20% relative risk reduction *vs.* placebo (p = 0.0234) and a 23% relative risk reduction *vs.* amlodipine (p = 0.0064).

In IRMA 2, subjects in the 300 mg irbesartan regimen had a 70% relative risk reduction for progressing from microalbuminuria to overt proteinuria compared with placebo. The risks for hyperkalemia appeared to be minimal and not dose related. Overall, the safety profile of irbesartan was similar to placebo in IRMA 2.

Table F translates the results of IDNT into tangible outcomes when treating 100 patients for 3 years.

Table F: Benefits of Irbesartan Treatment in Comparison with Placebo or Amlodipine

	Total Incidence of Events per 100 Patients in IDNT			Reduction in the Number of Patients with Outcome on Irbesartan	
	Placebo[a]	Irbesartan	Amlodipine	vs. Placebo	vs. Amlodipine
Double serum creatinine	27	19	28	8	9
ESRD	19	14	18	5	4
Death	16	14	13	2	-1
ESRD or doubling of serum creatinine	29	22	32	7	10

Note: The numbers in this table were derived from the Kaplan-Meier estimates of cumulative event rate at 36 months in IDNT

[a] Placebo actually represents a several classes of antihypertensive agents except RAS inhibitors and CCBs.

These data show that for 100 patients with type 2 diabetes, hypertension, and overt nephropathy treated with irbesartan, there would be 7 and 10 fewer cases of doubling of serum creatinine or development of ESRD as compared with the placebo or amlodipine groups, respectively. Based upon these results, irbesartan would provide a substantial slowing of the progression of renal disease in type 2 diabetic patients with overt proteinuria.

Risk

The risks of irbesartan in the IDNT population appear to be minimal. From a cardiovascular standpoint, there were similar cardiovascular AEs, SAEs, and deaths by body system in all three treatment groups. For the secondary cardiovascular endpoint, differences in treatment effect were not significant among all three treatment groups. Note that the placebo treatment group was not without therapy for hypertension. Since all three treatment groups had reductions in blood pressure, it is not surprising that there were no differences in cardiovascular events observed among the treatment groups. Indeed, four other trials compared different classes of antihypertensive medications in high-risk hypertensive patients. These four studies enrolled 34,781 subjects (3,302 of whom had diabetes). No significant differences were observed in cardiovascular endpoints in either the entire study population or in the diabetic hypertensive patients.

Hyperkalemia was not a problem for subjects with early diabetic renal disease like those in IRMA 2. However, in the IDNT population hyperkalemia is a potential concern. The magnitude of this concern is greatly dampened by the general appreciation among physicians that monitoring serum creatinine and serum potassium is a clinical necessity and standard of care, irrespective of drug therapy, in patients with underlying renal impairment. This is especially important for those patients with baseline impairment of renal function treated with an RAS inhibitor. The treatment-emergent AE data in IDNT indicate that hyperkalemia is a readily manageable, anticipated consequence of RAS inhibition in type 2 diabetic patients with overt proteinuria. The majority of these events were considered mild or moderate in intensity. Hyperkalemia events that the investigator classified as severe or very severe in intensity required no dose reduction, interruption, or discontinuation of study drug in one-half of these events. Thus, only a small number of events required an adjustment to dose, an interruption of drug, a discontinuation of drug or were classified as an SAE. Of note, for those events that did require discontinuation of

study drug due to hyperkalemia, the hyperkalemia was reversible upon drug withdrawal. Similarly, SAEs that required immediate intervention to correct the serum potassium were infrequent and required only routine (potassium binding resin and diuretic therapy) corrective measures.

Finally, while there was no risk for the addition of amlodipine to type 2 diabetic patients with overt proteinuria with respect to hyperkalemia, there also was no benefit for amlodipine (above that resulting from BP reduction) for renal disease compared with placebo. It is therefore the mechanism of AT_1 blockade through the use of irbesartan that has demonstrated clear benefit in patients with type 2 diabetes and overt proteinuria. Irbesartan-induced hyperkalemia in this population is an anticipated, readily manageable, consequence of RAS inhibition in type 2 diabetic patients with overt nephropathy.

Overall Benefit:Risk Assessment

Approximately 43% of all new cases of ESRD in the United States is attributed to diabetes, with the majority of patients having type 2 diabetes. Of these patients with diabetic ESRD, approximately 40% die annually. Chronic renal failure is a disease with rising prevalence, high patient morbidity and mortality, and high economic costs. Previously, no agent of any therapeutic class has demonstrated efficacy in the progression of renal disease in type 2 diabetic subjects with overt proteinuria. IDNT demonstrated that irbesartan offers a substantial reduction in the progression of renal disease in type 2 diabetic patients with overt proteinuria, and therefore represents a new treatment for an unmet medical need of significant import. Standard of care dictates the use of antihypertensive agents in these hypertensive patients. Thus the issue is in the choice of the specific antihypertensive therapy. Evidence now exists for mechanistic-based benefits of RAS inhibition with irbesartan-benefits above and beyond blood pressure reduction alone. Hyperkalemia does occur in these patients, but it is an anticipated, readily manageable, consequence of RAS inhibition in type 2 diabetic patients with overt nephropathy. Logically, intervening at an earlier phase of the same disease process, at a time prior to deterioration of renal function, but while there is evidence of disease (i.e., microalbuminuria stage) would likely offer the largest benefits in preserving renal function long-term. Indeed, pharmacological intervention at the microalbuminuria stage in hypertensive diabetic patients is recommended by the American Diabetes Association.

From a clinical perspective, the empiric view among treating physicians is that early intervention in a progressively deleterious disease process is often beneficial to patients. Taken together IDNT and IRMA 2 provide important information about the renoprotective benefits of irbesartan throughout the continuum of diabetic renal disease given the following points:

- IDNT and IRMA 2, conducted in different stages of type 2 diabetic renal disease, complement each other and provide strong evidence of the additional renoprotective benefit of AT_1 blockade with irbesartan, above and beyond that achieved with BP lowering.
- IDNT, in patients with advanced diabetic renal disease, included two comparator arms. Irbesartan was more effective than placebo ($p = 0.0234$) in reducing the risk of the primary composite endpoint consisting of doubling of serum creatinine, ESRD or all-cause mortality. Strengthening the results against placebo, irbesartan was also more effective than the active antihypertensive drug, amlodipine ($p = 0.0064$) on this composite endpoint.
- In IRMA 2, in patients at an earlier stage in the disease continuum, irbesartan 300 mg reduced the progression from incipient to overt nephropathy, as measured by urinary AER. It is well accepted that levels of urinary albumin and protein excretion predict progression to ESRD. The dose-response observed with the 150 mg and 300 mg doses of irbesartan demonstrates the consistency of the results in IRMA 2.
- In IRMA 2 an important new finding was observed in this patient population with early diabetic renal disease. At 4 weeks after study drug and other antihypertensive drugs were stopped, the urinary AER remained substantially below the baseline for subjects treated with irbesartan 300 mg. This new finding supports the view that irbesartan 300 mg affords a relative residual renoprotective effect once the drug is stopped. This finding is consistent with the view that RAS inhibition provides a fundamental change in the renal millieu in addition to and distinct from the reversible renal hemodynamic effects resulting from changes in BP alone.

In addition, the efficacy results in IDNT with irbesartan are very consistent with those of recently published results with another ARB in patients with type 2 diabetes and overt nephropathy.

1 INTRODUCTION

The clinical data presented support the indication of irbesartan in the treatment of diabetic renal disease in hypertensive type 2 diabetic patients. The recommended starting dose is 150 mg, and the preferred maintenance dose is 300 mg once daily.

2 DESCRIPTION OF IRBESARTAN

2.1 Pharmacology

Avapro® (irbesartan or BMS-186295-SR47436) is a long-acting, insurmountable angiotensin II receptor blocker (ARB) that demonstrates highly selective blockade of the AT_1 receptor subtype. Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity.

Angiotensin II (AII) is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). AII is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of AII by selectively binding to the AT_1 angiotensin II receptor. There is also an AT_2 receptor in many tissues, but the role of this receptor subtype in cardiovascular physiology has not been fully elucidated.

Blockade of the AT_1 receptor removes the negative feedback of AII on renin secretion, but the resulting increased plasma renin activity and circulating AII do not overcome the effects of irbesartan on BP.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the regulation of BP and sodium homeostasis.

2.2 Regulatory Status

Irbesartan (Avapro™) has been approved in the United States and other countries worldwide for the treatment of hypertension since 1997.

3 SCIENTIFIC RATIONALE FOR USE OF IRBESARTAN IN HYPERTENSIVE TYPE 2 DIABETIC PATIENTS

3.1 Overview of Hypertensive Type 2 Diabetic Renal Disease

Introduction

Diabetic renal disease is a significant unmet medical need in a high risk population. Because of the scope of this problem, it represents a serious public health concern.

Hypertensive patients with type 2 diabetes and diabetic renal disease are at high risk for renal and cardiovascular morbidity and mortality.[1] In these patients, therapeutic interventions which are safe, effective, and well tolerated are needed to slow the decline in renal function that often culminates with end-stage renal disease (ESRD).

An estimated 135 million people worldwide have diabetes. That figure is expected to more than double to nearly 300 million by the year 2025.[2] More than 16 million people in the United States alone have diabetes, the majority of whom (approximately 70 to 95% depending on race) are suffering from type 2 diabetes.[3] The prevalence of type 2 diabetes is expected to grow over the next decade, as the incidence increases due to aging and obesity, and the life-span of diabetic patients increases due to improvement in their care. As the prevalence of type 2 diabetes increases, the prevalence of diabetic renal disease is expected to increase as well with an incidence of approximately 9% per year.[4]

By the time patients are diagnosed with type 2 diabetes, hypertension is very common, especially among diabetic patients with evidence of renal disease, as manifested by increased urinary albumin excretion.[4,5] As levels of urinary albumin excretion increase, the prevalence of hypertension increases in these patients.

In patients with type 2 diabetes, the simultaneous presence of hypertension and renal disease, as manifested by increased urinary excretion of albumin and protein, increases the risk of mortality. In one study of type 2 diabetic patients, men had a 5-fold and women had an 8-fold increase in mortality risk when proteinuria coexisted with hypertension.[6] The combination of type 2 diabetes, hypertension and diabetic renal

disease places patients at high risk of morbidity and mortality. Once ESRD develops, average life span is dramatically reduced compared to age-matched controls without ESRD. ESRD is defined by the need for dialysis or transplantation. The average survival time for patients with ESRD is 4-5 years.[1] Furthermore, mortality among diabetics with ESRD is approximately 1.5 to 2.5 times greater than that among nondiabetics with ESRD. Less than 20% of diabetics with ESRD survive 5 years after initiation of dialysis.[7] The most common cause of death among diabetic patients with ESRD is cardiovascular disease.[8]

Currently, the most common cause of ESRD is diabetes, accounting for approximately 42–45% of all new cases of ESRD reported in the United States.[7]. Within the cases of ESRD due to diabetes, type 2 diabetes is a more common cause of diabetic ESRD than type 1 diabetes.[4,9] The dramatic increase in numbers of patients with type 2 diabetic renal disease reflects both an increase in the prevalence of diabetes in the general population as well as improved survival of patients with type 2 diabetes in recent years. With a reduction in mortality from cardiovascular disease, patients with type 2 diabetes are now surviving long enough to develop diabetic renal disease and ESRD. Among patients who have had type 2 diabetes for at least 25 years, the prevalence of nephropathy is 57%. Approximately 40% of patients with diabetic ESRD die annually with most deaths due to cardiovascular causes.[1,10]

Without specific interventions, type 2 diabetic patients with hypertension and diabetic renal disease experience a decline in renal function and develop chronic renal failure over time. Chronic renal failure can have a significant impact on quality of life. Clinic visits to control BP, and to receive dietary counseling can become more frequent as well as hospitalizations for other comorbidities associated with chronic renal failure. As the burden of illness increases with time and the decline in renal function, patients often become disabled and depressed, and the cost of their overall care gradually increases as they develop signs and symptoms of uremia with the approach of ESRD.

Diabetic ESRD is an important public health problem with financial implications that are staggering. The US Federal Government alone spent $44.9 billion dollars over the period from 1994 to 1997 for the direct care of patients with ESRD.[1] This estimate does not include costs from lost wages, disability payments and care for comorbid conditions.

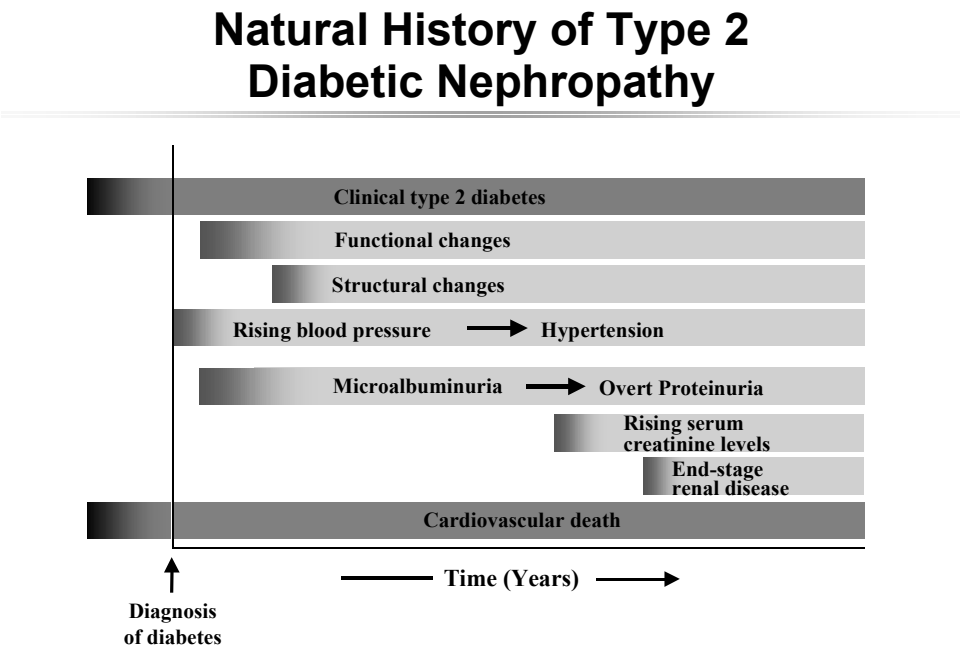
The average cost of hemodialysis in the U.S. is $52,000/year, and total spending for ESRD by all payers in the U.S. was estimated to be $15.6 billion in 1997.[1] The cost per patient-year at risk among all ESRD patients was higher for diabetics ($51,000) than for nondiabetics ($39,000).

Given the dramatically increasing worldwide incidence and prevalence of type 2 diabetes, the projected increased prevalence of ESRD in these patients, the high annual mortality rate in patients with diabetic ESRD, and the increasing costs of care for these high risk patients, new therapies are needed. Safe and effective therapy in diabetic renal disease has the potential to prevent major suffering and significantly reduce the costs involved with care of these ill patients, especially as they reach ESRD.

The Continuum of Diabetic Renal Disease

The natural history of diabetic renal disease is characterized by a continuum of renal abnormalities with altered glomerular morphology and function. This continuum of abnormalities is predictable, sequential and progressive, leading to proteinuria, decreased glomerular filtration rate, and ultimately to ESRD. (Figure 3.1)

Figure 3.1: Natural History of Type 2 Diabetic Nephropathy



Mogensen et al and many others have extensively characterized the natural history of type 1 diabetes. Type 2 diabetic patients, while a more heterogeneous population than type 1 diabetic patients, follow a similar natural history.[11,12]

One of the earliest clinical manifestations in the continuum of diabetic renal disease is the appearance of low but abnormal levels (≥ 30 mg per 24 hours) of albumin in the urine. This is referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient diabetic renal disease.[4] Microalbuminuria is a marker for both progressive kidney damage and cardiovascular disease. Presence of microalbuminuria in normotensive subjects with either type 1 or type 2 diabetes is associated with a three-to five-fold greater risk of cardiovascular mortality and a greater than tenfold risk of renal mortality (progression to dialysis) when compared with diabetic subjects without microalbuminuria.[13]

In patients with incipient diabetic renal disease, the glomerular filtration rate (GFR*)* can be either normal or supernormal (i.e., hyperfiltration is occurring). The decline in GFR during this phase of the continuum is relatively slow (approximately 2.4 mL/min/yr).[14] (Nielsen 1997) Without specific interventions, 20-40% of type 2 diabetic patients with sustained microalbuminuria progress to the next step in the continuum, to clinical (i.e., overt) proteinuria. Clinical (overt) proteinuria is defined as urinary albumin excretion rate (AER) ≥ 300 mg per 24 hours.[4] Other terms have been variably used to identify patients reaching this step on the continuum. These terms include clinical albuminuria, macroalbuminuria, diabetic nephropathy and overt nephropathy.

Once overt proteinuria occurs, without specific interventions, the GFR gradually declines over several years at a rate that is highly variable from individual to individual (2-20 mL per minute per year with an average value of 10 mL per minute per year).[4]

Also, along the continuum, glomerular morphologic changes occur which include mesangial expansion, glomerular basement membrane thickening, diffuse or nodular glomerulosclerosis, and microvascular changes, including arteriolar hyperplasia and hyalinosis. Angiotensin II (AII) is believed to be an important factor influencing these morphologic changes.

The types of glomerular lesions (i.e., diffuse or nodular glomerulosclerosis) are similar in type 1 and type 2 diabetes.[15,16,17] However, morphologic variability appears to be greater in type 2 diabetes than in type 1 diabetes. In particular, features of ischemia are more prevalent in type 2 diabetic renal disease.[16]

Of note, there is distinctly increasing mesangial expansion as patients progress from a normal urinary AER through microalbuminuria and overt proteinuria. Diabetic patients with incipient diabetic renal disease and microalbuminuria already have, on kidney biopsy, a larger fractional mesangial area (i.e., mesangial expansion) than diabetic patients with a normal urinary AER. Importantly, compared to those diabetic patients with microalbuminuria, patients with overt proteinuria have an even greater increased mesangial expansion which is likely due to the longer duration of disease.[18]

Once patients develop microalbuminuria, their glomerular collagen synthesis rates become very similar to that seen in patients with overt proteinuria, both rates quite elevated from that seen in patients with a normal urinary AER. Nevertheless, patients with a normal urinary AER and microalbuminuria have very similar creatinine clearance.[18]

Thus, increasing urinary albumin excretion, which is clinically easy to measure and monitor, reflects worsening abnormalities at the glomerular level.

Overt proteinuria is a modifiable marker that predicts progression to ESRD.[19,20] The magnitude of proteinuria is directly correlated with risk for ESRD and the rate of progression to renal failure.[21] In addition, at any given level of proteinuria, the higher the blood pressure, the more detrimental is the effect of proteinuria on progression to renal insufficiency and renal failure.

When renal insufficiency progresses, as manifested by increasing serum creatinine levels, patients are at increased risk for ESRD. Increasing serum creatinine levels correlate with loss of GFR. In particular, when a patient's serum creatinine doubles from a baseline value, that patient has lost one half of their renal function. In a clinical trial with captopril in type 1 diabetic patients with overt proteinuria, once serum creatinine levels doubled from baseline, the median time from doubling to ESRD was only 9.3 months.[22]

Thus, doubling of serum creatinine represented a very advanced worsening of renal insufficiency in these patients.

The median time to the development of ESRD after the onset of overt proteinuria in type 2 diabetic patients appears to be generally consistent with the above data in type 1 diabetic patients. Registry data from Minnesota in predominantly Caucasians with type 2 diabetes showed the median duration from onset of proteinuria to the development of ESRD to be 7 years.[23] In the PIMA Indians the cumulative incidence of chronic renal failure in type 2 diabetic patients who developed persistent proteinuria was 40% at 10 years and 61% at 15 years after the diagnosis of proteinuria. The incidence of ESRD was significantly related to the duration of diabetes, duration of proteinuria, extent of hyperglycemia, type of diabetes treatment, and presence of retinopathy.[24]

Once ESRD develops, average life span is dramatically reduced. As stated earlier, the average survival time for patients with ESRD is 4-5 years.[1] Furthermore, mortality among diabetics with ESRD is approximately 1.5 to 2.5 times greater than that among nondiabetics with ESRD. Less than 20% of diabetics with ESRD survive 5 years after initiation of dialysis.[7]

Thus, diabetic renal disease is characterized by a predictable, sequential and progressive spectrum of abnormalities, ultimately ending in ESRD. One major goal of treatment is to prevent or slow the progression to ESRD.

3.2 Rationale for the Development of Irbesartan for Use in Hypertensive Type 2 Diabetic Renal Disease

Strategies to Prevent Progressive Diabetic Renal Disease

Current treatment options to slow the progression of diabetic renal disease include strict blood glucose and BP control and interventions to control increases in urinary albumin or protein excretion.[4] Irbesartan safely and effectively controls BP and has also been shown to reduce urinary albumin and protein excretion.

Benefits of BP Control in Diabetes

Effective BP control in hypertensive type 2 diabetic patients is thought to: 1) decrease the rate of decline in GFR;[25] 2) to decrease urinary albumin excretion rates;[26] and 3) to decrease cardiovascular events.[27]

Elevated systolic BP accelerates the progression of type 2 diabetic renal disease, and systolic BP is an excellent predictor of ESRD risk.[28,29] Effective BP control decreases the rate of fall of GFR and lowers AER in hypertensive patients with diabetes.[26,30] The combination of reduced urinary AER and lowered BP has been shown to delay the progression of diabetic renal disease.[4] To date, lowering BP with any antihypertensive medication is generally thought to protect kidneys from functional decline. In a landmark trial with captopril in type 1 diabetic patients with overt nephropathy, this concept was challenged.

Since angiotensin II (AII) is believed to be an important factor influencing pathologic glomerular morphologic changes, drugs which lower BP by inhibiting the action of AII were hypothesized to provide renal protection above and beyond that from BP reduction alone. Specifically, drugs such as captopril which lower BP by inhibiting the renin-angiotensin-aldosterone (RAS) system were prime candidates to study.

A randomized, controlled trial was conducted to compare the antihypertensive drug captopril, an angiotensin converting enzyme inhibitor (ACE-I) with placebo in 409 patients with type 1 diabetes, diabetic retinopathy, proteinuria $\geq$ 500 mg per day, and serum creatinine concentrations $\leq$ 2.5 mg/dL. For BP control those patients randomized to placebo were given a variety of adjunctive antihypertensive medications excluding ACE inhibitors.

Captopril reduced the rate of progression of diabetic nephropathy in type 1 diabetic patients to a greater degree than would be expected from BP reduction alone. Median follow-up was 3 years. The primary endpoint was a doubling of the baseline serum creatinine concentration. Captopril slowed the progression of diabetic nephropathy, reducing the risk of a doubling of serum creatinine by 48% ($p = 0.007$). Captopril was also associated with a 50% risk reduction of the composite endpoint of death, need for dialysis, or transplantation.[22]

By demonstrating the additional renoprotective benefit of captopril above and beyond that achieved from BP control alone, this landmark trial changed the treatment practices of physicians, especially in type 1 diabetic patients. However, until now, in type 2 diabetic patients with diabetic renal disease there has been a paucity of adequately-sized, prospective, randomized clinical trial data demonstrating greater renal protection from one drug class over another on clinically relevant renal outcomes. These outcomes include doubling of serum creatinine or ESRD when BP was controlled to the same level by drugs from different antihypertensive drug classes.

In contrast to renal disease, for cardiovascular disease, the benefits of BP control with a specific antihypertensive drug class have not been observed. Instead, for cardiovascular disease, the specific antihypertensive drug regimen used to control BP does not appear to make a difference in the outcome. Numerous large-scale trials have successfully demonstrated reductions in cardiovascular events such as stroke, congestive heart failure and myocardial infarction in hypertensive diabetic patients and other high-risk populations regardless of the class of antihypertensive regimen used to control BP.[27,31]

Understanding the relative renoprotective benefit from BP reduction itself *vs.* unique benefits of a specific antihypertensive drug class to lower BP was the objective for undertaking a clinical program with irbesartan in hypertensive patients with type 2 diabetic renal disease. A comparison of RAS blockade with an ARB, such as irbesartan, *vs.* non-RAS blockade with the calcium channel blocker (CCB) amlodipine was chosen for study. Non-RAS blockers such as CCBs were known to consistently lower BP in hypertensive diabetic patients; however, the known effects of CCBs on AER in these patients were inconsistent.[32,33]

Furthermore, for hypertensive type 2 diabetic patients with microalbuminuria and overt proteinuria, convincing clinical outcome data, including prevention of death or development of ESRD, from adequately-sized, prospective, randomized clinical trials were not available in this population to support the definitive use of any drug that lowers BP by inhibiting the RAS. Only one drug, captopril, was approved for treatment of diabetic nephropathy, and this approval was for type 1 not type 2 diabetic patients.

RAS Inhibition in Diabetic Renal Disease

The effects of RAS inhibition either with an ARB or an ACE-I have been studied in a variety of patient populations, including nondiabetic and diabetic renal disease.

Since at least 1986 AII has been implicated in the progression of renal failure in diabetic nephropathy.[34] In nondiabetic renal disease RAS inhibition with the ARB, losartan, has been shown to induce improvements in renal hemodynamics and proteinuria similar to those induced by the ACE-I enalapril.[35]

As described earlier, RAS inhibition with the ACE-I captopril is renoprotective in type 1 diabetes. Captopril reduced the rate of progression of diabetic nephropathy in type 1 diabetic subjects to a greater degree than predicted from BP reduction alone[22] Also, in type 2 diabetic patients with early diabetic renal disease and normal BP, RAS inhibition by the ACE-I enalapril stabilized urinary albumin excretion and kidney function. A randomized, double-blind, relatively small placebo-controlled trial evaluated the long-term effect of ACE inhibition with enalapril 10 mg/day on proteinuria and the rate of decline in kidney function in 94 normotensive patients with type 2 diabetes, microalbuminuria, and normal renal function. Patients were followed for 5 years.

Urinary albumin excretion increased in the placebo group but remained stable in the ACE-I group throughout the study. The difference between the 2 groups became statistically significant after the first year. Kidney function, expressed as reciprocal creatinine (100/cr), decreased by 13% in the placebo group but remained stable in the enalapril group ($p < 0.05$). Risk of progression to clinical albuminuria (> 300 mg/24 h) within 5 years of follow-up was 42% on placebo and 12% with enalapril ($p < 0.001$). Thus, in normotensive patients during early stages of type 2 diabetic renal disease, ACE inhibition stabilized urinary albumin excretion and kidney function.[26]

However, in hypertensive type 2 diabetic patients there remains no conclusive evidence that ACE-Is provide protection against clinically relevant renal outcomes such as doubling of serum creatinine or ESRD.[36]

RAS Inhibition with Irbesartan

Irbesartan blocks the RAS cascade at its final step, the AII (AT_1) receptor. Like an ACE-I, irbesartan inhibits the effects of an activated RAS; however, unlike an ACE-I, which potentially allows the generation of AII through alternative chymostatin sensitive pathways, irbesartan more completely blocks the effects of AII by selectivity binding to the AT_1 angiotensin II receptor. Irbesartan was hypothesized to provide benefits similar to or better than those observed with ACE inhibitors in nondiabetic and diabetic renal disease.

