

**MERCK**

Research Laboratories

**NDA 20-386/S-028:  
COZAAR™ (losartan potassium)**

**FDA Advisory Committee  
Background Information**

Presented to:  
Cardiovascular and Renal Drugs Advisory  
Committee

April 12, 2002

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation</b>	<b>Definition</b>
AII	Angiotensin II
AIIA	Angiotensin II receptor antagonist
ACE	Angiotensin converting enzyme
ADA	American Diabetes Association
Adj.	Adjusted
ANCOVA	Analysis of covariance
AT1	Angiotensin II (Type AT1) receptor
BL	Baseline
BP	Blood pressure
CI	Confidence interval
CT	Conventional therapy
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
Enal.	Enalapril
ESRD	End stage renal disease
Est.	Estimation
et al	And others
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GM	Geometric mean
GMR	Geometric mean ratio
HBA <sub>1c</sub>	Hemoglobin A <sub>1c</sub>
HF	Heart failure
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment Study
IDNT	Irbesartan Diabetic Nephropathy Trial
ITT	Intention-to-treat
LIFE	Losartan Intervention for Endpoint Reduction in Hypertension Study
LOS	Losartan
MAP	Mean arterial pressure
MI	Myocardial infarction
NDA	New Drug Application
NIDDM	Non-insulin dependent diabetes mellitus
PAI-1	Plasminogen activator inhibitor-1
PDGF	Platelet derived growth factor
PBO	Placebo
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system

**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT.)**

<b>Abbreviation</b>	<b>Definition</b>
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
RR	Relative risk
sCr	Serum creatinine
SD	Standard deviation
sNDA	Supplemental New Drug Application
TGF- $\beta$	Transforming growth factor-beta
TIA	Transient ischemic attack
UA	Urinalysis
UA/Cr	Urinary albumin / creatinine ratio
UAE	Urinary albumin excretion
UKPDS	United Kingdom Prospective Diabetes Study
WAES	Worldwide Adverse Experience System
1/sCr	Slope of the reciprocal of serum creatinine

## I. INTRODUCTION AND ORGANIZATION OF THE DOCUMENT

### NDA 20-386/S-028

#### Use of Losartan to Delay Progression of Renal Disease in Type 2 Diabetic Patients With Nephropathy<sup>1</sup>

##### FDA Advisory Committee Background Information

COZAAR<sup>TM2</sup> (losartan potassium) is an angiotensin II receptor (type AT<sub>1</sub>) antagonist (AIIA) that is currently approved for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents at doses of 25, 50, and 100 mg. The usual starting dose of COZAAR<sup>TM</sup> is 50 mg once daily.

The studies described in this document were designed to evaluate the renal protective effects of losartan in patients with type 2 diabetes and nephropathy (defined as the presence of proteinuria; nephropathy and proteinuria are used interchangeably throughout the document). Despite the medical need to delay the progression of renal disease in these patients, at present there are no drugs approved to delay the progression of renal disease in type 2 diabetic patients with proteinuria.

Merck Research Laboratories has submitted a supplemental NDA for the use of COZAAR<sup>TM</sup> 50 mg (starting dose) to delay progression of renal disease in type 2 diabetic patients with proteinuria. This supplemental application is based largely on the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study which was designed to investigate the renal protective effects of losartan in patients with type 2 diabetes with nephropathy. The study evaluated whether losartan reduces the number of patients experiencing the primary composite endpoint of doubling of serum creatinine, end-stage renal disease (ESRD) (need for chronic dialysis or transplantation), or death (all-cause) in patients with type 2 diabetes and nephropathy. In addition, the secondary endpoints included progression of renal disease measured as the slope of the reciprocal of serum creatinine, changes in proteinuria and cardiovascular morbidity and mortality.

As will be shown, the results of the RENAAL study provide convincing evidence that losartan delays the progression of renal disease in this patient population. Based on the data presented herein, the proposed indication for COZAAR<sup>TM</sup> is as follows:

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<sup>1</sup> Nephropathy is defined as the presence of proteinuria; nephropathy and proteinuria are used interchangeably throughout this document.

<sup>2</sup> COZAAR<sup>TM</sup> is a registered trademark of E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA; COPYRIGHT © MERCK & CO., Inc., 1995, Whitehouse Station, NJ, USA.

*Renal Protection in Type 2 Diabetic Patients with Proteinuria*

*COZAAR™ is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end-stage renal disease (need for dialysis or renal transplantation) or death.*

The consistent and significant treatment effects of losartan across multiple endpoints in the RENAAL study promote confidence in its findings and provide confirmatory evidence that the results of this large single study are scientifically sound. Separately, preclinical studies have demonstrated the renal protective effects of losartan and data from both clinical and preclinical studies have documented the efficacy of losartan in reducing proteinuria. Together, these studies provide confirmatory evidence for the renal protective effectiveness of losartan observed in RENAAL. Furthermore, the results of RENAAL confirm that the safety profile of losartan in type 2 diabetic patients with proteinuria is consistent with that presented in the currently approved U.S. prescribing information for losartan.

This document describes the clinical development program undertaken to demonstrate the safety and efficacy of losartan to delay progression of renal disease in type 2 diabetic patients with proteinuria. Following a brief synopsis of the overall document, the Comprehensive Background section reviews the natural history of diabetic nephropathy, discusses the current management of type 2 diabetic patients with nephropathy, provides the rationale for the use of losartan in this population, and describes in detail the design of the RENAAL study and the efficacy and safety data from the study. Confirmatory evidence supporting the observed renal protective benefits of losartan therapy in the RENAAL study is discussed, along with a presentation of the positive benefit/risk evaluation for losartan therapy in patients with type 2 diabetes with nephropathy. The document ends with the overall conclusions from the program.

A list of references, denoted in the text by numbers within brackets [ ], follows the conclusions. A copy of the currently approved U.S. labeling for COZAAR™ is enclosed as Appendix 1.

The Synopsis that immediately follows distills this document into a comprehensive summary intended to orient the reader to the key elements of this document. The Synopsis is cross-referenced to the Comprehensive Background where appropriate.

## II. SYNOPSIS

### Use of Losartan to Delay Progression of Renal Disease in Type 2 Diabetic Patients With Nephropathy<sup>3</sup>

#### FDA Advisory Committee Background Information

##### 1. Introduction and Background (See Section III.1.)

Diabetes mellitus is one of the most common diseases worldwide [1]. It is the fourth or fifth leading cause of death in most developed countries and there is strong evidence that its prevalence is increasing [2]. It has been estimated that the total number of diabetic patients worldwide will increase from 123 million (1997) to 220 million by the Year 2010 [2], with ~97% being type 2 diabetic patients. Diabetic patients commonly develop renal and cardiovascular disease, which can result in considerable morbidity and mortality. One of the most devastating complications of diabetes is nephropathy, which occurs in 10 to 40% of this population [2]. Thus, the number of patients with type 2 diabetes and nephropathy is expected to continue to rise, increasing the burden of this disease on healthcare systems worldwide. [3; 2].

However, at present there are no approved drugs in the U.S. for delaying the progression of renal disease in type 2 diabetic patients with nephropathy.

In 1994, the FDA granted a claim for the angiotensin converting enzyme (ACE) inhibitor CAPOTEN<sup>TM</sup><sup>4</sup> (captopril) for treatment of type 1 diabetic patients with nephropathy (proteinuria >500 mg/day) and retinopathy. However, because there were no data in type 2 diabetic patients with nephropathy, the FDA did not grant a claim for CAPOTEN<sup>TM</sup> (captopril) in this patient population [4]. To date, no renal outcomes data with an ACE inhibitor in type 2 diabetic patients with nephropathy are available. Despite this, treatment guidelines recommending the use of ACE inhibitors in these patients were published in the 1990's [5; 6; 7]. In the absence of outcomes data in type 2 diabetic patients, these guidelines were used to support the concept that ACE inhibitors (in general) would provide renal protection in both type 1 and type 2 diabetic patients. These recommendations also relied upon reductions of microalbuminuria or proteinuria by ACE inhibitors in type 2 diabetic patients as evidence of renal protection [8; 9].

Merck Research Laboratories has submitted a supplemental NDA (sNDA) for the use of COZAAR<sup>TM</sup> 50 mg (starting dose) to delay progression of renal disease in type 2 diabetic patients with proteinuria. This supplemental application is largely based on the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study findings.

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<sup>3</sup> Nephropathy is defined as the presence of proteinuria; nephropathy and proteinuria are used interchangeably throughout this document.

<sup>4</sup> CAPOTEN<sup>TM</sup> is a registered trademark of the Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.

COZAAR™ (losartan potassium), an angiotensin II receptor (type AT<sub>1</sub>) antagonist, is approved in the U.S. for the treatment of hypertension.

The usual starting dose of COZAAR™ is 50 mg once daily (25 mg and 100 mg are also available) and COZAAR™ may be used alone or in combination with other antihypertensive agents. Based on the data presented in our sNDA and outlined in this document, the proposed indication for COZAAR™ is as follows:

*Renal Protection in Type 2 Diabetic Patients with Proteinuria*

*COZAAR™ is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end-stage renal disease (need for dialysis or renal transplantation) or death.*

Of note, the most recently updated guideline, the 2002 American Diabetes Association (ADA) Position Statement, recommends angiotensin II receptor antagonists for the initial treatment of hypertensive type 2 diabetic patients with nephropathy, based on the very recent results of the losartan RENAAL Trial [10] and Irbesartan Diabetic Nephropathy Trial (IDNT) [11].

Prior to initiation of the RENAAL study, renal outcome data in patients with type 2 diabetes with nephropathy did not exist. However, tight blood pressure control has been accepted as an important therapeutic goal to reduce the risk of macrovascular and microvascular complications in type 2 diabetes. Furthermore, blockade of angiotensin II (AII) may be more effective in delaying the progression of diabetic nephropathy than other antihypertensive therapies [12]. Preclinical studies have provided evidence that angiotensin II (AII) may play an important role in the progression of glomerular injury through both hemodynamic mechanisms, such as regulating intraglomerular pressure, and nonhemodynamic mechanisms, such as tubulo-interstitial injury, mesangial proliferation and expansion, production of growth factors (e.g., transforming growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor [PDGF]), and superoxide production [13; 14; 15; 16]. Therefore, it has been postulated that blockade of AII would offer renal protection beyond that expected by reducing systemic blood pressure alone.

## **2. The Losartan RENAAL Study**

### **2.1 Overview of Study Design (See Section III.2.1)**

The RENAAL study was a placebo-controlled, double-blind, multinational, randomized trial of 1513 patients with type 2 diabetes with nephropathy designed to investigate the long-term renal protective effects of using losartan to block the angiotensin II receptor (type AT<sub>1</sub>). RENAAL also included pre-specified analyses to specifically address whether blockade of the AT<sub>1</sub> receptor by losartan would offer renal protection beyond that attributable to blood pressure reduction alone.

The primary hypothesis was that long-term treatment with losartan (+/- conventional anti-hypertensive therapy) compared to placebo (+/- conventional anti-hypertensive therapy) in patients with type 2 diabetes with nephropathy would increase the time to the first

event of the combined endpoint of doubling of serum creatinine, end-stage renal disease (ESRD) (need for chronic dialysis or transplantation), or death.

In order to conclusively demonstrate that the treatment effect on progression of renal disease was beyond that attributable to blood pressure efficacy alone, tight blood pressure control, with equivalent blood pressure control between the 2 treatment groups, was important. To achieve this goal, treatment with losartan or placebo was on a background of conventional antihypertensive therapy (diuretics, calcium channel blockers, beta blockers, alpha blockers, and/or centrally acting agents, excluding ACE inhibitors and AIIAs).

The secondary hypotheses were that losartan (+/- conventional anti-hypertensive therapy) would (a) slow the rate of loss of renal function, as measured by the reciprocal of serum creatinine; (b) reduce proteinuria compared to placebo during the course of the study; and (c) increase the time to first event and decrease the incidence of cardiovascular morbidity/mortality (defined as myocardial infarction (MI), stroke, first hospitalization for heart failure (HF) or first hospitalization for unstable angina, revascularization (coronary or peripheral), or cardiovascular (CV) deaths) compared to placebo (+/- conventional anti-hypertensive therapy).

To be included in the study, patients had to have type 2 diabetes defined as: (1) diabetes diagnosed after the age of 30; (2) insulin not required within the first 6 months of diagnosis; and (3) no history of diabetic ketoacidosis. Patients between the ages of 31 and 70, with a serum creatinine between 1.3 (1.5 for males >60 kg) and 3.0 mg/dL and a first morning urinary albumin/creatinine ratio (UA/Cr) of  $\geq 300$  mg/g (or a 24-hour urine total protein of >500 mg/day) were eligible to participate in the study. Patients could be normotensive or hypertensive.

Patients with type 1 diabetes were excluded from the study. In general, patients with known high risk for cardiovascular disease who may have required ACE inhibitor therapy were excluded from participation. A history of myocardial infarction or coronary artery bypass graft surgery within 1 month prior to study start, cerebral vascular accident or percutaneous transluminal coronary angioplasty within 6 months prior to study start, and history of transient ischemic attacks (TIA) within the year prior to study start precluded a patient from participation. Another key exclusion criterion was a known history or current diagnosis of nondiabetic renal disease such as chronic glomerulonephritis or polycystic kidney disease. Patients with uncontrolled diabetes, i.e., hemoglobin A<sub>1c</sub> (HBA<sub>1c</sub>) >12%, were also excluded.

Patients with heart failure not requiring ACE inhibitors were initially allowed to enroll. However, early in the study several of these patients discontinued study therapy due to heart failure adverse experiences and were placed on other therapies to treat their heart failure. This observation resulted in a protocol amendment that excluded all patients with heart failure from randomization (86 patients with heart failure [43 patients in each treatment group] were randomized prior to implementation of the amendment and are included in all analyses).

After a 6-week screening period, patients were randomized to either losartan 50 mg once daily or placebo. At the onset of the screening phase, patients on ACE inhibitors or AIIAs were taken off these therapies and placed on conventional antihypertensive therapy, if needed, to control blood pressure. Because proteinuria has been demonstrated to be an independent risk factor for progression of renal disease in type 1 diabetic and nondiabetic patients [17; 18], patients were stratified by baseline proteinuria (UA/Cr <2000 mg/g or UA/Cr ≥2000 mg/g) at randomization. Study therapy was added in a double-blind fashion to each patient's usual antihypertensive therapy (excluding ACE inhibitors and angiotensin II antagonists). Study medication was increased to losartan 100 mg once daily (or matching placebo) after 4 weeks if the patient's trough sitting blood pressure did not reach the goal of <140/90 mm Hg. Thereafter, at any point during the study, the patient's usual open-label antihypertensive drug therapy could be increased, or any of the following open-label antihypertensive agents (diuretic, calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent) could be added at the discretion of the investigator to obtain the target blood pressure (excluding ACE inhibitors and angiotensin II antagonists).

Important aspects of the conduct of the RENAAL study to bear in mind are that the protocol required patients to continue study therapy regardless of whether an endpoint was reached. If patients discontinued study therapy, they were required to return for regular clinic visits to ensure that all primary and secondary endpoints were captured. If patients could not return to clinic after discontinuation, regular telephone contact was instituted to follow those patients for the hard outcomes of ESRD and death. Note that doubling of serum creatinine and cardiovascular morbidity outcomes were not collected during telephone follow-up. As a result of the rigorous procedures used for patient follow-up after discontinuation, there were no patients lost to follow-up, (ESRD and/or death status was ascertained on all patients randomized).

## **2.2 Independent Oversight Committees (See Section III.2.1.2)**

Three independent oversight committees were involved in the conduct of RENAAL. The Steering Committee was responsible for staying abreast of current research in the field, continually reevaluating the ethical context of the trial, and making potential decisions regarding continuation of the study. An unblinded Data Safety Monitoring Board (DSMB) monitored the ongoing safety of the patients and interim efficacy and safety results. Additionally, an independent Endpoint Adjudication Committee, consisting of 3 nephrologists, 2 cardiologists and 1 endocrinologist, was responsible for adjudicating every potential primary endpoint and secondary cardiovascular endpoint by a consensus process. No committee member was on more than one committee. Both the Steering and Endpoint Committees remained blinded throughout the study.

The study was planned to be completed in Mar-2002. This planned termination date was based on 3.5 years of follow-up of the last patient randomized, preceded by a 2-year enrollment period, yielding an expected average 4.5 years of follow-up (required to achieve 95% power). On 10-Feb-2001, the Steering Committee voted unanimously to end the RENAAL study prior to its planned completion of Mar-2002; its decision was

based on increasing evidence suggesting that ACE inhibitors, which were excluded by design from RENAAL, may be effective in reducing cardiovascular events in patients with cardiovascular risk factors and/or diabetes with renal impairment [19]. The new data that prompted termination of RENAAL was from a subset of patients from the Heart Outcomes Prevention Evaluation (HOPE) study [19; 20].

### **2.3 Summary of Statistical Methods (See Section III.2.2)**

The primary analyses of the primary composite endpoint of doubling of serum creatinine, ESRD, or death, and the secondary composite endpoint of cardiovascular events were based on the intention-to-treat (ITT) principle; all randomized patients were included from randomization through the study termination date regardless of compliance with study therapy. Prespecified supportive analyses included analyses of components of the composites, and 2 sensitivity analyses (per protocol and lagged censoring) intended to reduce the impact of study drug discontinuation on the intention-to-treat results. The per-protocol analysis excluded patients who violated the inclusion/exclusion criteria (6 patients) and censored patients' data 14 days after they permanently discontinued study therapy, while the 6-month lagged censoring analysis included all randomized patients and censored patients' data 6 months after permanent discontinuation of study therapy. A Cox regression model, including baseline level of proteinuria as a stratification factor (UA/Cr <2000 or UA/Cr ≥2000 mg/g) and geographic region (i.e., indicator variables for 4 regions) as a covariate, was used to determine the hazard ratio (losartan relative to placebo) and 95% confidence interval. (Post hoc analyses included the urine albumin/creatinine ratio as an additional continuous covariate.) The risk reduction was calculated as 100 percent x (1-hazard ratio). In analyses of nonfatal endpoints, patients who died were considered censored: that is, these patients were considered to be at risk of a nonfatal event only through their date of death. Event curves were based on the Kaplan-Meier procedure.

Due to one interim efficacy analysis and periodic interim safety analyses during the course of the study by the DSMB, a critical p-value of 0.048 was required for the primary hypothesis. For other outcomes, a p-value of less than 0.05 was considered to indicate statistical significance.

### **2.4 Baseline Characteristics and Patient Disposition (See Section III.2.3 and Section III.2.4)**

The study enrolled 1513 patients, of which 63.2% were male and 36.8% were female, with a mean age of 60 years. For the overall population, mean serum creatinine, urinary albumin:creatinine ratio, and HBA<sub>1c</sub> were 1.9 mg/dL, 1808 mg/g, and 8.5%, respectively. Baseline characteristics generally were similar between the 2 treatment groups. However, despite stratification by baseline proteinuria (UA/Cr <2000 or UA/Cr ≥2000 mg/g), there was a difference in mean baseline proteinuria (a known risk factor for the progression of renal disease) of ~130 mg/g, with the losartan group having the higher value (1873 mg/g in losartan versus 1743 mg/g in placebo). While nonsignificant, this difference has implications for the evaluation of losartan's effects and will therefore be discussed later in this document. More importantly, there was an imbalance in the

distribution of patients in the  $\geq 2000$  mg/g stratum of proteinuria, a difference that is discussed further in Section III, Comprehensive Background, Section 2.5.1.1.

The average duration of follow-up (mean time from randomization through February 10, 2001) was 3.4 years. No patients were lost to follow-up; outcomes of ESRD and/or death information were available in all randomized patients.

Because of the long duration of the study, and the high number of patients with comorbid conditions, it was expected that many patients would discontinue study therapy. In fact, the overall number of patients who discontinued study drug prior to a primary event (443, 29.3%) is consistent with the pre-specified estimated discontinuation rate (prior to primary event) of 13% per year (~30% cumulative rate). Of the 751 patients in the losartan group and 762 patients in the placebo group, 202 (26.9%) and 241 (31.6%) patients, respectively, discontinued from study drug prior to reaching a primary endpoint; while 142 (18.9%) and 162 (21.2%) patients, respectively, discontinued study drug after reaching a primary event.

The protocol required that patients who discontinued from study therapy be followed in the clinic (clinic follow-up) every 3 months until the end of the study (10-Feb-2001). In these patients, all primary and secondary endpoint information was collected, as if they were still on study drug. Of the 202 patients in the losartan group and 241 in the placebo group who discontinued prior to reaching a primary endpoint, 73 (36%) and 93 (39%), respectively, were followed in clinic.

For those patients in whom clinic follow-up was not feasible, regular telephone contact was performed to determine whether the patient had reached ESRD and/or death. Once in telephone contact, doubling of serum creatinine and cardiovascular morbidity outcomes were not collected. Of the 202 patients in the losartan group and 241 in the placebo group who discontinued study drug prior to reaching a primary endpoint, 129 (64%) and 148 (61%), respectively, were followed by telephone.

It is important to note that patients could have been followed in the clinic for a period of time, then by telephone until study completion. Because there were a variety of scenarios with regard to the mode of follow-up after discontinuation, the average patient years of follow-up was calculated to provide a more accurate reflection of the follow-up phase. With regard to clinic follow-up, average patient years of follow-up were 173 in the losartan group and 234 patient years of clinic follow-up in the placebo group. With regard to telephone follow-up, average patient years of follow-up were 122 in the losartan group and 177 in the placebo group. In both treatment groups, patients were in clinic follow-up a longer period of time compared to telephone follow-up. It is important to note that all discontinued patients regardless of the mode of follow-up were followed for ESRD and death outcomes.

## **2.5 Key Efficacy Results (See Section III.2.5)**

In the text below, primary and secondary renal efficacy results will be discussed first, followed by discussion of the secondary cardiovascular outcomes.

### **2.5.1 Primary Composite Endpoint (See Section III.2.5.1)**

By the intention-to-treat analysis, the primary composite endpoint was reached in 327 patients (43.5% of total 751 patients) given losartan versus 359 (47.1% of total 762 patients) given placebo. Losartan treatment resulted in a risk reduction of 16.1% ( $p=0.022$ ). The 95.2% confidence interval (corresponding to the 4.8% significance level for the primary analysis) for the risk reduction was (2.3%, 27.9%). Furthermore, 2 pre-defined supportive analyses were conducted, a 6-month lagged-censoring approach which included all randomized patients and censored data on 10-Feb-2001, or 6 months after study drug discontinuation, whichever came first, and a per-protocol approach which excluded protocol violators and censored data on 10-Feb-2001, or 14 days after study drug discontinuation, whichever came first. Both supportive analyses confirmed the results of the primary analysis. By the 6-month lagged censoring analysis, losartan treatment resulted in a risk reduction of 18.8% ( $p=0.017$ ) and by the per-protocol analysis, losartan conferred a 22.5% ( $p=0.007$ ) risk reduction. As compared with the results from the ITT approach, the risk reductions were larger for the lagged censoring and per-protocol approaches, suggesting that discontinuation of study therapy diminished losartan's treatment effect.