One of the proposed mechanisms for progression of renal failure in diabetic renal disease is an increase in intraglomerular capillary pressure due to AII-mediated vasoconstriction of the efferent arteriole. Increased intraglomerular capillary pressure results in hyperfiltration in the surviving glomeruli and eventual glomerular scarring.[37] Pharmacologic reductions in intraglomerular capillary pressure are associated with glomerular structural changes which reduce proteinuria. Reductions in intraglomerular pressure with irbesartan are associated with reductions in proteinuria.[38]

The mechanism of renoprotection by drugs such as irbesartan which block the action of AII may involve hemodynamic factors that lower intraglomerular pressure,[34] the possible beneficial effects of diminished proteinuria[39] and protein trafficking through the glomerulus, and diminished collagen formation, perhaps related to decreased stimulation of transforming growth factor–B by angiotensin.[40]

Once-daily administration of irbesartan has been shown to safely and effectively lower BP in clinical studies in hypertensive subjects. A 7-day dose-finding study in mild-to-moderate hypertensive subjects demonstrated a dose-related effect of irbesartan (1 mg, 25 mg, and 100 mg daily) on trough seated diastolic BP. Phase II-III studies in mild-to-moderate hypertensive subjects demonstrated that irbesartan is well-tolerated and exhibits dose-dependent effects on BP with once-daily dosing of up to 300 mg for 8-10 weeks. The development program in hypertension studied doses up to 900 mg and demonstrated that antihypertensive efficacy plateaus at 300 mg and safety is maintained up to 900 mg. Hepatic metabolism and biliary excretion are the major routes of elimination of irbesartan, suggesting that similar doses would be effective and well-tolerated in subjects

with and without impaired renal function (serum creatinine 1.5 to 3.0 mg/dL), including subjects with type 2 diabetes and hypertension.

Finally, irbesartan reduces urinary albumin and protein excretion in both experimental and clinical models of type 2 diabetes.[38,41,42]

As outlined in Section 4, a comprehensive development program in hypertensive type 2 diabetic patients with diabetic renal disease was designed to test the hypothesis that RAS inhibition by irbesartan provides definitive renal protection across the continuum of diabetic renal disease. Based on favorable preclinical[38] and clinical pilot data[42] obtained with irbesartan in hypertensive diabetic renal disease, this development program was initiated.

4 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The clinical development program was designed to encompass the spectrum of type 2 diabetic renal disease and consists of two randomized, comparative, adequate and well-controlled studies: CV131-048, hereafter referred to as **IDNT (I**rbesartan **D**iabetic **N**ephropathy **T**rial) and Protocol EFC2481, hereafter referred to as **IRMA 2** (**IR**besartan **M**icro**A**lbuminuria in type **2** Diabetes). IRMA 2 was designed to evaluate benefits of irbesartan on the progression from microalbuminuria to overt proteinuria. IDNT was designed to evaluate the benefits of irbesartan on the progression from overt proteinuria to a clinical composite endpoint of doubling of serum creatinine, development of ESRD, and all cause mortality. Together these two clinical studies evaluated the renoprotective effects of irbesartan in two separate phases of the same disease process.

The designs of IDNT and IRMA 2 are presented in Table 4.0.

Table 4.0: Summary of Irbesartan Study Designs in Hypertensive Type 2 Diabetic Patients

Protocol	Design	Objective	Treatment (mg)	Titration (mg)	Duration (months)	Total Randomized
Primary Effectiveness Studies						
IDNT	Double Blind Placebo Controlled Parallel Group Randomized Multicenter	Evaluate the effects of irbesartan (above blood pressure reduction alone) on the preservation of renal function in patients with hypertension, type 2 diabetes mellitus and overt proteinuria	Placebo Irbesartan Amlodipine	Wk 0→2→4 Placebo 75→150→300 2.5→5→10	Up to 57	1715
IRMA 2	Double Blind Placebo Controlled Parallel Group Randomized Multicenter	Evaluate effects of irbesartan on progression from microalbuminuria to overt proteinuria. The GFR substudy was conducted to evaluate the changes in GFR after 3 and 24 months. An extension of the GFR substudy was performed to evaluate the effects of withdrawal of study drug and all antihypertensive medications on GFR at one month.	Placebo Irbesartan 150 mg Irbesartan 300 mg	Wk 0→2→4 Placebo 75→150→150 75→150→300	24	611[a]

[a] At the enrollment visit, 1469 patients were eligible. A total of 858 patients were excluded during the placebo run-in period. A total of 611 patients were randomized, of whom 18 had no measurement of albuminuria and 3 received no study medication. A total of 590 randomized patients were followed for a median of 2 years of double-blind treatment.

Three supportive studies (Protocols CV131-047, CV131-046, and CV131-093) were also conducted. Protocol CV131-047 was the pilot study for IDNT; Protocols CV131-046 and CV131-093 were renal hemodynamics studies. A total of 97 subjects were exposed to study drug in the three supportive studies with duration of treatment ranging from a single dose to 14 weeks. The optional long term extensions in Protocols CV131-046 (N = 37) and CV131-047 (N = 5) ranged from one year to a maximum of three years. The relatively small collective size of these 3 supportive studies, the inclusion of healthy volunteers, and the limited exposure of some of these subjects to irbesartan (e.g., single-dose administration of irbesartan in Protocol CV131-093) in these supportive studies do not provide sufficient additional information to warrant a detailed presentation of these data in this Briefing Document.

5 IDNT

5.1 Design

IDNT was a prospective, multicenter, multinational, parallel group, double-blind, placebo and active-controlled* study design in hypertensive patients with type 2 diabetes and overt proteinuria.[43,44] The study assessed the effects of the ARB irbesartan, the calcium channel blocker (CCB) amlodipine, and placebo (receiving conventional antihypertensive treatment) on the preservation of renal function as evidenced by a reduction of events in the primary composite endpoint of: doubling of serum creatinine, development of ESRD, or all-cause mortality. Subjects evaluated were hypertensive (SeSBP > 135 mmHg and/or SeDBP > 85 mmHg for untreated patients, or receiving antihypertensive medication) with type 2 diabetes. Type 2 diabetes was defined by the same criteria as in the IRMA 2 study (Section 6.1). Subjects had proteinuria (24-hour urine protein excretion ≥ 900 mg) and a serum creatinine between 1.0 and 3.0 mg/dL in women and 1.2 and 3.0 mg/dL in men.

Subjects were randomized 1:1:1 to regimens of irbesartan, amlodipine, or placebo. The doses of study drug administered initially were irbesartan 75 mg, or amlodipine 2.5 mg, or placebo once daily. 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. The dose of study drug was further increased at the end of Week 4 to irbesartan 300 mg, or amlodipine 10 mg, or placebo in all subjects, as tolerated. Eight weeks after randomization, subjects entered a maintenance period in which they were seen every 3 months for 21-57 months. Additional visits to optimize BP control could be scheduled during the titration period. Randomized subjects who discontinued study drug were still followed for clinical event or vital status. Subjects who underwent renal transplantation or chronic dialysis were followed for vital status only thereafter.

The design strategy was to isolate the incremental effects of AT_1 blockade with irbesartan, above and beyond the beneficial effects of BP lowering with other methods of BP control. The attempt was to bring all treatment groups to the same BP goal in IDNT.

* Active control is with respect to hypertension only as no drug of any class has previously demonstrated efficacy in delaying diabetic renal disease in subjects with type 2 diabetes and overt proteinuria.

In this way the treatment differences on progression of type 2 diabetic renal disease, attributable only to the additional effects of AT_1 blockade, could be observed.

IDNT had an independent Executive Committee and the study was conducted under the auspices of the Collaborative Study Group. In addition, the study was overseen by several other independent committees. The Outcome Confirmation and Classification Committee (OCCC) adjudicated cardiovascular events and hospitalizations. The Mortality Committee (a subcommittee of the OCCC) adjudicated all deaths. Discontinuations were adjudicated by the Clinical Management Committee (CMC) to determine reasons for study drug discontinuation. Finally, a Data Safety Monitoring Board (DSMB) reviewed accumulated patient safety data at periodic intervals.

Extensive efforts were made by the CMC to oversee BP values for subjects in this study and recommend protocol allowed concomitant medications to reduce BPs to target levels in patients within all three treatment groups. Subjects in the placebo group were receiving antihypertensive agents excluding RAS inhibitors (ACE-I and ARB) and calcium channel blockers (CCBs). In this regard, placebo subjects were not untreated subjects, just not treated with RAS inhibition or calcium channel blockade. Oversight of BP management allowed for the prospective evaluation of the hypothesis that the mechanism by which BP is reduced and not BP reduction alone is important for maximizing the preservation of renal function.

5.2 Outcome Measures

Primary Composite Endpoint: Defined as the time from randomization to the first occurrence of:

1) doubling of baseline serum creatinine, or
2) end-stage renal disease (defined as renal transplantation or need for dialysis or serum creatinine ≥ 6.0 mg/dL), or
3) death (all-cause mortality).

The choice of a composite endpoint is relevant in this study population since such a composite captures the effect of treatment on death or progression to a state of advanced renal disease. The effect of treatment with irbesartan in subjects with advanced overt diabetic renal disease on three clinically meaningful and closely interrelated outcome

measures is appropriate to capture the overall effect of treatment. The outcome measure, death, is increased in frequency in diabetics and markedly increased in frequency in diabetics with even early manifestations of renal disease. The two renal outcome measures, ESRD and doubling of serum creatinine, are complementary and overlapping.

Though historically defined as a state of renal failure that is incompatible with life, with the availability of life-prolonging treatment for renal failure, ESRD has become synonymous with the initiation of renal replacement therapy for advanced uremic symptoms or reduction in GFR to less than 10-15 mL/minute. ESRD is highly significant from a clinical point of view because of the morbidity associated with dialysis and transplantation, and from a public health and policy point of view because of the cost associated with dialysis and transplantation. ESRD is not an ideal outcome measure for clinical studies because it is a subjective parameter. The timing of initiation of renal replacement therapy is physician dependent, with some physicians favoring initiation of therapy early, to limit the extent of malnutrition and metabolic bone disease, and others favoring initiation of therapy only for highly symptomatic disease.

The doubling of serum creatinine is a laboratory measure that represents a loss of 50% of baseline renal filtration function and is a more objective parameter. In patients with normal renal function, loss of 50% of baseline function produces no clinical findings. In patients with renal disease, however, a doubling of serum creatinine is clinically important and reflects progression to a state of advanced renal impairment.

Secondary Cardiovascular Composite Endpoint: Defined as the time from randomization to the first occurrence of:

1) cardiovascular death,
2) non-fatal myocardial infarction,
3) heart failure resulting in hospitalization,
4) permanent neurological deficit due to cerebrovascular event, or
5) above the ankle amputation.

Tertiary Cardiovascular Composite Endpoint: Defined as the time from randomization to the first occurrence of:

1) cardiovascular death,
2) non-fatal myocardial infarction,
3) heart failure resulting in hospitalization,
4) permanent neurological deficit due to cerebrovascular event,
5) above the ankle amputation,
6) unplanned coronary artery revascularization procedure,
7) heart failure requiring therapy with an ACE-I or ARB,
8) below the ankle amputation, or
9) unplanned peripheral artery revascularization procedure.

The secondary and tertiary cardiovascular endpoints did not overlap the primary renal composite endpoint except in mortality. The results for the renal endpoints would not be expected to predict the results for the cardiovascular endpoints.

5.3 Dose Selection

The IDNT trial design limited the dose experience with irbesartan to a single maintenance dose regimen of 300 mg. The 300 mg dose of irbesartan provides 100% blockage of the AT_1 receptor. The clinical pharmacology of irbesartan shown in hypertensive subjects and data with irbesartan in subjects with severe renal insufficiency suggested that the 300 mg dose would be well tolerated in this trial of hypertensive diabetic subjects with renal insufficiency.[45]

The choice of the irbesartan maintenance dose in IDNT represented a decision to explore the comparative efficacy of irbesartan 300 mg with amlodipine 10 mg. Amlodipine 10 mg is the highest approved dose for hypertension.

5.4 Comparator Selection

IDNT examined the potential renal benefits of RAS inhibition (i.e., blockade) in type 2 diabetic patients with overt proteinuria. The intent was to show that the renal benefits of irbesartan exist above and beyond its ability to lower BP.

In IDNT, the drugs chosen to compare against irbesartan were placebo and amlodipine with all arms on a background of standard antihypertensive therapy to control BP.

IDNT directly compared the clinical benefits of irbesartan on the kidney to those of other antihypertensive regimens. Comparisons of irbesartan with placebo added to the validity of the results. The comparison of irbesartan and amlodipine added critical information to support the hypothesis that inhibition of the RAS is beneficial in diabetes compared with effective antihypertensive agents using different mechanisms of action.

The relative renoprotective benefit from BP reduction itself *vs.* unique benefits of a specific antihypertensive class (i.e., blockers of the renin-angiotensin system [RAS] *vs.* Non-RAS blockers such as amlodipine) was tested.

RAS Blockade *vs.* Non-RAS Blockade

The two distinct mechanisms of antihypertensive action tested in IDNT are RAS blockade and calcium channel blockade. ARBs , such as irbesartan, and ACE-Is both act by interrupting the effects of an activated RAS whereas the calcium channel blocker (CCB) amlodipine, a very effective antihypertensive drug, has a different mechanism of blood pressure control. Demonstrating similar effects of an ARB and an ACE-I might provide reassurance that RAS blockade is beneficial in diabetic patients; however, a comparison of an ARB with a CCB, a drug class with a different mechanism of action, provides additional information for the prescribing physician, especially for the management of this type 2 diabetic patient population in whom BP is often difficult to control.

In IDNT the purpose of including a group treated with a CCB was to evaluate the hypothesis that blocking the AII receptor with irbesartan will delay the progression of diabetic renal disease to a greater degree than reducing BP through calcium antagonism. In addition to BP lowering efficacy, irbesartan would be expected to delay the progression of diabetic renal disease by its effect on glomerular hemodynamics and matrix metabolism.

CCBs consistently lower BP in hypertensive diabetic patients; however, the known effects of CCBs on proteinuria in these patients were inconsistent.[32,46]

CCBs, which have excellent antihypertensive efficacy, are frequently used in diabetic patients whose BP is difficult to control. CCBs elicit their antihypertensive effect by inhibiting the transmembrane influx of calcium ions in vascular smooth muscle, leading to systemic vasodilation and a reduction in peripheral vascular resistance. In the kidney these agents block tubuloglomerular feedback and preferentially dilate the preglomerular circulation, therefore affecting regulation of afferent arteriolar resistance and intraglomerular pressure.[32]

With the exception of the short-acting dihydropyridine CCB nifedipine, the use of CCBs has been associated with either improvement in or no impact on urine protein excretion and glomerular filtration rate in diabetic patients.[46] In several experimental models of diabetic nephropathy the use of CCBs has been reported to preserve renal function. However, in subjects with diabetic nephropathy, improvement in urine protein excretion or preservation of GFR have been less consistently observed.

The long term effects of CCBs on renal outcomes of doubling of serum creatinine and ESRD have not been previously reported.

5.5 Demography

Table 5.5 presents baseline demography for subjects randomized in IDNT by treatment group.

Table 5.5: Baseline Characteristics of Subjects Randomized in IDNT

	Number (%) of Subjects			
	Placebo N = 569	**Irbesartan N = 579**	**Amlodipine N = 567**	**Total N = 1715**
Mean Age (years) ± SD	58.3 ± 8.2	59.3 ± 7.1	59.1 ± 7.9	58.9 ± 7.8
Gender				
Male	403 (70.8)	378 (65.3)	359 (63.3)	1140 (66.5)
Female	166 (29.2)	201 (34.7)	208 (36.7)	575 (33.5)
Race/Ethnic Group				
White	415 (72.9)	438 (75.6)	389 (68.6)	1242 (72.4)
Black	78 (13.7)	63 (10.9)	87 (15.3)	228 (13.3)
Hispanic	26 (4.6)	28 (4.8)	29 (5.1)	83 (4.8)
Asian/Pacific	27 (4.7)	24 (4.1)	34 (6.0)	85 (5.0)
Other	23 (4.0)	26 (4.5)	28 (4.9)	77 (4.5)
Body Mass Index (BMI) (mean ± SD)	N = 569 30.54 ± 5.89	N = 579 31.03 ± 5.55	N = 566 30.90 ± 5.93	N = 1714 30.82 ± 5.79
Seated Blood Pressure (mm Hg)				
Systolic BP, Mean ± SD	158.2 ± 20.5	160.5 ± 19.5	158.6 ± 19.1	159.1 ± 19.7
Diastolic BP, Mean ± SD	86.9 ± 10.9	86.8 ± 11.3	87.0 ± 10.8	86.9 ± 11.0
Medical History				
Known Duration of Diabetes Mean (years) ± SD	N = 569 15.03 ± 7.89	N = 579 15.45 ± 8.53	N = 566 13.87 ± 7.79	N =1714 14.79 ± 8.11
Insulin Use	330 (58.6)	323 (56.0)	315 (56.4)	968 (56.4)
History of CV Disease	249 (43.8)	276 (47.7)	254 (44.8)	779 (45.4)
Laboratory Values:				
Serum creatinine (mg/dL) Mean ± SD	N = 567 1.7 ± 0.6	N = 578 1.7 ± 0.5	N = 564 1.7 ± 0.6	N = 1709 1.7 ± 0.6
Urinary protein excretion (mg/24 h) Mean ± SD	N = 534 3087.7±2496.6	N = 549 3051.1±2383.1	N = 528 2878.0±2251.6	N = 1611 3005.1±2376.4
Urinary albumin excretion[a] (mg/24h) Geometric Mean± SD	N = 532 1937.8±1691.4	N = 549 1941.5±1673.8	N = 527 1820.1±1550.5	N = 1608 1899.6±1638.1
HbA_{1c} (%) Mean ± SD	N = 513 8.2 ± 1.8	N = 527 8.1 ± 1.7	N = 515 8.1 ± 1.7	N = 1555 8.1 ± 1.7

[a] To convert urinary albumin excretion from mg/24h to µg/min these values must be divided by a factor of 1.44.

In IDNT, there were no imbalances among the treatment groups in the various demographic and baseline characteristics deemed large enough to affect the efficacy comparisons.

5.6 Efficacy

The primary renal composite endpoint was analyzed as time to the occurrence of doubling of baseline serum creatinine, development of end-stage renal disease (ESRD), or all-cause mortality, whichever happened first. The primary analysis was by Kaplan-Meier method using log-rank test for comparisons between treatment groups, and the relative risk reductions were estimated by Cox regression. The secondary and tertiary cardiovascular composite endpoints were analyzed similarly. For all analyses the primary comparison was irbesartan *vs.* placebo and the secondary comparison was irbesartan *vs.* amlodipine. The results presented here are ITT analyses.

Treatment effects on each of the three individual components of the primary composite endpoint, on the combination of ESRD or all-cause death, and on the combination of doubling of serum creatinine or ESRD, were assessed separately. In addition to these analyses, subgroup analyses of the renal composite endpoint were performed on sub-populations defined by baseline factors and geographic region.

Each patient could potentially have more than one event from the primary composite endpoint (e.g., starting with doubling of serum creatinine, progressing to ESRD, and ultimately dying). Tabulation of this total incidence of the individual renal components of doubling of serum creatinine and ESRD is included below.

5.6.1 Renal Primary Analysis

5.6.1.1 Time to Renal Composite Endpoint - Irbesartan Vs. Placebo and Vs. Amlodipine

Irbesartan significantly increased the time to the primary (renal) composite endpoint of doubling of serum creatinine, ESRD, or all-cause mortality in hypertensive subjects with type 2 diabetes and overt proteinuria, demonstrating a 20% relative risk reduction *vs.* placebo ($p = 0.0234$) and a 23% relative risk reduction *vs.* amlodipine ($p = 0.0064$) (Table 5.6.1.1A).

A total of 644/1715 (37.6%) randomized subjects reached the renal composite endpoint: 189/579 (32.6%) subjects in the irbesartan group; 222/569 (39.0%) in the placebo group.

Table 5.6.1.1A: IDNT: Primary Composite Endpoint: Irbesartan vs. Placebo - ITT analysis

Event	Number (%) of Subjects[a]		Relative Risk[b]		p[c]
	Placebo N = 569	Irbesartan N = 579	Estimate	95% Confidence Interval	
Primary Composite Endpoint[d]	222 (39.0)	189 (32.6)	0.80	0.66 - 0.97	0.0234

Dataset: Randomized Subjects

a One subject in the placebo group with unknown event date for ESRD was included in the event counts, but excluded from the time-to-event analysis.

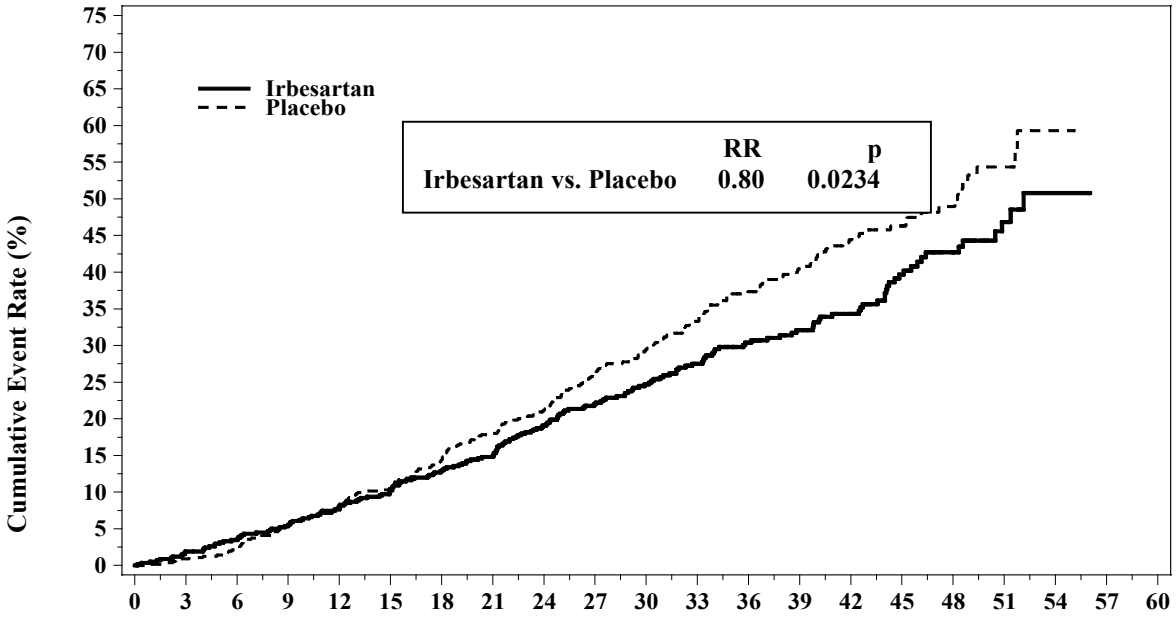
b For irbesartan relative to placebo (determined from Cox proportional hazards model)

c From log-rank test

d Counts and treatment comparisons are based on the first occurrence of the composite event. Each subject is counted no more than once.

Figure 5.6.1.1A displays the time-to-event analysis. The cumulative event rate curves for the primary composite endpoint begin to separate between irbesartan and placebo groups as early as 15 months and the difference becomes more pronounced during the course of the study.

Figure 5.6.1.1A: IDNT: Kaplan-Meier Curves for Primary Composite Endpoint (Irbesartan vs. Placebo) – all Randomized Subjects – ITT Analysis



N at risk

Irbesartan	**579**	**567**	**556**	**544**	**528**	**513**	**497**	**479**	**409**	**352**	**308**	**258**	**219**	**189**	**151**	**105**	**69**	**29**	**5**
Placebo	**569**	**560**	**552**	**532**	**515**	**500**	**474**	**457**	**407**	**337**	**289**	**237**	**194**	**161**	**126**	**85**	**59**	**23**	**4**

Irbesartan also significantly increased the time to the primary (renal) composite endpoint *vs.* amlodipine, demonstrating a 23% relative risk reduction (p = 0.0064). (Table 5.6.1.1B).

Irbesartan significantly reduced the number of subjects reaching the primary composite endpoint of doubling of serum creatinine, ESRD, or all-cause mortality in hypertensive subjects with type 2 diabetes and diabetic renal disease compared to amlodipine treatment. A total of 644/1715 (37.6%) randomized subjects reached the renal composite endpoint: 189/579 (32.6%) subjects in the irbesartan group and 233/567 (41.1%) in the amlodipine group.

Table 5.6.1.1B: IDNT: Primary Composite Endpoint: Irbesartan vs. Amlodipine – ITT analysis

Event	Number (%) of Subjects[a]		Relative Risk[b]		p[c]
	Amlodipine N = 567	Irbesartan N = 579	Estimate	95% Confidence Interval	
Primary Composite Endpoint[d]	233 (41.1)	189 (32.6)	0.77	0.63 - 0.93	0.0064

a Two subjects in the amlodipine group with unknown event date for ESRD were included in the event counts, but excluded from the time-to-event analysis.