As will be discussed in Section III, the Comprehensive Background section, baseline proteinuria in RENAAL was a strong predictor for primary events. Despite stratification of this important prognostic variable (UA/Cr  $<2000$  or  $\geq 2000$  mg/g), there was an imbalance in baseline mean proteinuria between the 2 treatment groups (1873 mg/g in losartan versus 1743 mg/g in placebo). More importantly, there was an imbalance in the distribution of patients in the  $\geq 2000$  mg/g stratum of proteinuria, a difference that is discussed further in Section III, Comprehensive Background, Section 2.5.1.1. To explore the effect of this imbalance, it was reasonable to adjust post hoc the primary composite endpoint using baseline proteinuria as a continuous covariate. This correction increased the magnitude and significance of the risk reduction for the primary composite endpoint (22.2%;  $p=0.001$ ).

### **2.5.2 Components of the Primary Composite Endpoint (See Section III.2.5.1)**

Examination of the components of the primary composite endpoint using the ITT approach indicates that the risk of doubling of serum creatinine concentration was reduced by 25.3% ( $p=0.006$ ) and the risk of ESRD was reduced by 28.6% ( $p=0.002$ ) in patients treated with losartan. Approximately 20% of patients died, with no difference between the 2 treatment groups ( $p=0.884$ ). Losartan reduced the risk of the combined component endpoint of ESRD or death by 19.9% ( $p=0.009$ ), and the combined component endpoint of ESRD or doubling of serum creatinine concentration by 21.0% ( $p=0.010$ ). The prespecified supportive 6-month lagged censoring and per-protocol approaches showed that losartan produced a stronger treatment effect and a greater risk

reduction than in the intention-to-treat analysis for every component of the primary composite endpoint, again suggesting that discontinuation of losartan diminished losartan's treatment effect. To explore the effect of the imbalance in baseline proteinuria, it was reasonable to perform a post hoc analysis of the combined component of ESRD or death, using baseline proteinuria as a continuous covariate. This correction increased the magnitude and significance of the risk reduction for the primary endpoint to  $p < 0.001$ .

### **2.5.3 Impact of Blood Pressure Control on Primary Endpoint (See Section III.2.5.1.2)**

Blood pressure was aggressively treated with standard antihypertensive drugs in all patients in RENAAL in order to achieve comparable blood pressure control in both treatment groups. Overall, patients assigned to losartan achieved a slightly lower mean arterial pressure (MAP) (~2 mm Hg) compared to patients assigned to placebo. During the first year, the difference in MAP between losartan and placebo was consistently >2 mm Hg; thereafter, differences between treatment groups were small over the course of the study.

Although blood pressure control is important in renal protection, the beneficial effects on renal protection observed with losartan in RENAAL were found to be beyond those attributable to reduction in blood pressure alone, based on a pre-defined analysis that adjusts for achieved MAP over the course of the trial. This finding is further supported by the results of IDNT, in which the calcium channel blocker, amlodipine, and the AIIA, irbesartan, lowered blood pressure to nearly identical levels, yet irbesartan demonstrated a beneficial effect on renal protection, whereas amlodipine did not [11].

### **2.5.4 Rate of Loss of Renal Function (Slope of 1/Cr) (See Section III.2.5.2.1)**

The rate of loss of renal function measured by the slope of the reciprocal of serum creatinine (1/sCr) over time is commonly used by clinical nephrologists to predict long-term renal outcome and time to ESRD [21]. The importance of this analysis is that it takes into consideration all patients, not just those who had a renal event. As compared with placebo, treatment with losartan reduced the rate of loss in renal function by 18.5% ( $p = 0.011$ ).

This secondary outcome demonstrated that losartan significantly reduced the rate of progression of renal disease, and underscores the consistency of the beneficial effect of losartan on renal protection in this population.

### **2.5.5 Reduction in Proteinuria (See Section III.2.5.2.2)**

Reduction of proteinuria has been a therapeutic goal in the treatment of diabetic nephropathy among practicing nephrologists. In RENAAL, proteinuria (urine albumin to urine creatinine ratio from a first morning void), a widely accepted marker of progressive glomerular injury, was reduced within 3 months of initiation of losartan compared to placebo and the reduction was sustained over the course of the study. Overall proteinuria was significantly reduced by 34.3% with losartan ( $p < 0.001$ ).

Notably, after the pre-specified adjustment for achieved blood pressure over the course of the trial, the reductions in proteinuria with losartan remained significant.

### **2.5.6 Secondary Composite Endpoint of Cardiovascular Morbidity and Mortality (See Section III.2.5.2.3)**

For the secondary endpoint of cardiovascular morbidity and mortality, there was no statistically significant difference between losartan and placebo. It is important to note that the RENAAL study was powered to evaluate renal outcomes. Neither the sample size nor the duration of the study were designed to assess cardiovascular outcomes. Since type 2 diabetic patients are at risk for cardiovascular events, prespecified cardiovascular morbidity and mortality events were recorded, adjudicated, and analyzed as a secondary comparison.

By the intention-to-treat analysis, the composite endpoint of cardiovascular morbidity and mortality was reached in 247 patients (32.9% of total 751 patients) given losartan versus 268 patients (35.2% of total 762 patients) given placebo. Losartan treatment resulted in an estimated reduction of risk of 9.6% ( $p=0.253$ ) with 95% confidence interval (-7.5%, 24.0%). For the components of the combined cardiovascular morbidity and mortality endpoint, there were no significant differences in the effect of losartan versus placebo, with one exception: first hospitalization for heart failure (89 patients with losartan versus 126 patients with placebo), for which the risk was reduced by 31.6% ( $p=0.006$ ).

Based on discussions that occurred during the 17-Jan-2002 FDA Cardio-Renal Advisory Committee Meeting, a post hoc analysis was performed to ascertain the effect of losartan treatment on the composite of the primary (renal) endpoint and the secondary (cardiovascular) endpoints. The results of this analysis show that the losartan treatment effect persists, with a risk reduction of 16.6% ( $p=0.008$ ). Furthermore, a greater treatment effect is observed in an analysis (post hoc) of the composite of the hard endpoints of ESRD, MI, stroke, or death (whichever occurred first) (risk reduction: 21.2%;  $p=0.003$ ). The results of this analysis indicate that the benefits of losartan on renal outcomes were not at the expense of an increased risk of cardiovascular events, and are supportive of an overall benefit of losartan treatment.

Confirmation of the impact of losartan on cardiovascular outcomes must await the availability of results from larger clinical trials that were designed to evaluate cardiovascular outcomes, particularly the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, which includes diabetic patients [22].

### **2.5.7 Analysis of Primary Composite Endpoint by Baseline Subgroups (See Section III.2.5.3)**

The primary composite endpoint was explored in subgroup analyses using the intention-to-treat approach. These analyses explored whether or not the effect of losartan compared to placebo was consistent in 18 predefined subgroups of patients at baseline. There were no significant interactions (nominal  $p$ -value  $\geq 0.10$ ) observed for: age, gender, race, body mass index, duration of hypertension, sitting systolic blood pressure, prior dihydropyridine use, prior insulin use, prior ACE inhibitor or angiotensin II use,

smoking, or pre-defined levels of baseline proteinuria (UA/Cr), serum creatinine, hemoglobin, HBA<sub>1c</sub>, serum albumin, serum uric acid, or total cholesterol.

Without any adjustment for multiplicity, only the apparent interaction between region and treatment was statistically significant ( $p=0.044$ ). However, it is not unexpected, when testing as many as 18 subgroups, that one subgroup would have a significant interaction with treatment by chance alone. It is important to note that the treatment effect favored losartan in all regions. Furthermore, there was no significant treatment-by-region interaction for the combined component of ESRD or death.

### **2.5.8 Summary of RENAAL Efficacy Results (See Section III.2.5.8)**

Overall, treatment with losartan resulted in a significant delay in the progression of renal disease in type 2 diabetic patients with proteinuria, as evidenced by 16.1% ( $p=0.022$ ) risk reduction of experiencing the primary composite endpoint of doubling of serum creatinine, ESRD, or death. The validity and importance of this observation is supported by the significant risk reductions also observed for ESRD (28.6%,  $p=0.002$ ) and ESRD or death (19.9%,  $p=0.009$ ) in patients treated with losartan. Furthermore, to explore the effect of the imbalance in baseline proteinuria observed in RENAAL, the primary composite endpoint was adjusted post hoc by baseline proteinuria as a continuous covariate, which increased the risk reduction (22.2%;  $p=0.001$ ). Likewise, post hoc adjustment of the combined component of ESRD or death by baseline proteinuria as a continuous covariate increased the risk reduction (25.7%;  $p<0.001$ ).

Losartan significantly reduced both proteinuria (34.3%,  $p<0.001$ ) and the rate of loss in renal function (18.5%,  $p=0.011$ ); these data are supportive of the results observed for the primary composite endpoint.

For the secondary endpoint of cardiovascular morbidity and mortality, there was no statistically significant difference between losartan and placebo. A significant treatment effect with losartan was observed in a post hoc analysis of the composite of the hard endpoints of ESRD, MI, stroke, or death (whichever occurred first) (risk reduction: 21.2%;  $p=0.003$ ). The results of this analysis indicate that the benefits of losartan on renal outcomes were not at the expense of an increased risk of cardiovascular events and are supportive of an overall benefit of losartan treatment.

### **2.6 Summary of Safety Results (See Section III.2.6)**

In this population of type 2 diabetic patients with underlying kidney disease, many had complications of diabetes and other progressive, co-morbid conditions. Also, many of the patients were taking multiple drugs for those conditions, which would have predisposed them to an increased incidence of adverse experiences, especially over the extended time-frame of the study. The extent of exposure to losartan was a mean of 913 days, and the duration of exposure to placebo was mean of 845 days.

The overall incidence of patients reporting at least one clinical adverse experience, regardless of relationship to study drug, was high and similar between losartan and placebo (95.3 and 95.7%, respectively). Overall, the incidence of patients reporting at

least one laboratory adverse experience was 49.5% in the losartan group and 42.4% in the placebo group. There were more drug-related laboratory adverse experiences in the losartan group due to more reports of hyperkalemia. Overall reports of hyperkalemia as a laboratory adverse experience were 20% versus 10% for losartan and placebo, respectively; of these, 12% of the losartan adverse experiences and 5% of the placebo adverse experiences were considered drug related, which is not unexpected in this patient population.

According to the Data Analysis Plan, formal statistical testing was performed for 6 adverse experiences of prespecified special interest, based on the disease history of this population (anemia, acute renal failure, hypo- / hyperkalemia, hypo- / hyperglycemia). There were no statistically significant differences between the 2 treatment groups for anemia, acute renal failure, hyperglycemia, or hypoglycemia.

Patients in this study were at increased risk of hyperkalemia by virtue of their diabetes and underlying kidney disease, as evidenced by the high incidence of hyperkalemia in the placebo group. The risk of hyperkalemia increases when a drug that blocks the renin-angiotensin-aldosterone system is administered. As expected, hyperkalemia occurred significantly more with losartan compared to placebo ( $p < 0.001$ ) and hypokalemia occurred more with placebo ( $p = 0.013$ ). Discontinuations due to hyperkalemia were small and comparable between losartan ( $n = 10$ ) and placebo ( $n = 6$ ) indicating that hyperkalemia with losartan is manageable. In RENAAL, no deaths were attributed to hyperkalemia. Overall, losartan was generally well tolerated in the RENAAL study. Furthermore, the results of RENAAL confirm that the safety profile of losartan in type 2 diabetic patients with proteinuria is consistent with that presented in the currently approved U.S. product circular for losartan.

## **2.7 Summary of the RENAAL Study (See Section III.2.7)**

In summary, the RENAAL Study demonstrated that:

1. Losartan is renal protective by delaying the onset of the primary composite endpoint of doubling of serum creatinine, ESRD (need for chronic dialysis or transplantation), or all-cause mortality.
2. Losartan reduces the rate of decline in renal function as measured by the slope of  $1/sCr$ .
3. Losartan reduces proteinuria.
4. The beneficial effects of losartan on the primary endpoint and proteinuria are beyond that attributable to its beneficial effect on blood pressure.
5. Losartan appears to offer renal protection in all subgroups of patients.
6. There is no significant difference on cardiovascular morbidity and mortality with losartan compared to placebo.
7. Losartan is generally well tolerated in this population of type 2 diabetic patients with proteinuria. As expected with AIIAs and other agents that interrupt the RAAS,

losartan is associated with a higher incidence of hyperkalemia compared to conventional therapy.

### **3. Confirmatory Evidence and Benefit/Risk Evaluation (See Section III.3.)**

#### **3.1 Confirmatory Evidence (See Section III.3.1)**

Regulatory decisions sometimes must be made using information primarily from a single study. This is often the case for large outcomes trials, when ethical and practical considerations make it impossible and/or impractical to conduct a second study to provide independent substantiation of the first study. In such cases, it is important to consider what supportive and confirmatory evidence may be available to provide reassurance that the results of the single study are scientifically sound and not due to chance alone. Such evidence may come from within the single study and/or from sources external to the main study.

Confirmatory evidence from data within the RENAAL study as well as data external to the RENAAL study will be presented below, demonstrating the effectiveness of losartan on the progression of renal disease.

##### **3.1.1 Confirmatory Evidence Within RENAAL (See Section III.3.1.1)**

Looking within the RENAAL study, the consistent and significant treatment effects across multiple outcomes (the primary composite endpoint, ESRD, ESRD or death, proteinuria, rate of loss of renal function) in the study promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound.

Perhaps most persuasive are the findings on the relationship between baseline proteinuria and risk for a primary composite event. Because of the known effects of proteinuria on renal progression in type 1 diabetics and non-diabetics, RENAAL patients were stratified at randomization based on baseline proteinuria, i.e., UA/Cr <2000 mg/g and UA/Cr  $\geq$ 2000 mg/g. Despite this stratification, by chance there was a slight imbalance in baseline proteinuria between the 2 treatment groups (1873 mg/g in losartan group, 1743 mg/g in placebo group). More importantly, there was an imbalance in the distribution of patients in the  $\geq$ 2000 mg/g stratum of proteinuria. This imbalance in distribution mainly occurred in the  $\geq$ 4000 mg/g category, where there were 21 more losartan patients compared to placebo patients (n=92 losartan, n=71 placebo). After correcting for this imbalance, the relative risk of patients in the losartan group experiencing the primary composite endpoint increased from a 16.1% risk reduction (p=0.022) to a 22.2% risk reduction (p=0.001). In addition to demonstrating that even small differences in baseline proteinuria are associated with large differences in risk, these results provide compelling confirmatory evidence for the renal protective benefits of losartan in type 2 diabetic patients with proteinuria.

In addition, 2 pre-specified supportive analyses that accounted for patients that discontinued study drug confirmed the results of the primary analysis, and also indicated a stronger treatment effect of losartan on the primary composite endpoint (per-protocol: risk reduction=22.5%, p=0.007; 6-month lagged censoring: risk reduction=18.8%,

p=0.017) and ESRD or death (per-protocol: risk reduction=32.0%, p=0.001; 6-month lagged censoring: risk reduction=26.0%, p=0.003).

### **3.1.2 Confirmatory Evidence from Studies External to RENAAL (See Section III.3.1.2)**

#### **3.1.2.1 Preclinical Studies (See Section III.3.1.2.1)**

Losartan has been shown to offer renal protection in several different experimental models of renal disease in rats. In nondiabetic, 5/6 nephrectomized rats, Lafayette et al. [23] demonstrated that 10-week administration of pharmacological doses of losartan were renal protective, in that greater reductions in glomerulosclerosis, glomerular transcapillary pressure, and proteinuria were observed in losartan-treated rats than in rats treated with triple antihypertensive therapy (i.e., reserpine, hydralazine, and hydrochlorothiazide) [23]. This demonstrated that the antiproteinuric and renal protective effect of losartan were beyond that attributable to its antihypertensive efficacy alone. Likewise, in long-term experimental diabetic models, losartan has been shown to attenuate glomerulosclerosis and urinary protein. Remuzzi et al. have shown that after a 1-year observation period, proteinuria in losartan-treated diabetic rats was significantly less than that seen in diabetic control rats, and comparable to that of normal control rats [24]. More importantly, glomerulosclerosis was prevented by specific AII blockade with losartan in these animals [24]. These data were confirmed in a long-term 1-year Merck study, where glomerulosclerosis and proteinuria were significantly reduced in losartan-treated diabetic rats compared to diabetic control rats [25].

These animal studies have demonstrated that losartan exerts renal protective effects and reduces proteinuria in experimental nondiabetic and diabetic renal disease, and provide confirmatory evidence for the renal protection benefits of losartan therapy seen in the RENAAL study.

#### **3.1.2.2 Clinical Studies (See Section III.3.1.2.2)**

Following initiation of the RENAAL study, several studies were conducted with losartan demonstrating its antiproteinuric effects in diabetic patients with proteinuria. In type 1 and type 2 diabetic patients with microalbuminuria, losartan has consistently demonstrated efficacy in reducing albuminuria. Andersen et al. compared the renal and hemodynamic effects of losartan to enalapril in type 1 diabetic patients [26]. The study demonstrated that losartan 100 mg once daily is as effective as enalapril 20 mg once daily in reducing albuminuria and blood pressure in this group of patients [26]. Chan and colleagues reported that treatment of type 2 diabetic patients with losartan for 12 weeks reduced albuminuria by 24% from baseline when compared to the calcium channel blocker, felodipine (11%) [27]. Interestingly, felodipine was associated with a greater degree of blood pressure reduction compared to losartan (p=NS), but reduced albuminuria to a lesser degree. Similar results were observed in an unpublished study in microalbuminuric type 2 diabetic patients comparing losartan to amlodipine [28]. Following 12 weeks of treatment, blood pressure was significantly lowered in both groups, but to a greater extent with amlodipine. Despite the larger reduction in blood

pressure, albumin excretion was unaffected by amlodipine treatment, whereas losartan was associated with a significant decrease in albumin excretion relative to baseline [28]. This finding suggests a disassociation between the antiproteinuric and antihypertensive effects of these compounds.

Additional studies assessing the antiproteinuric effects of losartan in type 2 diabetic patients have followed. de Pablos Velasco and Martin reported significant reductions in urinary albumin excretion (UAE) compared to baseline in both losartan and diltiazem groups after 12 weeks of therapy [29]. In more recent open-label studies, losartan again has been shown to effectively reduce albumin excretion in type 2 diabetic patients with microalbuminuria [30; 31]. Lozano et al. have demonstrated that after 6 months of therapy, losartan induced a 43% reduction in UAE [30]. In a smaller, shorter-term study, Esmatjes et al. reported a 33% decrease in UAE after 8 weeks of losartan treatment [31].

In a longer-term (1-year duration) double-blind study, Lacourciere et al. have demonstrated that daily treatment of type 2 diabetic patients with losartan 50 mg significantly reduced proteinuria relative to baseline, and similarly to an ACE inhibitor. Furthermore, by end of study, both losartan and ACE inhibition had similar changes in glomerular filtration rate [32].

In summary, the evidence of effectiveness of losartan in renal protection from both within RENAAL and external to RENAAL, provide convincing confirmatory evidence that the observed results are scientifically sound.

### **3.2 Benefit/Risk Evaluation (See Section III.3.2)**

Currently, there are no approved agents in the U.S. to delay progression of renal disease in type 2 diabetes with proteinuria. The results of the RENAAL study have clearly established that losartan provides renal protection in patients with type 2 diabetes and proteinuria by delaying the progression of renal disease. Compared to placebo, losartan significantly reduced the incidence of, and delayed the time to, the primary composite endpoint of doubling of serum creatinine concentration, ESRD, or death (risk reduction=16.1%;  $p=0.022$ ; after adjustment for baseline proteinuria as a continuous covariate, risk reduction=22.2%,  $p=0.001$ ). Treatment with losartan significantly reduced the incidence of and delayed the time to ESRD or death (risk reduction=19.9%;  $p=0.009$ ; after adjustment for baseline proteinuria as a continuous covariate, risk reduction=25.7%,  $p<0.001$ ). It is estimated from the results of RENAAL that 1 case of ESRD would be prevented for every 16 patients treated with losartan over a 3.5-year period. In addition, the treatment effect of losartan was more clearly established by the performance of 2 supportive analyses that accounted for patients who discontinued study drug. These supportive analyses not only confirmed the results of the primary analysis, but also indicated a stronger treatment effect as evidenced by higher risk reductions for the primary composite endpoint and the combined component of ESRD or death.

With respect to the secondary renal endpoints, losartan significantly reduced the rate of progression of renal disease (i.e., slope of reciprocal of serum creatinine). Furthermore, proteinuria, a widely accepted marker of progressive glomerular injury, was reduced

within 3 months of initiation of losartan compared to placebo and the reduction was sustained over the course of the study.

With respect to cardiovascular morbidity and mortality, no significant differences between the 2 treatment groups were observed in RENAAL.

Nonetheless, post hoc analyses were performed taking into consideration renal and major cardiovascular outcomes, which are competing events in this population. The results of the post hoc analysis of the composite of the primary (renal) endpoint and the secondary (cardiovascular) endpoints show that losartan treatment was associated with a risk reduction of 16.6% ( $p=0.008$ ). Furthermore, a greater treatment effect is observed in a post hoc analysis of the hard endpoints of ESRD, MI, Stroke, or Death (whichever occurred first) (risk reduction: 21.2%;  $p=0.003$ ). The results of these analyses indicate that the benefits of losartan on renal outcomes were not at the expense of an increased risk of cardiovascular events and are supportive of an overall benefit of losartan treatment in these patients.

Confirmation of the impact of losartan on cardiovascular outcomes must await the availability of results from larger clinical trials specifically designed to address cardiovascular outcomes. For example, the results of the LIFE study will be presented at the March, 2002 American College of Cardiology meeting, and published soon thereafter in the *Lancet*. The LIFE study was specifically designed to address cardiovascular outcomes, and included diabetic patients. Although confidentiality rules prevent disclosure of the LIFE study results here, Merck will be prepared to summarize at the upcoming Advisory Committee Meeting the relevant data and its impact on our assessment of the benefit/risk assessment for the use of losartan to delay progression of renal disease in type 2 diabetic patients with proteinuria. It is important to note that the FDA will not have access to the primary data from the LIFE study until after the 12-Apr-2002 Advisory Committee Meeting and thus could not provide the Committee with their full assessment of the study results.

The consistent and significant treatment effects across multiple endpoints in the RENAAL study promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound.

The safety profile of losartan in this study did not uncover any unusual or unexpected adverse experiences. In fact, the vast majority of adverse experiences reported occurred in a similar number of patients in the losartan and placebo groups. This finding is consistent with what has been previously reported in numerous clinical studies [33]. In addition, no differences were observed in  $HBA_{1c}$  between the losartan and placebo groups. No reports of adverse experiences demonstrating an interaction of losartan with commonly used oral hypoglycemic agents or insulin were observed.

In order to more specifically assess the safety of losartan in diabetic patients with proteinuria, several adverse experiences most likely to occur in this patient population were pre-specified for statistical analysis: acute renal failure, anemia, hyperglycemia, hypoglycemia, hyperkalemia, and hypokalemia. With the exceptions of hyperkalemia

and hypokalemia, there were no significant differences in the incidence of these events between treatment groups. The findings of this analysis support the fact that diabetic patients with renal disease are at higher risk for potassium imbalances. It is also known that drugs that block the RAAS are associated with increases in serum potassium. Therefore, it is not surprising that the number of patients reporting hyperkalemia was ~2-fold higher in the losartan group (24.2%), compared to patients taking placebo (12.3%), in whom the risk also was elevated, reflecting characteristics of the underlying disease state. Conversely, hypokalemia was ~2-fold higher in the placebo group (4.7%) compared to the losartan group (2.5%). The concurrent use of diuretics, necessary for the treatment of hypertension and edema in patients with nephropathy, is most likely accountable for the increased incidence of hypokalemia in this group. As would be expected, diuretic use was similar in both groups; however, the effect of diuretics on potassium excretion may have been counteracted by the addition of losartan.

Despite the observed effects on potassium in this patient population, the study shows that these electrolyte imbalances are manageable, evidenced by the very low proportion of patients discontinuing due to hyperkalemia, and no discontinuations due to hypokalemia. There were no deaths attributed to hyperkalemia or hypokalemia. Hyperkalemia and hypokalemia can be treated using dietary and/or pharmacologic means. In general, these findings further substantiate what is already known by physicians: that potassium levels should be evaluated in patients with nephropathy if they are treated with agents that block the RAAS.

The safety findings of this study accord well with the overall summary of spontaneous postmarketing adverse experiences in diabetic patients with renal disease reported to Merck & Co., Inc. Similar to the RENAAL findings, there were no unexpected adverse experiences reported by the general public, in that the reports appeared to be a consequence of the underlying disease. Given that a relatively limited number of spontaneous adverse events were reported in diabetic patients with renal disease, and that millions of patients worldwide with various disease histories have been exposed to losartan, the summary of the spontaneous postmarketing adverse experiences supports the drug's favorable tolerability profile.

The risks of losartan in this type 2 diabetic population were clearly defined in RENAAL and are considered manageable, as evidenced by the type and number of adverse event reports in the losartan versus placebo groups.

Given the strong renal protective effects and documented safety and tolerability profile of losartan in patients with type 2 diabetes and proteinuria, the benefits of losartan therapy in this population clearly outweigh the risks.

**4. Overall Conclusions (See Section III.4)**

1. The results on the RENAAL study provide convincing evidence that losartan delays the progression of renal disease in type 2 diabetic patients with proteinuria. The consistent and significant beneficial effects of losartan across multiple endpoints in the large multi-center RENAAL trial promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound. Additionally, the pre-specified supportive analyses (6-month lagged censoring and per protocol) and the post hoc adjustment using baseline proteinuria as a continuous covariate all support the renal protective effects of losartan in this population.
2. Additional confirmatory evidence for the findings of RENAAL come from:
  - a. Several clinical studies of losartan in diabetic and non-diabetic patients with renal disease that demonstrated reductions in proteinuria. [34; 35; 26; 8; 27; 29; 30; 31].
  - b. Long-term preclinical studies that have demonstrated the renal protective benefits of losartan treatment in preventing glomerulosclerosis and reducing proteinuria in animal models of diabetic nephropathy [24; 25].
3. The results of RENAAL confirm that the safety profile of losartan in type 2 diabetic patients with proteinuria is consistent with that presented in the currently approved U.S. prescribing information for losartan.
4. Given the strong renal protective effects and documented safety and tolerability profile of losartan in this population, the benefits of losartan clearly outweigh the risks.

### **III. COMPREHENSIVE BACKGROUND**

#### **Use of Losartan to Delay Progression of Renal Disease in Type 2 Diabetic Patients With Nephropathy<sup>5</sup>**

##### **1. Introduction and Background**

Diabetes mellitus is one of the most common diseases worldwide [1]. It is the fourth or fifth leading cause of death in most developed countries and there is evidence that its prevalence is increasing [2]. It has been estimated that the total number of diabetic patients worldwide will increase from 123 million (1997) to 220 million by the year 2010 [2], with ~97% being type 2 diabetic patients. Diabetic patients commonly develop renal and cardiovascular disease, which can result in considerable morbidity and mortality. One of the most devastating complications of diabetes is nephropathy, which occurs in 10 to 40% of this population [2]. Thus, the number of patients with type 2 diabetes and nephropathy is expected to continue to rise, increasing the burden of this disease on healthcare systems worldwide [3; 2]

However, at present there are no approved drugs in the U.S. to delay progression of renal disease in type 2 diabetic patients with proteinuria. Merck Research Laboratories has submitted a supplemental NDA for the use of COZAAR™ (losartan potassium) to delay progression of renal disease in type 2 diabetic patients with proteinuria. Of note, the recently published 2002 American Diabetes Association (ADA) Position Statement recommends angiotensin II receptor antagonists for the initial treatment of hypertensive type 2 diabetic patients with proteinuria [36], based on the very recent results of the losartan RENAAL study [10] and Irbesartan Diabetic Nephropathy Trial (IDNT) [11].

In 1994, the FDA granted a claim for the angiotensin converting enzyme (ACE) inhibitor CAPOTEN™<sup>6</sup> (captopril) for treatment of type 1 diabetic patients with nephropathy (proteinuria >500 mg/day) and retinopathy. However, because there were no data in type 2 diabetic patients with nephropathy, the FDA did not grant a claim for CAPOTEN™ (captopril) in this patient population [4]. To date, no renal outcomes data with an ACE inhibitor in type 2 diabetic patients with nephropathy is available. Despite this, treatment guidelines recommending the use of ACE inhibitors in these patients were published in the 1990's. In the absence of outcomes data in type 2 diabetic patients, these guidelines were used to support the concept that ACE inhibitors (in general) would provide renal protection in both type 1 and type 2 diabetic patients.

These recommendations also relied upon reductions of microalbuminuria or proteinuria by ACE inhibitors in type 2 diabetic patients as evidence of renal protection.

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study in patients with type 2 diabetes with nephropathy was designed to

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<sup>5</sup> Nephropathy is defined as the presence of proteinuria; nephropathy and proteinuria are used interchangeably throughout this document.

<sup>6</sup> CAPOTEN™ is a registered trademark of the Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.

investigate the long-term renal protective effects of losartan. The study results demonstrate that losartan significantly delays the progression of renal disease in type 2 diabetic patients with nephropathy.

### **1.1 Natural History of Diabetic Nephropathy**

Approximately 10 to 40% of diabetic patients develop kidney disease [2]. Diabetic nephropathy is primarily a glomerular disease. It has been hypothesized that many factors, both hemodynamic and non-hemodynamic, may contribute to the development of glomerular injury. As a result of the original insult to the glomerulus and loss of nephrons, the remaining nephrons increase their work, via a state of hyperfiltration, in order to maintain glomerular filtration. This adaptation occurs as a result of increased resistance in the post glomerular vessel (efferent arteriole). In diabetic patients, the resistance in preglomerular vessels (afferent arteriole) is also reduced. This combination contributes to an increase in intraglomerular pressure or glomerular hypertension. This short-term gain has long-term detrimental effects on the nephron and initiates an up-regulation of a series of non-hemodynamic factors such as growth factor mediators of fibrosis, e.g., TGF-beta and PAI-1. The end result is glomerulosclerosis and death of the nephron; this cycle continues until all nephrons are lost, i.e., ESRD occurs.

Initially, diabetic nephropathy is characterized by structural changes to the kidney such as glomerular basement membrane thickening and mesangial expansion with either no changes in overall renal function or modest adaptive increases in renal blood flow and glomerular filtration rate (GFR). The next stage of the disease is incipient nephropathy, usually characterized by hyperfiltration, gradual increases in blood pressure, and microalbuminuria. In patients with type 2 diabetes, albuminuria increases ~20% per year and is often associated with elevated blood pressure [37]. Type 2 diabetic patients may have pre-existing hypertension at the time of development of renal disease. Furthermore, albuminuria exceeding 15 µg/mL is predictive of clinical proteinuria and early mortality [38], with cardiovascular disease being the major cause of death [39]. Incipient nephropathy progresses with the appearance of overt proteinuria, hypertension, declining GFR, and rising serum creatinine [37]. Persistent gross proteinuria is associated with increased hospitalization [40], and is predictive of development of chronic renal failure [41]. In fact, proteinuria is considered an important, independent, and *modifiable* risk factor for progression of renal disease, and as such, is a therapeutic target among practicing nephrologists [17; 18; 42], although not considered a surrogate for renal protection from a U.S. regulatory perspective.

Ultimately, end-stage renal disease (ESRD) develops between 5 and 15 years after the onset of gross proteinuria [43]. At this stage, the renal replacement interventions of either dialysis or transplantation are required to maintain life. Despite these measures, ~40% of diabetics who undergo dialysis die within the first 2 years [44].

The progressive stages of diabetic nephropathy documented for type 1 diabetes are well described in the literature [45; 46; 47; 43]. Similarities exist in the natural course of progression of renal disease in type 1 and type 2 diabetes, such as microalbuminuria progressing to macroalbuminuria, and ultimately ESRD, and the corresponding

pathological renal lesions of basement membrane thickening and ultimate glomerulosclerosis. Despite these similarities, substantial differences exist between patients with type 1 and type 2 diabetes. Patients with type 2 diabetes are typically older, obese, have long-standing hypertension, advanced atherosclerotic changes throughout the vasculature, insulin resistance, and a high incidence of morbidity and mortality from cardiovascular disease and its sequelae. Although the glomerular pathology in type 1 and type 2 diabetic patients may be similar, there are morphological differences in the kidney of type 2 patients that may represent long-standing hypertension and older age, such as the presence of tubulo-interstitial lesions in the early stages of nephropathy in patients with type 2 diabetes. Given the differences between type 1 and type 2 diabetic patients, differences in the magnitudes of effect when evaluating therapeutic agents for treatment of nephropathy in these populations would be expected.

Recent estimates by the National Institutes of Health indicate that diabetes represents the single largest cause of ESRD, accounting for ~44% of all cases of ESRD in the U.S. between 1994 and 1999 [48]. Despite the variable prevalence rates of patients with diabetes and ESRD around the world, there has been a remarkable increase in the global incidence of diabetic patients with ESRD in the past decade, in regions such as Europe, Australia, and Asia [3]. With a much higher proportion of diabetics being diagnosed as type 2, it can be inferred that the majority of diabetic patients with ESRD have type 2 diabetes.

## **1.2 Current Management of Diabetic Patients With Nephropathy**

Prior to RENAAL, no conclusive data showing a benefit of treatment on ESRD/death were available in patients with type 2 diabetes and nephropathy. Therefore, therapeutic approaches to treatment of diabetic nephropathy focused on metabolic control, blood pressure control, and blockade of the renin-angiotensin system [49; 50; 51; 52; 17; 53]. Strict glycemic control in patients with type 1 and type 2 diabetes has demonstrated a benefit in early stages of diabetic nephropathy. Restricted dietary protein intake of 0.6 to 0.8 g/kg/day has been shown to stabilize or slow the rate of decline of renal function in type 1 diabetic patients with proteinuria [54; 55]. However, there are no data demonstrating that strict glycemic control or restricted dietary protein intake has an impact on ESRD/death in patients with established renal disease.

The benefits of conventional antihypertensive therapy for treatment of diabetic nephropathy, regardless of class, have been demonstrated in numerous studies. The importance of tight blood pressure control in reducing the risk of macrovascular and microvascular complications in type 2 diabetes was illustrated by the findings of the United Kingdom Prospective Diabetes Study (UKPDS) and Hypertension Optimal Treatment (HOT) study [53; 56]. The UKPDS is a multicenter, randomized, controlled study that showed tight blood pressure control (mean blood pressure, 144/82 mm Hg) in patients with type 2 diabetes and early nephropathy achieved a clinically important reduction in the risk of death and complications related to diabetes (e.g., nonfatal myocardial infarction, angina, heart failure, renal failure, and amputations) and progression of diabetic retinopathy [53]. The HOT study also provided evidence in 1501

diabetic patients, the majority of whom were type 2 diabetic, that strict blood pressure control plays an important role in reducing cardiovascular complications of diabetes. In this study, a 51% reduction in major cardiovascular events (including myocardial infarction, stroke, and cardiovascular mortality) was observed in patients with diabetes whose diastolic blood pressure was  $\leq 80$  mm Hg [56]. With respect to progression of nephropathy, Parving et al. demonstrated that antihypertensive therapy produced a reduction in blood pressure and albuminuria, as well as an attenuation in the decline of glomerular filtration rate (GFR) in patients with type 1 diabetes [57]. A reduction in systemic blood pressure and the associated fall in intraglomerular pressure may be an important mechanism by which antihypertensive agents attenuate the progression of diabetic nephropathy. It is important to note that there are no data on the effect of blood pressure control on the renal outcomes of ESRD or death in patients with type 2 diabetes and nephropathy.

### **1.2.1 Blockade of Renin-Angiotensin System**

It has been suggested that antihypertensive drugs that block the renin-angiotensin system (RAS) may have a specific renal protective benefit in patients with diabetic nephropathy [12]. Angiotensin II (AII) plays an important role in the progression of renal injury through hemodynamic mechanisms such as regulating intraglomerular pressure, and nonhemodynamic mechanisms such as increased mesangial proliferation and expansion, tubulo-interstitial injury and, production of growth factors such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor (PDGF), and stimulation of superoxide production [13; 14; 15; 16]. Therefore, it has been postulated that blockade of AII would offer renal protection beyond that expected by reducing systemic blood pressure alone. Studies in patients with type 1 diabetes have shown that angiotensin converting enzyme (ACE) inhibitors effectively diminish the progression of nephropathy above and beyond their blood pressure lowering effects [12]. In young, type 1 diabetic patients with retinopathy and overt nephropathy, captopril therapy was shown to have a beneficial effect on the combined endpoint of ESRD or death [12]. These findings demonstrate that blockade of the RAS offers renal protection in patients with type 1 diabetes. Because similarities exist in the mechanism of glomerular injury and progression of renal disease between type 1 and type 2 diabetic patients, it was believed that blockade of the RAS would also afford renal protection in type 2 diabetic patients.

However, data examining the effects of ACE inhibitors on the progression of renal disease to ESRD or death in type 2 diabetic patients are not presently available. As a result, ACE inhibitors are not currently approved in the U.S. for treatment of type 2 diabetes with proteinuria to delay progression of renal disease. Some studies involving ACE inhibitor treatment in patients with type 2 diabetes have demonstrated reductions in proteinuria; however, they have not consistently demonstrated a beneficial effect on progression of renal disease, and few studies have evaluated ESRD in diabetic patients with renal disease. The majority of studies with ACE inhibitors in type 2 diabetes included patients with early stages of nephropathy or were of small sample size [58; 8;

59; 9; 60; 61; 62; 63; 64; 65; 66; 67]. A summary of the findings of ACE inhibitor studies of at least 2 years in duration is shown in Table 1.

Table 1

Prior Studies on the Effect of ACE Inhibitors on Proteinuria  
 and Progression of Renal Disease in Type 2 Diabetes

	N	Treatment	Proteinuria	Renal Function <sup>†</sup>	ESRD
Walker [58]	134	Enal. vs. diuretic	No difference	No difference	NA
Ravid [8]	94	Enal. vs. placebo	Decreased	Improved	NA
Lacourciere [67]	74	Los. and/or Enal vs. CT	Decreased	No difference	NA
Lebovitz [59]	121	Enal. vs. CT	Decreased	Improved <sup>‡</sup> No difference <sup>§</sup>	NA NA
Bakris [9]	52	Lisinopril vs. verapamil vs. atenolol	No difference  Decreased	No difference  Improved	NA  NA
Ahmad [60]	103	Enal. vs. placebo	Decreased	No difference	NA
Nielsen [61]	43	Lisinopril vs. atenolol	Decreased	No difference	NA
UKPDS [62]	758	Captopril vs. atenolol	No difference	No difference	NA
Fogari [63]	107	Ramipril vs. nitrendipine	Decreased	No difference	NA
Estacio [64]	470	Enal. vs. nisoldipine	No difference	No difference	NA
Ruggenenti [65]	27	Ramipril vs. CT	NA	Decreased	No difference
Micro-HOPE [66]	3577	Ramipril vs. placebo	Decreased	NA	No difference

<sup>†</sup> Serum creatinine or GFR.

<sup>‡</sup> In patients with BL UA ≤300 mg/d.

<sup>§</sup> In patients with BL UA >300 mg/d.

“No Difference” = Differences between treatment groups were not significant.

“Decreased” = Refers to ACE inhibitor group relative to comparator treatment.

CT = Conventional therapy.

NA = Not applicable.

### **1.2.2 Treatment Recommendations of Published Hypertension and Renal Guidelines**

Professional guidance that has been provided to physicians treating hypertension in diabetic patients with proteinuria has been generalized to the overall diabetic population, and may not necessarily have differentiated between type 1 and type 2 diabetes. The published guidelines could not make evidence-based recommendations regarding type 2 diabetic patients with proteinuria, due to the lack of appropriate data in this population. Therefore, in the absence of definitive clinical studies, expert opinion, rather than outcome data, is frequently used to develop guidelines. Guidelines in general have recommended first-line use of ACE inhibitors by extrapolating from renal protection studies in patients with type 1 diabetes and from studies in type 2 diabetes where reduction of microalbuminuria or proteinuria were used as surrogates for renal protection [5; 6; 7]. Ravid et al. [8], one of the studies on which the guidelines are based, demonstrated reductions in microalbuminuria with ACE inhibitor treatment in 94 normotensive type 2 diabetic patients, while renal function (as assessed by reciprocal of serum creatinine) remained stable with ACE inhibitor and decreased with placebo treatment. Another study, not referenced in the guidelines, in a similar population and duration of follow-up, also demonstrated decreases in microalbuminuria with an ACE inhibitor compared to placebo; however, no differences were observed in the rate of change in glomerular filtration rate (GFR) between groups [60].

Until the recent results of the RENAAL [10] and IDNT [11] studies, definitive data on the treatment of type 2 diabetic patients with nephropathy did not exist. Furthermore, there has been no study to conclusively show that reduction of proteinuria leads to a reduction in renal outcomes. The American Diabetes Association (ADA) has recognized the outcome of these 2 large studies, and has modified its guidelines accordingly. The recently published 2002 ADA Position Statement now recommends AIIAs for the initial treatment of hypertensive, type 2 diabetic patients with nephropathy [36], based on the recent results of the losartan RENAAL Study [10] and the IDNT [11]. Previous ADA statements recommended the initial treatment of these patients with ACE inhibitors [7], while recognizing that there were no data to indicate that any antihypertensive agent is renal protective in this population [68].

### **1.3 Rationale for the Use of Losartan in Diabetic Patients With Proteinuria and Supportive Literature**

In young type 1 diabetic patients with retinopathy and overt nephropathy, captopril therapy has been shown to have a beneficial effect on the combined endpoint of ESRD or death [12]. These findings demonstrated that blockade of the RAS offers renal protection in patients with type 1 diabetes. Because similarities exist in the mechanism of glomerular injury and progression of renal disease between type 1 and type 2 diabetic patients, it was believed that blockade of the RAS would also afford renal protection in type 2 diabetic patients. However, when the RENAAL program was developed, data examining the effects of ACE inhibitors or other therapeutic classes on the progression of renal disease to ESRD or death in type 2 diabetic patients were not available.

The results of studies in animals and humans have provided evidence to suggest losartan is efficacious in diabetic nephropathy. This section will describe preclinical and clinical studies that have demonstrated losartan's ability to effectively reduce proteinuria, while preserving renal structure in animal models. The AIIA, losartan, is an orally active, highly specific antagonist that blocks the binding of AII to the AT<sub>1</sub> receptor subtype. Losartan was approved by the FDA for the treatment of hypertension, and has a favorable tolerability profile [69; 70; 71; 72]. Studies have demonstrated that losartan is generally well tolerated in the elderly and in patients with underlying renal disease, including diabetics (original NDA).

Therefore, the existing evidence in preclinical studies in animal models of diabetic kidney disease and clinical studies in non-diabetic patients with proteinuria supported the biologic plausibility of the renal protective effect of losartan, and allowed for the initiation of RENAAL.

#### Summary of Renal Protective Effects in Experimental Models of Kidney Disease and Diabetes

Losartan has been shown to offer renal protection in several different experimental models of renal disease in rats. In nondiabetic, 5/6 nephrectomized rats, Lafayette et al. [23] demonstrated that 10-week administration of pharmacological doses of losartan were renal protective, in that greater reductions in glomerulosclerosis, glomerular transcapillary pressure and proteinuria were observed in losartan-treated rats than in rats treated with triple antihypertensive therapy (i.e., reserpine, hydralazine, and hydrochlorothiazide) [23]. This demonstrated that the antiproteinuric and renal protective effect of losartan was beyond its antihypertensive efficacy. Likewise, in long-term experimental diabetic models, losartan has been shown to attenuate glomerulosclerosis and urinary protein. Remuzzi et al. have shown that after a 1-year observation period, proteinuria in losartan-treated diabetic rats was significantly less than that seen in diabetic control rats, and comparable to that of normal control rats [24]. More importantly, glomerulosclerosis was prevented by specific AII blockade with losartan in these animals [24]. These data were confirmed in a long-term 1-year Merck study, where glomerulosclerosis and proteinuria were significantly reduced in losartan-treated diabetic rats compared to diabetic control rats [25].

These animal studies have demonstrated that losartan exerts renal protective effects and reduces proteinuria in experimental nondiabetic and diabetic renal disease, and therefore losartan therapy may be beneficial in slowing the progression of nephropathy in humans.

#### The Antiproteinuric Effect of Losartan in Patients With Proteinuria

Early in the development of losartan, the antiproteinuric effect of losartan in patients with proteinuria was studied. In patients with non-diabetic renal disease, losartan significantly reduced proteinuria while maintaining GFR and increasing renal blood flow [34]. In another study of non-diabetic patients with proteinuria, losartan and amlodipine resulted in comparable reductions in blood pressure, yet only losartan reduced proteinuria [35], indicating that losartan's antiproteinuric effect is beyond blood pressure control.