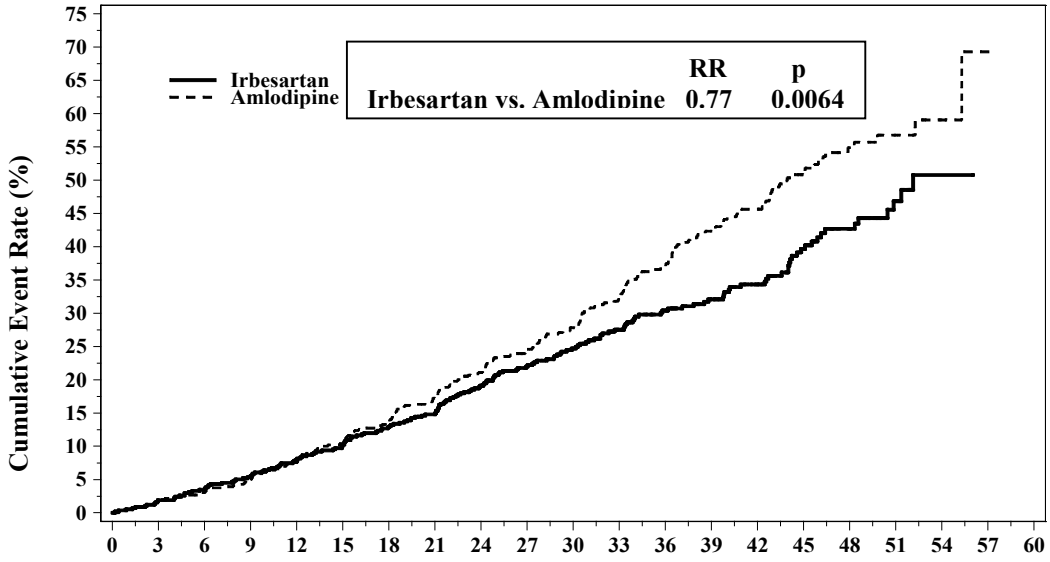
b For irbesartan relative to amlodipine (determined from Cox proportional hazards model)

c From log-rank test

d Counts and treatment comparisons are based on the first occurrence of the composite event. Each subject is counted no more than once.

The cumulative event rate curves for the primary composite endpoint begin to diverge between irbesartan and amlodipine groups as early as 15 months and the difference becomes more pronounced during the course of the study (Figure 5.6.1.1B).

Figure 5.6.1.1B: IDNT: Kaplan-Meier Curves for Primary Composite Endpoint (Irbesartan vs. Amlodipine – all Randomized Subjects - ITT Analysis)



N at risk

Irbesartan	579	567	556	544	528	513	497	479	409	352	308	258	219	189	151	105	69	29	5
Amlodipine	567	553	544	531	513	499	479	455	399	341	299	247	200	161	132	93	51	26	9

5.6.1.2 Primary Composite Endpoint and Individual Events

The breakdown of the first occurrence of primary composite endpoint and the total incidence of events are presented in Table 5.6.1.2A.

Table 5.6.1.2A: IDNT: Primary Composite Endpoint: By Treatment Group

	Number (%) of Subjects		
	Placebo Group N = 569	**Irbesartan Group N = 579**	**Amlodipine Group N = 567**
Primary Composite Endpoint	222 (39.0)	189 (32.6)	233 (41.1)
Breakdown of the First Occurring Primary Event			
Doubling of Serum Creatinine	111 (19.5)	82 (14.2)	129 (22.8)
ESRD[a]	47 (8.3)	43 (7.4)	50 (8.8)
All-cause Mortality	64 (11.2)	64 (11.1)	54 (9.5)
Total Incidence of[b]			
Doubling of Serum Creatinine	135 (23.7)	98 (16.9)	144 (25.4)
ESRD	101 (17.8)	82 (14.2)	104 (18.3)
All-cause Mortality	93 (16.3)	87 (15.0)	83 (14.6)

[a] There were 55 subjects (24 placebo, 16 irbesartan and 15 amlodipine) who had ESRD and doubling of baseline serum creatinine occurring on the same day. These subjects are included in ESRD and are not counted towards doubling of serum creatinine in this breakdown of the first primary composite endpoint.

[b] The total incidence counts the first occurrence of each individual component event, rather than just the first occurrence of the primary composite endpoint. Therefore, the total incidences of the components add up to more than the overall incidence of the primary composite endpoint.

As observed in Table 5.6.1.2A, many subjects reached doubling of serum creatinine earlier than ESRD or death, which may not be surprising given the natural progression of the renal disease in type II diabetes. All subjects were followed until death or until study completion to characterize the renal deterioration, and thus observing the components of the primary composite endpoint. Due to natural progression of the renal disease and due to the competing risk of cardiovascular mortality in these subjects with type 2 diabetes, after subjects reached doubling of baseline serum creatinine, they could subsequently develop ESRD or die due to any cause. In other words, each subject could have had more than one primary component event occur during the study: doubling of serum creatinine, ESRD or death. In order to assess the impact of treatment on the individual components of the primary composite endpoint, the total incidence of each component is also summarized in Table 5.6.1.2A.

In the time to event analysis for an individual component event, all first occurrences of that component event were included, regardless of whether a different component event occurred previously. All renal events (doubling and ESRD), however, were obviously censored at the time of death. For example, in the time to event analysis of ESRD, a subject should not be censored when he/she reached doubling of serum creatinine. All subjects with ESRD should be considered to have an ESRD event, regardless of whether the subjects had reached doubling of serum creatinine. The analysis results of the individual components are presented in Tables 5.6.1.2B and C.

Table 5.6.1.2B: Primary Event Comparison: Irbesartan vs. Placebo (ITT Analysis)

	Number (%) of Subjects[a]		Relative Risk[b]		
Event	**Placebo N = 569**	**Irbesartan N = 579**	**Estimate**	**95% Confidence Interval**	**p[c]**
Doubling of Serum Creatinine[d]	135 (23.7)	98 (16.9)	0.67	0.52 - 0.87	0.0027
ESRD[d]	101 (17.8)	82 (14.2)	0.77	0.57 - 1.03	0.0731
Death (all causes)[d]	93 (16.3)	87 (15.0)	0.92	0.69 - 1.23	0.5683

[a] One subject in placebo group with unknown event date for ESRD was included in the event counts, but excluded from the time-to-event analyses.

[b] For irbesartan relative to placebo (determined from Cox proportional hazards model)

[c] From log-rank test

[d] Represents total number of occurrences of each event. Treatment comparisons are based on analysis of time to first occurrence of the individual component.

Table 5.6.1.2C: Primary Event Comparison: Irbesartan vs. Amlodipine (ITT Analysis)

	Number (%) of Subjects[a]		Relative Risk[b]		
Event	**Amlodipine**	**Irbesartan**	**Estimate**	**95% Confidence**	**p[c]**
	N = 567	**N = 579**		**Interval**	
Doubling of Serum Creatinine[d]	144 (25.4)	98 (16.9)	0.63	0.49 - 0.81	0.0003
ESRD[d]	104 (18.3)	82 (14.2)	0.77	0.57 - 1.03	0.0746
Death (all causes)[d]	83 (14.6)	87 (15.0)	1.04	0.77 - 1.40	0.8083

[a] Two subjects with unknown event dates for ESRD were included in the event counts, but excluded from the time-to-event analyses.

[b] For irbesartan relative to amlodipine (determined from Cox proportional hazards model)

[c] From log-rank test

[d] Represents total number of occurrences of each event. Treatment comparisons are based on analysis of time to first occurrence of the individual component.

There was a consistent trend of a favorable relative risk reduction for irbesartan in the individual renal components of doubling of serum creatinine or ESRD. The observed renal benefit was not out-weighed by a risk of mortality due to any cause.

Doubling of Baseline Serum Creatinine

Irbesartan significantly decreased the total incidences of the individual component of doubling of baseline serum creatinine (SrCr). A total of 377/1715 (22%) randomized subjects reached doubling of baseline serum creatinine. The incidence rate of doubling of SrCr was 16.9% in the irbesartan group compared with 23.7% in the placebo group and 25.4% in the amlodipine group. The relative risks of SrCr doubling for irbesartan *vs.* placebo were 0.67 (95% CI 0.52-0.87) and 0.63 (95% CI 0.49-0.81) for irbesartan *vs.* amlodipine. Irbesartan demonstrated a statistically significant 33% relative risk reduction in SrCr doubling compared to placebo ($p = 0.0027$) and a 37% relative risk reduction compared to amlodipine ($p = 0.0003$). Of the 377 subjects whose SrCr doubled from baseline, 202 (53.6%) progressed to ESRD later in the trial. The median follow-up time to ESRD after doubling was 9.8 months.

End Stage Renal Disease (ESRD)

Irbesartan also decreased the total incidences of the individual component of ESRD. The relative risks of ESRD for irbesartan *vs.* placebo and for irbesartan *vs.* amlodipine were both 0.77 (95% CI: 0.57 - 1.03).

All-Cause Mortality

A total of 263/1715 (15.3%) subjects died during the trial, 87/579 (15%) in the irbesartan group, 93/569 (16.3%) in the placebo group, and 83/567 (14.6%) in the amlodipine group (Tables 5.6.1.2B and 5.6.1.2C). The relative risks for all-cause mortality were 0.92 (95% CI: 0.69-1.23) for irbesartan *vs.* placebo, and 1.04 (95% CI: 0.77-1.40) for irbesartan *vs.* amlodipine. There was no significant difference in risk of all-cause mortality between irbesartan and placebo or amlodipine.

5.6.1.3 Risk Reduction of the Primary Composite Endpoint Adjusted for Baseline Prognostic Factors

It is of interest to assess whether the benefit of irbesartan compared with placebo persists despite adjustment for possible differences in baseline prognostic factors. Thus, Cox regression models adjusting individually for baseline prognostic factors, were used to calculate the relative risk of irbesartan compared with placebo adjusting for the prognostic factor. A separate Cox model was fit for each covariate with factors including the treatment and the covariate. Seventeen *a priori* specified baseline prognostic factors were considered: gender (male, female), race (white and non-white), age, duration of diabetes, seated mean arterial pressure (MAP), serum creatinine, albumin excretion rate, protein excretion rate, glycosylated hemoglobin, total cholesterol, prior ACE-I use, use of insulin, BMI, history of cardiovascular disease, baseline abnormal ECG, use of sulfonylureas, and use of metformin.

In the following discussion, Table 5.6.1.3A (irbesartan *vs.* placebo) focuses on the impact of the most clinically relevant (rather than statistically important) baseline factors: gender, race, age, duration of diabetes, seated mean arterial pressure (MAP), serum creatinine, albumin excretion rate, and protein excretion rate.

Table 5.6.1.3A: IDNT Study: Effect of Potential Prognostic Baseline Factors on Relative Risk for Primary Composite Endpoint (Irbesartan vs. Placebo)

	Irbesartan vs. Placebo
Baseline Factors[a]	**Relative Risk (95% CI)**[b]
Gender (male)	0.79 (0.65 – 0.96)
Race (white)	0.81 (0.67 – 0.98)
Age (yr)	0.80 (0.66 – 0.97)
Duration of diabetes (yr)	0.79 (0.65 – 0.96)
Seated MAP (mmHg)	0.79 (0.65 – 0.96)
Serum creatinine (mg/dL)	0.80 (0.66 – 0.97)
Albumin excretion rate[c]	0.77 (0.63 – 0.94)
Protein excretion rate [c]	0.80 (0.66 – 0.98)

[a] Each regression model included terms for treatment group and baseline factor.

[b] Risk for irbesartan relative to placebo, after adjustment for the baseline factor.

[c] Logarithm transformation was applied to AER and PER.

Overall, based on Table 5.6.1.3A, treatment with irbesartan compared with placebo provides significant risk reductions of 19%-23% after adjustment for the baseline factors, thus suggesting a consistent treatment benefit of irbesartan for the primary composite endpoint.

5.6.2 Antihypertensive Efficacy: Irbesartan *vs.* Placebo and *vs.* Amlodipine

The majority of subjects required two to four concomitant antihypertensive drugs during the double-blind period to control pressure. As expected patients in the placebo group required more adjunctive therapy than patients in the irbesartan or amlodipine groups.

Beta-blockers were the most commonly used adjunctive agents and were used by 52%, 43.5% and 40.6% of the placebo, irbesartan and amlodipine groups, respectively. Alpha/beta adrenergic blockers were used by 48.1%, 43.2% and 41.5% of patients in these groups, respectively.

BP was reduced in all three treatment groups to 145.2/79.3 mmHg, 141.8/77.0 mmHg, and 141.9/76.4 mmHg in the placebo, irbesartan, and amlodipine groups, respectively at the last visit. Table 5.6.2 displays the change from baseline to last observation in seated blood pressure.

Table 5.6.2: IDNT: Change from Baseline to Last Observation in Seated Blood Pressures

Treatment Group Number Randomized		**Placebo N = 569**	**Irbesartan N = 579**	**Amlodipine N = 567**
Seated Systolic BP (mmHg)	n	565	576	562
	Baseline Mean (SD)	158.2 (20.5)	160.4 (19.5)	158.5 (19.1)
	Last Observation Mean (SD)	145.2 (20.6)	141.8 (20.9)	141.9 (19.1)
	Adjusted[a] Mean Change (SE)	-13.6 (0.8)	-17.7 (0.8)	-17.0 (0.8)
	p value: Comparison vs. Irbesartan	< 0.001		0.566
Seated Diastolic BP (mmHg)	n	565	576	562
	Baseline Mean (SD)	86.9 (11.0)	86.8 (11.3)	87.0 (10.8)
	Last Observation Mean (SD)	79.3 (11.9)	77.0 (10.6)	76.4 (10.8)
	Adjusted[a] Mean Change (SE)	-7.6 (0.4)	-9.8 (0.4)	-10.5 (0.4)
	p value: Comparison vs. Irbesartan	< 0.001		0.249
Seated MAP[b] (mmHg)	n	565	576	562
	Baseline Mean (SD)	110.7 (12.0)	111.3 (11.9)	110.8 (11.4)
	Last Observation Mean (SD)	101.3 (12.9)	98.6 (12.2)	98.2 (11.7)
	Adjusted[a] Mean Change (SE)	-9.6 (0.5)	-12.4 (0.5)	-12.7 (0.5)
	p value: Comparison vs. Irbesartan	< 0.001		0.714

[a] Adjusted via analysis of covariance

[b] MAP - Mean Arterial Pressure

Clinically meaningful reductions in BP were achieved during the course of IDNT. The adjusted mean change to last visit in SeSBP was -13.6, -17.7, and -17.0 mmHg for the placebo, irbesartan and amlodipine groups, respectively; the adjusted mean change in SeDBP was -7.6, -9.8, and -10.5, respectively; and the adjusted mean change in MAP was -9.6, -12.4, and -12.7, respectively. For each of the seated BP parameters, the decrease from baseline was statistically significantly greater for irbesartan than for placebo ($p < 0.001$) even though the placebo group was actively treated by adjunctive antihypertensive medications. However, the differences between irbesartan and amlodipine in mean change in BP were not statistically significant. In addition, repeated measures mixed model ANOVAs were performed to assess whether the treatment groups were similar in attained BP over the course of the study. These analyses served to determine whether Cox regression was needed to remove the effect of systemic BP when assessing the treatment effect on the efficacy composite endpoints. After adjustment for the effect of MAP, the treatment benefit of irbesartan in relative risk reduction for the primary composite endpoint compared to either placebo or amlodipine was still statistically significant.

If BP control was the sole mechanism of action responsible for the significant renoprotective effects achieved with irbesartan, the same favorable effects on kidney function should have been evident with amlodipine. The renoprotective effects of irbesartan are independent of BP reduction.

5.6.3 Renal Outcomes: Irbesartan vs. Placebo and vs. Amlodipine

Given that the effects of irbesartan vs placebo on mortality during the relatively few years of this trial were likely to be small, one planned analysis focused on renal outcomes alone. Doubling of serum creatinine and ESRD are complementary and overlapping measures of progression to a state of advanced renal failure; 140 subjects developed end stage renal disease before serum creatinine doubled or on the same day.

Combination of Doubling of Serum Creatinine or ESRD

Irbesartan significantly reduced the time to the combined endpoint of doubling of serum creatinine or ESRD (i.e., the first occurrence of either event). The p value *vs.* placebo was 0.0116 and *vs.* amlodipine was 0.0003. The relative risks were 0.74 (95% CI: 0.59-0.94) for irbesartan *vs.* placebo and 0.66 (95% CI: 0.53-0.83) for irbesartan *vs.* amlodipine. Irbesartan demonstrated significant relative risk reductions of 26% compared with placebo and 34% compared with amlodipine (Table 5.6.3A).

Table 5.6.3A: IDNT: Comparison (Irbesartan vs. Placebo and vs. Amlodipine) of Renal Outcomes - ITT Analysis

Event	Number (%) of Subjects[a]			Irbesartan *vs.* Placebo		Irbesartan *vs.* Amlodipine	
	Placebo N = 569	Irbesartan N = 579	Amlodipine N = 567	RR (95% CI)[b]	p[c]	RR (95% CI)[b]	p[c]
Doubling of Serum Creatinine or ESRD[d]	158 (27.8)	125 (21.6)	179 (31.6)	0.74 (0.59-0.94)	0.0116	0.66 (0.53-0.83)	0.0003

[a] One subject in the placebo group and 2 subjects in the amlodipine group with unknown event date for ESRD were included in the event counts, but excluded from the time-to-event analyses.

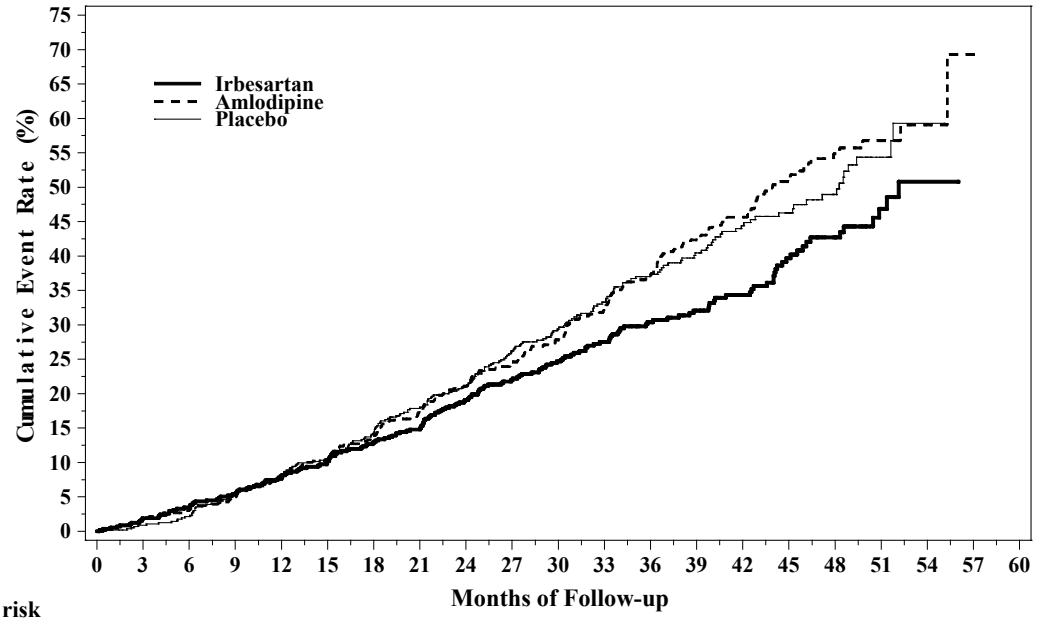
[b] Determined from Cox proportional hazards model.

[c] From log-rank test

[d] Counts and treatment comparisons are based on the first occurrence of either event. Each subject is counted no more than once.

5.6.4 RAS Blockade *Vs.* Non-RAS Blockade: Relative Risk Analysis

Figure 5.6.4: IDNT: Kaplan Meier Curves for Primary Composite Endpoint-all Randomized Subjects



N at risk																			
Irbesartan	579	567	556	544	528	513	497	479	409	352	308	258	219	189	151	105	69	29	5
Amlodipine	567	553	544	531	513	499	479	455	399	341	299	247	200	161	132	93	51	26	9
Placebo	569	560	552	532	515	500	474	457	407	337	289	237	194	161	126	85	59	23	4

Since the objective of IDNT was to compare the effects of BP reduction by RAS inhibition with irbesartan to those of BP reduction utilizing different mechanisms to lower BP, a post-hoc analysis of the primary endpoint was performed in which irbesartan was compared with the placebo and amlodipine groups combined. The fact that the two non-RAS groups exhibit similar effects in terms of the primary endpoint, as demonstrated by overlapping Kaplan-Meier curves (Figure 5.6.4), confirms the clinical validity of this post-hoc analysis. As shown in Table 5.6.4A, the frequency of subjects reaching the primary composite endpoint of doubling of serum creatinine, ESRD, or all-cause mortality was significantly lower in the irbesartan group compared with the combined data from the placebo and amlodipine groups.

Table 5.6.4A: IDNT Study: Primary Composite Endpoint Comparison: Irbesartan vs. Placebo and Amlodipine

Event	Number (%) of Subjects[a]		Relative Risk[b]		
	Placebo and Amlodipine N = 1136	Irbesartan N = 579	Estimate	95% Confidence Interval	p[c]
Primary Composite Endpoint[d]	455 (40.1)	189 (32.6)	0.78	0.66 - 0.93	0.0041

[a] One subject in the placebo group and 2 subjects in the amlodipine group with unknown event date for ESRD were included in the event counts, but excluded from the time-to-event analyses.

[b] For irbesartan relative to placebo and amlodipine (determined from Cox proportional hazards model)

[c] From log-rank test

[d] Counts and treatment comparisons are based on the first occurrence of the composite event. Each subject is counted no more than once.

Table 5.6.4B: Comparison (Irbesartan vs. Placebo and Amlodipine) of Primary Composite Endpoint - ITT Analysis

	Number (%) of Subjects[a]		Relative Risk[b]		
Event	**Placebo and Amlodipine**	**Irbesartan**	**Estimate**	**95% Confidence**	**p[c]**
	N = 1136	**N = 579**		**Interval**	
Primary Composite Endpoint	455 (40.1)	189 (32.6)	0.78	0.66 - 0.93	0.0041
Breakdown of the First Occurring Primary Event					
Doubling of Serum Creatinine	240 (21.1)	82 (14.2)			
ESRD[d]	97 (8.5)	43 (7.4)			
All-Cause Mortality	118 (10.4)	64 (11.1)			
Total Incidence of					
Doubling of Serum Creatinine[e]	279 (24.6)	98 (16.9)	0.65	0.51 - 0.81	0.0002
ESRD[e]	205 (18.0)	82 (14.2)	0.77	0.59 - 0.99	0.0422
All-Cause Mortality[e]	176 (15.5)	87 (15.0)	0.98	0.75 - 1.26	0.8476
ESRD or Doubling of Serum Creatinine[e]	337 (29.7)	125 (21.6)	0.70	0.57 - 0.85	0.0005

[a] One subject in placebo group and two subjects in amlodipine group with unknown ESRD event dates were reflected in the event counts, but excluded from the time-to-event analyses.

[b] For irbesartan relative to placebo and amlodipine (determined from Cox proportional hazards model)

[c] From log-rank test

[d] There were 55 subjects (24 placebo, 16 irbesartan and 15 amlodipine) who had ESRD and doubling of baseline serum creatinine occurring on the same day. These subjects are included in ESRD and are not counted towards doubling of serum creatinine in this breakdown of the first primary composite endpoint.

[e] The total incidence counts the first occurrence of each individual component event, rather than just the first occurrence of the primary composite endpoint. Therefore, the total incidences of the components add up to more than the overall incidence of the primary composite endpoint. For the combination of ESRD or doubling of serum creatinine, the first occurrence of this combination event is counted.

End Stage Renal Disease (ESRD)

In a post hoc analysis, irbesartan demonstrated a statistically significant 23% relative risk reduction in ESRD compared to the combined placebo and amlodipine groups ($p = 0.0422$ for irbesartan *vs.* the combined placebo and amlodipine groups).

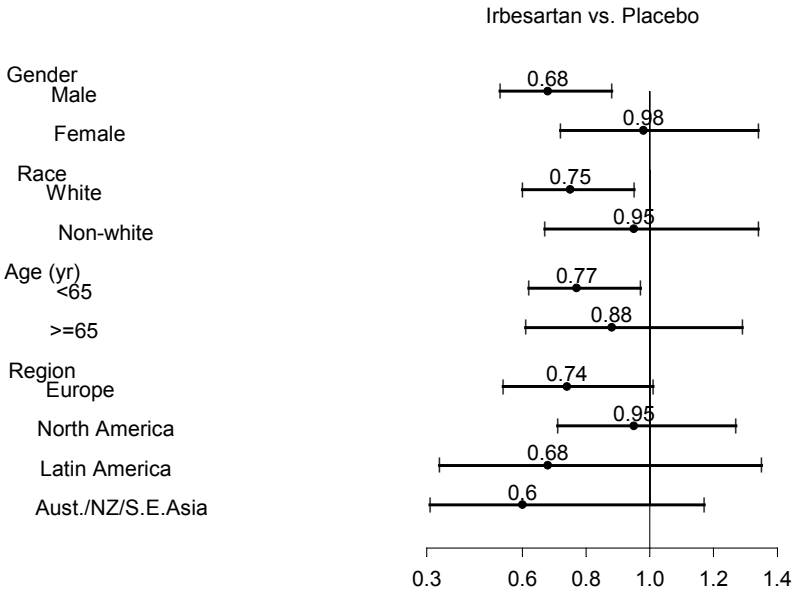
Combination of Doubling of Serum Creatinine or ESRD

Irbesartan significantly reduced the time to the combined endpoint of doubling of serum creatinine or ESRD ($p = 0.0005$) *vs.* placebo and amlodipine combined. The relative risk was 0.70 (95% CI 0.57-0.85). See text after Table 5.6.1.2A for an explanation of the counting rules in Table 5.6.4B.

5.6.5 Subgroups within Baseline Prognostic Factors

At the outset of IDNT, a sample size of at least 1650 was determined to be required to detect significant differences in treatment effect of the magnitude expected. The trial was not designed to detect treatment effect within subgroups. Nevertheless, subgroups were evaluated to explore the consistency of the results. Subgroups were identified from the 17 baseline prognostic factors considered above. Figure 5.6.5A presents the analyses of gender, race, age and region.

Figure 5.6.5A: IDNT: Primary Efficacy Outcome: Relative Risk (with 95 Percent Confidence Intervals) within Subgroups (Irbesartan vs. Placebo)



The point estimates of relative risk for irbesartan *vs.* placebo for all subgroups were below one, thus favoring irbesartan. The confidence intervals are necessarily wider than for the entire study population, since subgroups are by definition smaller. The confidence intervals of relative risk of irbesartan *vs.* placebo for gender, race, age and region subgroups overlapped each other (see Figure 5.6.5A). It is of particular interest that all these confidence intervals covered the value 0.80, which was the estimated relative risk for the overall subject sample. This indicates that the subgroup results were consistent with the overall results for the primary composite endpoint in the comparison of irbesartan *vs.* placebo.