Furthermore, in an open-label study of antihypertensive efficacy and safety in patients with different degrees of renal impairment, losartan reduced blood pressure and proteinuria [73]. These data [74; 73] were included in the original hypertension NDA for losartan. At the time of RENAAL program development, evidence of losartan's antiproteinuric effects was mainly limited to non-diabetic patients [35; 74; 73]. However, subsequent to the initiation of RENAAL, many studies in the literature have confirmed these findings with losartan in diabetic patients with renal disease and some of these studies have clearly demonstrated that the antiproteinuric effect of losartan is beyond its antihypertensive efficacy. These studies will be described in Section 3.1.

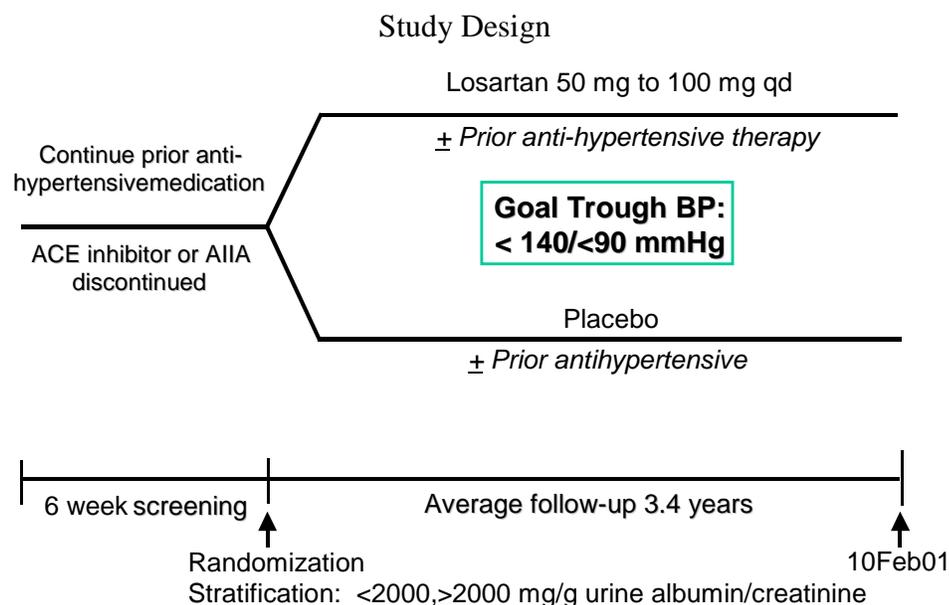
## **2. Summary of RENAAL**

### **2.1 Overview of Study Design**

To investigate the long-term renal protective effects of losartan, the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study was initiated in patients with type 2 diabetes with nephropathy. The study investigated whether losartan reduces the number of patients experiencing the primary composite endpoint of doubling of serum creatinine, ESRD (need for chronic dialysis or transplantation), or death (all-cause) in patients with type 2 diabetes. In order to conclusively demonstrate that the treatment effect on progression of renal disease was beyond that attributable to blood pressure control alone, equivalent blood pressure control between the 2 treatment groups was important. To achieve this goal, treatment with losartan or placebo was on a background of conventional antihypertensive therapy (diuretics, calcium channel blockers, beta blockers, alpha blockers, and/or centrally acting agents, excluding ACE inhibitors and AIIAs).

In addition, the study assessed the effects of losartan (versus placebo) on progression of renal disease measured as the slope of the reciprocal of serum creatinine, changes in proteinuria, cardiovascular morbidity and mortality. The RENAAL study design is depicted in Figure 1.

Figure 1



This double-blind, multicenter, randomized study enrolled 1513 patients from 250 investigative centers in 28 countries. Patients must have had type 2 diabetes defined as: (1) diabetes diagnosed after the age of 30; (2) insulin not required within the first 6 months of diagnosis; and (3) no history of diabetic ketoacidosis. Patients between the ages of 31 and 70, with a serum creatinine between 1.3 (1.5 for males >60 kg) and 3.0 mg/dL and a first morning urinary albumin/creatinine ratio (UA/Cr) of ≥300 mg/g (or a 24-hour urine total protein of >500 mg/day) were eligible for the study. Patients could be normotensive or hypertensive.

Patients with type 1 diabetes were excluded from the study. In general, patients with known high risk for cardiovascular disease who may have required ACE inhibitor therapy were excluded from participation. A history of myocardial infarction or coronary artery bypass graft surgery within 1 month prior to study start, cerebral vascular accident or percutaneous transluminal coronary angioplasty within 6 months prior to study start, and history of transient ischemic attacks (TIA) within the year prior to study start precluded a patient from participation. Another key exclusion criterion was a known history or current diagnosis of nondiabetic renal disease such as chronic glomerulonephritis or polycystic kidney disease. Patients with uncontrolled diabetes, i.e., HBA<sub>1c</sub> >12%, were also excluded.

Patients with heart failure not requiring ACE inhibitors were initially allowed to enroll. However, early in the study several of these patients discontinued study therapy due to

heart failure adverse experiences and were placed on other therapies to treat their heart failure. This observation resulted in a protocol amendment that excluded all patients with heart failure from randomization (86 patients with heart failure [43 patients in each treatment group] were randomized prior to implementation of the amendment and are included in all analyses).

After a 6-week screening period, patients were randomized to either losartan 50 mg once daily or placebo. At the onset of the screening phase, patients on ACE inhibitors or AIIAs were taken off these therapies and placed on conventional antihypertensive therapy, if needed, to control blood pressure. At randomization, patients were stratified by baseline proteinuria (UA/Cr <2000 mg/g or UACr  $\geq$ 2000 mg/g). Study therapy was added in a double-blind fashion to each patient's usual antihypertensive therapy (excluding ACE inhibitors and angiotensin II antagonists). Study medication was increased to losartan 100 mg once daily (or matching placebo) after 4 weeks if the patient's trough sitting blood pressure did not reach the goal of <140/90 mm Hg. Thereafter, at any point during the study, the patient's usual open-label antihypertensive drug therapy could be increased, or any of the following open-label antihypertensive agents added at the discretion of the investigator to obtain the target blood pressure: a diuretic, calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent. At the investigator's discretion, patients with possible intravascular volume depletion (due to high-dose diuretic) or a history of hypotension could receive double-blind losartan 25 mg or placebo during the first week of the study with titration to losartan 50 mg or placebo after the first week.

The primary efficacy parameter in RENAAL, the one on which the sample size was based, was the time to the composite endpoint of doubling of serum creatinine concentration, ESRD (need for chronic dialysis or transplantation), or death. To evaluate the effect of a pharmacologic intervention on renal protection, it is necessary to demonstrate a treatment effect on ESRD or death. In the development of the RENAAL study design, it was felt that many patients would die prior to reaching ESRD, since they had significant disease at the time of randomization. Therefore, to capture renal outcome, doubling of serum creatinine, which reflects a clinically important progression towards ESRD (>50% loss of renal function), was included as a component of the primary endpoint. Hence, the composite of doubling of serum creatinine, ESRD, or death was established as the primary endpoint in this study. For a given patient, multiple components of the primary endpoint could have been captured. Doubling of serum creatinine endpoints were not collected after patients reached ESRD.

Once a patient reaches ESRD, dialysis or transplantation is required. In fact, dialysis is a life-support therapy without which patient death would undoubtedly occur. Thus, in a population of patients with type 2 diabetes and proteinuria, death and ESRD are competing events because patients may die before reaching ESRD or die as a result of requiring, but not receiving, dialysis.

The secondary hypotheses were that losartan would (a) slow the rate of loss of renal function, as measured by the reciprocal of serum creatinine; (b) reduce proteinuria

compared to placebo during the course of the study; and (c) increase the time to first event and decrease the incidence of cardiovascular morbidity/mortality (defined as myocardial infarction (MI), stroke, first hospitalization for heart failure (HF) or first hospitalization for unstable angina, revascularization (coronary or peripheral), or cardiovascular (CV) deaths) compared to placebo.

Investigators were to maintain their patients on study therapy throughout the duration of the study, regardless of whether a primary endpoint was reached. For instance, if a patient reached doubling of serum creatinine, the investigator was to maintain that patient on study drug until the patient died or until completion of the study. It should be noted, however, that the decision to discontinue study therapy was left solely to the discretion of investigators. The protocol required that all discontinued patients be followed in the clinic every 3 months until the end of the study. In those patients who were in clinic follow-up, all primary endpoint data, including doubling of serum creatinine, and secondary cardiovascular endpoint data were collected. For those patients in whom clinic follow-up was not feasible, regular follow-up through telephone contacts was required. Once in telephone follow-up, doubling of serum creatinine endpoints and cardiovascular morbidity outcomes were not collected, however; data on ESRD and death were collected for all patients randomized to the study. It is important to note that the patients in clinic and telephone follow-up were not exclusive to either form of follow-up, i.e., patients could have been followed in clinic for a period of time, then by telephone until study completion.

### **2.1.1 Important Aspects of RENAAL Study Design**

RENAAL had several important aspects in its study design. The protocol required patients to continue study therapy regardless of whether an endpoint was reached. If patients discontinued study therapy, they were required to return for regular clinic visits to ensure that all primary and secondary endpoints were captured. If patients could not return to the clinic after discontinuation, regular telephone contact was instituted to follow those patients for the hard outcomes of ESRD and death (doubling of serum creatinine and cardiovascular morbidity outcomes were not collected in telephone follow-up). As a result of RENAAL's rigorous procedures for follow-up after discontinuation, there were no lost-to-follow-up patients at study end, in that ESRD and/or death status was ascertained on all patients randomized.

### **2.1.2 Independent Oversight Committees**

The study was overseen by a Steering Committee. An Endpoint Committee was responsible for adjudicating every potential primary endpoint and secondary cardiovascular endpoint by a consensus process. Both the Steering and Endpoint Committees remained blinded throughout the study. No member served on more than one committee.

An unblinded Data Safety Monitoring Board (DSMB) monitored the ongoing safety of the patients. For the purposes of the DSMB review only, an interim analysis for efficacy was prespecified and was to be performed when half of the expected events (246 of

492 events) associated with the sample size and event rate estimates were observed or the last patient entered was followed for 1.75 years, whichever came first. In actuality, 309 primary events were included in the interim efficacy analysis.

The study was planned to be completed in Mar-2002. This planned termination date was based on 3.5 years of follow-up of the last patient randomized, preceded by a 2-year enrollment period, yielding an expected average 4.5 years of follow-up (required to achieve 95% power). However, on 10-Feb-2001, the Steering Committee, whose role included staying abreast of current research in the field and continually reevaluating the ethical context of the study, voted unanimously to end the study prior to its planned completion of March, 2002. Its decision was based on increasing evidence suggesting that ACE inhibitors, which were excluded by design from RENAAL, may be effective in reducing cardiovascular events in patients with cardiovascular risk factors and/or diabetes with renal impairment [19]. The new data that prompted termination of RENAAL was in a subset of patients from the Heart Outcomes Prevention Evaluation (HOPE) study [19; 20].

## **2.2 Summary of Prespecified Statistical Methods**

The primary analyses of the primary composite endpoint of doubling of serum creatinine, ESRD, or death, and the secondary composite endpoint of cardiovascular events were based on the intention-to-treat (ITT) principle; all randomized patients were included from randomization through the study termination date in their randomized treatment group regardless of compliance with study therapy. Supportive analyses included analyses of components of the composites, and 2 sensitivity analyses (per protocol and lagged censoring) intended to reduce the impact of study drug discontinuation on the intention-to-treat results. The per-protocol analysis excluded patients who violated the inclusion/exclusion criteria and censored patients' data 14 days after they permanently discontinued study therapy, while the 6-month lagged censoring analysis included all randomized patients and censored patients' data 6 months after permanent discontinuation of study therapy. (See Table 2 for a description of these 2 analytical approaches.)

A Cox regression model, including baseline level of proteinuria as a stratification factor (i.e., indicator variable for UA/CR, <2000 mg/g and  $\geq$ 2000 mg/g) and geographic region (i.e., indicator variables for 4 regions) as a covariate, was used to determine the hazard ratio (losartan relative to placebo) and 95% confidence interval. (Additional post hoc analyses included the UA/Cr as an additional continuous covariate.) The risk reduction was calculated as 100 percent x (1-hazard ratio). In analyses of nonfatal endpoints, patients who died were considered censored; that is, these patients were considered to be at risk of a nonfatal event only through their date of death. Event curves were based on the Kaplan-Meier procedure.

Table 2

Description of Analytical Approaches for the Primary Composite Endpoint and Individual Components

Analytical Approach	Patients Excluded	Time of Data Censoring
<b>Primary</b>		
Intention-to-Treat	None	10-Feb-2001 (i.e., study end)
<b>Supportive</b>		
Lagged Censoring	None	10-Feb-2001, or 6 months after study drug discontinuation <sup>†</sup> , whichever came first
Per Protocol	Protocol Violators	10-Feb-2001, or 14 days after study drug discontinuation <sup>†</sup> , whichever came first
<sup>†</sup> Defined as the date of permanent discontinuation from study therapy, or an interruption lasting at least 6 months.		

Since patients were followed after the occurrence of a nonfatal primary endpoint, many patients experienced multiple endpoints. In these cases, the principles applied were that a patient counted as having had an endpoint in *all* relevant analyses, and that a patient counted *only once* in any analysis. For example, suppose a patient experienced all 3 components: doubling of serum creatinine followed by ESRD followed by death. In the analysis of the composite endpoint, the doubling of serum creatinine endpoint would count; in the analysis of the death component, the death endpoint would count; and in the analysis of the combined component of ESRD or death, the ESRD endpoint would count.

The impact of between-group differences in blood pressure control was examined in a pre-defined analysis by adding mean arterial pressure as a time-varying covariate in the Cox regression model, and comparing the estimated effect of losartan from this model with that from the primary analysis.

Because the secondary endpoints of renal disease progression (slope of reciprocal of serum creatinine) and changes in proteinuria were derived from laboratory measurements, their corresponding analyses were based on a prespecified on-treatment approach, as these measurements may not have been consistently collected in patients who discontinued from study therapy. For renal disease progression, the slopes of the reciprocal of serum creatinine concentration were compared between the 2 treatment groups using a linear random effects model, adjusting for region, baseline proteinuria stratum, and baseline serum creatinine concentration. Changes in proteinuria were compared between the 2 treatment groups using a mixed-effects model with terms including treatment, region, and baseline proteinuria stratum.

In order to explore the degree to which the reduction in proteinuria (losartan versus placebo) over time is explained by changes in blood pressure, a prespecified ANCOVA

model was used with independent variables of treatment, region, baseline proteinuria (on the logarithm scale), and both diastolic and systolic blood pressure, and the dependent variable of proteinuria (on the logarithm scale) at each time point of Month 3, Month 6, Year 1, Year 2, Year 3, and the last. At each point, the last observation available up to and including this time point was used. Therefore, the last analysis contains all patients who had postrandomization values under each approach. At each scheduled visit, where a proteinuria value was available, a blood pressure value was selected either at this time point or at previous visits using the last-observation-carried-forward method. Most patients had blood pressure measurements at each visit.

Due to one prespecified interim efficacy analysis and periodic interim safety analyses during the course of the study by the DSMB, a critical p-value of 0.048 was required for the primary hypothesis. For other outcomes, a p-value of less than 0.05 was considered to indicate statistical significance. All statistical tests were two-sided. Assuming that the 5-year composite event rate would be 58% in the placebo group, and that this rate would be reduced by 20% (absolute percentage of 46.4%) in the losartan group, a total sample size of 1320 patients (660 per group) was proposed to achieve 95% power at the 4.8% significance level (two-sided, adjusted for interim analyses). This calculation for power of the study was based on a 2-year enrollment period, 3.5 years of follow-up for the last randomized patient, and 13% per year rate of discontinuation from study therapy.

The protocol originally planned for 1520 patients to be enrolled over a 1-year period but was amended (147-03) to 1320 patients when it became clear that enrollment would take 2 years. The study actually over-enrolled with 1513 patients due to a larger than anticipated number of screened patients successfully qualifying during the final months of the 2-year recruitment period.

Prespecified evaluation of safety included tabulating all adverse experiences that occurred during the double-blind study period or within 14 days following cessation of double-blind treatment, whether or not related to the investigational product. For an adverse experience having a total number of events greater than 22, as specified in the Data Analysis Plan, a 95% confidence for relative risk was also provided.

For adverse experiences of special interest (e.g., hyperkalemia), a Cox regression analysis was used to compare the treatment groups including only the treatment term (losartan versus placebo). Patients who did not have one of the prespecified adverse experiences until either death or the end of the double-blind treatment period plus 14 days following discontinuation of therapy were censored at that time point. The analysis takes into account time to first event, regardless of whether the event was reported as a clinical or a laboratory adverse experience.

### **2.3 Patient Disposition**

As summarized in Figure 2, 3893 patients were screened for the study and 1513 were allocated to either losartan (751) or placebo (762).

The average duration of follow-up (mean time from randomization through February 10, 2001) was 3.4 years. No patients were lost to follow-up and the outcome of ESRD and/or

death was available in all randomized patients. The protocol required patients to remain on study drug even after experiencing a primary endpoint. Because of the long duration of the study, and the high number of patients with co-morbid conditions, it was expected that many patients would discontinue study therapy. In fact, the overall number of patients who discontinued prior to a primary event (443, 29.3%) is consistent with the pre-specified estimated discontinuation rate (prior to primary event) of 13% per year (~30% cumulative rate). Of the 751 patients in the losartan group and 762 patients in the placebo group, 202 (26.9%) and 241 (31.6%) patients, respectively, discontinued from study drug prior to reaching a primary endpoint; while 142 (18.9%) and 162 (21.2%) patients, respectively, discontinued after reaching a primary event.

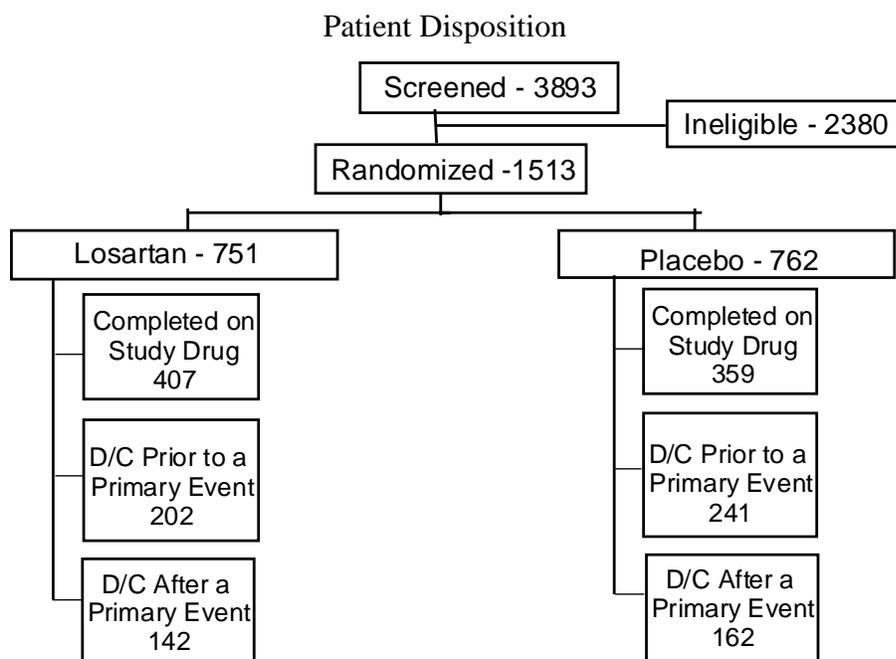
The protocol required that patients who discontinued from study therapy be followed in the clinic (clinic follow-up) every 3 months until the end of the study (10-Feb-2001). In those patients, all primary and secondary endpoint information was collected, as if they were still on study drug. Of the 202 patients in the losartan group and 241 in the placebo group who discontinued study drug prior to reaching a primary endpoint, 73 (36%) and 93 (39%), respectively, were followed in clinic.

For those patients in whom clinic follow-up was not feasible, regular telephone contact was performed to determine whether the patient had reached ESRD or death. Once in telephone contact, doubling of serum creatinine and cardiovascular morbidity outcomes were not collected. Of the 202 patients in the losartan group and 241 in the placebo group who discontinued study drug prior to reaching a primary endpoint, 129 (64%) and 148 (61%), respectively, were followed by telephone.

It is important to note that the patients in clinic and telephone follow-up were not exclusive to either form of follow-up. For instance, after a patient discontinued study drug, he/she may have entered clinic follow-up for a period of time. While in clinic follow-up, the patient may have reached the primary endpoints of doubling of serum creatinine and ESRD. After initiating dialysis, the patient may have opted to be contacted by telephone every 3 months rather than attending clinic visits. At study end, it would have been determined through telephone contacts whether this patient reached death. Therefore, any given patient in clinic or telephone follow-up reported above could have been in one or both forms of follow-up until study end.

Because there were a variety of scenarios with regard to the mode of follow-up after discontinuation, the average patient years of follow-up were calculated to provide a more accurate reflection of the follow-up phase. With regard to clinic follow-up, average patient years of follow-up were 173 in the losartan group and 234 in the placebo group. With regard to telephone follow-up, average patient years of follow-up were 122 in the losartan group and 177 in the placebo group. In both treatment groups, patients were in clinic follow-up a longer period of time compared to telephone follow-up. It is important to note that all discontinued patients, regardless of the mode of follow-up, were followed for ESRD and death outcomes.

Figure 2



#### 2.4 Demographic and Other Baseline Characteristics

The study enrolled 1513 patients, of which 63.2% were male and 36.8% were female, with a mean age of 60 years. For the overall population, mean serum creatinine, urinary albumin:creatinine ratio, and HBA<sub>1c</sub> were 1.9 mg/dL, 1808 mg/g, and 8.5%, respectively. Baseline characteristics generally were similar between the 2 treatment groups and are summarized in Table 3. However, despite stratification by baseline proteinuria (UA/Cr <2000 or UA/Cr ≥2000 mg/g), there was a difference in mean baseline proteinuria, a known risk factor for the progression of renal disease, of ~130 mg/g, with the losartan group having the higher value (1873 mg/g in losartan versus 1743 mg/g in placebo). While nonsignificant, this difference has implications for the evaluation of losartan's effect that will be discussed in Section 2.5.1.1. Also summarized in Table 3 are secondary diagnoses, and prior and concomitant therapies.