Table 5.6.5: Primary Composite Endpoint (Irbesartan vs. Placebo): Subgroup Analyses

	Placebo		Irbesartan		Relative Risk	
	Total	Incidence	Total	Incidence		95% Confidence
Baseline Factors	**N**	**n (%)**	**N**	**n (%)**	**Estimate**	**Interval**
Gender						
Male	403	148 (36.7)	378	104 (27.5)	0.68	(0.53-0.88)
Female	166	74 (44.6)	201	85 (42.3)	0.98	(0.72-1.34)
Race						
White	415	155 (37.3)	438	129 (29.5)	0.75	(0.60-0.95)
Non-white	154	67 (43.5)	141	60 (42.6)	0.95	(0.67-1.34)
Age (yr)						
< 65	414	165 (39.9)	431	137 (31.8)	0.77	(0.62-0.97)
≥ 65	155	57 (36.8)	148	52 (35.1)	0.88	(0.61-1.29)
Region						
Europe	268	87 (32.5)	274	68 (24.8)	0.74	(0.54-1.01)
North America	197	92 (46.7)	204	92 (45.1)	0.95	(0.71-1.27)
Latin America	46	18 (39.1)	51	15 (29.4)	0.68	(0.34-1.35)
Austr./N.Z./S.E.A.	58	25 (43.1)	50	14 (28.0)	0.60	(0.31-1.17)

It should be noted that females make up only 32%, non-whites 26%, and North-Americans 35% of the irbesartan and placebo treatment groups (see Table 5.6.5). Based on the observed event rates for placebo subjects and sample sizes in the relevant

subgroups, the post-hoc power to detect 20% treatment benefit with irbesartan compared with placebo (the same as observed overall) is 29% for females, 24% for nonwhites and 32% for North Americans.

Thus, there is no evidence for lack of a treatment benefit in females, nonwhites and North-Americans. For these subgroups, the calculated risk reduction ("point estimate") is modest. However, a point estimate fails to account for the variability in the data and the resulting uncertainty in actual risk reduction. This uncertainty is captured by the confidence interval for the risk reduction, which states plausible values for the true risk reduction, given the data.

An exhaustive search was made of possible and probable factors within each subgroup to assess whether the subgroup results represent true differences or chance effects, and detailed below.

Assessment by Gender

Additional analyses were performed to examine whether demography, dose of study drug, the blood pressure control, glycemic control, or any baseline prognostic factors could explain the apparent modest treatment effect observed in females.

There was no meaningful imbalance observed between gender groups at baseline. There were similar percentages of male (85%) and female (81%) irbesartan treated subjects on the maintenance dose of 300 mg/day. There were no clear differences observed between gender subgroups in the time-pattern of response for blood pressure control nor clinically meaningful differences in HbA_{1c}.

An adjustment to attained mean arterial blood pressure (MAP) or HbA_{1c} was performed and the results essentially remain unchanged.

Moreover, the classes of concomitant medication used during the study were reviewed, and no clinically important differences were found between males and females.

The albumin and protein excretion rates (AER and PER, respectively) followed similar time courses for both genders. As AER and PER are widely regarded as indicators for renal damage, these results suggest that the observed modest result in the primary renal composite endpoint for females may be an artifact.

Finally, creatinine clearance corrected for BSA and serum creatinine, both in females and males, showed similar trends over time for all three treatment groups. These results in creatinine parameters are to be expected as creatinine is highly correlated with the primary renal endpoint.

Different subgroups constituted from gender and race were examined for any indication of an explanation for the possible differences in treatment effect of irbesartan.

There is no indication of a detrimental effect of irbesartan in females among any of the race groups.

Thus, the quantitative difference between gender subgroups in treatment effect on the primary composite endpoint cannot be explained by dose of study drug, by differences in BP response or glycemic control during the trial, or baseline demography nor by concomitant medication or by other baseline prognostic factors defined *a priori.*

A thorough search of the medical literature suggests that the observed results in women are not based on physiological differences. Also, in the IRMA 2 study, no differences between gender subgroups were observed on the main efficacy endpoint, overt proteinuria**.** Furthermore, previous clinical trials conducted by BMS with irbesartan have shown that men and women have similar pharmacokinetic and pharmacodynamic responses to irbesartan. Interpretation of underpowered subgroup results must be made with caution. An example in the literature to support this view is the initial subgroup analysis for females in some of the major trials[47,48] demonstrating the benefit of BP control. The initial subgroup analysis of these trials suggests that women either were harmed by BP control or had no benefit from BP control.

In summary, the apparent gender differences in efficacy appear to be due to chance because of the lack of adequate power to detect differences within any of the subgroups, including that for gender.

Assessment By Race

Previous studies in hypertension have shown that blacks respond less well than whites to treatment with RAS inhibitors. This observation may be related to a generally lower level of plasma renin in black patients. This could explain the modest overall treatment effect observed among non-whites.

As with gender, there were no clear differences among racial subgroups in the time-course of response for blood pressure control or for glycosylated hemoglobin.

The albumin and protein excretion rates (AER and PER, respectively) followed similar time courses among the racial subgroups. As AER and PER are widely regarded as indicators for renal damage, these results suggest that the observed modest result in the primary renal endpoint for non-whites may be due to the lack of adequate power to detect differences within any of the subgroups, including that for race.

Finally, creatinine clearance corrected for BSA and serum creatinine in non-whites generally showed similar trends over time for all three treatment groups. These results in creatinine parameters are to be expected as creatinine is highly correlated with the primary renal endpoint.

Assessment By Region

Figure 5.6.5B examines the treatment effect between the two major geographical subgroups.

Figure 5.6.5B: Primary Efficacy Outcome: Relative Risk with 95 Percent Confidence Intervals for Whites and Males

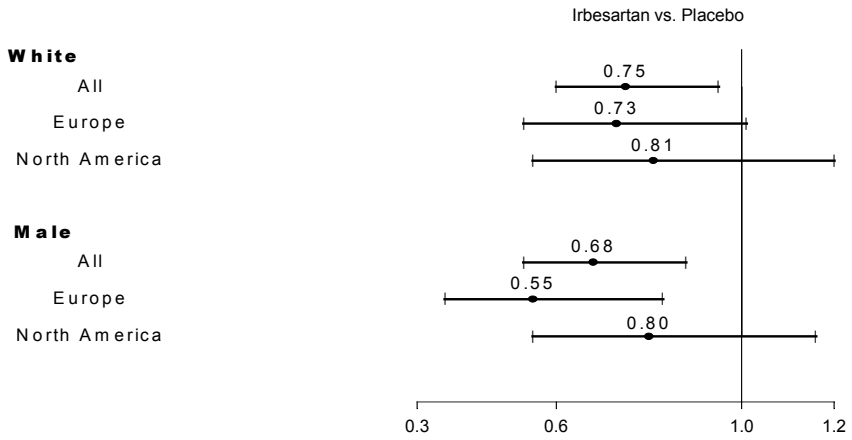


Figure 5.6.5B suggests that in both North America and Europe, irbesartan is effective in comparison to placebo among whites and males. The wide confidence intervals are the result of the small sample sizes. This suggests that a possible explanation for the modest overall irbesartan effect in North America was the relative representation of the various demographic subgroups in the two regions, rather than any effect of the regions themselves.

The percentage of non-whites in the subject sample was much higher in North America (47.3%) than in Europe (6.3%). In North America, non-whites were mainly composed of blacks. This disparity in racial mix lends credence to the idea that the overall result for North America may be influenced by such differential representation.

As was done for gender and race, the time-course of BP control (seated systolic and diastolic BP) and important laboratory parameters (HbA_{1c}, albumin excretion rate (AER), protein excretion rate (PER), creatinine clearance corrected for BSA, and serum creatinine) for each region were evaluated.

The results were similar to those observed in the race subgroups. Thus the observed modest treatment benefit in the primary renal endpoint for North Americans may be due to chance.

Conclusions Regarding Subgroup Efficacy

The subgroup results were consistent with the overall results for the primary composite endpoint in the comparison of irbesartan *vs.* placebo.

5.6.6 Progressive Measures of Renal Function

Regarding laboratory parameters of renal function, irbesartan had a positive effect compared with placebo and amlodipine. The annual increase in serum creatinine was lower in the irbesartan group (0.42 mg/dL) compared with both the placebo group (0.55 mg/dL; $p = 0.004$) and the amlodipine group (0.53 mg/dL; $p = 0.013$). Also, the annual decrease in creatinine clearance was lower in the irbesartan group (-5.27 mL/min/1.73m^2/yr) than in both the placebo group (-6.30 mL/min/1.73m^2/yr; $p = 0.043$) and the amlodipine group (-6.53 mL/min/1.73m^2/yr; $p = 0.014$). After one year of follow-up, proteinuria was statistically significantly reduced ($p < 0.001$) on average by 42% in the irbesartan group compared to 12% in the amlodipine group and 15% in the placebo group (adjusted geometric mean percent changes), with for the most part similar results thereafter.

5.6.7 All-Cause Mortality Outcome: Irbesartan *vs.* Placebo and *vs.* Amlodipine

A total of 263 (15.3%) subjects died during the study, 87 (15%) in the irbesartan group, 93 (16.3%) in the placebo group, and 83 (14.6%) in the amlodipine group. The relative risks for all-cause mortality were 0.92 (95% CI: 0.69-1.23) for irbesartan *vs.* placebo, and 1.04 (95% CI: 0.77-1.40) for irbesartan *vs.* amlodipine. There was no significant difference in risk of all-cause mortality between irbesartan and placebo or amlodipine. This study was not powered to analyze differences in incidence of death and these differences in all-cause mortality were not statistically significant. The addition of all-cause mortality as a component of the primary composite endpoint provided evidence that the positive effect of irbesartan on renal outcomes is not offset by a negative effect on mortality.

5.6.8 Cardiovascular Outcomes: Irbesartan *vs.* Placebo and *vs.* Amlodipine

Cardiovascular outcomes included secondary and tertiary cardiovascular composite endpoints. The secondary composite endpoint was based on the time to any of the following outcomes: cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurologic deficit attributed to stroke, or above-the-ankle amputation. The tertiary composite endpoint was based on the time to any of the following outcomes: cardiovascular death, nonfatal myocardial infarction, heart failure requiring hospitalization or therapy with an ACE inhibitor or ARB, permanent neurologic deficit attributed to stroke, above-or-below-the-ankle amputation, unplanned coronary artery revascularization procedure or unplanned peripheral artery revascularization procedure.

A total of 416 (24.3%) subjects reached the secondary composite endpoint in the study, 141 (24.4%) subjects in the irbesartan group, 146 (25.7%) in the placebo group, and 129 (22.8%) were in the amlodipine group (Tables 5.6.8A and 5.6.8B). The relative risks were 0.92 (95% CI: 0.73-1.15) for the irbesartan *vs.* placebo group and 1.05 (95% CI: 0.83-1.33) for the irbesartan *vs.* amlodipine group.

Table 5.6.8A: IDNT: Secondary Cardiovascular Composite Endpoint Comparison: Irbesartan vs. Placebo

Event	Number (%) of Subjects		Relative Risk[a]		p[b]
	Placebo N = 569	Irbesartan N = 579	Estimate	95% Confidence Interval	
Secondary Cardiovascular Endpoint	146 (25.7)	141 (24.4)	0.92	0.73 - 1.15	0.4537

[a] Determined using the Cox proportional hazards model

[b] From log-rank test

Table 5.6.8B: IDNT: Secondary Cardiovascular Composite Endpoint Comparison: Irbesartan vs. Amlodipine

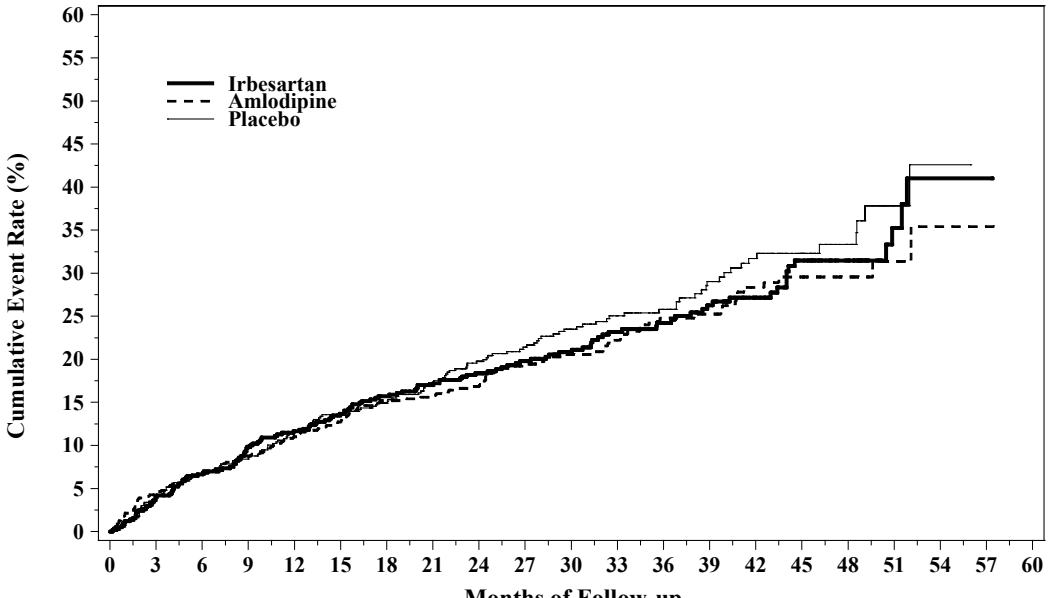
Event	Number (%) of Subjects		Relative Risk[a]		p[b]
	Amlodipine N = 567	Irbesartan N = 579	Estimate	95% Confidence Interval	
Secondary Cardiovascular Endpoint	129 (22.8)	141 (24.4)	1.05	0.83 - 1.33	0.6935

a Determined using the Cox proportional hazards model

b From log-rank test

Figure 5.6.8 presents the Kaplan-Meier curves for time to first occurrence of the secondary cardiovascular composite endpoint. There were no significant differences among treatment groups for the secondary cardiovascular composite endpoint.

Figure 5.6.8: IDNT: Kaplan-Meier Curves for Secondary Cardiovascular Composite Endpoint all Randomized Subjects



N at risk																			
Irbesartan	579	548	529	504	486	466	449	439	378	322	286	234	198	169	137	95	63	22	4
Amlodipine	567	534	515	495	476	455	434	418	368	309	268	224	186	156	126	91	47	18	7
Placebo	569	539	519	501	477	453	433	413	365	310	264	216	175	145	113	78	49	17	2

A total of 518 (30.2%) subjects reached the tertiary cardiovascular composite endpoint in the study, 172 (29.7%) subjects were in the irbesartan group, 185 (32.5%) subjects were in the placebo group, and 161 (28.4%) subjects were in the amlodipine group. The relative risks were 0.88 (95% CI 0.72-1.08) for irbesartan *vs.* placebo, and 1.03 (95% CI: 0.83-1.27) for irbesartan *vs.* amlodipine.

Components of Cardiovascular Composite Endpoints

Table 5.6.8C shows the distribution of the individual components for the secondary cardiovascular composite endpoint.

Table 5.6.8C: IDNT: Components of Secondary Cardiovascular Composite Endpoint

Event [a]	Number (%) of Subjects		
	Placebo N = 569	Irbesartan N = 579	Amlodipine N = 567
Secondary			
Cardiovascular Death	46 (8.1)	52 (9.0)	37 (6.5)
Nonfatal Myocardial Infarction	41 (7.2)	39 (6.7)	25 (4.4)
Hospitalization for Heart Failure	71 (12.5)	58 (10.0)	86 (15.2)
Stroke[b]	21 (3.7)	21 (3.6)	11 (1.9)
Above-ankle Amputation	8 (1.4)	8 (1.4)	9 (1.6)

[a] The numbers in the table indicate the total incidence of each event. A subject could have more than one type of event; therefore, the total incidence of all events adds up to more than the overall incidence of the secondary cardiovascular composite endpoint shown in Tables 5.6.8 A and B.

[b] Permanent neurological deficit attributed to stroke

The observed incidences of non-fatal myocardial infarction and stroke were numerically smaller in the amlodipine group compared to either irbesartan or placebo groups, while the number of patients hospitalized for heart failure was higher in the amlodipine groups compared to either irbesartan or placebo groups.

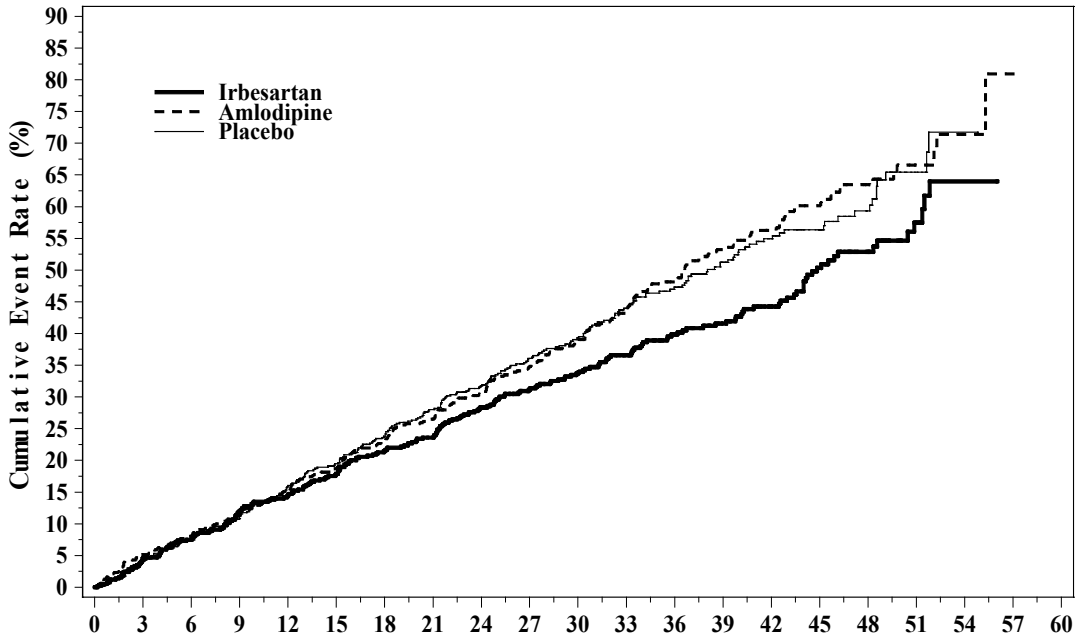
5.6.9 Renal Benefit in Relation to Cardiovascular Outcomes

The primary composite endpoint in IDNT (i.e., doubling of serum creatinine, development of ESRD, or all-cause mortality) demonstrates the renoprotective benefit of irbesartan above and beyond BP control alone in hypertensive, type 2 diabetic patients with proteinuria. The secondary cardiovascular (CV) composite endpoint was prospectively evaluated because these patients have a high risk for CV morbidity and mortality. In IDNT, there were no significant differences between irbesartan and placebo, or irbesartan and amlodipine in the secondary cardiovascular composite endpoint. Since all 3 treatment groups had similar BPs, it is not surprising that there were no differences in cardiovascular events observed among the treatment groups. Indeed, 4 other trials[49,50,51,52*] compared different classes of antihypertensive medications in high-risk antihypertensive patients. These 4 studies enrolled 34,781 subjects (3,302 of whom had diabetes) and no significant differences were observed in cardiovascular endpoints in either the entire study population or in the diabetic hypertensive subjects (Julius, 2001).

To fully evaluate the renal benefits and cardiovascular outcomes together in IDNT, a post-hoc analysis was performed by combining the primary and secondary endpoints of IDNT. In this fashion, the renal and cardiovascular events are given equal weight. The results of this analysis is presented in Figure 5.6.9.

* CAPPP, Captopril Prevention Project; NORDIL, Nordic Diltiazem study; STOP2, Swedish Trial in Old Patients with hypertension-2; INSIGHT, International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment

Figure 5.6.9: Kaplan-Meier Curve of the Combined Primary and Secondary Composite Endpoint for all Randomized Subjects (ITT Analysis)



N at risk																			
Irbesartan	579	547	528	500	482	460	437	422	355	303	265	220	183	157	125	82	51	18	2
Amlodipine	567	533	513	492	470	449	423	399	349	290	247	198	159	129	104	75	39	18	6
Placebo	569	540	520	497	470	446	416	393	346	289	245	194	159	127	96	64	40	14	2

This analysis demonstrates a benefit for irbesartan with a relative risk of 0.81 (95% CI: 0.68-0.97; p = 0.0187) compared with placebo and 0.79 (95% CI: 0.67-0.94; p = 0.0078) compared with amlodipine. The relative risk reduction for the primary composite endpoint of irbesartan compared with placebo or amlodipine was 20% and 23%, respectively; the relative risk reduction for the combined primary-secondary composite endpoints was 19% and 21%, respectively. These significant findings in the combined analysis of the primary and secondary composite endpoints are therefore very consistent with the primary endpoint alone.

5.7 Safety

The incidence of AEs, ADEs, SAEs, discontinuations for a clinical AE, and deaths in IDNT are presented in Table 5.7A.

Table 5.7A: Summary of Safety for IDNT

	Number (%) of Subjects		
	Placebo N = 563	**Irbesartan N = 577**	**Amlodipine N = 559**
AEs	524 (93.1)	540 (93.6)	526 (94.1)
ADEs	225 (40.0)	266 (46.1)	285 (51.0)
SAEs	363 (64.5)	358 (62.0)	361 (64.6)
Discontinuations	36 (6.4)	43 (7.5)	44 (7.9)
Deaths	90 (16.0)	86 (14.9)	79 (14.1)

5.7.1 Treatment-Emergent Adverse Events

The most commonly reported treatment-emergent clinical adverse event was edema which occurred more frequently in amlodipine-exposed (60.3%) subjects than in placebo- (37.5%) or irbesartan-exposed (38.5%) subjects. This observation most likely reflects the peripheral vasodilatory properties of this calcium channel blocker. Of note, edema is the most common dose-related clinical adverse event that occurs with amlodipine treatment.

Musculoskeletal pain ranked as the second most common AE in IDNT and was reported similarly between irbesartan- (37.8%) and placebo-exposed (38.2%) subjects.

Dizziness, orthostatic dizziness, and orthostatic hypotension all tended to occur more frequently in irbesartan-exposed subjects than in placebo- or amlodipine-exposed subjects. Anemia was reported as an AE slightly more frequently in irbesartan-exposed (9.2%) subjects than in placebo- (7.1%) or amlodipine-exposed (7.3%) subjects.

Heart failure tended to occur more frequently in the amlodipine-exposed (13.8%) subjects in IDNT as compared to either irbesartan- (9.9%) or placebo-exposed (10.7%) subjects.

The remainder of adverse events occurred similarly across treatment groups with the exception of diarrhea (17.7% *vs.* 14.7%) and dyspepsia/heartburn (12.7% *vs.* 10.5%) that tended to occur slightly more often in irbesartan-exposed subjects compared with placebo-exposed subjects.

5.7.2 Adverse Drug Experiences

The most common clinical adverse drug experiences are presented in Table 5.7.2.

Table 5.7.2: IDNT: Most Common Clinical Adverse Drug Experiences (Reported in ≥ 2% of Subjects in any Treatment Group) During and Up to 14 Days Post Double-Blind Therapy, by Primary Term

Adverse Event by Primary Term	Number of Events (% of Subjects)		
	Placebo N = 563	Irbesartan N = 577	Amlodipine N = 559
Edema	84 (14.9)	75 (13.0)	154 (27.5)
Dizziness	34 (6.0)	59 (10.2)	38 (6.8)
Fatigue	34 (6.0)	38 (6.6)	35 (6.3)
Orthostatic Dizziness	15 (2.7)	31 (5.4)	21 (3.8)
Headache	36 (6.4)	31 (5.4)	22 (3.9)
Orthostatic Hypotension	18 (3.2)	31 (5.4)	32 (5.7)
Musculoskeletal Pain	16 (2.8)	22 (3.8)	17 (3.0)
Nausea/Vomiting	19 (3.4)	19 (3.3)	19 (3.4)
Diarrhea	9 (1.6)	17 (2.9)	8 (1.4)
Abdominal Pain	13 (2.3)	11 (1.9)	3 (0.5)
Dyspnea	13 (2.3)	11 (1.9)	14 (2.5)
Angina Pectoris	5 (0.9)	8 (1.4)	15 (2.7)
Heart Failure	10 (1.8)	6 (1.0)	18 (3.2)
Overall Total Events	560	601	629
Overall Total Subjects with at Least One ADE	225 (40.0)	266 (46.1)	285 (51.0)

Overall, ADEs were reported in 40.0%, 46.1%, and 51.0% of the placebo-, irbesartan, and amlodipine-exposed subjects, respectively. Clinical ADEs that tended to be reported more frequently in irbesartan-exposed subjects as compared with placebo-exposed subjects were dizziness, orthostatic dizziness, and orthostatic hypotension. The incidence of ADEs related to orthostatic hypotension tend to be higher in both the irbesartan- and amlodipine-exposed subjects compared with placebo-exposed subjects. Adverse drug experiences that tended to occur with higher frequencies in the amlodipine-exposed subjects in comparison with the placebo-exposed subjects (> 2%) include edema, and orthostatic hypotension. The remainder of the ADEs occurred similarly across treatment groups. No additional adverse events were identified in ADEs from those events previously identified in AEs.

5.7.3 Serious Adverse Events

The SAEs for IDNT are presented in primary terms as adjudicated outcome. These adjudicated outcomes, however, generally represent a larger number of events than the reported SAEs by Investigators because events for cardiovascular endpoints were collected and adjudicated until a subject developed ESRD or death. The adjudicated data are presented in this fashion to parallel the data presented in the Efficacy section

Of the 1699 exposed subjects in IDNT, 1082 (63.7%) experienced at least one serious adverse event (SAE). The overall incidence of all SAEs by primary term was less frequently reported in irbesartan-exposed subjects (62.0%) as compared with placebo- (64.5%) or amlodipine-exposed (64.6%) subjects. Amlodipine-exposed subjects tended to have an increased frequency of reported SAEs by primary term for increased serum creatinine (21.5%) whereas irbesartan-exposed subjects had a lower frequency of reported SAEs for increased serum creatinine (12.7%) as compared with placebo-exposed subjects (19.0%). Amlodipine-exposed subjects also tended to have more frequent reporting of heart failure (15.9%) as compared with irbesartan- or placebo-exposed subjects (10.4% and 11.5%, respectively). Conversely, amlodipine-exposed subjects (5.2%) tended to have a lower incidence of myocardial infarction (8.1%), as compared with placebo- (7.3%) or irbesartan-exposed subjects.

5.7.4 Discontinuation Due to an AE

All permanent study drug discontinuations in IDNT were adjudicated by the Clinical Management Committee (CMC) to determine the reason for study drug discontinuation. Overall, the incidence of study drug discontinuations due to clinical adverse events was similar in subjects receiving placebo (6.4%), irbesartan (7.5%), or amlodipine (7.9%). In IDNT, the only discontinuations for a clinical adverse event that occurred with a frequency of > 1% were edema and fatigue. Discontinuations for edema occurred in 7 (1.2%), 4 (0.7%), and 14 (2.5%) in the placebo, irbesartan, and amlodipine treatment groups, respectively. Fatigue resulted in the discontinuation of six subjects, all on placebo.