Table 3

Patient Demographic and Other Baseline Characteristics

	Losartan (N=751)		Placebo (N=762)		Total (N=1513)	
	n	(%)	n	(%)	n	(%)
<b>Age (yr)<sup>†</sup></b>						
≤50 yr	89	(11.9%)	83	(10.9%)	172	(11.4%)
50 to 54 yr	83	(11.1%)	84	(11.0%)	167	(11.0%)
55 to 59 yr	142	(18.9%)	141	(18.5%)	283	(18.7%)
60 to 64 yr	189	(25.2%)	194	(25.5%)	383	(25.3%)
65 to 69 yr	200	(26.6%)	193	(25.3%)	393	(26.0%)
≥70 yr	48	(6.4%)	67	(8.8%)	115	(7.6%)
Mean (SD)	60 (7.4)		60 (7.5)		60 (7.4)	
Median	61		62		61	
Range	36.0 to 74.0		31.0 to 73.0		31.0 to 74.0	
<b>Gender</b>						
Female	289	(38.5%)	268	(35.2%)	557	(36.8%)
Male	462	(61.5%)	494	(64.8%)	956	(63.2%)
<b>Race</b>						
Asian	117	(15.6%)	135	(17.7%)	252	(16.7%)
Black	125	(16.6%)	105	(13.8%)	230	(15.2%)
Hispanic	140	(18.6%)	137	(18.0%)	277	(18.3%)
Other	11	(1.5%)	8	(1.0%)	19	(1.3%)
White	358	(47.7%)	377	(49.5%)	735	(48.6%)
<b>Height (cm)</b>						
Mean (SD)	165.7 (10.7)		166.2 (10.5)		165.9 (10.6)	
Median	166		166		166	
Range	123.0 to 194.9		134.6 to 195.6		123.0 to 195.6	
<b>Weight (kg)</b>						
Mean (SD)	82.6 (20.6)		81.7 (20.9)		82.2 (20.7)	
Median	80.51		78.97		79.83	
Range	32.0 to 159.7		37.2 to 161.0		32.0 to 161.0	
<b>Body Mass Index (kg/m<sup>2</sup>)</b>						
Mean (SD)	30.0 (6.4)		29.4 (6.2)		29.7 (6.3)	
Median	29		28.18		28.63	
Range	15.6 to 56.3		16.2 to 59.6		15.6 to 59.6	
<b>Sitting Systolic BP (mm Hg)</b>						
Mean (SD)	151.8 (18.7)		153.2 (19.9)		152.5 (19.3)	
Median	150		152		151	
Range	105.0 to 220.0		97.0 to 226.0		97.0 to 226.0	
<b>Sitting Diastolic BP (mm Hg)</b>						
Mean (SD)	82.4 (10.3)		82.4 (10.6)		82.4 (10.4)	
Median	82		82		82	
Range	37.0 to 111.0		49.0 to 120.0		37.0 to 120.0	

Table 3 (Cont.)

Patient Demographic and Other Baseline Characteristics

	Losartan (N=751)		Placebo (N=762)		Total (N=1513)	
	n	(%)	n	(%)	n	(%)
<b>Mean Arterial Pressure (mm Hg)</b>						
Mean (SD)	105.5 (10.9)		106.0 (11.6)		105.8 (11.3)	
Median	105.67		106.33		106	
Range	61.3 to 137.7		73.3 to 148.7		61.3 to 148.7	
<b>Region</b>						
Asia	125	(16.6%)	132	(17.3%)	257	(17.0%)
Europe	151	(20.1%)	144	(18.9%)	295	(19.5%)
Latin America	137	(18.2%)	137	(18.0%)	274	(18.1%)
North America	338	(45.0%)	349	(45.8%)	687	(45.4%)
<b>Proteinuria Level (UA/Cr in mg/g)</b>						
Mean (SD)	1873 (1831)		1743 (1543)		1808 (1693)	
Median	1237		1260.5		1245.5	
Range	31.0 to 12208		44.5 to 10151		31.0 to 12208	
<b>Serum Creatinine (mg/dL)<sup>†</sup></b>						
Mean (SD)	1.9 (0.5)		1.9 (0.5)		1.9 (0.5)	
Median	1.75		1.8		1.8	
Range	0.9 to 3.6		0.9 to 3.2		0.9 to 3.6	
<b>HBA<sub>1C</sub> (%)</b>						
Mean (SD)	8.5 (1.7)		8.4 (1.6)		8.5 (1.6)	
Median	8.25		8.20		8.20	
Range	5.2 to 17.5		4.8 to 15.2		4.8 to 17.5	
<b>Medical History</b>						
<b>Duration of Diabetes</b>						
Not Available	1	(0.1%)	2	(0.3%)	3	(0.2%)
<5 yr	74	(9.9%)	74	(9.7%)	148	(9.8%)
Duration ≥5 yr	676	(90.0%)	686	(90.0%)	1362	(90.0%)
<b>Duration of Hypertension</b>						
Not Available	112	(14.9%)	110	(14.4%)	222	(14.7%)
<10 yr	387	(51.5%)	409	(53.7%)	796	(52.6%)
Duration ≥10 yr	252	(33.6%)	243	(31.9%)	495	(32.7%)
<b>Treatment for Hypertension</b>	<b>694</b>	<b>(92.4%)</b>	<b>721</b>	<b>(94.6%)</b>	<b>1415</b>	<b>(93.5%)</b>
<b>Prior Amputation</b>						
No	686	(91.3%)	692	(90.8%)	1378	(91.1%)
Yes	65	(8.7%)	70	(9.2%)	135	(8.9%)
<b>Prior Anemia</b>						
No	590	(78.6%)	594	(78.0%)	1184	(78.3%)
Yes	161	(21.4%)	168	(22.0%)	329	(21.7%)

Table 3 (Cont.)

Patient Demographic and Other Baseline Characteristics

	Losartan (N=751)		Placebo (N=762)		Total (N=1513)	
	n	(%)	n	(%)	n	(%)
<b>Prior Angina</b>						
No	685	(91.2%)	687	(90.2%)	1372	(90.7%)
Yes	66	(8.8%)	75	(9.8%)	141	(9.3%)
<b>Prior Laser Therapy, Eye</b>						
No	701	(93.3%)	707	(92.8%)	1408	(93.1%)
Yes	50	(6.7%)	55	(7.2%)	105	(6.9%)
<b>Prior MI</b>						
No	663	(88.3%)	657	(86.2%)	1320	(87.2%)
Yes	88	(11.7%)	105	(13.8%)	193	(12.8%)
<b>Prior Neuropathy</b>						
No	374	(49.8%)	382	(50.1%)	756	(50.0%)
Yes	377	(50.2%)	380	(49.4%)	757	(50.0%)
<b>Prior Retinopathy</b>						
No	256	(34.1%)	290	(38.1%)	546	(36.1%)
Yes	495	(65.9%)	472	(61.9%)	967	(63.9%)
<b>Prior Stroke</b>						
No	751	(100.0%)	761	(99.9%)	1512	(99.9%)
Yes	0	(0.0%)	1	(0.1%)	1	(0.1%)
<b>Prior Insulin</b>						
No	290	(38.6%)	313	(41.1%)	603	(39.9%)
Yes	461	(61.4%)	449	(58.9%)	910	(60.1%)
<b>Prior ACE Inhibitor</b>						
No	375	(49.9%)	401	(52.6%)	776	(51.3%)
Yes	376	(50.1%)	361	(47.4%)	737	(48.7%)
<b>Prior AIIA</b>						
No	722	(96.1%)	742	(97.4%)	1464	(96.8%)
Yes	29	(3.9%)	20	(2.6%)	49	(3.2%)
<b>Prior Oral-Antidiabetics</b>						
No	390	(51.9%)	381	(50.0%)	771	(51.0%)
Yes	361	(48.1%)	381	(50.0%)	742	(49.0%)
<b>Prior Aspirin</b>						
No	496	(66.0%)	518	(68.0%)	1014	(67.0%)
Yes	255	(34.0%)	244	(32.0%)	499	(33.0%)
<b>Prior Lipid-Lowering Agents</b>						
No	477	(63.5%)	487	(63.9%)	964	(63.7%)
Yes	274	(36.5%)	275	(36.1%)	549	(36.3%)
† Some patients were randomized who did not meet entry criteria for age or serum creatinine.						
SD = standard deviation.						

## **2.5 Summary of Efficacy**

### **2.5.1 Summary of Primary Efficacy Parameters**

#### Composite Endpoint of Doubling Serum Creatinine, ESRD, or Death

Table 4 shows results for the primary composite endpoint. By the intention-to-treat analysis, 327 patients (43.5% of total 751 patients) given losartan versus 359 (47.1% of total 762 patients) given placebo experienced the primary endpoint. Losartan treatment resulted in a risk reduction of 16.1% ( $p=0.022$ ) adjusted (pre-defined) for region and baseline proteinuria stratum (UA/Cr <2000 mg/g or UA/Cr  $\geq$ 2000 mg/g). The 95.2% confidence interval (corresponding to the 4.8% significance level for the primary analysis, due to adjustment for the interim efficacy analysis) for the risk reduction was (2.3%, 27.9%).

The Kaplan-Meier curves for the primary composite endpoint using the intention-to-treat approach are shown in Figure 3. Note that the risk reduction and p-value were obtained from the primary analysis when adjusted for region and baseline proteinuria stratum (UA/Cr <2000 mg/g or UA/Cr  $\geq$ 2000 mg/g). The sample sizes below the curves represent the number of patients at risk at various time points; i.e., the number of patients with the corresponding months of follow-up who had not yet had an event. Losartan treatment had lower event rates than placebo treatment over the entire study. With regard to Figure 3, the convergence of the losartan and placebo curves after Month 36 is probably due to the small numbers of patients at risk in both treatment groups at the later time points of the study.

Furthermore, 2 pre-defined supportive analyses were conducted, the 6-month lagged-censoring approach which censored patients on 10-Feb-2001, or 6 months after study drug discontinuation, whichever came first, and the per-protocol approach which excluded protocol violators and censored patients on 10-Feb-2001, or 14 days after study drug discontinuation, whichever came first (Table 4). Both supportive analyses confirmed the results of the primary analysis. By the 6-month lagged censoring analysis, losartan treatment resulted in a risk reduction of 18.8% ( $p=0.017$ ), and by the per-protocol analysis, losartan conferred a 22.5% ( $p=0.007$ ) risk reduction. As compared with the results from the ITT approach, the risk reductions were larger for the lagged censoring and per-protocol approaches, suggesting that discontinuation of study therapy diminished losartan's treatment effect.

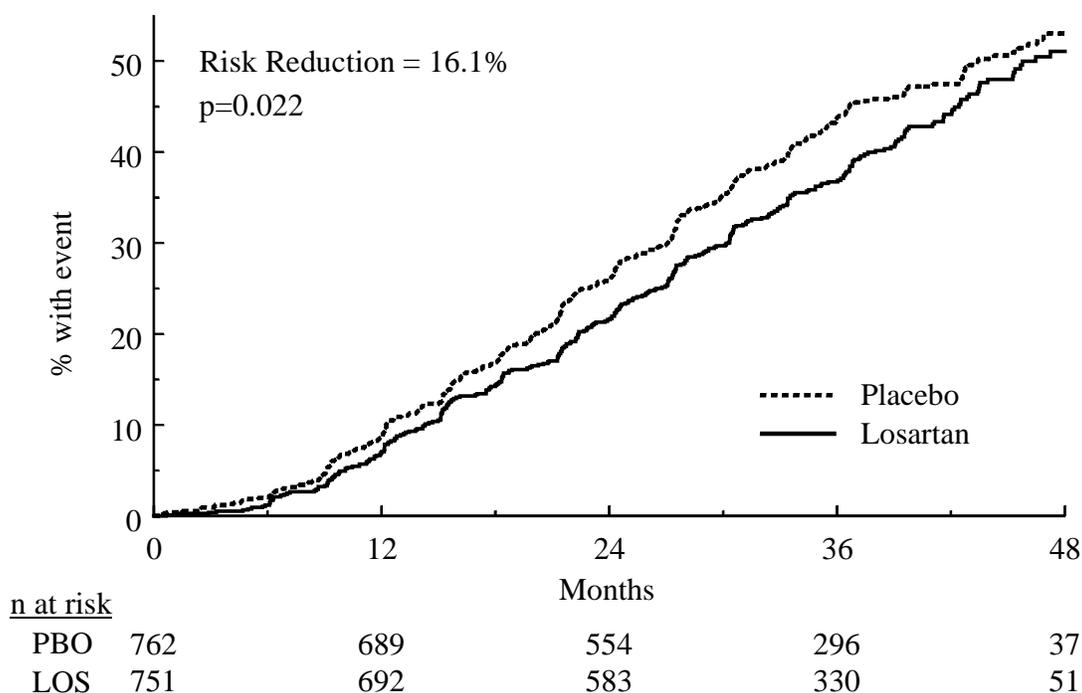
Table 4

Composite Endpoint of Doubling Serum Creatinine,  
 End-Stage Renal Disease (ESRD), or Death

Approach	Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95.2% CI	p-Value
<b>Primary Analysis</b>					
Intention-to-treat	327/751 (43.5)	359/762 (47.1)	16.1%	(2.3%, 27.9%)	0.022
<b>Supportive Analyses</b>					
Six-month lagged censoring	254/751 (33.8)	276/762 (36.2)	18.8%	(3.5%, 31.7%)	0.017
Per protocol	215/747 (28.8)	240/760 (31.6)	22.5%	(6.7%, 35.7%)	0.007
n/N = number of patients who had an event/total number of patients pertaining to each approach. Est. = estimation using a proportional hazards regression model with pre-specified adjustment for region and baseline proteinuria stratum (UA/Cr <2000 mg/g or ≥2000 mg/g). CI = confidence interval. The 95.2% CI corresponds to the 4.8% significance level for the primary analysis, due to adjustment for the interim efficacy analysis.					

Figure 3

Kaplan-Meier Curve for Composite Endpoint of Doubling Serum Creatinine, End-Stage Renal Disease (ESRD), or Death (Intention-to-Treat)



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Components of the Composite Endpoint: Doubling Serum Creatinine, ESRD, or Death

Analyses were also performed to compare the losartan treatment effect on the following 3 individual components of the composite endpoint and on 2 combined components of the primary endpoint: (a) time to doubling of serum creatinine concentration (censoring patients at the time of ESRD or death), (b) time to ESRD (ignoring any events of doubling of serum creatinine and censoring patients at time of death), (c) time to death (ignoring any events of doubling of serum creatinine and ESRD), (d) time to the combined component endpoint of ESRD or death (ignoring any events of doubling of serum creatinine), and (e) time to the combined component endpoint of ESRD or doubling of serum creatinine concentration (censoring patients at the time of death).

Table 5 shows that the risk of doubling of serum creatinine concentration was reduced by 25.3% (p=0.006) and the risk of ESRD was reduced by 28.6% (p=0.002) in patients treated with losartan. Approximately 20% of patients died, with no difference between the 2 treatment groups (p=0.884). Losartan reduced the risk of the combined component endpoint of ESRD or death by 19.9% (p=0.009), and the combined component endpoint

of ESRD or doubling of serum creatinine concentration by 21.0% (p=0.010). The raw cumulative event rates for the 2 individual components of ESRD and death, and the combined component of ESRD or death are shown in Figure 4, based on the Kaplan-Meier curve using the intention-to-treat analysis.

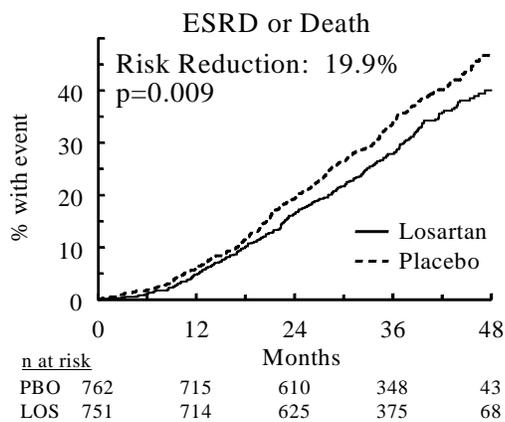
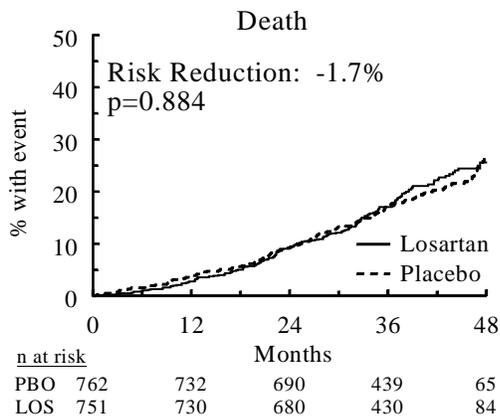
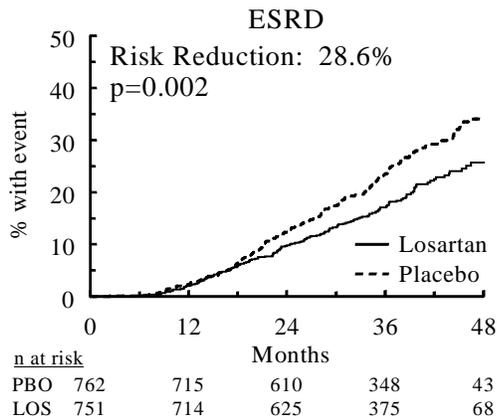
Also provided in Table 5 are the risk reductions of the 3 individual components and 2 combined components using the prespecified, supportive 6-month lagged censoring and per-protocol approaches, which were described for the primary endpoint. As described previously for the composite endpoint, a stronger treatment effect with a higher risk reduction was observed for every component, suggesting that discontinuation of losartan diminished losartan’s treatment effect.

Table 5

Individual or Combined Components of Doubling of Serum Creatinine (sCr), End-Stage Renal Disease (ESRD), or Death (Results of Intention-to-Treat [ITT], Lagged Censoring, and Per-Protocol Analyses)

Component	Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95% CI	p-Value
<b>Primary—ITT</b>					
Doubling of sCr	162/751 (21.6)	198/762 (26.0)	25.3%	(7.8%, 39.4%)	0.006
ESRD	147/751 (19.6)	194/762 (25.5)	28.6%	(11.5%, 42.4%)	0.002
Death	158/751 (21.0)	155/762 (20.3)	-1.7%	(-26.9%, 18.6%)	0.884
ESRD or death	255/751 (34.0)	300/762 (39.4)	19.9%	(5.3%, 32.3%)	0.009
Doubling of sCr or ESRD	226/751 (30.1)	263/762 (34.5)	21.0%	(5.6%, 33.9%)	0.010
<b>Six-Month Lagged Censoring</b>					
Doubling of sCr	145/751 (19.3)	175/762 (23.0)	28.1%	(10.2%, 42.5%)	0.003
ESRD	100/751 (13.3)	136/762 (17.8)	35.4%	(16.2%, 50.1%)	<0.001
Death	100/751 (13.3)	100/762 (13.1)	6.5%	(-23.5%, 29.1%)	0.638
ESRD or death	174/751 (23.2)	210/762 (27.6)	26.0%	(9.4%, 39.5%)	0.003
Doubling of sCr or ESRD	184/751 (24.5)	209/762 (27.4)	23.0%	(6.1%, 36.9%)	0.010
<b>Per Protocol</b>					
Doubling of sCr	137/747 (18.3)	163/760 (21.4)	28.5%	(10.0%, 43.2%)	0.004
ESRD	73/747 (9.8)	105/760 (13.8)	41.1%	(20.4%, 56.3%)	<0.001
Death	64/747 (8.6)	70/760 (9.2)	16.6%	(-17.2%, 40.6%)	0.296
ESRD or death	125/747 (16.7)	160/760 (21.1)	32.0%	(14.0%, 46.2%)	0.001
Doubling of sCr or ESRD	167/747 (22.4)	189/760 (24.9)	24.4%	(6.8%, 38.7%)	0.009
n/N = number of patients who had an event/total number of patients pertaining to each approach. Est. = estimation using a proportional hazards regression model with adjustment for region and stratum. CI = confidence interval.					

Figure 4  
 Kaplan-Meier Curves for End-Stage Renal Disease (ESRD),  
 Death, and ESRD or Death (Intention-to-Treat)



### **2.5.1.1 The Impact of Baseline Proteinuria on the Primary Endpoint**

In type 1 diabetic and nondiabetic patients with proteinuria, it has been demonstrated that proteinuria is an independent risk factor for progression of renal disease [17; 42; 18]. As illustrated in Figure 5, RENAAL also has demonstrated that in type 2 diabetic patients with proteinuria, there is a strong relationship between baseline proteinuria and the risk of having a primary outcome. For the overall population, patients with higher baseline proteinuria, relative to 300 mg/g as a reference, were at increased risk for having a primary event during the course of follow-up and that even relatively small increases in baseline proteinuria translate into substantial increases in risk of primary events.

Because of the known effects of proteinuria on renal progression in type 1 diabetics and non-diabetics, patients were stratified in the present study at randomization based on baseline proteinuria, i.e., UA/Cr <2000 mg/g and UA/Cr ≥2000 mg/g. Despite this stratification, as summarized earlier (Section 2.4), there was a slight imbalance in baseline proteinuria between the 2 treatment groups (1873 mg/g in losartan group, 1743 mg/g in placebo group). More importantly, there was an imbalance in the distribution of patients in the ≥2000 mg/g stratum of proteinuria. As seen in Figure 6, this imbalance in distribution mainly occurred in the ≥4000 mg/g category, where there were 21 more losartan patients compared to placebo patients (n=92 losartan, n=71 placebo). To explore the effect of this imbalance in baseline proteinuria, it was reasonable to adjust post hoc the primary composite endpoint for baseline proteinuria as a continuous covariate, which increased the magnitude and significance of the risk reduction (22.2%; p=0.001) (Table 6).