While the frequency of AEs reported for dizziness, orthostatic dizziness, and orthostatic hypotension all tended to occur more frequently in irbesartan-exposed subjects than in placebo- or amlodipine-exposed subjects, these symptoms infrequently led to discontinuation of study drug. Similarly, the frequency of AEs reported for anemia tended to be higher in irbesartan-exposed subjects than in placebo- or amlodipine-exposed subjects, but decreased hemoglobin resulted in discontinuation of study drug in only one (0.3%) subject.

The most frequently reported discontinuation due to a laboratory adverse event in irbesartan-exposed subjects was for persistent hyperkalemia, which was reported in 2 (0.4%), 12 (2.1%) and 3 (0.54%) of the placebo-, irbesartan-, and amlodipine-exposed subjects, respectively. A more detailed discussion of hyperkalemia is presented in Section 5.7.9.1.

5.7.5 Deaths

The cause of death was adjudicated by the Mortality Committee and all reported deaths during and post double-blind therapy are discussed in this section. The total number of deaths in the safety dataset include 255 exposed subjects for IDNT. There were 8 additional subjects who died after randomization, but never received study drug. These 8 subjects are therefore included in the ITT efficacy analyses, but not the safety analyses.

Of the 255 subjects who died during and post double-blind therapy, 90 (16.0%) were in the placebo group, 86 (14.9%) were in the irbesartan group, and 79 (14.1%) were in the

amlodipine group. The most common adjudicated causes of death occurred in the cardiovascular, general, nervous, renal/genitourinary, and respiratory body systems. There was no overall difference observed across the treatment groups for cause of death.

5.7.6 Laboratory Adverse Events

Laboratory AEs were defined as those designated by the investigator as AEs, regardless of the actual laboratory value, and recorded on the AE page of the CRF. In IDNT, the incidence of laboratory AEs tended to be slightly higher in the irbesartan- (54.1%) and amlodipine-exposed (51.0%) groups compared with the placebo group (48.5%). The higher incidence of laboratory AEs in the irbesartan-exposed subjects is largely attributed to a more frequent incidence of increased serum potassium. A total of 23.2% of subjects receiving irbesartan had a laboratory AE for increased serum potassium; while the frequency was 9.4% and 8.1% in the placebo and amlodipine groups, respectively.

5.7.7 Safety in Sub-Populations: Gender, Race, Age

There were 376 males and 201 females treated with irbesartan in the IDNT study. The extent of exposure was slightly longer for males than females (mean duration of exposure of 851 and 748 days, respectively). Orthostatic hypotension was reported more frequently by males, while edema and dizziness were reported more frequently in female subjects.

Myocardial infarction was reported most frequently in irbesartan-exposed female subjects (9.0%) as compared with female placebo-exposed (4.3%), male irbesartan-exposed (6.6%), and male placebo-exposed (8.5%) subjects. The higher frequency of reported events for myocardial infarction in female irbesartan-exposed subjects in IDNT lacks mechanistic basis, was not observed in a similar fashion in IRMA 2 (see Section 6.7.7), and therefore likely represents variability in an underpowered subgroup analysis.

There were no gender-specific differences in marked laboratory abnormalities.

In IDNT, there were 436 white subjects and 63 black subjects treated with irbesartan; the remaining subjects were divided evenly among Asian/Pacific Islanders, Hispanics and other races or ethnicities. Analysis of these clinical AEs by primary term in black subjects, however, is hampered by the relative low numbers of black subjects and frequently these “differences” involve a single or few subjects between these two groups.

Consequently, the frequencies of the reported events are difficult to interpret and it is not possible to conclude that any meaningful differences exist. The clinical AEs that tended to occur more frequently in irbesartan-exposed black subjects as compared with placebo-exposed black subjects included: angina pectoris, orthostatic hypotension, renal failure, bruit, weakness, and pain. Conversely, there were clinical AEs that tended to occur less frequently in irbesartan-exposed black subjects as compared with placebo-exposed black subjects, including: pruritus, sexual dysfunction, constipation, dry mouth, musculoskeletal pain, rhinitis, sinus abnormality, vision disturbance, retinal abnormality and other eye disturbance.

Generally the magnitude and direction of the frequencies of reported marked laboratories abnormalities was unremarkable across race.

There were 431 subjects aged < 65 years and 146 subjects aged ≥ 65 years in IDNT. Older subjects received less duration of exposure to irbesartan (788 days compared with 824 days). In subjects < 65 years of age, dizziness was reported in 19.8%, 25.3%, and 17.7% in the placebo-, irbesartan-, and amlodipine-exposed subjects, respectively. Several clinical AEs tended to occur more frequently in irbesartan-exposed subjects ≥ 65 years of age compared with placebo-exposed subjects ≥ 65 years of age, including: diarrhea, peripheral vascular disease, and infection. Conversely, dyspnea was reported less frequently in the irbesartan-exposed subjects ≥ 65 years of age as compared with placebo-exposed subjects ≥ 65 years of age. Analysis of these clinical AEs by primary term in subjects ≥ 65 years of age, however, is hampered by the relative low numbers of these subjects. Consequently, the frequencies of the reported events are difficult to interpret and it is not possible to conclude that any meaningful differences exist.

No relationship of marked laboratory abnormalities with age was observed.

5.7.8 Drug-Drug Interactions

Drug-drug interaction safety data for selected therapeutic classes were evaluated in irbesartan-exposed subjects who were treated with specified concomitant medications any time during the double-blind therapy in the clinical safety/efficacy studies. Selected drug classes included antihyperglycemics (insulin, sulfonylureas, metformin), antihypertensive agents (beta blockers, alpha/beta blockers, loop diuretics), aspirin/antiplatelet, and NSAIDs/analgesics. Potential drug-interactions that were

identified in IDNT included orthostatic symptoms (dizziness, orthostatic dizziness, or orthostatic hypotension) that occurred more frequently in irbesartan-exposed subjects using either concomitant insulin, beta blockers, NSAIDs/analgesics or loop diuretics as compared to placebo-exposed subjects using these concomitant drugs.

5.7.9 Additional Safety Considerations

5.7.9.1 Hyperkalemia

Hyperkalemia is a well-recognized complication of renal insufficiency and ESRD, and also occurs in patients with disease- or drug-induced hypoaldosteronism. Drugs that inhibit the renin-angiotensin system (RAS), such as ACE inhibitors (ACE-I) or angiotensin II receptor antagonists (ARB) can cause elevations of serum potassium through a combination of decreasing serum aldosterone and through a mild reduction in glomerular filtration rate (GFR). The risk for RAS blockade-induced hyperkaliemia increases with renal hypoperfusion (particularly bilateral renal artery stenosis).

The incidence of RAS blockade-induced hyperkalemia in patients with type 2 diabetes and overt proteinuria has heretofore been unknown. In general, however, the incidence of ACE-I-induced hyperkalemia appears to be relatively low in patients with normal renal function (0-6%), but occurs much more commonly in patients with renal insufficiency (5-50%). Specifically, in a case controlled study serum creatinine was shown to be an independent factor predicting ACE-I-induced hyperkalemia. In that study, a serum creatinine of 1.1-1.5 mg/dL was associated with an odds ratio of 1.5 (95% confidence interval: 0.9-2.6) and a serum creatinine $\geq$ 1.6 mg/dL was associated with an odds ratio of 4.6 (95% confidence interval: 1.8-12.0) for the development of ACE-I-induced hyperkalemia.[53] Importantly, the presence of baseline renal insufficiency does not abrogate the beneficial effects of ACE-I in delaying the progression of renal disease; in fact, the relative risk reduction increases with higher levels of baseline serum creatinine in type 1 diabetes or baseline urinary protein excretion in non-diabetic nephropathy.

Because of the potential for RAS inhibitors to cause hyperkalemia, a special discussion regarding these events in IDNT is presented in this Section. Because irbesartan inhibits the RAS, it was expected that subjects in IDNT could develop hyperkalemia. Due to the higher anticipated baseline serum creatinine in IDNT (a risk factor for development of

RAS-inhibitor induced hyperkalemia), the overall frequency of hyperkalemia was expected to be higher in both placebo- and irbesartan-exposed subjects as compared with subjects in IRMA 2. Accordingly, in IDNT, events of increased serum potassium were systematically captured in treatment-emergent laboratory adverse events, laboratory marked abnormalities, and mean change from baseline analyses. Hyperkalemia was defined as a threshold value for serum potassium of ≥ 6.0 mEq/L for clinical intervention for hyperkalemia in IDNT. In the event that a subject had a single elevation of serum potassium that was ≥ 6.0 mEq/L clinical interventions, by protocol, were to be carried out to determine the cause of the serum potassium elevation and institute corrective actions including temporary discontinuation of study drug. With respect to discontinuations from adverse events, hyperkalemia was emphasized, by segregation, from other adverse events in IDNT. Finally, clinically relevant events associated with hyperkalemia captured as SAEs were specifically reported.

5.7.9.1A Summary of Clinical Events and Laboratory Abnormalities for Elevated Serum Potassium or Hyperkalemia: IDNT

Treatment emergent AEs, laboratory marked abnormalities, discontinuations for hyperkalemia, SAEs for hyperkalemia and deaths due to hyperkalemia in IDNT are presented in Table 5.7.9.1A.

Table 5.7.9.1A: Summary of Clinical Events and Laboratory Abnormalities (During and Greater Than or Equal to 14 Days Post Double-Blind Therapy) for Elevated Serum Potassium or Hyperkalemia in IDNT

	Number (%) of Subjects		
	Placebo N = 563	**Irbesartan N = 577**	**Amlodipine N = 559**
Treatment-emergent AEs	53 (9.4)	134 (23.2)	45 (8.1)
Elevated Serum Potassium ($K^+ \geq 6.0$ mEq/L)	40 (7.1)	124 (21.5)	37 (6.6)
Elevated Serum Potassium ($K^+ \geq 6.0$ mEq/L) on 2 or more occasions	9 (1.6)	26 (4.5)	2 (0.4)
Study drug discontinuations	2 (0.4)	12 (2.1)	3 (0.5)
SAEs	1 (0.2)	5 (0.9)	3 (0.5)
Any sudden death[a]	16 (2.8)	12 (2.1)	8 (1.4)

[a] Sudden death may potentially reflect undiagnosed hyperkalemia; however, serum potassium was unknown at the time of each of these specific events.

Subjects in the placebo group experienced treatment-emergent AEs and laboratory marked abnormalities for hyperkalemia at a frequency of 9.4% and 6.0%, respectively in IDNT; these events were not observed in placebo-exposed subjects in IRMA 2.

A rise in serum potassium would not be an expected occurrence with a calcium-channel antagonist such as amlodipine. It was therefore not surprising that the frequency of treatment emergent AEs, laboratory marked abnormalities, study drug discontinuations, and SAEs for hyperkalemia were reported similarly between placebo and amlodipine-exposed subjects in IDNT. In contrast, RAS inhibition by irbesartan can produce an elevation of serum potassium in these subjects by its mechanism of action. Thus, there were more frequently reported treatment-emergent AEs, laboratory marked abnormalities, study drug discontinuations, and SAEs for hyperkalemia in irbesartan-exposed subjects. These events are described in further detail in the following sections.

5.7.9.1B Treatment-Emergent Adverse Events in IDNT

Treatment-emergent AEs for hyperkalemia were reported in 53 (9.4%), 134 (23.2%) and 45 (8.1%) of placebo-, irbesartan-, and amlodipine-exposed subjects, respectively. Treatment-emergent AEs for hyperkalemia were thought by the investigator to be related to study drug in 60.8% of placebo-exposed subjects and 58.3% of irbesartan-exposed subjects who had a such an event. No event was thought to be certainly related to study drug. In all 3 study groups, similar events were considered related to study drug.

The most clinically significant elevations in potassium were considered to be those ≥ 6.0 mEq/L and those resulting in discontinuation of treatment. These are discussed in Sections 5.7.9.1C and 5.7.9.1D, respectively.

5.7.9.1C Hyperkalemia (Greater Than or Equal to 6.0 mEq/L) in IDNT

A single serum value of ≥ 6.0 mEq/L was obtained in 40 (7.1%), 124 (21.5%), and 37 (6.6%) of the subjects in the placebo, irbesartan, and amlodipine groups, respectively.

Very few subjects in IDNT, however, in any treatment group had two (or more) consecutive serum potassium values of ≥ 6.0 mEq/L. Specifically, there were 9 (1.6%), 26 (4.5%), and 2 (0.4%) of subjects in the placebo, irbesartan, and amlodipine treatment groups, respectively. The observed occurrences of persistent hyperkalemia ≥ 6.0 mEq/L (4.5%) was therefore, far less than the occurrences for a single laboratory value ≥ 6.0 mEq/L (21.5%).

Clinically relevant outcomes of the subjects that had two (or more) consecutive serum potassium values of ≥ 6.0 mEq/L is presented in Table 5.7.9.1C.

Table 5.7.9.1C: Clinically Relevant Outcomes of the Subjects That had Two (or more) Consecutive Serum Potassium Values of Greater Than or Equal to 6.0 mEq/L

	Number (%) of Subjects						
	Doubling of Serum Creatinine[a]	ESRD[a]	Doubling of Serum Creatinine or ESRD[a]	Sudden Death[a]	CV Death[a]	Any Death[a]	Doubling of Serum Creatinine or ESRD or Any Death
Placebo n = 9	5 (55.6)	2 (22.2)	5 (55.6)	0	0	2 (22.2)	6 (66.7)
Irbesartan n = 26	7 (26.9)	5 (19.2)	9 (34.6)	0 (0)	0 (0.0)	1 (3.9)	9 (34.6)
Amlodipine n = 2	1 (50.0)	1 (50.0)	1 (50.0)	0	0	0	1 (50.0)

[a] As adjudicated by the OCCC

These clinically relevant outcomes in subjects that have 2 (or more) consecutive serum potassium values of ≥ 6.0 mEq/L suggests that irbesartan-exposure has a safety profile similar to placebo with respect to death in this high risk subgroup. One irbesartan-exposed subject (Subject 188/006) experienced investigator-reported sudden death that was adjudicated to ESRD. Of note, the last dose of study drug for this patient was on 03AUG98. Source documents verify a serum potassium of 4.9 mEq/L on 02AUG99 and the subject subsequently died on 21SEP99 (more than one year after discontinuing study drug) of sudden death. This event of sudden death, was therefore not related to irbesartan exposure.

5.7.9.1D Discontinuations of Study Drug Due to Hyperkalemia in IDNT

Discontinuations* of study drug due to hyperkalemia occurred in 2 (0.4%), 12 (2.1%), and 3 (0.5%) of the subjects receiving placebo, irbesartan, or amlodipine, respectively (discontinuations in irbesartan group are 11 (1.9%) in the database as one additional subject was not recorded as a discontinuation - further details can be found in the IDNT Clinical Study Report Errata Table). These discontinuations occurred throughout the trial with a mean ± std. dev. of 312.5 ± 398.1 (range: 31-594), 411.5 ± 318.6 (range: 9-919), and 309.3 ± 334.0 (range: 114-695) days from initiation of study drug to clinical AE in the placebo, irbesartan and amlodipine treated groups, respectively. The mean ± std. dev. for serum potassium immediately prior to study drug discontinuation was 5.3 ±1.1 mEq/L (range: 4.5-6.1 mEq/L), 6.4 ± 0.7 mEq/L (range: 5.6-7.4 mEq/L), and 5.5 ± 0.2 mEq/L (range: 5.3-5.6 mEq/L) in the placebo, irbesartan and amlodipine groups, respectively. Upon discontinuation of study drug in irbesartan-exposed subjects, serum potassium declined to a mean ± std. dev of 5.2 ± 0.4 (range: 4.8-6.1) at the first serum potassium value obtained after discontinuation of study drug and declined to 5.1 ± 0.4 (range: 4.6-5.9) at the first serum potassium value obtained after one week following study drug discontinuation (a sufficient time for elimination of study drug). This decline in serum potassium reflects the reversibility of the elevations in serum potassium as would be expected through RAS inhibition.

5.7.9.1E Serious Adverse Events for Hyperkalemia in IDNT

Adjudicated* SAEs for hyperkalemia occurred in 1 (0.2%), 5 (0.9%), and 3 (0.5%) of the subjects receiving placebo, irbesartan, or amlodipine, respectively. Treatment for these SAEs in irbesartan-exposed subjects involved administration of oral potassium binding resin and/or furosemide administration that corrected the electrolyte disturbance. One irbesartan-exposed subject discontinued study drug and one other subject required an interruption of study medication for the SAE. Overall, SAEs for hyperkalemia were infrequent and required only routine corrective measures.

* Adjudicated events included all hospitalizations, cardiovascular events and deaths. In addition, study drug discontinuations were adjudicated to the primary reason for discontinuation of study drug. Treatment emergent AEs were not adjudicated. The reported frequencies between the Investigator reported and adjudicated SAEs differ in some cases.

5.7.9.1F Deaths Attributed to Hyperkalemia in IDNT

There were no deaths attributed to hyperkalemia in any treatment group in IDNT.

Because the first clinical manifestation of unknown, very severe elevations of serum potassium may be sudden death, these events were evaluated in IDNT for the entire study duration, during and 14 days post double-blind therapy, and > 14 days post double-blind therapy and are summarized in Table 5.7.9.1F

Table 5.7.9.1F: Events of Adjudicated Sudden Death that Occurred in IDNT

	Number (%) of Subjects		
	Total Events	**During + 14 days Post Double-blind Therapy**	**> 14 Days Post Double-blind Therapy**
Placebo N = 563	30 (5.3)	16 (2.8)	14 (2.5)
Irbesartan N = 577	29 (5.0)	12 (2.1)	17 (2.9)
Amlodipine N = 559	23 (4.1)	8 (1.4)	15 (2.7)

Overall, sudden death occurred similarly in all treatment groups and sudden death that occurred while subjects were receiving double-blind therapy was lower in the irbesartan and amlodipine groups, as compared with the placebo group.

5.7.9.1G Hyperkalemia Summary

Irbesartan-induced elevations of serum potassium occur in a mechanistic fashion through inhibition of the RAS. The placebo rate of AEs and laboratory abnormalities for serum potassium demonstrates the importance of monitoring serum potassium, irrespective of drug therapy, in all patients with type 2 diabetes and overt proteinuria. In the higher risk group (IDNT), however, investigator reported treatment-emergent adverse events for hyperkalemia were of little clinical consequence as most were mild to moderate in intensity and few patients discontinued therapy or required intervention for hyperkalemia.

5.7.9.2 Orthostatic Symptoms

Table 5.7.9.2 presents a summary of the treatment-emergent clinical adverse events, adverse drug experiences, serious adverse events, and study drug discontinuations due to an AE for dizziness, orthostatic dizziness, and orthostatic hypotension in IDNT.

Table 5.7.9.2: Reported Occurrences of Treatment-Emergent Events for Dizziness, Orthostatic Dizziness, and Orthostatic Hypotension in IDNT

	Number (%) of Subjects		
	Placebo n = 563	**Irbesartan n = 577**	**Amlodipine n = 559**
Dizziness			
Clinical AE	111 (19.7)	143 (24.8)	97 (17.4)
Clinical ADE	34 (6.0)	59 (10.2)	38 (6.8)
SAE	0	0	0
Discontinuation	3 (0.5)	2 (0.3%)	0
Orthostatic Dizziness			
Clinical AE	53 (9.4)	74 (12.8)	39 (7.0)
Clinical ADE	15 (2.7)	31 (5.4)	21 (3.8)
SAE	0	0	0
Discontinuation	0	1 (0.2%)	2 (0.4%)
Orthostatic Hypotension			
Clinical AE	51 (9.1)	65 (11.3)	50 (8.9)
Clinical ADE	18 (3.2)	31 (5.4)	32 (5.7)
SAE	0	0	0
Discontinuation	0	0	1 (0.2%)

Treatment-emergent AEs for dizziness, orthostatic dizziness, and orthostatic hypotension occur with greater frequency in this population and is evidenced by the frequency of reported AEs for dizziness (19.7%), orthostatic dizziness (9.4%), and orthostatic hypotension (9.1%) in placebo-exposed subjects. This observation is likely a reflection of the presence of long-standing advanced type 2 diabetes mellitus and its sequelae (i.e., peripheral and autonomic neuropathy) in the IDNT study population. In addition, these subjects were typically prescribed several open label antihypertensive agents for blood pressure control and it is likely that these additional antihypertensive agents are contributing to these symptoms in all 3 treatment groups. Orthostatic symptoms occurred at a numerically greater incidence in irbesartan-exposed subjects as compared with

placebo-exposed or amlodipine-exposed subjects in IDNT. The observation that orthostatic symptoms tend to occur more often in irbesartan-exposed subjects compared with amlodipine-exposed subjects may be related to the relative physiological importance of the renin angiotensin system in these subjects and different pharmacokinetic properties of these agents. Notably, peak plasma concentrations of irbesartan are reached within 1.5–2 hours after dosing (Avapro Label) whereas the peak plasma concentrations for amlodipine are not reached until 6–12 hours after oral administration. (Norvasc label) The intensity of treatment-emergent AEs for dizziness and orthostatic dizziness were similar between all 3 treatment groups. The large majority of events were considered mild to moderate in intensity by the investigator. There were no reported SAEs related to dizziness, orthostatic dizziness, and orthostatic hypotension in any treatment group in IDNT. Collectively, these symptoms were infrequently associated with a need for study drug discontinuation (≤ 0.3 % for irbesartan-exposed subjects) and were comparable across all treatment groups. Thus, these orthostatic symptoms were of marginal clinical significance to the patient.

5.8 Overall Conclusions

The overall conclusions that can be drawn from IDNT are:

- Irbesartan significantly reduces the risk of the primary renal composite endpoint events (consisting of doubling of serum creatinine, ESRD, and all cause mortality) by 20% ($p = 0.0234$) relative to placebo and by 23% ($p = 0.0064$) relative to amlodipine.
- The significantly better renal outcome in the irbesartan-treated group can not be explained solely on the basis of BP control. The treatment benefit with irbesartan remained statistically significant with adjustment for the mean arterial pressures achieved in the three treatment groups.
- No differences were observed among the three randomized treatment groups in the risk of all cause mortality.
- In the subgroups analyzed by Cox regression models, quantitative, but not qualitative, differences in risk reductions with treatment were observed for the primary renal composite endpoint for irbesartan *vs.* placebo.

- No clinically or statistically significant differences were observed among the three randomized treatment groups in the risk of the secondary cardiovascular composite endpoint.
- Overall, irbesartan was safe and well tolerated in IDNT subjects. Hyperkalemia and orthostatic symptoms were reported more frequently among irbesartan exposed subjects in IDNT.

6 IRMA 2

6.1 Design

IRMA 2 was a multicenter, multinational, randomized, parallel group, double-blind study comparing irbesartan or placebo (conventional antihypertensive therapy excluding ACE-I, ARBs or dihydropyridine calcium channel antagonists) in hypertensive subjects with type 2 diabetes, microalbuminuria (AER between 20-200 μg/minute) and normal renal function.[54] The study assessed the benefits of two irbesartan regimens (150 mg and 300 mg) compared with placebo on the progression from microalbuminuria to overt proteinuria in these subjects. The subjects evaluated were hypertensive (SeSBP > 135 mmHg and/or SeDBP > 85 mmHg, or if receiving antihypertensive medication SeSBP ≤ 160 mmHg and/or SeDBP ≤ 90 mmHg) with type 2 diabetes. Type 2 diabetes was defined as:

1) type 2 diabetes not requiring insulin: hyperglycemia requiring treatment with an oral hypoglycemic agent, and/or fasting plasma glucose ≥ 140 mg/dL on 2 occasions, and/or fasting C peptide level exceeding the normal level of the local laboratory; or
2) type 2 diabetes requiring insulin: time between diagnosis of type 2 diabetes and insulin use greater than 1 year, or fasting C peptide level exceeding the normal level of the local laboratory.

Subjects had microalbuminuria (AER: 20-200 μg/min on a single-timed overnight collection) and normal renal function (serum creatinine ≤ 130 μmoles/L [1.5 mg/dL] in males and 100 μmoles/L [1.1 mg/dL] in females).

After randomization, subjects entered a 4-week titration. During the first 2 weeks, subjects randomized to irbesartan received a 75 mg dose once daily. At Week 2, the dose was titrated to 150 mg once daily. At Week 4, subjects who were randomized to 150 mg once daily remained on that dose, and subjects who were randomized to 300 mg irbesartan were titrated to 300 mg once daily. Subjects remained on this daily dosing regimen until Month 24 in the double-blind maintenance period. Use of other antihypertensive medication was permitted to maintain BP control with the exception of RAS inhibitors (ACE-I and ARB) and dihydropyridine calcium antagonists.

The design strategy was to isolate the incremental effects of AT_1 blockade with irbesartan, above and beyond the beneficial effects of BP lowering with other methods of BP control. The attempt was to bring all treatment groups to the same BP goal in IRMA 2. In this way the treatment differences on progression of type 2 diabetic renal disease, attributable only to the additional effects of AT_1 blockade, could be observed.

The primary objective was to evaluate the effects of irbesartan on progression from microalbuminuria (AER: 20-200 μg/min on a single - timed overnight collection) to overt proteinuria (AER > 200 μg/min and an increase of at least 30% from baseline).

Secondary objectives included the evaluation of change from baseline in overnight urinary AER and the change from baseline in estimated creatinine clearance using the Cockcroft and Gault formula.[55]

A glomerular filtration rate (GFR) sub-study was performed at selected centers on a subset of the main study population. This study was designed to evaluate the changes from baseline in GFR after 24 months of double-blind treatment. GFR was measured using the total plasma clearance of ^{51}Cr-EDTA. A total of 133 subjects were included in this sub-study. A one-month extension of the sub-study was performed to evaluate the effects of withdrawal (after 4 weeks) of study drug and other antihypertensive treatments on GFR.

A Scientific Committee was responsible for the protocol and established guidelines for the ethics, science and policy for the overall conduct of the study. An independent Data Safety Monitoring Committee (DSMC) reviewed accumulated patient safety data generated by an independent statistical center at periodic intervals. Finally, an independent Adjudication Event Committee (AEC) reviewed blinded adjudication dossiers to validate the diagnoses of major cardiovascular serious adverse events.

6.2 Outcome Measures

Primary Efficacy Endpoint: The time to the first occurrence of clinical proteinuria, defined as urinary AER (overnight urine collection) exceeding 200 μg/minute and an increase of urinary AER of at least 30% from baseline. The study endpoint was reached if clinical proteinuria was observed at two successive evaluations. The time of the event was the date of the first evaluation of the two successive positive evaluations.

Secondary Efficacy Endpoints: Change from baseline in the incidence of clinical proteinuria at 2 years with each treatment and change in estimated creatinine clearance using the Cockcroft and Gault formula after one and two years of treatment.

6.3 Dose Selection

IRMA 2 evaluated two effective antihypertensive doses of irbesartan. IRMA 2 was initiated to verify the potential prevention of overt nephropathy by long term RAS inhibition with irbesartan in a dose- related manner independent of the BP lowering effect of irbesartan.

The starting 75 mg dose in IRMA 2 was up titrated to 150 mg or 300 mg to achieve a maintenance dose at 150 mg or 300 mg if each dose was well tolerated. Other antihypertensive treatments were added when BP targets were not achieved. The use of two different doses of irbesartan helped demonstrate a dose-response of irbesartan on the primary endpoint.

6.4 Comparator Selection

In IRMA 2, two irbesartan regimens (150 mg and 300 mg) were compared with a placebo regimen. In all three arms, patients received background therapy with a variety of standard antihypertensive drugs to control BP.

6.5 Demography

Table 6.5: Baseline Characteristics of Subjects Randomized in IRMA 2

	Number (%) Subjects			
	Placebo N = 207	**Irbesartan 150 mg N = 203**	**Irbesartan 300 mg N = 201**	**Total N = 611**
Mean Age (years) ± SD	58.4 ± 8.6	58.3 ± 7.9	57.3 ± 7.8	58.0 ± 8.1
Gender				
Male (%)	142 (68.6)	134 (66.0)	140 (69.7)	416 (68.1)
Female (%)	65 (31.4)	69 (34.0)	61 (30.3)	195 (31.9)
Race/Ethnic Group				
Black (%)	0	2 (1.0)	0	2 (0.3)
Caucasian (%)	203 (98.1)	198 (97.5)	194 (96.5)	595 (97.4)
Oriental (%)	2 (1.0)	1 (0.5)	1 (0.5)	4 (0.7)
Other Race (%)	2 (1.0)	2 (1.0)	6 (3.0)	10 (1.6)
Body Mass Index (BMI) Mean ± SD	30.3 ± 4.5	29.8 ± 3.8	30.0 ± 4.3	30.0 ± 4.2
Seated Blood Pressure (mmHg)				
Systolic BP, Mean ± SD	N = 206 153.3 ± 14.7	N = 202 153.2 ± 14.0	N = 200 153.0 ± 14.5	N = 608 153.2 ± 14.4
Diastolic BP, Mean ± SD	N = 206 89.7 ± 8.8	N = 202 89.7 ± 8.5	N = 200 90.9 ± 10.1	N = 608 90.1 ± 9.1
Medical History				
Known Diabetes Duration Mean (years) ± SD	10.5 ± 8.5	9.7 ± 7.1	9.4 ± 7.1	9.9 ± 7.6
Insulin Use	82 (39.6)	68 (33.5)	62 (30.8)	212 (34.7)
Known Cardiovascular Disease (%)	50 (24.2)	62 (30.5)	53 (26.4)	165 (27.0)
Laboratory Variables				
Serum creatinine (mg/dL) Mean ± SD	1.06 ± 0.18	1.04 ± 0.18	1.07 ± 0.19	1.06 ± 0.18
Urinary albumin excretion (μg/min)[a] GM[b] ± SD	56.4 ± 39.5	58.6 ± 38.3	52.8 ± 31.4	55.9 ± 36.4
HbA_{1c} (%) Mean ± SD	7.2 ± 1.6	7.3 ± 1.7	7.0 ± 1.7	7.2 ± 1.7

[a] To convert urinary albumin excretion from μg/min to mg/24h these values must be multiplied by a factor of 1.44.

[b] Geometric mean

In IRMA 2, there were no imbalances among the treatment groups in the various demographic and baseline characteristics deemed large enough to affect the efficacy comparisons.

6.6 Efficacy

All IRMA 2 analyses were performed on the per-protocol population in the primary analysis and in the intention-to-treat population (ITT) in the secondary analysis. The analysis results presented here for the ITT population were similar to those observed for the per-protocol population.

At the enrollment visit, 1469 patients were eligible. A total of 858 patients were excluded during the placebo run-in period. A total of 611 patients were randomized, of whom 18 had no measurement of albuminuria and 3 received no study medication. A total of 590 randomized patients were followed for a median of 2 years of double-blind treatment.

The primary objective was to evaluate the effects of irbesartan compared to placebo on progression to macroalbuminuria, referred to as clinical proteinuria, in hypertensive subjects with type 2 diabetes and microalbuminuria, but without renal insufficiency. Coagulation parameters, lipid profile and glycosylated hemoglobin were also analyzed. In a sub-study of this protocol, GFR, extracellular fluid volume (ECV), pro-renin, active renin, and angiotensin II measurements were evaluated. In addition, 4 weeks after all study medication and concomitant antihypertensive medications were discontinued at Month 24, GFR and AER were assessed at the last visit of this sub-study extension.

6.6.1 Primary Renal Results

Treatment with irbesartan resulted in a dose-dependent decrease in the incidence of the primary endpoint, clinical proteinuria. Time to the progression of proteinuria was significantly prolonged in a dose dependent manner. In the ITT population analysis, a 70% relative risk reduction *vs*. placebo ($p = 0.0004$) was demonstrated in the irbesartan 300 mg group and a 39% relative risk reduction *vs.* placebo ($p = 0.085$) was demonstrated in the irbesartan 150 mg group (Table 6.6.1).

Table 6.6.1: IRMA 2: Primary Endpoint - Irbesartan vs. Placebo Comparison: Intention-to-Treat Population

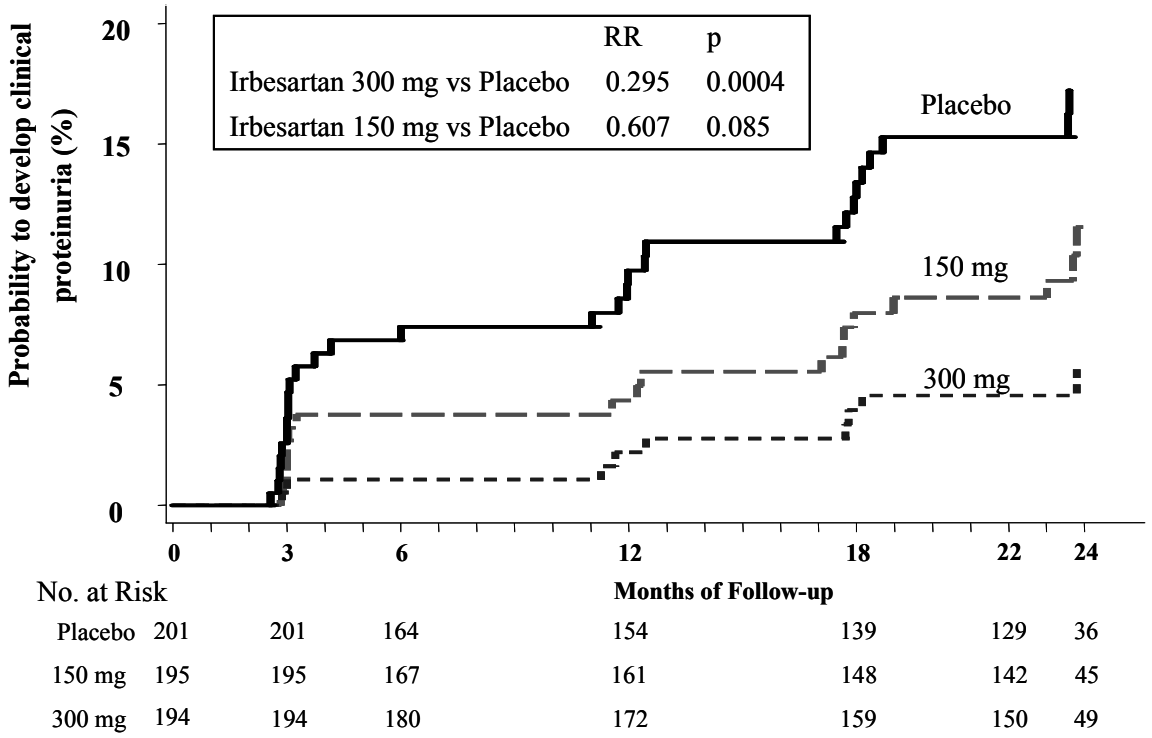
	Placebo N = 201	Irbesartan 150 mg N = 195	Irbesartan 300 mg N = 194
Number (%) of Subjects	30 (14.9)	19 (9.7)	10 (5.2)
Relative Risk[a] vs. placebo	N/A	0.607	0.295
95% Confidence Interval	N/A	0.341, 1.079	0.144, 0.606
p[b]	N/A	0.085	0.0004

[a] From Cox model with treatment as the only covariate

[b] From Mantel-Haenszel log-rank test

The results show a progressive separation relative to the probability of developing clinical proteinuria among all three groups. This effect begins at Month 3 (the first visit at which an assessment occurred) and continues through Month 24. Therapy with irbesartan lowers the risk of developing clinical proteinuria relative to placebo in a dose-dependent manner, and this benefit becomes more pronounced with time (Figure 6.6.1).

Figure 6.6.1: IRMA 2: Time to Occurrence of Clinical Proteinuria: Kaplan-Meier Curves Intent to Treat Population



Note: The sample size at Month 24 declines because most subjects completed Visit 9 at Month 22. Thus, this decline in sample does not indicate premature discontinuation of these subjects from the study.

The results for the per-protocol population were similar to those observed for the ITT population, with a 69% relative risk reduction in the 300 mg dose group (p = 0.0013) and a 39% relative risk reduction in the 150 mg dose group (p = 0.096).

6.6.1.1 Risk Ratio Adjusted for Baseline Prognostic Factors

A total of nine baseline factors were analyzed for significance in predicting the risk of developing clinical proteinuria. Albumin excretion rate (AER) was the only factor statistically significant as a prognostic factor for both the irbesartan 150 mg and placebo integrated group (p = 0.00001) and the irbesartan 300 mg and placebo integrated group (p = 0.00005) in the ITT population.

Table 6.6.1.1: IRMA 2: Risk Ratio of the Primary Endpoint After Adjusting for Albumin Excretion Rate and Mean Arterial Pressure - Intention-to-Treat Subjects

	Placebo	Irbesartan	RR	95% CI	p value
	N n (%)	N n (%)			
150 mg/placebo					
Unadjusted[a]	201 30 (14.9)	195 19 (9.7)	0.607	0.341-1.079	0.085
Adjusted[b]	201 30 (14.9)	194 19 (9.8)	0.556	0.311-0.993	0.047
300 mg/placebo					
Unadjusted[a]	201 30 (14.9)	194 10 (5.2)	0.295	0.144-0.606	0.0004
Adjusted[b]	201 30 (14.9)	191 10 (5.2)	0.316	0.153-0.653	0.0018

Note: N = Total sample of the population; n = subgroup of the total sample

[a] Mantel Haenszel Log rank test

[b] Cox's model adjustment on baseline AER and MAP time dependent variables.

AER as a risk factor reached statistical significance in the irbesartan 300 mg and placebo integrated group with an increase of the risk of developing clinical proteinuria 9.08 times higher in subjects with AER > 53 μg/min than in subjects with AER ≤ 53 μg/min.

The estimated risk ratio was re-analyzed by restricting the adjustment for the two major factors i.e., baseline AER as a fixed co-variable, which is a highly significant baseline risk factor in the previous model, and mean arterial pressure (MAP) as a time-dependent co-variable, which is the major treatment effect that could influence the results.

The risk ratio resulting from the Cox model analysis adjusted for AER and MAP is similar to the risk ratio resulting from the unadjusted analysis in both treatment groups. Consequently, the observed effect of irbesartan on reducing the risk to develop clinical proteinuria is not explained by differences in the level of baseline AER or the BP-lowering effect of irbesartan at the 2 doses tested (Table 6.6.1.1).

6.6.1.2 Analysis of Prognostic Factors by Sub-Group

To assess the consistency of treatment effects, eleven baseline prognostic factors and three time dependent factors were included into sub-group analyses for the primary

endpoint with comparisons of irbesartan 300 mg *vs.* placebo and irbesartan 150 mg *vs.* placebo. The risk ratio is always below one in any stratum of sub-groups for any irbesartan doses and in intention-to-treat and per-protocol populations. These results suggest that there was no difference in treatment effect in any sub-group and there was no interaction between treatment groups and sub-group populations.

6.6.2 Other Renal and Cardiovascular Results

6.6.2.1 Blood Pressure Measurements

SeDBP, SeSBP, and MAP decreased from baseline in all treatment groups at 1 and 2 years (Table 6.6.2.1). In the comparison between placebo and irbesartan doses, there were no statistically significant differences in mean change from baseline to 2 years. However at one year and for SeSBP and MAP in irbesartan 300 mg only, the decrease of pressure *vs.* placebo was significantly more marked.

Table 6.6.2.1: IRMA 2: Overall Change in Seated Diastolic and Systolic Blood Pressure (Irbesartan vs. Placebo) at 1 and 2 Years: Intention-to-Treat Population

Change	Placebo	Irbesartan 150 mg	Irbesartan 300 mg	Irbesartan 150 mg *vs.* Placebo		Irbesartan 300 mg *vs.* Placebo	
	Mean (SD)	Mean (SD)	Mean (SD)	Estimate Difference [95% CI]	p	Estimate Difference [95% CI]	p
After 1 Year in:	**N = 161**	**N = 171**	**N = 177**				
SeDBP (mmHg)	-8.16 (10.02)	-6.96 (9.06)	-9.77 (9.31)	1.202 [-0.84, 3.24]	0.25	-1.607 [-3.63, 0.42]	0.12
SeSBP (mmHg)	-11.72 (16.15)	-12.30 (14.83)	-15.24 (13.83)	-0.584 [-3.80, 2.64]	0.72	-3.552 [-6.72, -0.33]	0.031
MAP (mmHg)	-9.35 (10.70)	-8.74 (9.63)	-11.59 (9.60)	0.607 [-1.54, 2.76]	0.58	-2.245 [-4.38, -1.11]	0.039
After 2 Years in:	**N = 136**	**N = 145**	**N = 162**				
SeDBP (mmHg)	-7.84 (10.10)	-7.46 (10.27)	-8.85 (9.37)	0.380 [-1.94, 2.70]	0.75	-1.004 [-3.27, 1.26]	0.38
SeSBP (mmHg)	-9.59 (16.57)	-9.97 (17.17)	-12.36 (14.47)	-0.381 [-4.14, 3.38]	0.84	-2.776 [-6.43, 0.90]	0.14

Table 6.6.2.1: IRMA 2: Overall Change in Seated Diastolic and Systolic Blood Pressure (Irbesartan vs. Placebo) at 1 and 2 Years: Intention-to-Treat Population

	Placebo	Irbesartan 150 mg	Irbesartan 300 mg	Irbesartan 150 mg *vs.* Placebo		Irbesartan 300 mg *vs.* Placebo	
Change	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Estimate Difference [95% CI]**	**p**	**Estimate Difference [95% CI]**	**p**
MAP (mmHg)	-8.43 (10.59)	-8.30 (11.31)	-10.59 (9.74)	0.126 [-2.34, 2.60]	0.92	-1.591 [-4.00, 0.82]	0.19

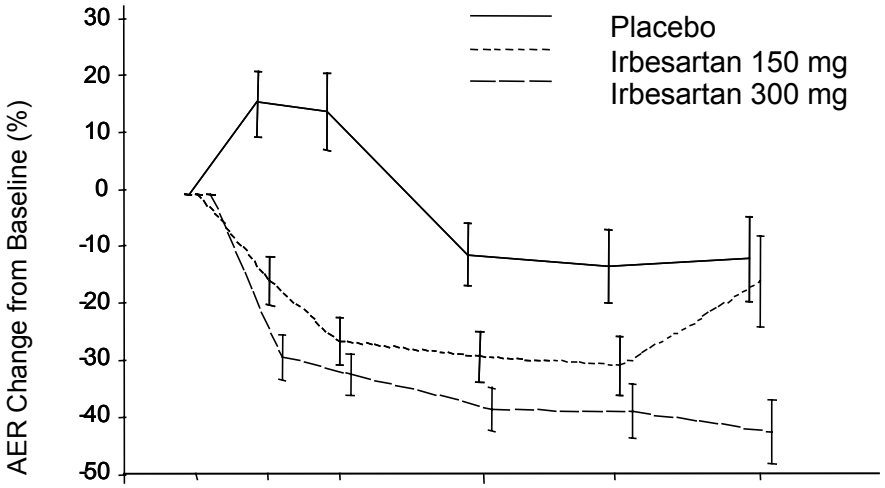
At 1 year, the SeSBP/SeDBP mean values were almost comparable across treatment groups: 141.8/81.9, 140.6/82.7, and 138.1/81.7 mmHg, in the placebo, irbesartan 150 mg, and irbesartan 300 mg groups, respectively.

At 2 years (end of study), the SeSBP/SeDBP mean values were very similar between treatment groups: 143.5/82.6, 143.5/82.5, and 140.9/82.6 mmHg, in the placebo, irbesartan 150 mg, and irbesartan 300 mg groups, respectively.

6.6.2.2 Clinical Proteinuria

Irbesartan in both treatment groups demonstrated a significant and consistent dose-dependent reduction in the geometric mean percentage changes from baseline in urinary AER *vs.* placebo. Figure 6.6.2.2 shows the percentage decrease from baseline in each treatment group in the ITT population. The geometric mean percentage changes (SE) were at one year: 11.5 (5.4), 29.3 (4.7) and 38.6 (3.8) in placebo, irbesartan 150 mg, and irbesartan 300 mg groups, respectively and, at 2 years, 12.1 (7.3), 16.1 (7.8) and 42.7 (5.5), respectively.

Figure 6.6.2.2: IRMA 2: Secondary Endpoint - Percentage Geometric Mean Change in Urinary Albuminuria Excretion Rate from Baseline: Intention-to-Treat Population.



Placebo	206	192	180	159	147	164
Irbesartan 150	201	185	175	167	158	169
Irbesartan 300	197	187	181	169	165	166

The irbesartan groups and the placebo group did not exhibit the same AER decrease profile. In the first 6-month period, the percentage change of AER was positive in the placebo group and negative in the irbesartan groups. These differences could be a consequence of the better blood pressure lowering effect of irbesartan groups within that 6-month period.

This hypothesis is not verified by the treatment effect adjusted to the blood pressure as a time dependent co-variate. The differences between groups in blood pressure are not sufficient for explaining AER differences. A complementary analysis was performed on primary endpoint in the population who reached the targeted BP (SBP ≤ 135 mmHg or DBP ≤ 85 mmHg) and in the population who did not.

Table 6.6.2.2A shows that efficacy in the irbesartan 300 mg group does not depend on targeted blood pressure. In both sub-populations, the percentage of patients who reached

the stage of overt proteinuria in the irbesartan 300 mg group remained statistically lower than in the placebo group.

Table 6.6.2.2A: IRMA 2: Percentage of Subjects who Reached the Stage of Clinical Proteinuria in 2 Sub-populations Defined According to Targeted Blood Pressure During the Study – Intent-to-Treat Population

Subjects Below Targeted Blood Pressure at Any Time					
	Number (%) of Subjects		Relative Risk[a] irbesartan *vs.* placebo		
	n/N	%	Estimate	95% Confidence Interval	P[b]
Placebo	6/46	13.0	-	-	-
Irbesartan 150 mg	6/73	8.2	0.629	0.203, 1.950	0.42
Irbesartan 300 mg	1/53	1.9	0.146	0.018, 1.213	0.039
Subjects Above Targeted Blood Pressure at Least Once					
	Number (%) of Subjects		Relative Risk[a] irbesartan *vs.* placebo		
	n/N	%	Estimate	95% Confidence Interval	P[b]
Placebo	24/155	15.5	-	-	-
Irbesartan 150 mg	13/122	10.7	0.611	0.311, 1.201	0.15
Irbesartan 300 mg	9/141	6.4	0.312	0.140, 0.695	0.0026

[a] From Cox model with treatment as the only covariate

[b] From Mantel-Haenszel log-rank tes

In the per-protocol population the differences between the irbesartan groups and the placebo group were statistically significant throughout the study, with the greatest difference (-47.15 %) occurring in the irbesartan 300 mg group at Month 24 ($p = 0.0001$ *vs* placebo). The mean decrease from baseline to Month 24 in the irbesartan 150 mg group was 30.48 %; this change was statistically significantly different from the one observed with placebo ($p = 0.046$). Table 6.6.2.2B describes these results.

Table 6.6.2.2B: IRMA 2: Secondary Endpoint Comparison - Geometric mean Percentage Change (SEM) in Urinary AER (Irbesartan vs. Placebo): Per-Protocol Population

Treatment Regimen	Visit	N	Baseline		Change from Baseline		Difference *vs.* Placebo		
			GM	SEM	GMPC	SEM	Estimate[a]	95% Confidence Interval	p
Placebo	Month 3	170	55.7	2.67	14.75	6.28			
	Month 6	157	53.3	2.61	13.87	7.11			
	Month 12	140	52.5	2.71	-10.46	5.83			
	Month 18	129	49.8	2.62	-10.52	7.04			
	Month 24	107	49.2	2.83	-7.55	8.95			
Irbesartan 150 mg	Month 3	157	57.7	2.83	-16.59	4.62	-27.31	[-38.08,-14.68]	0.0001
	Month 6	150	57.9	2.87	-28.03	4.39	-36.80	[-46.65,-25.14]	< 0.0001
	Month 12	140	56.2	2.81	-30.72	4.81	-22.63	[-35.92,-6.58]	0.0078
	Month 18	134	54.8	2.79	-34.49	5.48	-26.79	[-42.13,-7.39]	0.0094
	Month 24	109	54.3	2.99	-30.48	6.80	-24.79	[-43.12,-0.56]	0.046
Irbesartan 300 mg	Month 3	160	54.1	2.38	-32.56	4.27	-41.23	[-49.89,-31.06]	< 0.0001
	Month 6	155	53.8	2.40	-33.70	3.91	-41.77	[-50.78,-31.12]	< 0.0001
	Month 12	145	54.3	2.54	-39.84	4.07	-32.81	[-44.26,-19.01]	< 0.0001
	Month 18	144	53.1	2.41	-39.73	5.19	-32.64	[-46.53,-15.13]	0.0008
	Month 24	121	52.3	2.61	-47.15	5.27	-42.83	[-56.46,-24.94]	0.0001

Note: Parameter log-transformed: GMPC = geometric mean percent change

[a] Between-group percentage effect, calculated from the ratio of within-group ratios associated with geometric mean percent changes, current to baseline

The geometric mean (SEM) of AER at baseline was comparable in the placebo, irbesartan 150 mg, and irbesartan 300 mg groups. At 1 year and similarly at 2 years, the results were considerably different across the three groups.

A post hoc analysis was performed on the normalized AER defined as AER < 20 μg/min at the last visit.

Thirty-four percent of the subjects had normalized AER in the irbesartan 300 mg group compared with 21% and 24% in the placebo and irbesartan 150 mg groups, respectively.

The results for the per-protocol population were similar to those of the ITT population for the normalized AER. Treatment with irbesartan resulted in a dose-dependent normalized AER by 24% and 33% with 150 mg and 300 mg, respectively, compared with a 17% decrease in AER in the placebo group.

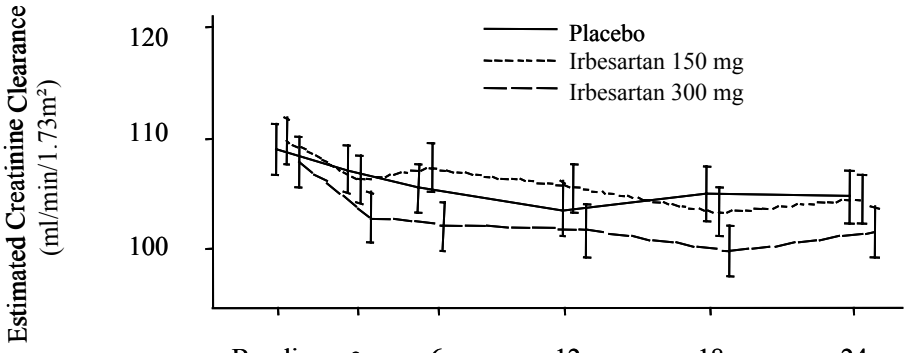
6.6.2.3 Creatinine Clearance

In this population without renal insufficiency at baseline, mean decreases from baseline were observed in estimated creatinine clearance for all treatment groups at all timepoints. There were no statistically significant differences between both irbesartan doses and placebo at any timepoint.

The geometric mean baseline values (SE) of estimated creatinine clearance in each group were comparable: 108.9 (2.19), 109.4 (1.99) and 107.7 (2.27) mL/min/1.73m^2 in placebo, irbesartan 150 mg and irbesartan 300 mg respectively.

Figure 6.6.2.3 shows the geometric mean values ± SEM of creatinine clearance estimated by the Cockcroft and Gault formula at each time point in the intention-to-treat population.

Figure 6.6.2.3: IRMA 2 Estimated Creatinine Clearance in Intention-to-Treat Population (mL/min/1.73m^2)



No. At Risk

Placebo	200	193	180	156	148	159
Irbesartan 150 mg	194	187	177	166	158	167
Irbesartan 300 mg	194	188	183	175	169	169

Previous studies suggest that the faster initial decline in creatinine clearance (or GFR) is due to a functional (hemodynamic) effect of antihypertensive treatment, which does not attenuate over time, while the sustained slower decline reflects the beneficial effect on progression of diabetic renal disease. In a complementary analysis, the mean decline of creatinine clearance per month were analyzed from baseline to 3-month and from 3-month to end of the study and is presented in Table 6.6.2.3. This analysis shows a marked mean decrease in calculated creatinine clearance in all treatment groups from baseline to Month 3 that was more pronounced in irbesartan treated groups, and especially in the irbesartan 300 mg group. This finding is in contrast to what is observed during months 3 through 24, where the magnitude of monthly decrease is far less important, without any clear differences between groups. Moreover, the decrease is within the same order of magnitude as the one observed in the healthy aging subjects.