Figure 5

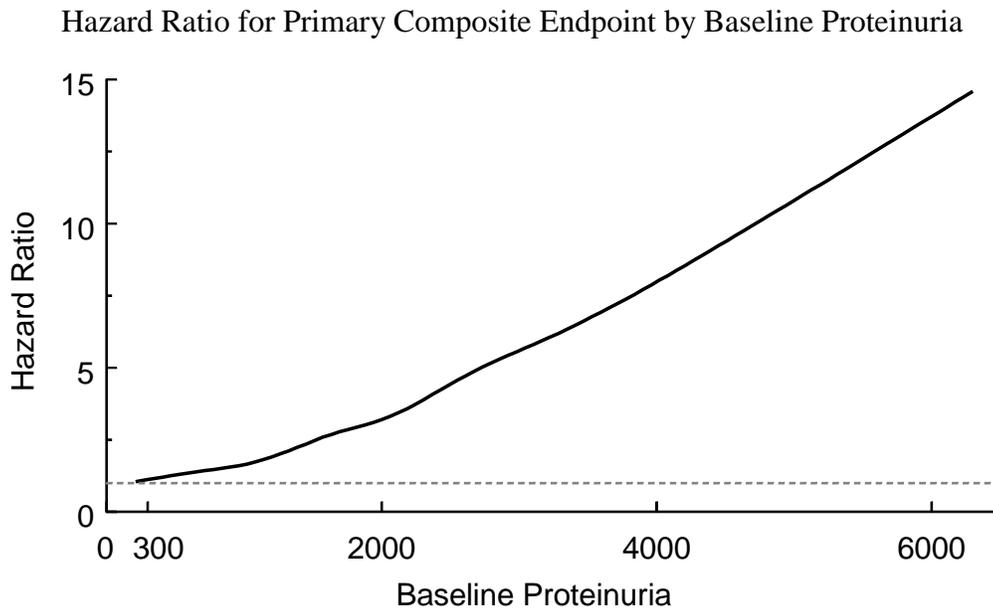


Figure 6

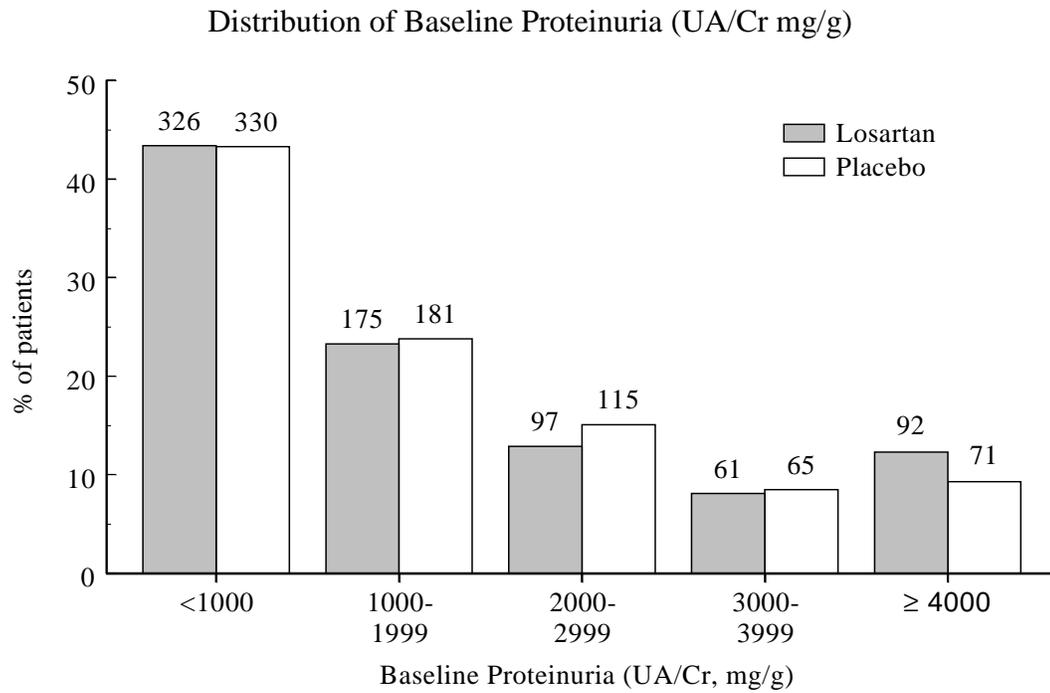


Table 6

Primary Composite Endpoint of Doubling of Serum Creatinine,  
 ESRD or Death Adjusted for Baseline Proteinuria (Continuous Covariate)

Approach	Original			Adjusted for Baseline Proteinuria		
	Est. Risk Reduction	95.2% CI	p-Value	Est. Risk Reduction	95.2% CI	p-Value
<b>++Primary Analysis</b>						
Intention-to-treat	16.1%	2.3, 27.9	0.022	22.2%	9.4, 33.2	0.001
<b>Supportive Analysis</b>						
Per protocol	22.5%	6.7, 35.7	0.007	29.0%	14.3, 41.2	<0.000
The 95.2% CI corresponds to the 4.8% significance level for the primary analysis, due to adjustment for the interim efficacy analysis						

Similarly, when adjusting the analysis of the individual components and combined components of the primary composite endpoint, particularly ESRD or death, for the imbalances in baseline proteinuria, increases in risk reductions were observed (Table 7).

Table 7

Individual or Combined Components of Doubling of Serum Creatinine (sCr),  
 End-Stage Renal Disease (ESRD), or Death: Adjusted for Baseline Proteinuria  
 (Continuous Covariate)

Approach	Original			Adjusted for Baseline Proteinuria		
	Est. Risk Reduction	95% CI	p-Value	Est. Risk Reduction	95% CI	p-Value
<b>Primary—ITT</b>						
ESRD	28.6%	11.5, 42.4	0.002	36.7%	21.3, 49.0	<0.001
Death	-1.7%	-26.9, 18.6	0.884	1.3%	-23.3, 21.0	0.907
ESRD or death	19.9%	5.3, 32.3	0.009	25.7%	12.1, 37.3	<0.001
Doubling of sCr or ESRD	21.0%	5.6, 33.9	0.010	28.4%	14.4, 40.2	<0.001
<b>Per Protocol</b>						
ESRD	41.1%	20.4, 56.3	<0.001	45.4%	26.2, 59.6	<0.001
Death	16.6%	-17.2, 40.6	0.296	18.5%	-14.6, 42.0	0.240
ESRD or death	32.0%	14.0, 46.2	<0.001	35.5%	18.4, 49.1	<0.001
Doubling of sCr or ESRD	24.4%	6.8, 38.7	0.009	32.3%	16.4, 45.2	<0.001

### 2.5.1.2 Blood Pressure Control and Its Impact on the Primary Endpoint

#### Mean Profile Over Time

Blood pressure was aggressively treated with standard antihypertensive drugs in all patients in RENAAL in order to achieve comparable blood pressure control in the 2 treatment groups.

Table 8 shows mean arterial pressure (MAP) over time for each treatment group, and difference of means between losartan- and placebo-treated groups. Overall, patients assigned to losartan achieved a slightly lower MAP (~2 mm Hg) compared to patients assigned to placebo. During the first year, the differences in MAP between losartan and placebo were consistently >2 mm Hg; thereafter, differences between treatment groups were smaller over the course of the study.

Table 8

Mean Arterial Pressure (MAP) (mm Hg) Prior to Primary Endpoint (Intention-to-Treat)

Time	Losartan			Placebo			Mean Difference (Losartan-Placebo)	p-Value
	n	Mean	SD	n	Mean	SD		
Baseline	751	105.53	10.92	762	106.03	11.60	-0.50	0.387
Week 1	731	103.24	11.47	738	105.74	11.86	-2.50	<0.001
Month 1	721	103.16	11.79	732	106.03	12.00	-2.87	<0.001
Month 3	734	102.84	12.62	731	105.66	12.01	-2.81	<0.001
Month 6	714	102.04	11.45	705	105.24	11.52	-3.20	<0.001
Month 9	691	102.17	12.04	670	104.35	11.75	-2.17	<0.001
Month 12	662	100.75	11.50	641	103.09	11.45	-2.34	<0.001
Month 15	617	100.05	11.03	599	101.78	10.79	-1.74	0.006
Month 18	589	99.10	11.09	553	101.35	10.96	-2.25	<0.001
Month 21	559	99.75	12.24	523	101.22	10.30	-1.48	0.033
Month 24	529	98.91	11.30	491	99.80	10.33	-0.89	0.192
Month 27	498	96.69	10.30	453	99.22	10.26	-2.52	<0.001
Month 30	443	97.00	10.39	401	98.55	10.07	-1.55	0.028
Month 33	374	96.15	10.81	320	98.92	10.63	-2.77	<0.001
Month 36	295	95.77	10.10	247	99.32	10.14	-3.55	<0.001
Month 39	226	96.37	10.14	185	97.89	9.82	-1.51	0.128
Month 42	164	95.42	9.49	133	97.11	9.92	-1.69	0.136
Month 45	101	94.83	9.79	86	96.77	10.06	-1.93	0.186
Month 48	44	93.07	10.48	30	96.58	7.31	-3.51	0.117

SD denotes standard deviation.

### Pre-Specified Correction for Mean Arterial Pressure (MAP) on the Primary Endpoint Analysis

The treatment effect on the primary composite endpoint was adjusted for MAP, a prespecified time-varying covariate. This analysis showed that the treatment effect was relatively unaffected by small differences in MAP, with a risk reduction of 15.2% ( $p=0.033$ ). After adjusting the ESRD component by MAP, the treatment effect was only slightly affected with a risk reduction of 26.1% ( $p=0.006$ ). When the combined component of ESRD or death was adjusted by MAP, again, the treatment effect was only slightly affected with a risk reduction of 19.1% ( $p=0.013$ ).

These results indicate that renal protection conferred by losartan exceeded that attributable to any small differences in blood pressure over the course of the study. Thus, although blood pressure control is important in renal protection, the beneficial effects on renal protection observed in RENAAL are beyond that attributable to a reduction in blood pressure alone.

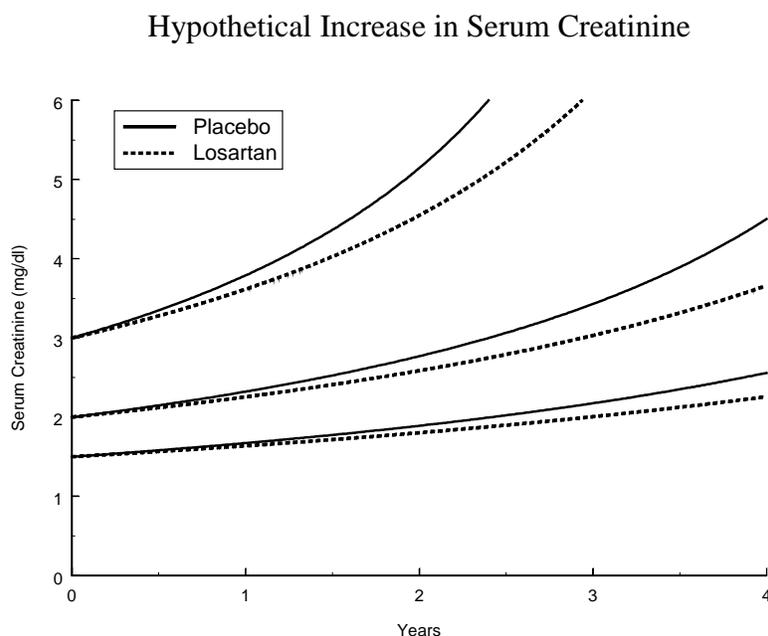
### **2.5.2 Summary of Secondary Efficacy Parameters**

#### **2.5.2.1 Rate of Loss of Renal Function (Slope of 1/Cr)**

One of the secondary objectives was the evaluation of renal disease progression. Renal disease progression was defined as the rate of loss of renal function measured by the slope of the reciprocal of serum creatinine ( $1/sCr$ ) across time (year) during the study. This measure is commonly used by clinical nephrologists to predict long-term renal outcome and time to ESRD [21]. The importance of this analysis is that it takes into consideration all patients who had a renal event. A negative slope indicates a loss of renal function. The more negative the slope, the faster the loss of renal function occurred. As compared with placebo, treatment with losartan reduced the rate of loss in renal function. The median on-treatment slopes of  $1/sCr$  were  $-0.0573$  in the losartan group and  $-0.0703$  in the placebo group. Thus, the reduction in the rate of loss of renal function associated with losartan is 18.5% ( $p=0.011$ ). This secondary outcome demonstrated that losartan significantly reduced the rate of progression of renal disease, and underscores the consistency of the beneficial effect of losartan on renal protection in this study of type 2 diabetic patients.

To illustrate the clinical impact of a difference in slope of  $1/sCr$  as large as was observed in RENAAL, Figure 7 depicts the progression of serum creatinine of *hypothetical* patients treated with placebo or losartan. Each pair of lines starting from a common value at 0 years represents patients with the same starting serum creatinine values (starting values of 1.5, 2, and 3 are used for illustration). The curves represent the progression of serum creatinine values in these patients assuming that the slope of  $1/sCr$  values (i.e., the Mitch curve) [21] is linear, the slope of  $1/sCr$  in the losartan group is  $-0.0573$  dL/mg/yr, and the slope in the placebo group is  $-0.0703$  dL/mg/yr (i.e., actual median values observed in RENAAL). Figure 7 illustrates the degree to which the rate of loss of renal function is greater in hypothetical patients taking placebo than that of patients taking losartan.

Figure 7



### 2.5.2.2 Reduction in Proteinuria

Another secondary hypothesis in the RENAAL study was that losartan would reduce proteinuria compared to placebo during the course of the study. Reduction of proteinuria has been a therapeutic target in the treatment of diabetic nephropathy among practicing nephrologists. In RENAAL, proteinuria was reduced within 3 months of initiation of losartan compared to placebo and the reduction was sustained over the course of the study.

It was prespecified that the proteinuria values would be log-transformed for the analysis. Table 9 summarizes differences in proteinuria between the 2 treatment groups over time, based on the pre-specified on-treatment approach. Because lab measurements were inconsistent after patients discontinued study drug, the on-treatment approach produced a more accurate assessment of changes in proteinuria. Table 9 summarizes the number of patients (n) whose postrandomization values of proteinuria were available for each time point; geometric mean (GM); and geometric mean when adjusted by baseline proteinuria (Adj. GM). The adjusted reductions in proteinuria between the 2 treatment groups were calculated as  $100 \times (1 - \text{Adj. GMR})\%$  (losartan versus placebo), where GMR refers to GM ratio. As seen in Table 9, losartan treatment led to an adjusted (for baseline) reduction in proteinuria over time from 29% at Month 3 to 44% after Year 3. The adjusted reduction is plotted for each treatment group in Figure 8.

Table 9

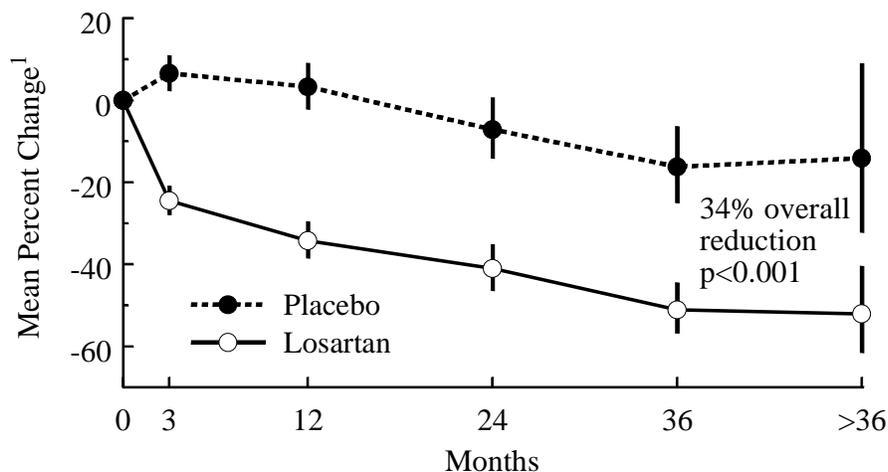
Summary of Proteinuria (mg/g) Over Time (On-Treatment)

Month	Losartan			Placebo			Reduction <sup>†</sup> (%)
	n	GM	Adj. GM	n	GM	Adj. GM	
0	751	1172.52	1.00	762	1148.50	1.00	0
3	719	885.33	0.75	710	1224.75	1.07	29
12	661	726.43	0.66	632	1146.26	1.03	36
24	558	596.69	0.59	529	951.68	0.93	37
36	432	448.87	0.49	389	768.85	0.84	42
>36	163	408.40	0.48	120	680.34	0.86	44

<sup>†</sup> Based on Adj. GM (losartan versus placebo).  
 n = Number of patients whose postrandomization values of proteinuria were available for each time-point.  
 GM = Geometric mean.  
 Adj. GM = Adjusted geometric mean.

Figure 8

Mean (95% CI) Percent Change of Proteinuria Over Time for Each Treatment Group (On-Treatment)



<sup>1</sup> Based on geometric mean. Vertical bars around mean percent change = 95% CI.

Table 10 shows model-based reductions in proteinuria over time (previously described in Section 2.2). This analysis was performed in order to determine the overall reduction in proteinuria, taking all time points into consideration. Overall, losartan treatment reduced proteinuria by 34.3% (p-value <0.001).

Table 10

Proteinuria: Model-Based Percent Reduction

	n	Est. Reduction	p-Value
<b>Primary Analysis (on -treatment)</b>			
Overall	1443	34.3%	<0.001
n = Number of patients who had postrandomization measurements of proteinuria. Est. = Estimated using a fixed effects model adjusted for region and baseline proteinuria.			

**2.5.2.2.1 Impact of Blood Pressure on Proteinuria Reduction**

In order to determine whether blood pressure reduction influenced proteinuria reduction during the course of the study, the effects of losartan on changes in proteinuria were analyzed after adjusting for blood pressure (pre-specified analysis). Table 11 shows reduction in proteinuria over time with and without blood pressure adjustment, using the on-treatment approach. The sample size (n) represents the number of patients with postrandomization values of proteinuria at or before each time point. With adjustment for both diastolic and systolic blood pressure, the reduction in proteinuria was diminished by 2 to 6% as compared with the reduction without the adjustment. The effect of losartan on proteinuria reduction remained significant after adjusting for the blood pressure differences between the treatment groups (p<0.001).

Table 11

Reduction in Proteinuria Over Time With or Without Adjustment for  
 Systolic and Diastolic Blood Pressure (BP) (On-Treatment)

Time	n	Reduction Without BP Adjustment		With BP Adjustment	
		Reduction in Proteinuria	p-Value	Reduction in Proteinuria	p-Value
Month 3	1371	27.5%	<0.001	25.2%	<0.001
Month 6	1431	31.3%	<0.001	29.1%	<0.001
Year 1	1444	33.6%	<0.001	31.3%	<0.001
Year 2	1445	32.8%	<0.001	30.0%	<0.001
Year 3	1445	35.5%	<0.001	30.3%	<0.001
Last	1445	36.7%	<0.001	32.4%	<0.001
n = Number of patients who had postrandomization measurements of proteinuria prior to and at each time interval.					

### **2.5.2.3 Composite Endpoint of Cardiovascular Morbidity and Mortality**

The third secondary endpoint was the composite of cardiovascular morbidity/mortality, which was prespecified in the Data Analysis Plan as myocardial infarction (MI), stroke, hospitalization for heart failure (HF) or unstable angina, revascularization (coronary or peripheral), or cardiovascular (CV) deaths. Since type 2 diabetic patients are at risk for cardiovascular events, cardiovascular morbidity and mortality events were recorded, adjudicated, and analyzed as a secondary comparison. The secondary hypothesis was that long-term treatment with losartan compared to placebo in patients with type 2 diabetes with nephropathy would increase the time to first composite event of cardiovascular morbidity and mortality. Confirmation of the impact of losartan on cardiovascular outcomes must await the availability of results from larger clinical trials that were designed to evaluate cardiovascular outcomes, particularly the LIFE study, which includes diabetic patients.

There was no statistically significant difference between losartan and placebo for this endpoint of cardiovascular morbidity and mortality (Table 12). By the intention-to-treat analysis, the composite endpoint of cardiovascular morbidity and mortality was reached in 247 patients (32.9% of total 751 patients) given losartan versus 268 patients (35.2% of total 762 patients) given placebo. Losartan treatment resulted in an estimated reduction of risk of 9.6% (p=0.253) with 95% confidence interval (-7.5%, 24.0%). The cumulative event rate for the secondary composite endpoint using the intention-to-treat approach is shown in Figure 9 based on the Kaplan-Meier curve.

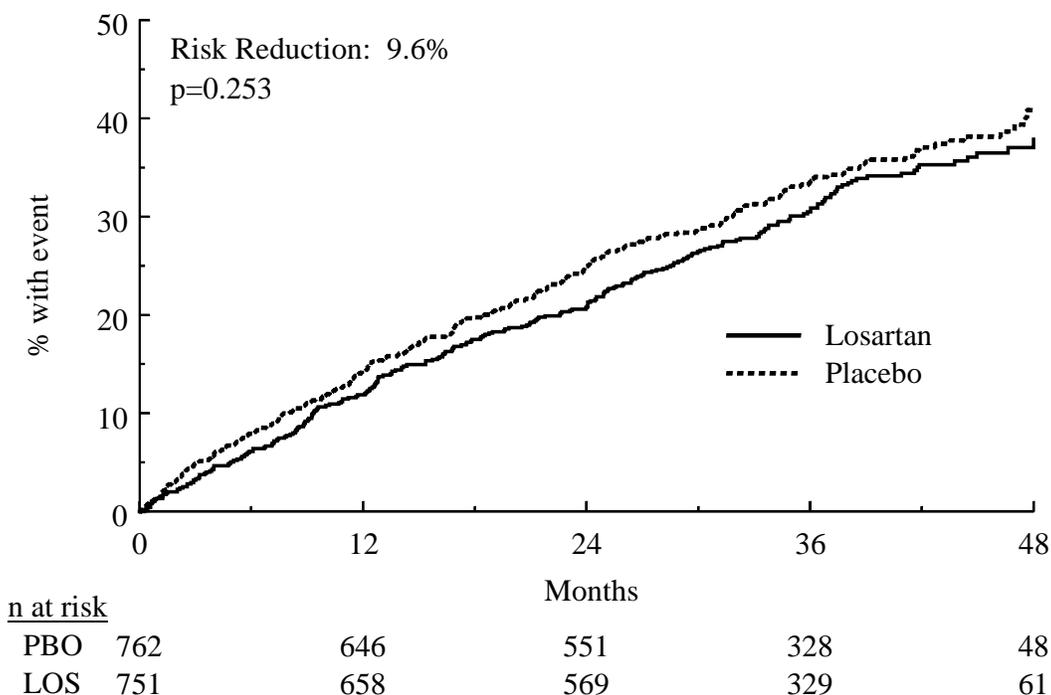
Table 12

Composite Endpoint of Cardiovascular Morbidity/Mortality

Approach	Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95% CI	p-Value
<b>Primary</b>					
Intention-to-treat	247/751 (32.9)	268/762 (35.2)	9.6%	(-7.5%, 24.0%)	0.253
n/N = Number of patients who had an event/total number of patients. Est. = Estimation using a proportional hazards regression model with adjustment for region and stratum. CI = Confidence interval.					

Figure 9

Kaplan-Meier Curves for Composite of  
 Cardiovascular Morbidity/Mortality (Intention-to-Treat)



Components of Cardiovascular Morbidity and Mortality

An analysis was also performed to compare the losartan treatment effect with respect to all 6 individual components of the cardiovascular morbidity and mortality composite. For the intention-to-treat analysis, there were no significant differences in the effect of losartan versus placebo on these cardiovascular components, with one exception: first hospitalization for heart failure (89 patients with losartan versus 126 with placebo), for which the risk was reduced by 31.6% (p=0.006) (Table 13). In addition, another difference that approached statistical significance (p=0.079) was found in the number of myocardial infarctions between the losartan (50 patients) and placebo (68 patients) groups (risk reduction = 28.0%).