Table 6.6.2.3: IRMA 2: Mean Decrease in Estimated Creatinine Clearance from Baseline or Month 3 During Acute (0 to Month 3) and Chronic (Month 3 to Month 24) Treatment: Per-Protocol Patients

	Calculated Creatinine Clearance (mL/min/1.73m^2/month)					
	Change from Baseline: 0 to Month 3			Change from Month 3: Month 3 to Month 24		
	N	Change in Creatinine Clearance	SEM	N	Change in Creatinine Clearance	SEM
Placebo	171	-0.91	0.54	107	-0.16	0.09
Irbesartan 150mg	158	-0.86	0.56	110	-0.19	0.09
Irbesartan 300 mg	160	-1.86	0.56	125	-0.19	0.09

Note: SEM = standard error of the mean

The mean change of estimated creatinine clearance per month during the sustained period 3-month to 24- month equivalent to 1.9 and 2.3 mL/min/1.73m^2 per year in placebo and in any irbesartan group respectively.

6.6.3 Glomerular Filtration Rate Substudy

A total of 133 subjects who were randomized to double-blind treatment participated in the GFR sub-study. Of those sub-study subjects, 115 completed the 2 years of double-blind treatment.

Of the 133 GFR sub-study subjects, 48 were randomized to placebo, 42 were randomized to irbesartan 150 mg and 43 were randomized to irbesartan 300 mg.

6.6.3.1 Glomerular Filtration Rate Results

GFR decreased modestly in all substudy groups over the course of the trial. There were no significant differences between treatment groups. These results are quite consistent with the results previously stated with respect to CrCl (Table 6.6.3.1).

Table 6.6.3.1: IRMA 2: Geometric Mean Percentage Change (SEM) in Glomerular Filtration Rate (mL/min/1.73 m^2) (Irbesartan vs. Placebo): GFR Sub-Study Population

Treatment Regiment	Visit	N	Change from Baseline		Difference vs Placebo		
			GMPC	SEM	Estimate[a] (GMPC)	95% Confidence Interval	p-value
Placebo	Month 3	37	-2.6	2.1			
	Month 24	32	-8.9	2.0			
Irbesartan 150 mg	Month 3	38	-3.2	2.1	-0.67	(-6.70, 5.76)	0.83
	Month 24	31	-10.0	2.5	-1.10	(-7.85, 6.14)	0.76
Irbesartan 300 mg	Month 3	37	-2.3	2.3	0.27	(-5.86, 6.80)	0.93
	Month 24	33	-12.1	2.2	-3.41	(-9.91, 3.55)	0.32

Note: Parameter log-transformed: GMPC = geometric mean percent change, SEM = standard error of the mean

[a] Between-group percentage effect, calculated from the ratio of within-group ratios associated with geometric mean percent changes, current to baseline

6.6.3.2 Active Renin, Pro-Renin, and Angiotensin II

As expected with an ARB, at Months 3 and 24 (end of the study), treatment with irbesartan resulted in a dose-dependent increase in the mean percentage change (SE) in renin, pro-renin, and angiotensin II. For the irbesartan 300 mg group, the differences *vs.* placebo were highly statistically significant in each parameter and at each timepoint.

These data are consistent with the fact that angiotensin II (subtype AT_1) receptors were blocked by irbesartan and not blocked in the placebo group.

Table 6.6.3.2: IRMA 2: Geometric Mean Percentage Change (SEM) in Angiotensin II (Irbesartan vs. Placebo): GFR Sub-Study Subjects

Treatment	Visit	N	Change from Baseline		Difference with Placebo		
			GMPC	SEM	Estimate[a] (GMPC)	95% Confidence Interval	P-value
Placebo	Month 3	12	-11.0	10.2			
	Month 24	25	4.4	16.2			
Irbesartan 150 mg	Month 3	14	56.9	18.7	76.4	(21.7, 155.5)	0.0037
	Month 24	27	97.8	24.5	89.5	(29.1, 178.2)	0.0014
Irbesartan 300 mg	Month 3	13	126.4	33.7	154.4	(74.4, 271.0)	< 0.0001
	Month 24	26	157.4	33.5	146.6	(67.4, 263.3)	< 0.0001

[a] Between-group percentage effect, calculated from the ratio of within-group ratios associated with geometric mean percent changes, current to baseline

6.6.3.3 GFR Sub-Study Extension

Ninety-one (91) subjects entered the 4-week extension period and 76 completed this extension. Fifteen patients prematurely discontinued their participation either for adverse event (7 patients) or for other cause (8 patients).

6.6.3.4 GFR/+Week 4

GFR increased in all groups after completion of the study. There were no statistically significant differences between either dose of irbesartan and placebo (Table 6.6.3.4).

Table 6.6.3.4: IRMA 2: Mean (SEM) Change in Glomerular Filtration Rate (mL/min/1.73 m^2) (Irbesartan vs. Placebo): GFR Sub-Study Extension Population

Treatment Regiment	Visit	N	Change from Baseline (Month 24)		Difference *vs.* Placebo		
			GMPC	SEM	Estimate[a] (GMPC)	95% Confidence Interval	P
Placebo	+Week 4	24	5.7	2.1			
Irbesartan 150 mg	+Week 4	18	1.2	2.4	-4.30	(-10.4, 2.2)	0.18
Irbesartan 300 mg	+Week 4	23	3.7	2.6	-1.90	(-7.8, 4.3)	0.53

Note: Parameter log-transformed: GMPC = geometric mean percent change, SEM = standard error of the mean

[a] Between-group percentage effect, calculated from the ratio of within-group ratios associated with geometric mean percent changes, current to baseline

6.6.3.5 Creatinine Clearance / +Week 4

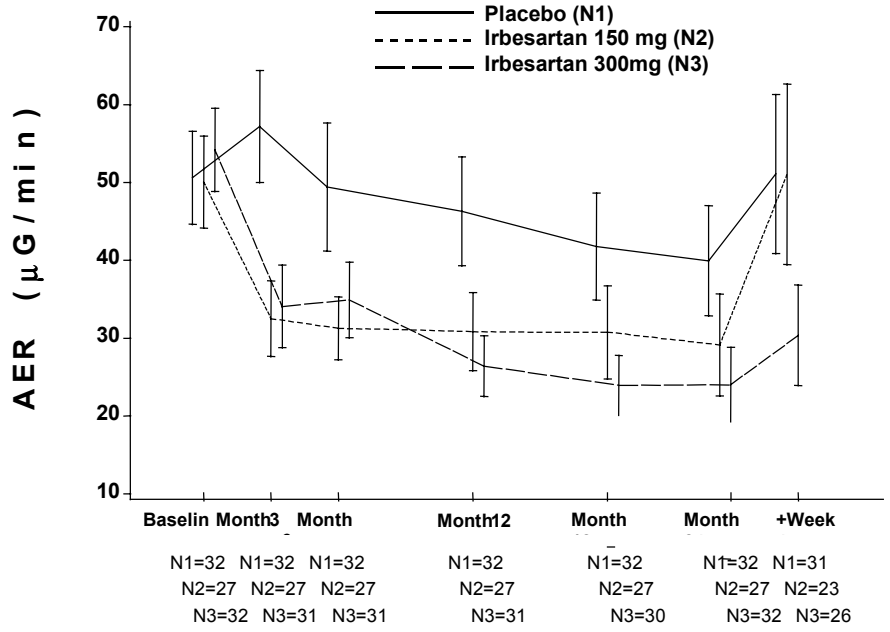
At Week + 4 the mean (SD) creatinine clearance increased to 89.3 (4.3), 90.9 (5.5), and 85.9 (6.7) mL/min/1.73m^2 in the placebo, irbesartan 150 mg, and irbesartan 300 mg groups, respectively. The increase of creatinine clearance reached the values observed at Month 12 for placebo [88.4 (5.0)], at baseline for irbesartan 150 mg [91.2 (3.9)], and at Month 3 for irbesartan 300 mg [86.3 (5.1)].

As expected the decline of GFR or estimated creatinine clearance was modest among all treatment groups in this population with incipient nephropathy. The initial drop at Month 3, which can be explained by the hemodynamic effect of the antihypertensive treatment, was steeper than the slow sustained decline (Month 3 to 24) which did not differ significantly in the 3 groups.

6.6.3.6 Urinary AER / +Week 4

At 4 weeks post discontinuation of study medications and other antihypertensive agents, AER remained substantially below baseline only for subjects who had been treated with irbesartan 300 mg (Figure 6.6.3.6).

Figure 6.6.3.6: IRMA 2: Mean (SE) AER (g/min) Over Time: GFR Sub-Study Extension

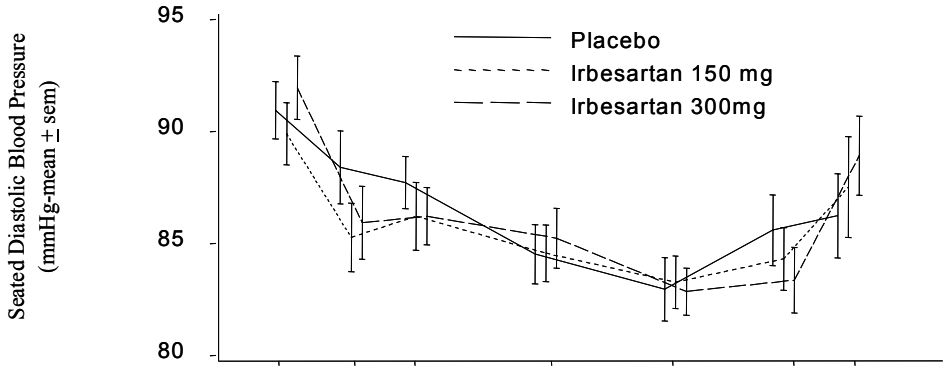


6.6.3.7 Blood Pressure / +Week 4

Mean BP values increased during the GFR sub-study extension (after withdrawal of study medication and other antihypertensive agents), approaching baseline values in the irbesartan 150 mg and irbesartan 300 mg groups. However, the mean BP increases observed in the placebo group did not approach baseline levels.

The Figure 6.6.3.7 shows the diastolic blood pressure changes overtime in all patients participating to the sub-study and the 4-week extension. In contrast to the AER changes at 4-week extension the increase of the diastolic blood pressure seems at the same level in the three groups.

Figure 6.6.3.7: IRMA 2: Mean (SE) SeDBP (mmHg) Over Time: GFR Sub-Study Extension



Placebo	48	48	44	43	42	43	32
Irbesartan 150 mg	42	42	40	39	37	40	24
Irbesartan 300 mg	43	43	40	38	38	40	31

6.6.3.8 GFR Substudy Conclusions

Patients in IRMA 2 treated with irbesartan did not demonstrate a substantial and sustained effect on GFR decline over the 2 year follow-up. Due to the early stage of disease studied, study duration, and low numbers of subjects, we did not expect to demonstrate a difference in GFR decline among the groups. The magnitude of the acute hemodynamic effect of RAS inhibition with irbesartan on GFR is in contrast with the subsequent slow decrease in GFR, which is similar in the three groups. The beneficial treatment effect of irbesartan on preventing clinical proteinuria (i.e., macroalbuminuria defined as urinary AER > 200 μg/min) may be occurring at the expense of the initial hemodynamic impact of the treatment. Overall, during the short 2-year time frame considered, it is not possible to differentiate the effect of irbesartan on GFR from that observed in the control group, given the slow decrease observed in the "chronic" phase of treatment, roughly in the same range as the decrease related to aging.

The results of the GFR sub-study and its extension suggest a relative residual renoprotective effect after withdrawal of study drugs and adjunctive antihypertensive medications in the group treated with 300 mg of irbesartan.

6.7 Safety

The incidence of treatment-emergent adverse events (AEs), adverse drug events (ADEs), serious adverse drug events (SAEs), discontinuations for a clinical AE, and deaths in IRMA 2 are presented in Table 6.7.

Table 6.7: Summary of Safety for IRMA 2

	Number (%) of Subjects			
	Placebo N= 206	**Irbesartan 150 mg N = 202**	**Irbesartan 300 mg N = 200**	**All Irbesartan N = 402**
AEs	141 (68.4)	129 (63.9)	149 (74.5)	278 (69.2)
ADEs	27 (13.1)	25 (12.4)	21 (10.5)	46 (11.4)
SAEs	47 (22.8)	32 (15.8)	30(15.0)	62 (15.4)
Discontinuations	19 (9.2)	18 (8.9)	11 (5.5)	29 (7.2)
Deaths	5 (2.4)	3 (1.5)	8 (4.0)	11 (2.7)

6.7.1 Treatment-Emergent Adverse Events

The most commonly reported treatment-emergent clinical adverse event in IRMA 2 was musculoskeletal pain that tended to occur more frequently in irbesartan-exposed subjects (11.4%) than in placebo-exposed subjects (9.7%). Subjects receiving the 150 mg irbesartan regimen tended to have a similar or less frequent reporting of clinical AEs compared with placebo-exposed subjects in all clinical AEs reported at ≥ 3% frequency except diarrhea (4.0% *vs.* 2.9%), bacterial skin infection (3.0% *vs.* 0.5%), and nausea/vomiting (3.5% *vs.*1.0%). Diarrhea may be dose related as it tends to occur more frequently in the 300 mg irbesartan regimen (6.5%) as compared with the 150 mg irbesartan regimen (4.0%). Nausea/vomiting, however, does not appear to be dose related as the reported occurrence in subjects receiving the 300 mg irbesartan regimen was equal to placebo-exposed subjects. Subjects receiving the 300 mg irbesartan regimen, tended to have more frequent reporting (≥ 2%) of musculoskeletal pain (12.5% *vs.* 9.7%), dizziness (6.5% *vs.* 2.9%), diarrhea (5.5% *vs.* 2.4%), pulmonary infection (5.0% *vs.* 1.9%), urination abnormality (3.5% *vs.* 1.0%), depression (4.0% *vs.* 1.9%), vertigo (3.0% *vs.* 1.0%), and sleep disturbance (3.0% *vs.* 0.0%) as compared with

placebo-exposed subjects. Of note, many of these events occurred similarly or less frequently in irbesartan-exposed subjects compared with placebo-exposed subjects in IDNT including musculoskeletal pain (37.8% *vs.* 38.2%), pulmonary infection (4.7% *vs.* 6.7%), urination abnormality (6.6% *vs.* 6.6%), and depression (5.9% *vs.* 5.0%).

6.7.2 Adverse Drug Experiences

The most common clinical adverse drug experiences are presented in Table 6.7.2.

Table 6.7.2: IRMA 2: Most Common Clinical Adverse Drug Experiences (Reported in ≥ 1% of Subjects in any Treatment Group) During and Up to 14 Days Post Double-Blind Therapy, by Primary Term

Adverse Event By Primary Term	Number of Events (% of Subjects)			
	Placebo N = 206	Irbesartan 75/150 mg N = 202	Irbesartan 75/150/300 mg N = 200	All Irbesartan N = 402
Dizziness	3 (1.5)	3 (1.5)	5 (2.5)	8 (2.0)
Fatigue	1 (0.5)	3 (1.5)	1 (0.5)	4 (1.0)
Nausea/Vomiting	0	4 (2.0)	0	4 (1.0)
Cough	2 (1.0)	2 (1.0)	1 (0.5)	3 (0.7)
Headache	2 (1.0)	0	3 (1.5)	3 (0.7)
Vertigo	0	1 (0.5)	2 (1.0)	3 (0.7)
Hypertension	6 (2.9)	2 (1.0)	0	2 (0.5)
Hypotension	0	0	2 (1.0)	2 (0.5)
Edema	2 (1.0)	0	1 (0.5)	1 (0.2)
Chest Pain	2 (1.0)	0	0	0
Dyspepsia/Heartburn	2 (1.0)	0	0	0
Overall Total Event	34	30	34	64
Overall Total Subjects with at Least One ADE	27 (13.1)	25 (12.4)	21 (10.5)	46 (11.4)

An adverse drug experience (ADE) is an adverse event that was deemed by the Investigator to be certainly, probably, possibly related to study drug or of unassessable or missing relationship. Therefore, ADEs are a subset of the treatment-emergent AEs.

Overall, ADEs were reported less frequently in irbesartan-exposed subjects as compared with placebo-exposed subjects. The most common ADE was dizziness and was reported in 1.5%, 1.5%, and 2.5% of the subjects in the placebo group, 150 mg irbesartan regimen, and 300 mg irbesartan regimen, respectively. The overall incidence of dizziness in all irbesartan-exposed subjects was 2% and was therefore similar to placebo (1.5%). The only adverse drug experience that tended to be reported more frequently (≥ 2% difference) in irbesartan exposed subjects was nausea/vomiting that was reported in 2% of the subjects receiving the 150 mg irbesartan regimen. This event does not appear to be dose related as it was not reported in the 300 mg irbesartan regimen; therefore, nausea/vomiting had an overall incidence of 1% in all irbesartan-exposed subjects and was similar to placebo. Overall, ADEs were reported similarly between placebo- and irbesartan-exposed subjects in IRMA 2 and no additional adverse events were identified in ADEs from these events previously identified in AEs.

6.7.3 Serious Adverse Events

A serious AE (SAE) was defined as an AE that met any of the following criteria: fatal, life-threatening, results in persistent or significant disability/incapacity, requiring inpatient hospitalization or prolongation of existing hospitalization, congenital anomaly/birth defect, cancer, or overdose (accidental or intentional).

Of the 608 exposed subjects, 109 experienced at least one SAE. The frequency of SAE occurrence was higher in placebo-exposed subjects (22.8%) as compared with irbesartan-exposed subjects (15.4%). Myocardial infarction was the event most frequently reported as a SAE which occurred similarly in the irbesartan-exposed (1.2%) subjects as compared with placebo-exposed (2.4%) subjects. The second most frequently reported SAE was heart failure which occurred in 1.5% of the irbesartan-exposed subjects, but was not reported in placebo-exposed subjects. The incidence of heart failure does not appear to be dose-related. Of the six heart failure SAEs, five were reported as not likely or unrelated to irbesartan. In one subject (801/039), severe heart failure was reported one week after double-blind treatment completion. The relationship to study

drug was reported as likely because the Investigator believed that the study drug (irbesartan 150 mg) protected the subject from heart failure while receiving treatment since heart failure developed one week post study. All reported cases of heart failure resolved.

6.7.4 Discontinuations Due to an Adverse Event

There were fewer discontinuation of study drug due to an AE in irbesartan-exposed subjects (7.2%) as compared with placebo-exposed subjects (9.2%). The total number of discontinuations due to adverse events in irbesartan-exposed subjects does not appear to be dose-related as discontinuations in the 150 mg irbesartan regimen (8.9%) was higher than the 300 mg irbesartan regimen (5.5%). The highest rate of discontinuation for a clinical adverse event was for nausea/vomiting (2%) and occurred in the 150 mg irbesartan-treatment group. Again, this finding does not appear to be dose-related as no subject in the 300 mg irbesartan-treatment group discontinued due to nausea/vomiting. Therefore, the incidence of nausea/vomiting in all irbesartan-exposed subjects was 1.0%. The remainder of discontinuations for clinical adverse events occurred with a frequency of 1% or less. Overall, the discontinuation due to a clinical adverse event were similar between irbesartan- and placebo-exposed subjects.

The most frequent cause of discontinuation for a laboratory AE was increased serum potassium that occurred in 2 (1%) of the subjects in the 150 mg irbesartan regimen and was not reported in the placebo or 300 mg irbesartan treatment groups. The overall incidence of discontinuation for elevated serum potassium in irbesartan-exposed subjects in IRMA 2 was 0.5%.

6.7.5 Deaths

The overall number of deaths in IRMA 2 was similar between irbesartan-exposed subjects (2.7%) and placebo-exposed subjects (2.4%). Of note, there was not any cause of death by primary term that occurred in more than one subject in each of the three treatment groups.

6.7.6 Laboratory Adverse Events

In IRMA 2, laboratory AEs tended to be similarly reported in the irbesartan-exposed (8.7%) subjects compared with placebo-exposed (10.7%) subjects.

6.7.7 Safety in Subpopulations: Gender, Race, Age

There were 273 males and 129 females treated with any dose of irbesartan in the IRMA 2 study. The extent of exposure to irbesartan was similar for males and females (mean duration of exposure of 623 and 614 days, respectively). Musculoskeletal pain tended to be more frequently reported in males, while females reported diarrhea and dermatitis more frequently. The total number of events in these subpopulations was, however, low and whether these event rates represent meaningful differences is uncertain. Overall, the results suggest no important gender-specific differences in clinical AEs by body system. Importantly, an increased incidence in myocardial infarction in female subjects in IDNT (see Section 5.7.7) was not observed in IRMA 2. Specifically, in IRMA 2, myocardial infarction was reported in 2.1%, 2.2%, 3.1% of male placebo-exposed, male irbesartan-exposed, and female placebo-exposed subjects, but there was no reported occurrence of myocardial infarction in female irbesartan-exposed subjects.

Almost all subjects (97%) in IRMA 2 were white so this study does not provide information on safety by race.

There were 305 subjects aged < 65 years and 97 subjects aged ≥ 65 years in IRMA 2. The mean duration of exposure was almost the same at 620 and 621 days, respectively. No significant differences were observed for patients ages less than 65 years. Edema was reported more frequently and in a dose-related manner for patients aged ≥ 65 years old (1.6%, 5.8% and 11.1% in the placebo, irbesartan 150 mg and irbesartan 300 mg groups, respectively).

6.7.8 Drug-Drug Interaction

Drug-drug interaction safety data for selected therapeutic classes were evaluated in irbesartan-exposed subjects who were treated with specified concomitant medications any time during the double-blind therapy in the clinical safety/efficacy studies. Selected drug classes included antihyperglycemics (insulin, sulfonylureas, metformin),

antihypertensive agents (beta blockers, loop diuretics), aspirin/antiplatelet, and NSAIDs/analgesics. Potential drug-interactions that were identified in IRMA 2 included increased dizziness in irbesartan-exposed subjects using concomitant NSAIDs/analgesics or beta blockers as compared with placebo-exposed subjects using concomitant NSAIDs/analgesics or beta blockers.

6.7.9 Additional Safety Considerations

6.7.9.1 Summary of Clinical Events and Laboratory Abnormalities for Elevated Serum Potassium or Hyperkalemia: IRMA 2

Treatment emergent AEs, laboratory marked abnormalities, discontinuations for hyperkalemia, SAEs for hyperkalemia and deaths due to hyperkalemia in IRMA 2 are presented in Table 6.7.9.1.

Table 6.7.9.1: Summary of Clinical Events and Laboratory Abnormalities for Elevated Serum Potassium or Hyperkalemia in IRMA 2

	Number (%) of Subjects		
	Placebo N = 206	**Irbesartan 150 mg N = 202**	**Irbesartan 300 mg N = 200**
Treatment-emergent AEs	0	2 (1.0)	0
Laboratory marked abnormalities ($K^+ \geq 6.0$ mEq/L)	0	4 (2.0)	0
Study drug discontinuations	0	2 (1.0)	0
SAEs	0	0	0
Sudden death	0	0	1 (0.5%)

The occurrence of elevated serum potassium in subjects in the IRMA 2 study was low and did not appear to be dose-related. There were no SAEs attributed to hyperkalemia in IRMA 2. Sudden death occurred in one irbesartan-exposed subject with a past medical history of ischemic heart disease, atrial fibrillation, angina pectoris and a cavitary lung lesion in IRMA 2. Overall, hyperkalemia in patient populations with type 2 diabetes and microalbuminuria is not common.

The frequency of observed clinical and laboratory abnormalities related to hyperkalemia (serum potassium ≥ 6.0 mEq/L) in IDNT, but not in IRMA 2, underscores the difference between type 2 diabetes with microalbuminuria and overt proteinuria.

6.7.9.2 Orthostatic Symptoms

Table 6.7.9.2 presents a summary of the treatment-emergent clinical adverse events, adverse drug experiences, serious adverse events, and study drug discontinuations due to an AE for dizziness (a symptom that may or may not be related to actual orthostasis), orthostatic dizziness, and orthostatic hypotension in IRMA 2.

Table 6.7.9.2: Reported Occurrences of Treatment-Emergent Events for Dizziness, Orthostatic Dizziness, and Orthostatic Hypotension in IRMA 2

	Number (%) of Subjects		
	Placebo N = 206	**Irbesartan 150 mg N = 202**	**Irbesartan 300 mg N = 200**
Dizziness			
Clinical AE	6 (2.9)	8 (4.0)	13 (6.5)
Clinical ADE	3 (1.5)	3 (1.5)	5 (2.5)
SAE	0	0	0
Discontinuation	1 (0.5)	0	0
Orthostatic Dizziness			
Clinical AE	1 (0.5)	1 (0.5)	1 (0.5)
Clinical ADE	1 (0.5)	1 (0.5)	1 (0.5)
SAE	0	0	0
Discontinuation	0	0	0
Orthostatic Hypotension			
Clinical AE	1 (0.5)	2 (1.0)	1 (0.5)
Clinical ADE	1 (0.5)	1 (0.5)	1 (0.5)
SAE	0	1 (0.5)	0
Discontinuation	0	0	0

Dizziness appears to occur with a numerically higher frequency in irbesartan-exposed subjects as compared to placebo-exposed subjects. Importantly, there were no reported discontinuations due to dizziness in either the 150 mg or the 300 mg irbesartan regimens and only one discontinuation was associated with dizziness in the placebo group. Finally,

there was no apparent increased frequency of clinical AEs, ADEs, SAEs, or discontinuations for an AE in irbesartan-exposed subjects as compared with placebo-exposed subjects for either orthostatic dizziness or orthostatic hypotension. These data suggest that orthostatic symptoms do not occur frequently in patient populations similar to the IRMA 2 study and are not commonly associated with SAEs or the need for study drug discontinuation.

6.8 Overall Conclusions

The results of the primary endpoint in this study were positive and dose-dependent in both the per-protocol and ITT populations. Irbesartan 300 mg significantly reduced the risk to reach clinical proteinuria by 70% ($p = 0.0004$) in the ITT population. Irbesartan 150 mg reduced the risk by 39%, but this reduction was not statistically significant. The effect of irbesartan in reducing the risk to develop clinical proteinuria is independent of the level of baseline AER and of the BP-lowering effect of irbesartan at the two doses tested. This benefit is observed in addition to the positive anti-hypertensive effect.

Additionally, the results observed for the major secondary endpoint were positive. Irbesartan, at the two doses tested, showed a statistically significant reduction in urinary AER at 1 and 2 years in both populations analyzed per-protocol and intent-to-treat.

The study also showed that:

- Irbesartan at 300 mg dose is renoprotective in the early stage of diabetic nephropathy with microalbuminuria. This kidney protection observed is in addition to the BP-lowering effect of irbesartan.
- Irbesartan, at both the 150 and 300 mg doses, is well tolerated and safe in hypertensive type 2 diabetic subjects with microalbuminuria.
- The results of the GFR sub-study extension showed a relative residual effect of irbesartan 300 mg on the post treatment withdrawal increase of AER.
- Irbesartan did not affect kidney function as evaluated by the estimated creatinine clearance in the main study and the GFR sub-study.