Table 13

Components of Cardiovascular Morbidity/Mortality

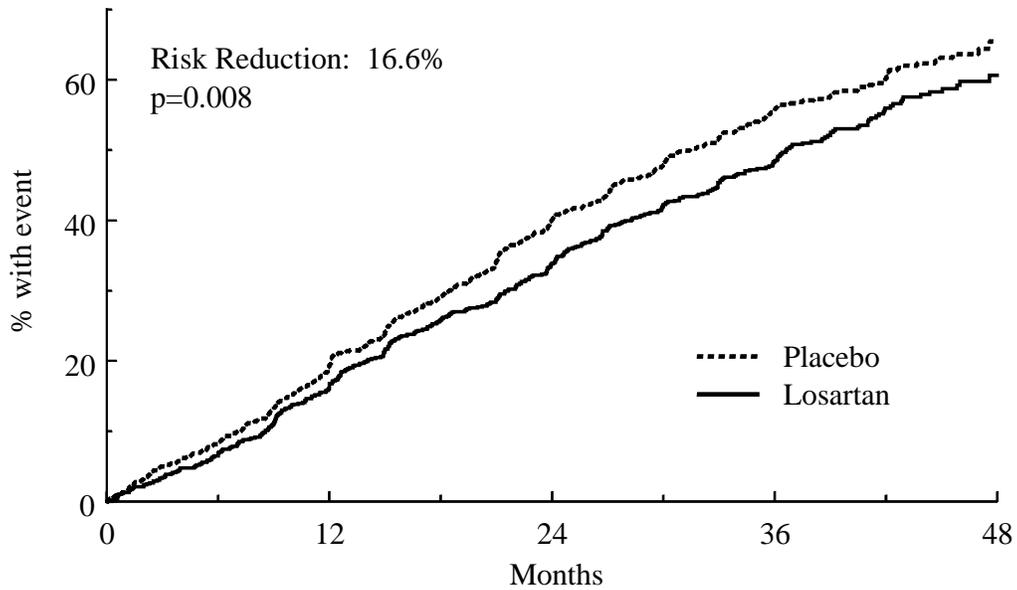
Components	Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95% CI	p-Value
<b>Intention-to-Treat</b>					
Hospitalization for heart failure	89/751 (11.9)	126/762 (16.5)	31.6%	(10.3%, 47.9%)	0.006
MI	50/751 (6.7)	68/762 (8.9)	28.0%	(-3.8%, 50.0%)	0.079
Revascularization	69/751 (9.2)	60/762 (7.9)	-18.5%	(-67.5%, 16.2%)	0.337
Stroke	47/751 (6.3)	50/762 (6.6)	5.5%	(-40.8%, 36.5%)	0.783
Hospitalization for unstable angina	42/751 (5.6)	41/762 (5.4)	-3.2%	(-58.6%, 32.9%)	0.888
Cardiovascular death	90/751 (12.0)	79/762 (10.4)	-12.3%	(-51.9%, 17.0%)	0.453
n/N = Number of patients that had an event/total number of patients. Est. = Estimation using a proportional hazards regression model with adjustment for region and stratum. CI = Confidence interval. MI = Myocardial infarction.					

Composite of the Primary Endpoint and the Secondary Cardiovascular Endpoints

Patients with type 2 diabetes may have numerous co-morbid conditions, one of which is cardiovascular disease. Patients in RENAAL were therefore not only at risk for renal outcomes, but also at risk for cardiovascular outcomes, rendering both competing events. Based on discussions that occurred during the 17-Jan-2002 FDA Cardio-Renal Advisory Committee Meeting, a post hoc analysis was performed to ascertain the effect of losartan treatment on the composite of the primary (renal) endpoint and the secondary (cardiovascular) endpoints (Figure 10). The results of this analysis show that losartan treatment was associated with a risk reduction of 16.6% (p=0.008).

Figure 10

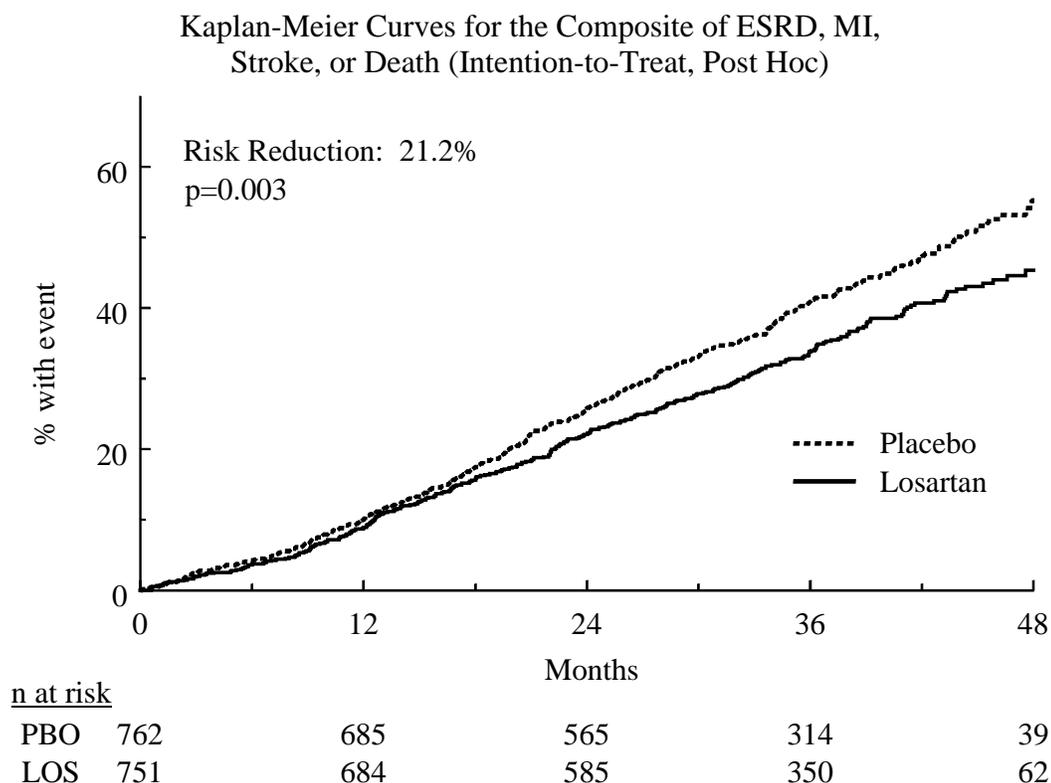
Kaplan-Meier Curves for the Composite of the Primary (Renal) and Secondary (Cardiovascular) Endpoints (Intention-to-Treat, Post Hoc)



<u>n at risk</u>					
PBO	762	614	456	234	30
LOS	751	625	497	272	40

Furthermore, a greater treatment effect is observed in an analysis (post hoc) of the composite of the hard endpoints of ESRD, MI, stroke, or death (whichever occurred first) (risk reduction: 21.2%; p=0.003) (Figure 11).

Figure 11



### **2.5.3 Additional Pre-Specified Analyses: Primary Composite Endpoint by Baseline Subgroups**

The primary composite endpoint was explored in subgroup analyses using the intention-to-treat approach. These analyses explored whether or not the effect of losartan compared to placebo was consistent in 18 predefined subgroups of patients (Table 14).

Consistent treatment effects were seen in all subgroups without any adjustment for multiplicity; only the interaction between region and treatment was statistically significant (p=0.044). However, it is not unexpected, when testing as many as 18 subgroups, that one would have a significant interaction by chance alone. It is important to note as well that the treatment effect favored losartan in all regions. Furthermore, there was no treatment-by-region interaction in the combined component of ESRD or death.

Table 14

Subgroup Analyses on Primary Composite Endpoint (Intention-to-Treat)

Subgroup (at Baseline)		Losartan		Placebo		Hazard Ratio (95% CI)	p-Value (Interaction)
		N	Event Rate n (%)	N	Event Rate n (%)		
Age	<65 years	503	222 (44.1)	502	246 (49.0)	0.784 (0.653, 0.941)	0.205
	≥65 years	248	105 (42.3)	260	113 (43.5)		
Body Mass Index	<30 kg/m <sup>2</sup>	416	185 (44.5)	457	221 (48.4)	0.850 (0.698, 1.034)	0.839
	≥30 kg/m <sup>2</sup>	314	132 (42.0)	291	133 (45.7)		
Dihydropyridine use	No	345	128 (37.1)	351	148 (42.2)	0.870 (0.687, 1.103)	0.773
	Yes	406	199 (49.0)	411	211 (51.3)		
Duration of hypertension	<10 yr	387	178 (46.0)	409	204 (49.9)	0.818 (0.669, 1.002)	0.807
	≥10 yr	252	105 (41.7)	243	105 (43.2)		
Gender	Female	289	138 (47.8)	268	145 (54.1)	0.762 (0.603, 0.962)	0.310
	Male	462	189 (40.9)	494	214 (43.3)		
Hemoglobin A <sub>1c</sub>	<10 %	600	248 (41.3)	621	285 (45.9)	0.812 (0.685, 0.964)	0.579
	≥10 %	142	74 (52.1)	133	72 (54.1)		
Hemoglobin	<12 gm/dL	296	158 (53.4)	284	167 (58.8)	0.766 (0.615, 0.953)	0.357
	≥12 gm/dL	436	164 (37.6)	452	181 (40.0)		
Insulin use	No	290	113 (39.0)	313	128 (40.9)	0.883 (0.685, 1.137)	0.563
	Yes	461	214 (46.4)	449	231 (51.4)		
Previous use of ACEI/AIIA <sup>†</sup>	No	351	146 (41.6)	386	180 (46.6)	0.832 (0.669, 1.036)	0.913
	Yes	400	181 (45.3)	376	179 (47.6)		
Proteinuria (UA/Cr)	<2000 mg/g	501	150 (29.9)	511	161 (31.5)	0.908 (0.727, 1.135)	0.301
	≥2000 mg/g	250	177 (70.8)	251	198 (78.9)		

Table 14 (Cont.)

Subgroup Analyses on Primary Composite Endpoint (Intention-to-Treat)

Subgroup (at Baseline)		Losartan			Placebo			Hazard Ratio (95% CI)	p-Value (Interaction)
		N	n	(%)	N	n	(%)		
Race	Asian	117	49	(41.9)	135	74	(54.8)	0.655 (0.453, 0.947)	0.344
	Black	125	50	(40.0)	105	41	(39.0)		
	Hispanic	140	77	(55.0)	137	74	(54.0)		
	White	358	145	(40.5)	377	163	(43.2)		
	Other	11	6	(54.5)	8	7	(87.5)		
Region	Asia	125	49	(39.2)	132	78	(59.1)	0.540 (0.376, 0.774)	0.044
	Latin America	137	78	(56.9)	137	80	(58.4)		
	Europe	151	58	(38.4)	144	51	(35.4)		
	North America	338	142	(42.0)	349	150	(43.0)		
Serum albumin	<3.6 mg/dL	192	134	(69.8)	191	141	(73.8)	0.792 (0.623, 1.006)	0.683
	≥3.6 mg/dL	544	184	(33.8)	560	214	(38.2)		
Serum creatinine	<2.0 mg/dL	482	174	(36.1)	483	173	(35.8)	0.945 (0.765, 1.167)	0.097
	≥2.0 mg/dL	269	153	(56.9)	279	186	(66.7)		
Serum uric acid	<7 mg/dL	459	197	(42.9)	448	203	(45.3)	0.899 (0.739, 1.095)	0.359
	≥7 mg/dL	292	130	(44.5)	314	156	(49.7)		
Sitting systolic blood pressure	<140 mm Hg	191	60	(31.4)	187	66	(35.3)	0.879 (0.619, 1.248)	0.624
	≥140 mm Hg	560	267	(47.7)	575	293	(51.0)		

Table 14 (Cont.)

Subgroup Analyses on Primary Composite Endpoint (Intention-to-Treat)

Subgroup (at Baseline)		Losartan		Placebo		Hazard Ratio (95% CI)	p-Value (Interaction)
		N	Event Rate n (%)	N	Event Rate n (%)		
Smoking	Nonsmoker	604	258 (42.7)	632	298 (47.2)	0.818 (0.692, 0.967)	0.555
	Smoker	145	69 (47.6)	128	60 (46.9)	0.940 (0.663, 1.333)	
Total cholesterol	<240 mg/dL	488	183 (37.5)	482	204 (42.3)	0.830 (0.679, 1.015)	0.815
	≥240 mg/dL	255	140 (54.9)	273	154 (56.4)	0.807 (0.641, 1.017)	

† ACEI refers to angiotensin converting enzyme inhibitor and AIIA refers to angiotensin II antagonist.

## **2.6 Summary of Safety**

In this population of type 2 diabetic patients with underlying kidney disease, many had complications of diabetes and other progressive, co-morbid conditions. Also, many patients were taking multiple drugs that would have predisposed them to an increased incidence of adverse experiences, especially over the extended time frame of the study. In addition to evaluating the prespecified tabulations of clinical and laboratory adverse experiences, 6 prespecified adverse experiences of special interest in this population were analyzed.

### **2.6.1 Summary of Clinical Adverse Experiences**

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a preexisting condition, temporally associated with the use of study drug, whether or not considered drug related. The summary of clinical adverse experiences that occurred on study therapy, or within 14 days of discontinuation of study therapy, is presented in Table 15. Overall, the incidence of patients reporting at least one adverse experience was similar between losartan and placebo (95.3% and 95.7%, respectively; relative risk (RR)=1.00;95%CI: 0.98, 1.02) even though the extent of exposure to losartan was longer (mean of 913 days) compared to placebo (mean of 845 days). No reports of adverse experiences demonstrating an interaction of losartan with commonly used oral hypoglycemic agents or insulin were observed.

Table 15

Clinical Adverse Experience Summary

	Losartan (N=751)		Placebo (N=762)		Relative Risk Losartan Versus Placebo
	n	(%)	n	(%)	(95% CI)
With one or more adverse experiences	716	(95.3)	729	(95.7)	1.00 (0.98, 1.02)
With no adverse experience	35	(4.7)	33	(4.3)	1.08 (0.68, 1.71)
With drug-related adverse experiences <sup>†</sup>	129	(17.2)	106	(13.9)	1.23 (0.97, 1.56)
With serious adverse experiences	481	(64.0)	487	(63.9)	1.00 (0.93, 1.08)
With serious drug-related adverse experiences	24	(3.2)	20	(2.6)	1.22 (0.68, 2.16)
Who died	68	(9.1)	70	(9.2)	0.99 (0.72, 1.35)
Discontinued due to adverse experiences	143	(19.0)	185	(24.3)	0.78 (0.65, 0.95)
Discontinued due to drug-related adverse experiences	14	(1.9)	18	(2.4)	0.79 (0.40, 1.57)
Discontinued due to serious adverse experiences	107	(14.2)	141	(18.5)	0.77 (0.61, 0.97)
Discontinued due to serious drug-related adverse experiences	6	(0.8)	12	(1.6)	

<sup>†</sup> Determined by the investigator to be possibly, probably, or definitely drug related.  
 Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.  
 CI = Confidence interval, 95% CI provided if total events were >22.

**2.6.1.1 Drug-Related Clinical Adverse Experiences**

Drug-related adverse experiences (i.e., possibly, probably, or definitely drug related as assessed by the investigator) occurred in 17.2% and 13.9% of patients in the losartan and placebo groups, respectively (RR=1.23; 95%CI: 0.97, 1.56); the higher percentage in the losartan group was attributable to more reports of hyperkalemia, a finding that is not unexpected with a drug that interrupts the renin-angiotensin aldosterone system. The 5 most frequent drug-related clinical adverse experiences reported in the losartan and placebo groups, respectively, were dizziness (4.5% versus 3.7%), hyperkalemia (3.7% versus 0.8%), hypotension (2.5% versus 1.3%), asthenia/fatigue (1.6% versus 0.8%), and hypertension (0.7% versus 1.0%).

**2.6.1.2 Serious Clinical Adverse Experiences**

The incidence of serious adverse experiences was similar in both groups: 64.0% and 63.9% in the losartan and placebo groups, respectively (RR=1.00; 95%CI: 0.93, 1.08). The most frequently occurring serious clinical adverse experiences in the losartan or placebo groups, respectively, were heart failure (11.3% versus 13.1%), end-stage renal disease (10.1% versus 13.3%), myocardial infarction (7.9% versus 8.8%), renal

insufficiency (7.2% versus 7.0%), and pneumonia (6.1% versus 6.0%). The incidence of serious drug-related clinical adverse experiences was also similar in both groups: 3.2% versus 2.6% for losartan and placebo, respectively (RR=1.22; 95%CI: 0.68, 2.16).

### **2.6.1.3 Discontinuations Due to Clinical Adverse Experiences**

The overall incidence of adverse experiences leading to discontinuation was lower in the losartan group (19.0%) compared to the placebo group (24.3%) (RR=0.78; 95%CI: 0.65, 0.95). This trend was numerically consistent for all adverse experiences leading to discontinuation (losartan versus placebo) including those that were serious (14.2 versus 18.5%; RR=0.77; 95%CI: 0.61, 0.97), drug-related (1.9 versus 2.4%; RR=0.79; 95%CI: 0.40, 1.57), or serious drug-related (0.8 versus 1.6%). The 5 most frequent clinical adverse experiences leading to discontinuation reported in the losartan and placebo groups, respectively, were heart failure (3.2% versus 6.6%), renal insufficiency (2.0% versus 2.3%), end-stage renal disease (1.5% versus 2.1%), myocardial infarction (1.6% versus 2.1%), and cerebrovascular accident (1.1% versus 1.2%).

### **2.6.1.4 Discontinuations Due to Death**

One hundred thirty-eight deaths occurred in the study during the double-blind treatment period, 68 (9.1%) in the losartan group and 70 (9.2%) in the placebo group (RR=0.99; 95%CI: 0.72, 1.35). Table 16 presents the counts of adverse experiences by body system that resulted in death. The causes of death, as determined by the investigator, are also listed. The most common causes of death in the losartan and placebo groups, respectively, were myocardial infarction (2.0% versus 2.1%), unknown cause of death (1.5% versus 0.7%), congestive heart failure (0.7% versus 0.7%), cerebrovascular accident (0.7% versus 0.3%), and pneumonia (0.7% versus 0.3%). It should be noted that the deaths represented in Table 16 occurred while on double-blind study therapy or within 14 days of discontinuation of therapy. There were no differences in overall deaths between losartan and placebo.

Table 16

Number (%) of Patients With Specific Clinical Adverse Experiences  
 Resulting in Death by Body System (On Treatment)

	Losartan (N=751)		Placebo (N=762)	
	n	(%)	n	(%)
Patients who died	68	(9.1)	70	(9.2)
<b>Body as a Whole/Site Unspecified</b>	<b>16</b>	<b>(2.1)</b>	<b>13</b>	<b>(1.7)</b>
Bacterial sepsi	2	(0.3)	2	(0.3)
Cardiopulmonary failure	0	(0.0)	3	(0.4)
Dehydration	1	(0.1)	0	(0.0)
Metastatic neoplasm of known primary	1	(0.1)	0	(0.0)
Sepsis	0	(0.0)	1	(0.1)
Septic shock	1	(0.1)	2	(0.3)
Unknown cause of death	11	(1.5)	5	(0.7)
<b>Cardiovascular System</b>	<b>35</b>	<b>(4.7)</b>	<b>44</b>	<b>(5.8)</b>
Arrhythmia	1	(0.1)	2	(0.3)
Cardiac arrest	5	(0.7)	5	(0.7)
Cardiogenic shock	0	(0.0)	6	(0.8)
Cerebrovascular accident	5	(0.7)	2	(0.3)
Congestive heart failure	5	(0.7)	5	(0.7)
Coronary artery disease	0	(0.0)	1	(0.1)
Hematoma	0	(0.0)	1	(0.1)
Hypertensive heart disease	0	(0.0)	2	(0.3)
Intracranial hemorrhage	0	(0.0)	2	(0.3)
Myocardial infarction†	15	(2.0)	16	(2.1)
Myocardial rupture	1	(0.1)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(0.1)
Third degree atrioventricular block	1	(0.1)	0	(0.0)
Ventricular arrhythmia	1	(0.1)	0	(0.0)
Ventricular fibrillation	1	(0.1)	1	(0.1)
<b>Digestive System</b>	<b>2</b>	<b>(0.3)</b>	<b>2</b>	<b>(0.3)</b>
Gastrointestinal bleeding	1	(0.1)	1	(0.1)
Pancreatic malignant neoplasm	0	(0.0)	1	(0.1)
Upper gastrointestinal hemorrhage	1	(0.1)	0	(0.0)
<b>Endocrine System</b>	<b>1</b>	<b>(0.1)</b>	<b>0</b>	<b>(0.0)</b>
Diabetic vascular disease	1	(0.1)	0	(0.0)
<b>Metabolism and Nutrition</b>	<b>0</b>	<b>(0.0)</b>	<b>1</b>	<b>(0.1)</b>
Acidosis	0	(0.0)	1	(0.1)

Table 16 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences  
 Resulting in Death by Body System (On Treatment)

	Losartan (N=751)		Placebo (N=762)	
	n	(%)	n	(%)
<b>Nervous System</b>	<b>3</b>	<b>(0.4)</b>	<b>0</b>	<b>(0.0)</b>
Anoxic brain damage	1	(0.1)	0	(0.0)
Brain death	2	(0.3)	0	(0.0)
<b>Respiratory System</b>	<b>6</b>	<b>(0.8)</b>	<b>5</b>	<b>(0.7)</b>
Lower respiratory infection	1	(0.1)	0	(0.0)
Pneumonia	5	(0.7)	2	(0.3)
Respiratory failure	0	(0.0)	3	(0.4)
<b>Urogenital System</b>	<b>5</b>	<b>(0.7)</b>	<b>5</b>	<b>(0.7)</b>
Chronic renal failure	1	(0.1)	2	(0.3)
End-stage renal disease	3	(0.4)	1	(0.1)
Ovarian malignant neoplasm	1	(0.1)	0	(0.0)
Renal failure	0	(0.0)	2	(0.3)

† Myocardial infarction includes acute myocardial infarction, 4 (0.5) and 4 (0.5), and myocardial infarction, 11 (1.5) and 12 (1.6).  
 Although a patient may have had 2 or more clinical adverse experiences that resulted in death, the patient was counted only once in a category. The same patient may appear in different categories.