7 RATIONALE FOR THE PRESCRIBED DOSE

Irbesartan has been approved since 1997 for the treatment of hypertension, with > 3.6 million patient-years of clinical experience since then. The usual recommended initial and maintenance dose is 150 mg once daily, with titration to 300 mg for patients requiring further blood pressure reduction. Over the past four years, irbesartan has been well recognized as an effective, safe and well-tolerated antihypertensive treatment at these doses, including hypertensive patients with type 2 diabetes mellitus. Most prescriptions are for the 150 mg once daily dose. Consistent with the dosing for hypertension, we recommend a starting dose of 150 mg once daily for treatment of diabetic renal disease in hypertensive type 2 diabetic patients.

The irbesartan clinical program in type 2 diabetic renal disease was planned in 1996, prior to the approval of irbesartan for hypertension. At that time, the recommended starting dose for the treatment of hypertension was not yet established. Irbesartan was subsequently approved for hypertension with a recommended starting dose of 150 mg once daily. Unfortunately, both IRMA 2 and IDNT had already begun with a starting dose for irbesartan of 75 mg once daily, creating an inconsistency between the recommended 150 mg starting dose for hypertension and the starting dose used in these two clinical trials.

A renoprotective benefit was demonstrated for irbesartan in both IRMA 2 and IDNT, independent of the effect of irbesartan on systemic blood pressure. In IRMA 2, subjects were initiated on 75 mg once daily and were titrated to either 150 mg or 300 mg of irbesartan. In IDNT, subjects were initiated on 75 mg once daily, and most patients were titrated to 300 mg once daily. Importantly, in both IRMA 2 and IDNT, the data suggest that 300 mg once daily is the dose required for optimal renoprotection.

The safety of irbesartan was established in both of these studies. In IRMA 2, adverse drug experiences were similar to those reported for hypertensive patients. During the initial period of treatment with 75 mg of irbesartan, prior to titration, 8 patients (2.0%) discontinued study drug prematurely in the irbesartan groups, compared with 7 patients (3.4%) in the placebo group. In IDNT, adverse drug experiences were similar to those reported for hypertensive patients, with the exception of orthostatic symptoms and hyperkalemia. However, very few patients in IDNT required discontinuation of study

drug for either orthostatic symptoms or hyperkalemia. Furthermore, patients randomized to irbesartan were not at an increased risk, compared with the placebo or amlodipine groups, of either orthostatic symptoms or hyperkalemia shortly after initiation of irbesartan. This was evaluated both within the full 2-week period of the initial dose of study drug, prior to titration, as well as within the first 5 days after the initiation of study drug, during which time most orthostatic symptoms caused by the initiation of antihypertensive therapy should be seen.

Unfortunately, in the real world, physicians frequently fail to titrate antihypertensive medicines to optimal doses necessary to achieve appropriate BP control. In one study, for about three quarters of patient visits in which elevated BP was recorded, physicians did not increase medications. Consequently, hypertension remains uncontrolled in over 70% of hypertensive patients.[56] Initiation at an irbesartan dose of 75 mg once daily, followed by two separate titration steps, may therefore actually impede physicians from attaining the appropriate renoprotective irbesartan dose of 300 mg.

In summary, based on the established safety and tolerability profile of irbesartan in hypertension and in the IRMA 2 and IDNT trials, as well as the need for patients to be appropriately treated with the renoprotective dose of 300 mg once daily, we recommend that irbesartan be initiated at 150 mg once daily. This dosing is consistent with the starting dose of irbesartan for hypertension and is only one titration step from the preferred maintenance dose of 300 mg once daily for the treatment of diabetic renal disease.

8 BENEFIT: RISK

Benefit

Irbesartan is the first drug of any class to demonstrate beneficial effects on slowing progression of renal disease above and beyond BP control in a high risk population with type 2 diabetes, hypertension and early and later stages of diabetic renal disease.

Evidence to Support Irbesartan Effectiveness

The results of IDNT and IRMA 2 complement each other and support both early and later intervention in the natural history of type 2 diabetic renal disease (see Table E). The results provide strong evidence to support the hypothesis that RAS inhibition with irbesartan has renoprotective effects above and beyond those from blood pressure reduction alone.

The pathophysiology of diabetic renal disease is well understood, and the proposed mechanism by which RAS inhibition would favorably alter the kidney is fairly well recognized. One of the proposed mechanisms for progression of renal failure in diabetic renal disease is an increase in intraglomerular capillary pressure due to AII-mediated vasoconstriction of the efferent arteriole which results in hyperfiltration in the surviving glomeruli and eventual glomerular scarring. The effects of AII may be abrogated by either reducing the generation of AII through ACEI use or by inhibition of AII binding to its receptor (AT1) through the use of an AII receptor antagonist, such as irbesartan.

In IRMA 2 in patients with microalbuminuria, irbesartan significantly reduced urinary albumin excretion and progression to clinical proteinuria, which predicts progression to ESRD. In IDNT, irbesartan reduced clinically relevant renal outcomes that occur later in the continuum of diabetic renal disease.

For IDNT, compared with placebo, irbesartan therapy was associated with a substantial treatment effect, namely a 20% reduction in the primary composite endpoint, a 33% reduction in doubling of serum creatinine, and a 23% reduction in ESRD. These overall results which are consistent within IDNT are complemented by the treatment effect observed with the 300 mg dose of irbesartan in IRMA 2, namely a 70% reduction in the incidence of overt proteinuria compared with placebo.

Taken together, IRMA 2 results on clinical proteinuria relate to the prevention of a disease with a potentially serious outcome, and IDNT results relate to protection of renal function once patients have advanced renal disease.

The chosen endpoints for IRMA 2 and IDNT were clinically appropriate to the stage of disease and could be objectively assessed (e.g., urinary albumin excretion rates and doubling of serum creatinine). The primary endpoints in the two studies, though different, are pathogenically related. A dose-response was observed in the IRMA 2 study with the 300 mg irbesartan dose showing statistically significant delay of progression from microalbuminuria to overt proteinuria.

IDNT demonstrated clinically relevant effects on irreversible morbidity, namely a permanent doubling of serum creatinine which represents halving of renal function. Furthermore, the trends in risk reduction for IDNT across all individual renal component endpoints of the primary renal outcome favor irbesartan for the comparison of irbesartan *vs.* placebo or amlodipine.

Importantly, the IDNT design included a comparison of irbesartan with another active comparator, namely amlodipine. The achieved mean arterial BPs in the irbesartan and amlodipine treatment groups were virtually identical, and lower than that achieved in the placebo treatment group. Unlike irbesartan, however, amlodipine did not have a renoprotective effect at the same level of achieved mean arterial BP. The comparable treatment benefit of irbesartan relative to placebo and amlodipine re-enforced the findings on the primary endpoint.

In IDNT the results for the critical renal outcomes (doubling of serum creatinine and ESRD) are accompanied by expected beneficial results on related outcomes of change in creatinine clearance and in urinary albumin and protein excretion.

In IRMA 2 an important new finding was observed in this patient population with early diabetic renal disease. At 4 weeks after study drug and other antihypertensive drugs were stopped, the urinary AER remained substantially below the baseline for subjects treated with irbesartan 300 mg. This new finding supports the view that irbesartan 300 mg affords a relative residual renoprotective effect once the drug is stopped. This finding is consistent with the view that RAS inhibition provides a fundamental change in the renal

millieu in addition to and distinct from the reversible renal hemodynamic effects resulting from changes in BP alone.

The results of IDNT with irbesartan are consistent with those in a recently published clinical trial with another member of the same pharmacologic class. This randomized, prospective trial comparing losartan with placebo used the identical primary composite endpoint as IDNT in type 2 diabetic patients with overt nephropathy. The magnitude of the beneficial treatment effect in the losartan trial (16%) is approximately that seen with irbesartan in IDNT (20%) with an identical p value of 0.02.

Table E: Summary of Primary Efficacy - IDNT and IRMA 2 (ITT Analysis)

	Placebo Regimen	Irbesartan 150 mg Regimen	Irbesartan 300 mg Regimen	Amlodipine Regimen
IDNT				
Primary Composite Endpoint[a]	222 (39.0)		189 (32.6)	233 (41.1)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			20% (0.0234)	
Irebesartan vs Amlodipine[b]			23% (0.0064)	
Total Incidence of Renal Endpoints				
Doubling of Serum Creatinine[a]	135 (23.7)		98 (16.9)	144 (25.4)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			33% (0.0027)	
Irbesartan vs Amlodipine[b]			37% (0.0003)	
End Stage Renal Disease[a]	101 (17.8)		82 (14.2)	104 (18.3)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			23% (0.0731)	
Irbesartan vs Amlodipine[b]			23% (0.0746)	
Total Incidence of All-Cause Mortality[a]	93 (16.3)		87 (15.0)	83 (14.6)
Relative Risk Reduction				
Irbesartan vs Placebo[b]			8% (0.5683)	
Irbesartan vs Amlodipine[b]			-4% (0.8083)	
IRMA 2				
Progression to Clinical Proteinuria[a,c]	30 (14.9)	19 (9.7)	10 (5.2)	
Relative Risk Reduction				
Irbesartan vs Placebo[b]		39% (0.085)	70% (0.0004)	

Note: Relative risk reduction and p-values are from time-to-first event analysis.

[a] Total number of subjects with the event (percent)

[b] Relative Risk Reduction (p value)

[c] Clinical proteinuria is defined as albumin excretion rate > 200 µg/min and an increase of at least 30% from baseline

In IDNT, irbesartan significantly increased the time to the primary (renal) composite endpoint of doubling of serum creatinine, ESRD, or all-cause mortality in hypertensive subjects with type 2 diabetes and overt proteinuria, demonstrating a 20% relative risk reduction *vs.* placebo (p = 0.0234) and a 23% relative risk reduction *vs.* amlodipine (p = 0.0064).

In IRMA 2, subjects in the 300 mg irbesartan regimen had a 70% relative risk reduction for progressing from microalbuminuria to overt proteinuria compared with placebo. The risks for hyperkalemia appeared to be minimal and not dose related. Overall, the safety profile of irbesartan was similar to placebo in IRMA 2.

Table F translates the results of IDNT into tangible outcomes when treating 100 patients for 3 years.

Table F: Benefits of Irbesartan Treatment in Comparison with Placebo or Amlodipine

	Total Incidence of Events per 100 Patients in IDNT			Reduction in the Number of Patients with Outcome on Irbesartan	
	Placebo[b]	Irbesartan	Amlodipine	vs. Placebo	vs. Amlodipine
Double serum creatinine	27	19	28	8	9
ESRD	19	14	18	5	4
Death	16	14	13	2	-1
ESRD or doubling of serum creatinine	29	22	32	7	10

Note: The numbers in this table were derived from the Kaplan-Meier estimates of cumulative event rate at 36 months in IDNT

[a] Placebo actually represents a several classes of antihypertensive agents except RAS inhibitors and CCBs.

These data show that for 100 patients with type 2 diabetes, hypertension, and overt nephropathy treated with irbesartan, there would be 7 and 10 fewer cases of doubling of serum creatinine or development of ESRD as compared with the placebo or amlodipine groups, respectively. Based upon these results, irbesartan would provide a substantial slowing of the progression of renal disease in type 2 diabetic patients with overt proteinuria.

Risk

The risks of irbesartan in the IDNT population appear to be minimal. From a cardiovascular standpoint, there were similar cardiovascular AEs, SAEs, and deaths by body system in all three treatment groups. For the secondary cardiovascular endpoint, differences in treatment effect were not significant among all three treatment groups. Note that the placebo treatment group was not without therapy for hypertension. Since all three treatment groups had reductions in blood pressure, it is not surprising that there were no differences in cardiovascular events observed among the treatment groups. Indeed, four other trials compared different classes of antihypertensive medications in high-risk hypertensive patients. These four studies enrolled 34,781 subjects (3,302 of whom had diabetes). No significant differences were observed in cardiovascular endpoints in either the entire study population or in the diabetic hypertensive patients.

Hyperkalemia was not a problem for subjects with early diabetic renal disease like those in IRMA 2. However, in the IDNT population hyperkalemia is a potential concern. The magnitude of this concern is greatly dampened by the general appreciation among physicians that monitoring serum creatinine and serum potassium is a clinical necessity and standard of care, irrespective of drug therapy, in patients with underlying renal impairment. This is especially important for those patients with baseline impairment of renal function treated with an RAS inhibitor. The treatment-emergent AE data in IDNT indicate that hyperkalemia is a readily manageable, anticipated consequence of RAS inhibition in type 2 diabetic patients with overt proteinuria. The majority of these events were considered mild or moderate in intensity. Hyperkalemia events that the investigator classified as severe or very severe in intensity required no dose reduction, interruption, or discontinuation of study drug in one-half of these events. Thus, only a small number of events required an adjustment to dose, an interruption of drug, a discontinuation of drug or were classified as an SAE. Of note, for those events that did require discontinuation of

study drug due to hyperkalemia, the hyperkalemia was reversible upon drug withdrawal. Similarly, SAEs that required immediate intervention to correct the serum potassium were infrequent and required only routine (potassium binding resin and diuretic therapy) corrective measures.

Finally, while there was no risk for the addition of amlodipine to type 2 diabetic patients with overt proteinuria with respect to hyperkalemia, there also was no benefit for amlodipine (above that resulting from BP reduction) for renal disease compared with placebo. It is therefore the mechanism of AT_1 blockade through the use of irbesartan that has demonstrated clear benefit in patients with type 2 diabetes and overt proteinuria. Irbesartan-induced hyperkalemia in this population is an anticipated, readily manageable, consequence of RAS inhibition in type 2 diabetic patients with overt nephropathy.

9 CONCLUSIONS

- IDNT and IRMA 2, conducted in different stages of the continuum of type 2 diabetic renal disease, complement each other and provide strong evidence of the additional renoprotective benefit of AT_1 blockade with irbesartan, above and beyond that achieved with BP lowering.
- IDNT, in patients with advanced diabetic renal disease, included two comparator arms. Irbesartan was more effective than placebo ($p = 0.0234$) in reducing the risk of the primary composite endpoint consisting of doubling of serum creatinine, ESRD or all-cause mortality. Strengthening the results against placebo, irbesartan was also more effective than the active antihypertensive drug, amlodipine ($p = 0.0064$) on this composite endpoint.
- In IRMA 2, in patients at an earlier stage in the disease continuum, irbesartan 300 mg reduced the progression from incipient to overt nephropathy, as measured by urinary AER. It is well accepted that levels of urinary albumin and protein excretion predict progression to ESRD. The dose-response observed with the 150 mg and 300 mg doses of irbesartan demonstrates the consistency of the results in IRMA 2.
- In IRMA 2 an important new finding was observed in this patient population with early diabetic renal disease. At 4 weeks after study drug and other antihypertensive drugs were stopped, the urinary AER remained substantially below the baseline for subjects treated with irbesartan 300 mg. This new finding supports the view that irbesartan 300 mg affords a relative residual renoprotective effect once the drug is stopped. This finding is consistent with the view that RAS inhibition provides a fundamental change in the renal millieu in addition to and distinct from the reversible renal hemodynamic effects resulting from changes in BP alone.
- The benefit:risk for irbesartan favors its use in type 2 diabetic renal disease.

10 REFERENCES

1. United States Renal Data System, USRDS 1999 Annual Data Report. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, April, 1999.

2. World Health Organization. *The World Health Report 1997: Conquering Suffering, Enriching Humanity*. Geneva, Switzerland. 1997.

3. National Diabetes Fact Sheet, 1998. Centers for Disease Control & Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes in the United States. Revised edition. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 1998.

4. American Diabetes Association. Diabetic nephropathy: clinical practice recommendations. *Diabetes Care* 2001; 24(suppl 1):S69-S72.

5. Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertension* 1992; 19:403-418.

6. Wang S-L, Head J, Stevens L, et al. Excess mortality and its relation to hypertension and proteinuria in diabetic patients. *Diabetes Care* 1996; 19:305-311.

7. United States Renal Data System, USRDS 2001 Annual Data Report. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2001.

8. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100:1134-1146.

9. Ismail N, Becker B, Strzelczyk P, Ritz E. Renal disease and hypertension in non-insulin-dependent diabetes mellitus. *Kidney Int* 1999; 55:1-28.

10. Mogensen, CE et al, The Kidney and Hypertension in Diabetes Mellitus Fifth Edition, Kluwer Academic Publishers, 2000, p 41, 171-175, 237, 529.

11. Nelson Robert G., Peter H. Bennett, Gerald J. Beck, min Tan, William C. Knowler, William E. Mitch, Gladys H. Hirschman, Bryan D. Myers. "Development and progrression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus." New England Journal of Medicine. No. 22 1996, 335:1636-1642.

12. Biesenbach G, Janko O, Zazgornik J. Similar rate of progression in predialysis phase in type I and type II diabetes mellitus. Nephrol Dial Transplant 1994;9:1097-1102.

13. Mogensen CE, Keane WF, Bennett PH, et al. Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; 346:1080-1084.

14. Nielsen S, Schmitz A, Rehling M, Mogensen CE: The clinical course of renal function in NIDDM patients with normo- and microalbuminuria. J. Intern Med 1997; 241:133-141.

15. Osterby R, Gall M-A, Schmitz A, et al. Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetiologia* 1993; 36:1064-1070.

16. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. *Am J Kid Dis* 1996; 27:167-194.

17. Schwartz MM, Lewis EJ, Leonard-Martin T, Breyer Lewis J, Battle D and the Collaborative Study Group. "Renal pathology patterns in type 2 diabetes mellitus: relationship with retinopathy." Nephrology Dialysis Transplantation 1998;13:2547-2552.

18. Adler S, Kang S, Feld S, Cha D, Barba L, et al. Glomerular mRNAs in human type 1 diabetes: biochemical evidence for microalbuminaria as a manifestation of diabetic nephropathy. *Kidney Inter* 2001; 60:2230-2336.

19. Bakris GL, Whelton P, Weir M, et al. The future of clinical trials in chronic renal disease: outcome of an NIH/FDA/physician specialist conference. *J Clin Pharmacol* 2000; 40:1-11.

20. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kid Dis* 1999; 33:1004-1010.

21. Ruggenenti P, Gambara V, Perna A, et al. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol* 1998; 9:2336-2343.

22. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, for the Collaborative Study Group: The Effect Of Angiotensin-Converting Enzyme Inhibition On Diabetic Nephropathy. N Engl J Med 1993; 329:1456-1462.

23. Humphrey LL, Ballard DJ, Frohnert PP, et al. Chronic renal failure in non-insulin dependent diabetes mellitus. *Ann Int Med* 1989; 111:788-796.

24. Nelson RG, Knowler WC, McCance DR, et al. Determinants of end-stage renal disease in Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus and proteinuria. *Diabetiologia* 1993; 36:1087-1093.

25. Bakris GL, Copley JB, Vicknair N, et al. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 1996; 50:1641-1650.

26. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993; 118:577-581.

27. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 2000; 356:1955-1964.

28. Gall M-A, Nielsen FS, Smidt UM, Parving H-H. The course of kidney function in type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. *Diabetologia* 1993; 36:1071-1078.

29. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; 334:13-18.

30. Parving H-H. Microalbuminuria in essential hypertension and diabetes mellitus. J Hypertens 1996; 14(suppl 2):S89-S94.

31. Julius, S, Majahalme S, Palatini P. Antihypertensive Treatment of Patients with Diabetes and Hypertension. AJH;14:310S-316S.

32. Bakris GL. The effects of calcium channel blockers on renal hemodynamics, urinary protein excretion, and glomerular morphology in diabetic states. J Am Soc Neph 1991; 2:S21-S29.

33. Parving HH, Rossing P. Calcium channel blockers and the diabetic hypertensive subject. Am. J. Kid. Dis. 1993;21,#6:47-52.

34. Zatz R, Dunn BR, Meyer TW, et al. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 1986; 77:1925-1930.

35. Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? *Kidney Int* 1994; 45:861-867.

36. Ruggenenti P, Perna A, Gheradi G, Gaspari F, Benini R, Remuzzi G, on behalf of the GISEN. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. The Lancet 1998;352:1252-1256.

37. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. AM. J. Med. 1982; 72:375-380. Editorial

38. O'Donnell MP, Crary GS, Oda H, Kasiske BL, et al. Irbesartan lowers blood pressure and ameliorates renal injury in experimental non-insulin-dependent diabetes mellitus. *Kidney Int* 1997; 52(suppl 63):S218-S220.

39. Abbate M, Zoja C, Corna D, Capitanio M, Bertani T, Remuzzi G: In proressive nephropathies, overload of tubular cells with filtered proteins translates glomerular permability dysfunction into cellular signals of interstitial inflammation. J Am Soc Nephrol 1998;9: 1213-1224.

40. Wu LL, Cox A, Roe CJ, Dziadek M, Cooper ME, Gilbert RE: Transforming growth factor beta 1 and renal injury following subtotal nephrectomy in the rat: Role of the rein-angiotensin system. Kidney Int 1997;51:1553-1567.

41. Pool JL, Guthrie RM, Littlejohn T, Raskin P, Shepard AMM, Weber MA, Weir MR Wilson TW, Wright JM, Deruyter H, and Reeves R. Antihypertensive effects of irbesartan in subjects with mild to moderate hypertension. AM J Hypertens 1996; 9(4 Part 2): 152A.

42. BMS-186295: "Pilot Study of the Safety and Efficacy of Irbesartan and Hypertensive Type 2 Diabetic Subjects With Proteinuria. Statistical report on Protocol CV131-047 (DCN 910057962), Bristol-Myers Squibb Internal Report. February 12, 1997

43. Rodby R, Rohde R, Clarke W, Hunsicker L, Anzalone D, Atkins R, Ritz E, Lewis E. The irbesartan type II diabetic nephropathy trial: study design and baseline patient characteristics. *Nephrol Dial Transpl* 2000; 15:487-497.

44. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345:851-860.

45. BMS-186295: "The safety and efficacy of Irbesartan in patients with hypertension and renal insufficiency". Statistical report on protocol CV131-033 (DCN 910057962), Bristol-Myers Squibb Internal Report. July 31,1996

46. Parving H-H, Smidt UM, Hommel E, et al. Effective antihypertensive treatment postpones renal insufficiency in diabetic nephropathy. *Am J Kid Dis* 1993; 22:188-195.

47. Hypertension Detection and Follow-up Program Cooperative Group. Five-Year Findings of the Hypertension Detection and Follow-up Program. Mortality by Race-Sex and Age. *JAMA* 1979; 242:23:2572-2577.

48. Hypertension Detection and Follow-up Program Cooperative Group. Five-Year Findings of the Hypertension Detection and Follow-up Program. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension. *JAMA* 1979; 242:23:2562-2571.

49. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) Randomized Trial. *Lancet* 1999a; 353:611-616.

50. Hansson L, Hedner T, Lund-Johansen P, et al. Randomized trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; 356:359-365.

51. Hansson L, Lindholm LH, Ekbom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999b; 354:1751-1756.

52. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356:366-372.

53. Reardon, Lawrence C., Macpherson David S.: Hyperkalemia in Outpatients Using Angiotensin-Converting Enzyme Inhibitors: Arch Intern Med 1998; 158:26-32.

54. Parving H-H, Lehnert H, Brochner-Mortensen, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001a; 345:870-878.

55. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

56. World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertension* 1999; 17:151-183.

LIST OF ABBREVIATIONS

Term	Definition
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ADE	adverse drug event
AE	adverse event
AEC	Adjudication Event Committee
AER	albumin excretion rate
AII	Angiotensin II
AIIRA	Angiotensin II Receptor Antagonist
ANOVA	analysis of variance
ARB	Angiotensin II Receptor Blocker
AUC	Area under the curve
Aust./Austr.	Australia
AT_1	angiotensin II receptor subtype 1
BB	Beta Blockers
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BP	blood pressure
BSA	body surface area
CAPPP	Captopril Prevention Project
CCB	Calcium Channel Blocker
CDC	Centers for Disease Control and Prevention
CHD	Congestive Heart Disease
CI	confidence interval
Cmax	Max Concentration
CMC	Clinical Management Committee

Term	Definition
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CST	Contraction stress testing
CV	Cardiovascular
CYP	Cytochrome
dL	deciliter
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECV	extracellular fluid volume
e.g.	for example
ESRD	End Stage Renal Disease
FDA	Food & Drug Administration
GFR	glomerular filtration rate
GM	geometric mean
GMPC	geometric mean percent change
HbA_{1c}	glycosylated hemoglobin
HCTZ	Hydrochlorothiazide
HDL	high-density lipoprotein
HDS	The Hypertension in Diabetes Study Group
HF	Heart Failure
HR	Heart Rate
HTN	Hypertension
IDNT	Irbesartan Diabetic Nephropathy Trial
i.e.	in other words
INSIGHT	International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment
ITT	intent-to-treat

Term	Definition
IRMA 2	IRbesartan MicroAlbuminuria in type 2 Diabetes
K+	Potassium
kg	kilogram
L	Liter
MAP	mean arterial pressure
mEq	milliequivalent
mg	milligram
min	minute
mL	milliLiter
mmHg	Millimeter of Mercury
MRD	Maximum recommended dose
MRHD	Maximum recommended human dose
N	Number
n	sub-group of number
NDC	National Drug Code
NIDDM	Non-Insulin Diabetes Mellitus
NIH	National Institutes of Health
Q	Nordic Diltiazem study
NSAID	non-steroidal anti-inflammatory drug
NST	non-stress test
NZ	New Zealand
OCCC	Outcome Confirmation and Classification Committee
PAI_1	plasminogen activator inhibitor-1
PDR	Physician's Desk Reference
PER	Protein Excretion Rate
RAS	renin angiotensin system
RR	Relative Risk

Term	Definition
SAE	serious adverse event
SD	standard deviation
S.E.A.	South East Asia
SeSBP	seated systolic blood pressure
SeDBP	seated diastolic blood pressure
SEM	standard error of the mean
SCAT	The simvastatin/enalapril coronary atherosclerosis trial
SrCr	Serum Creatinine
std. dev.	Standard Deviation
STOP2	Swedish Trial in Old Patients with hypertension-2
UAE	Urinary Albumin Excretion
USP	Unassisted Systolic pressure
UTI	Urinary Tract Infection
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study Group
US	United States
USRDS	United States Renal Data System
VHAS	The Verapamil in hypertension and atherosclerosis study
vs.	versus
WHO	World Health Organization
Wk/wk	Week