Table 17 presents the causes of death as determined by the Endpoint Adjudication Committee. There were no differences in overall deaths between losartan and placebo. By the on-treatment approach, there were 65 (8.7%) deaths on losartan and 70 (9.2%) on placebo. (Note: 68 deaths on losartan-treatment are reported in the previous table, Table 16, as opposed to 65 deaths in the following table, Table 17. The difference of 3 patients is due to the fact that they died after the 10-Feb-2001 study endpoint cut-off date; therefore, they are not included in the above table of adjudicated deaths on treatment.)

Table 17

Adjudicated Death on Treatment

Death Cause	Losartan		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Fatal myocardial infarction	12	(1.6)	14	(1.8)	26	(1.7)
Noncardiac, nonvascular	16	(2.1)	22	(2.9)	38	(2.5)
Not determined	1	(0.1)	2	(0.3)	3	(0.2)
Other cardiac causes	1	(0.1)	2	(0.3)	3	(0.2)
Other vascular causes	6	(0.8)	7	(0.9)	13	(0.9)
Progressive heart failure	2	(0.3)	6	(0.8)	8	(0.5)
Sudden cardiac death	27	(3.6)	17	(2.2)	44	(2.9)
Total	65	(8.7)	70	(9.2)	135	(8.9)

**2.6.2 Summary of Laboratory Adverse Experiences**

Laboratory adverse experiences were clinically significant changes in lab values that were considered by the investigators to be an adverse change from baseline. There were no prespecified values of lab parameters that were required to be reported as a laboratory adverse experience; therefore, laboratory adverse experiences were reported solely at the discretion of the investigators.

The summary of laboratory adverse experiences is presented in Table 18. A count and percentage of events are provided for each treatment group. Overall, the incidence of patients reporting at least one laboratory adverse experience was 49.5% in the losartan group and 42.4% in the placebo group (RR=1.17; 95%CI: 1.04, 1.30).

Table 18

Laboratory Adverse Experience Summary

	Losartan (N=750)		Placebo (N=761)		Relative Risk and 95% CI Losartan Vs. Placebo
	n	(%)	n	(%)	
With one or more adverse experiences	371	(49.5)	323	(42.4)	1.17 (1.04, 1.30)
With no adverse experience	379	(50.5)	438	(57.6)	0.88 (0.80, 0.96)
With drug-related adverse experiences <sup>†</sup>	111	(14.8)	57	(7.5)	1.98 (1.45, 2.66)
With serious adverse experiences	6	(0.8)	8	(1.1)	
With serious drug-related adverse experiences	3	(0.4)	0	(0.0)	
Who died	0	(0.0)	0	(0.0)	
Discontinued due to adverse experiences	20	(2.7)	16	(2.1)	1.27 (0.66, 2.39)
Discontinued due to drug-related adverse experiences	10	(1.3)	6	(0.8)	
Discontinued due to serious adverse experiences	1	(0.1)	2	(0.3)	
Discontinued due to serious drug-related <sup>†</sup> adverse experiences	1	(0.1)	0	(0.0)	

<sup>†</sup> Determined by the investigator to be possibly, probably, or definitely drug related.  
 N = Number of patients with at least one laboratory test postbaseline.  
 95% CI (confidence interval) provided if total events were >22.

Drug-related adverse experiences (i.e., possibly, probably, or definitely drug related as assessed by the investigator) occurred in 14.8% and 7.5% of patients in the losartan and placebo groups, respectively (RR=1.98; 95%CI: 1.45, 2.66). The higher percentage of drug-related adverse experiences in the losartan group is attributable to a greater number of reports of hyperkalemia.

The incidence of serious laboratory adverse experiences was approximately the same in the losartan and placebo groups (0.8% and 1.1%, respectively). The incidence of serious drug-related adverse experiences was also similar in both groups (0.4 versus 0.0%, losartan versus placebo, respectively).

No patients died as a result of a laboratory adverse experience.

Overall, the number of patients discontinued due to a laboratory adverse experience was low with no clinically meaningful differences observed between the treatment groups. In the losartan group, 2.7% of the patients were discontinued due to a laboratory adverse experience versus 2.1% in the placebo group (RR=1.27; 95%CI: 0.66, 2.39). Laboratory adverse experiences leading to discontinuation that were drug-related (1.3% versus 0.8%), serious (0.1% versus 0.3%), and serious drug-related (0.1% versus 0%) were low and not different between the losartan and placebo groups, respectively.

### **2.6.3 Summary of Adverse Experiences of Special Interest**

According to the Data Analysis Plan, formal statistical testing was performed for adverse experiences of prespecified special interest, based on the disease history of this population. Because these patients were diabetic, hyper- and hypoglycemia were clearly of special interest. Acute renal failure was included because it has been reported with ACE inhibitors and AII antagonists in patients with underlying renal disease. Hyper- and hypokalemia were of special interest due to potential imbalances in serum potassium in diabetic patients with renal disease, especially when using an agent that blocks the renin-angiotensin-aldosterone system. Anemia was also selected because it is associated with chronic renal disease. Anemia has been reported with ACE inhibitors and AII receptor antagonists and is noted in the U.S. prescribing information for losartan. Table 19 summarizes the incidences of, and hazard ratios for, the adverse experiences of special interest. There were more patients in the losartan group with reports of anemia and hypoglycemia, but overall there was no statistically significant difference between the 2 groups in the risk for these events. HBA<sub>1c</sub> was comparable between 2 treatment groups and there were no reports of interactions with insulin or oral hypoglycemic agents. There was also no statistically significant difference in acute renal failure or hyperglycemia.

With respect to hypokalemia, which was reported significantly more with placebo (p=0.013), the incidences of clinical adverse experiences were 2.4% with losartan versus 2.6% with placebo. The incidences of laboratory adverse experiences of hypokalemia were 1.3% with losartan versus 2.8% with placebo. Of the clinical adverse experiences of hypokalemia, 0.4% and 0.5% in the losartan and placebo groups, respectively, were considered serious; none were considered drug related or resulted in discontinuation. Of the laboratory adverse experiences of hypokalemia, 0% and 0.1% in the losartan and placebo groups, respectively, were serious; none were considered drug related or resulted in discontinuation. No patients died due to hypokalemia.

Hyperkalemia was reported significantly more in the losartan group compared to placebo (p<0.001) and is discussed in the following section.

Table 19

Prespecified Analysis of Adverse Experiences

Endpoints	Losartan (N=751) n (%)	Placebo (N=762) n (%)	Hazard Ratio (Losartan Versus Placebo)	95% CI for Hazard Ratio	p-Value
Acute renal failure	13 (1.7)	12 (1.6)	1.01	(0.46,2.21)	0.981
Hyperkalemia	182 (24.2)	94 (12.3)	2.00	(1.56,2.57)	<0.001
Hypokalemia	19 (2.5)	36 (4.7)	0.50	(0.28,0.86)	0.013
Anemia	106 (14.1)	82 (10.8)	1.25	(0.94,1.67)	0.126
Hyperglycemia	98 (13.0)	114 (15.0)	0.82	(0.63,1.08)	0.156
Hypoglycemia	112 (14.9)	90 (11.8)	1.21	(0.92,1.60)	0.174
Time to first clinical or laboratory adverse experience. Hazard ratio and 95% CI estimated using an unadjusted proportional hazards regression model.					

**2.6.3.1 Hyperkalemia**

Hyperkalemia is not unexpected in diabetic patients with underlying kidney disease especially when treated with an agent that blocks the renin-angiotensin system; therefore, it is important to examine the incidence of hyperkalemia as a clinical or laboratory adverse experience. Table 20 summarizes hyperkalemia reported as an adverse experience. There were no deaths attributed to hyperkalemia.

Table 20

Adverse Experiences of Hyperkalemia

	Losartan (n=751)	Placebo (n=762)
	N (%)	N (%)
Patients with one or more clinical and/or laboratory:		
Adverse experiences of hyperkalemia	202 (26.7)	100 (13.1)
Drug-related hyperkalemia	117 (15.6)	43 (5.6)
Serious hyperkalemia	20 (2.7)	10 (1.3)
Hyperkalemia causing discontinuation	10 (1.3)	6 (0.7)

**2.6.4 Postmarketing Experience in Diabetic Patients With Nephropathy**

The Merck & Co., Inc. Worldwide Adverse Experience System (WAES) database was searched to identify spontaneous reports from a patient population with underlying diabetes and renal disease, similar to the patients enrolled in the RENAAL study [75]. The time-frame of the search extended from the grant of licensure for sale of losartan potassium (2-Sep-1994) through 30-Jun-2001. For the 63 patients identified with diabetes and renal disease, there were no predominant events reported. It should be noted that 3 of 4 reports of “erythrocytosis decreased” were received from one clinician and involve patients with chronic renal failure. Reports of “hepatic disorder” and “hepatic function abnormality” generally were confounded by concurrent conditions that can be associated with hepatic function abnormalities, such as history of hepatitis, hyperlipidemia, and congestive heart failure. There were 8 reports of hyperkalemia, however, the occurrence of this event, along with the other reported adverse events, did not elucidate any pattern, or suggest that treatment with losartan predisposed diabetic patients with renal disease to any unexpected adverse experiences. There were also no post-marketing reports of death attributed to hyperkalemia. The data from postmarketing experience in diabetic patients with nephropathy do not suggest that the safety profile for losartan is different for diabetic patients with histories of renal diseases than for patients in general who are treated with losartan.

**2.7 Summary of the RENAAL Study**

In summary, the RENAAL Study demonstrated that:

1. Losartan is renal protective by delaying the onset of the primary composite endpoint of doubling of serum creatinine, ESRD (need for chronic dialysis or transplantation), or all-cause mortality.
2. Losartan reduces the rate of decline in renal function as measured by slope of 1/sCr.
3. Losartan reduces proteinuria.

4. The beneficial effects of losartan on the primary endpoint and proteinuria are beyond that attributable to its beneficial effect on blood pressure.
5. Losartan appears to offer renal protection in all subgroups of patients.
6. There is no significant difference on cardiovascular morbidity and mortality with losartan compared to placebo.
7. Losartan is generally well tolerated in this population of type 2 diabetic patients with proteinuria. As expected with AIIAs and other agents that interrupt the RAAS, losartan is associated with a higher incidence of hyperkalemia compared to conventional therapy.

### **3. Confirmatory Evidence and Benefit Versus Risk Relationship**

#### **3.1 Confirmatory Evidence**

Regulatory decisions sometimes must be made using information primarily from a single study. This is often the case for large outcomes trials, when ethical and practical considerations make it impossible and/or impractical to conduct a second study to provide independent substantiation of the first study. In such cases, it is important to consider what supportive and confirmatory evidence may be available to provide reassurance that the results of the single study are scientifically sound and not due to chance alone. Such evidence may come from within the single study and/or from sources external to the main study.

Confirmatory evidence from data within the RENAAL study as well as data external to the RENAAL study will be presented below, demonstrating the effectiveness of losartan on the progression of renal disease.

##### **3.1.1 Confirmatory Evidence Within RENAAL**

Looking within the RENAAL study, the consistent and significant treatment effects across multiple outcomes (the primary composite endpoint, ESRD, ESRD or death, proteinuria, rate of loss of renal function) in the study promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound.

Perhaps most persuasive are the findings on the relationship between baseline proteinuria and risk for a primary composite event. Because of the known effects of proteinuria on renal progression in type 1 diabetics and non-diabetics, RENAAL patients were stratified at randomization based on baseline proteinuria, i.e., UA/Cr <2000 mg/g and UA/Cr ≥2000 mg/g. Despite this stratification, by chance there was a slight imbalance in baseline proteinuria between the 2 treatment groups (1873 mg/g in losartan group, 1743 mg/g in placebo group). More importantly, there was an imbalance in the distribution of patients in the ≥2000 mg/g stratum of proteinuria. This imbalance in distribution mainly occurred in the ≥4000 mg/g category, where there were 21 more losartan patients compared to placebo patients (n=92 losartan, n=71 placebo). After correcting for this imbalance, the relative risk of patients in the losartan group experiencing the primary composite endpoint increased from a 16.1% risk reduction

( $p=0.022$ ) to a 22.2% risk reduction ( $p=0.001$ ). In addition to demonstrating that even small differences in baseline proteinuria are associated with large differences in risk, these results provide compelling confirmatory evidence for the renal protective benefits of losartan in type 2 diabetic patients with proteinuria.

In addition, 2 pre-specified supportive analyses that accounted for patients that discontinued study drug confirmed the results of the primary analysis, and also indicated a stronger treatment effect of losartan on the primary composite endpoint (per-protocol: risk reduction=22.5%,  $p=0.007$ ; 6-month lagged censoring: risk reduction=18.8%,  $p=0.017$ ) and ESRD or death (per-protocol: risk reduction=32.0%,  $p=0.001$ ; 6-month lagged censoring: risk reduction=26.0%,  $p=0.003$ ).

### **3.1.2 Confirmatory Evidence from Studies External to RENAAL**

#### **3.1.2.1 Preclinical Studies**

Losartan has been shown to offer renal protection in several different experimental models of renal disease in rats. In nondiabetic, 5/6 nephrectomized rats, Lafayette et al. [23] demonstrated that 10-week administration of pharmacological doses of losartan were renal protective, in that greater reductions in glomerulosclerosis, glomerular transcapillary pressure, and proteinuria were observed in losartan-treated rats than in rats treated with triple antihypertensive therapy (i.e., reserpine, hydralazine, and hydrochlorothiazide) [23]. This demonstrated that the antiproteinuric and renal protective effect of losartan were beyond that attributable to its antihypertensive efficacy alone. Likewise, in long-term experimental diabetic models, losartan has been shown to attenuate glomerulosclerosis and urinary protein. Remuzzi et al. have shown that after a 1-year observation period, proteinuria in losartan-treated diabetic rats was significantly less than that seen in diabetic control rats, and comparable to that of normal control rats [24]. More importantly, glomerulosclerosis was prevented by specific AII blockade with losartan in these animals [24]. These data were confirmed in a long-term 1-year Merck study, where glomerulosclerosis and proteinuria were significantly reduced in losartan-treated diabetic rats compared to diabetic control rats [25].

These animal studies have demonstrated that losartan exerts renal protective effects and reduces proteinuria in experimental nondiabetic and diabetic renal disease, and provide confirmatory evidence for the renal protection benefits of losartan therapy seen in the RENAAL study.

#### **3.1.2.2 Clinical Studies**

Following initiation of the RENAAL study, several studies were conducted with losartan demonstrating its antiproteinuric effects in diabetic patients with proteinuria. In type 1 and type 2 diabetic patients with microalbuminuria, losartan has consistently demonstrated efficacy in reducing albuminuria. Andersen et al. compared the renal and hemodynamic effects of losartan to enalapril in type 1 diabetic patients [26]. The study demonstrated that losartan 100 mg once daily is as effective as enalapril 20 mg once daily in reducing albuminuria and blood pressure in this group of patients [26]. Chan and colleagues reported that treatment of type 2 diabetic patients with losartan for 12 weeks

reduced albuminuria by 24% from baseline when compared to the calcium channel blocker, felodipine (11%) [27]. Interestingly, felodipine was associated with a greater degree of blood pressure reduction compared to losartan ( $p=NS$ ), but reduced albuminuria to a lesser degree. Similar results were observed in an unpublished study in microalbuminuric type 2 diabetic patients comparing losartan to amlodipine [28]. Following 12 weeks of treatment, blood pressure was significantly lowered in both groups, but to a greater extent with amlodipine. Despite the larger reduction in blood pressure, albumin excretion was unaffected by amlodipine treatment, whereas losartan was associated with a significant decrease in albumin excretion relative to baseline [28]. This finding suggests a disassociation between the antiproteinuric and antihypertensive effects of these compounds.

Additional studies assessing the antiproteinuric effects of losartan in type 2 diabetic patients have followed. de Pablos Velasco and Martin reported significant reductions in urinary albumin excretion (UAE) compared to baseline in both losartan and diltiazem groups after 12 weeks of therapy [29]. In more recent open-label studies, losartan again has been shown to effectively reduce albumin excretion in type 2 diabetic patients with microalbuminuria [30; 31]. Lozano et al. have demonstrated that after 6 months of therapy, losartan induced a 43% reduction in UAE [30]. In a smaller, shorter-term study, Esmatjes et al. reported a 33% decrease in UAE after 8 weeks of losartan treatment [31].

In a longer-term (1-year duration) double-blind study, Lacourciere et al. have demonstrated that daily treatment of type 2 diabetic patients with losartan 50 mg significantly reduced proteinuria relative to baseline, and similarly to an ACE inhibitor. Furthermore, by end of study, both losartan and ACE inhibition had similar changes in glomerular filtration rate [32].

Table 21 summarizes the studies conducted in type 2 diabetic patients, assessing losartan's effect on proteinuria and microalbuminuria.

Table 21

Summary of Studies Assessing the  
 Effect of Losartan on Proteinuria in Patients With Type 2 Diabetes

	N	Duration of Treatment	Treatment	Blood Pressure (Systolic/Diastolic)	Proteinuria/ Microalbuminuria
Chan [27]	12	12 weeks	Los vs BL Los vs Felodipine Felodipine vs baseline	Decreased (-19/-11) NA Decreased (-28/-20)	Decreased (24%) No Difference Decreased (11%)
Merck Statistical Report [28]	130	12 weeks	Los vs BL Los vs Amlodipine Amlodipine vs BL	Decreased (-11/-10) † Decreased (-17/-13)	Decreased <sup>‡</sup> (14%) No Difference No Difference (0%)
de Pablos Velasco [29]	40	12 weeks	Los vs BL Los vs Diltiazem Diltiazem vs BL	Decreased <sup>‡</sup> (-17/-8) NA Decreased <sup>‡</sup> (-23/-13)	Decreased <sup>‡</sup> (17%) No Difference Decreased <sup>‡</sup> (17%)
Ragonesi [76]	34	12 weeks	Los vs BL	Decreased <sup>‡</sup> (-18/-12)	Decreased <sup>‡</sup> (41%)
Lacourciere [32]	103	1 year	Los vs BL Los vs Enalapril Enalapril vs BL	Decreased <sup>‡</sup> (-15/-10) NA Decreased <sup>‡</sup> (-12/-11)	Decreased <sup>‡</sup> (35%) No Difference Decreased <sup>‡</sup> (55%)
Lozano [30]	424	6 months	Los vs BL	Decreased <sup>‡</sup> (-23/-14)	Decreased <sup>‡</sup> (43%)
Esmatjes [31]	14	8 weeks	Los vs BL	Decreased <sup>‡</sup> (-6/-3)	Decreased <sup>‡</sup> (33%)
<sup>†</sup> Significant difference in blood pressure between treatment groups. <sup>‡</sup> Significant change from baseline. Los = losartan; BL = baseline; NA = Statistical comparison Not Available. “No Difference” indicates differences between treatment groups or compared to baseline not significant.					

RENAAL was designed to evaluate the effect of losartan on the progression of renal disease. These external studies are supportive of RENAAL in that they provide evidence to support losartan’s intrinsic ability to reduce proteinuria. These data are consistent with the antiproteinuric effect of losartan and that the renal protective effect observed in RENAAL exceeds that attributable to a reduction of blood pressure alone.

In summary, the evidence of effectiveness of losartan in renal protection, from both within RENAAL and external to RENAAL, provide convincing confirmatory evidence that the observed results are scientifically sound.

### 3.2 Benefit Versus Risk Relationship

Currently, there are no approved agents in the U.S. to delay progression of renal disease in type 2 diabetes with proteinuria. The results of the RENAAL study have clearly established that losartan provides renal protection in patients with type 2 diabetes and proteinuria by delaying the progression of renal disease. Compared to placebo, losartan

significantly reduced the incidence of, and delayed the time to, the primary composite endpoint of doubling of serum creatinine concentration, ESRD, or death (risk reduction=16.1%;  $p=0.022$ ; after adjustment for baseline proteinuria as a continuous covariate, risk reduction=22.2%,  $p=0.001$ ). Treatment with losartan significantly reduced the incidence of and delayed the time to ESRD or death (risk reduction=19.9%;  $p=0.009$ ; after adjustment for baseline proteinuria as a continuous covariate, risk reduction=25.7%,  $p<0.001$ ). It is estimated from the results of RENAAL that 1 case of ESRD would be prevented for every 16 patients treated with losartan over a 3.5-year period. In addition, the treatment effect of losartan was more clearly established by the performance of 2 supportive analyses that accounted for patients who discontinued study drug. These supportive analyses not only confirmed the results of the primary analysis, but also indicated a stronger treatment effect as evidenced by higher risk reductions for the primary composite endpoint and the combined component of ESRD or death.

With respect to the secondary renal endpoints, losartan significantly reduced the rate of progression of renal disease (i.e., slope of reciprocal of serum creatinine). Furthermore, proteinuria, a widely accepted marker of progressive glomerular injury, was reduced within 3 months of initiation of losartan compared to placebo and the reduction was sustained over the course of the study.

With respect to cardiovascular morbidity and mortality, no significant differences between the 2 treatment groups were observed in RENAAL. Nonetheless, post hoc analyses were performed taking into consideration renal and major cardiovascular outcomes, which are competing events in this population. The results of the post hoc analysis of the composite of the primary (renal) endpoint and the secondary (cardiovascular) endpoints show that losartan treatment was associated with a risk reduction of 16.6% ( $p=0.008$ ). Furthermore, a greater treatment effect is observed in a post hoc analysis of the hard endpoints of ESRD, MI, Stroke, or Death (whichever occurred first) (risk reduction: 21.2%;  $p=0.003$ ). The results of these analyses indicate that the benefits of losartan on renal outcomes were not at the expense of an increased risk of cardiovascular events and are supportive of an overall benefit of losartan treatment in these patients.

Confirmation of the impact of losartan on cardiovascular outcomes must await the availability of results from larger clinical trials specifically designed to address cardiovascular outcomes. For example, the results of the LIFE study will be presented at the March, 2002 American College of Cardiology meeting, and published soon thereafter in the *Lancet*. The LIFE study was specifically designed to address cardiovascular outcomes, and included diabetic patients. Although confidentiality rules prevent disclosure of the LIFE study results here, Merck will be prepared to summarize at the upcoming Advisory Committee Meeting the relevant data and its impact on our assessment of the benefit/risk assessment for the use of losartan to delay progression of renal disease in type 2 diabetic patients with proteinuria. It is important to note that the FDA will not have access to the primary data from the LIFE study until after the 12-Apr-2002 Advisory Committee Meeting and thus could not provide the Committee with their full assessment of the study results.

The consistent and significant treatment effects across multiple endpoints in the RENAAL study promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound.

The safety profile of losartan in this study did not uncover any unusual or unexpected adverse experiences. In fact, the vast majority of adverse experiences reported occurred in a similar number of patients in the losartan and placebo groups. This finding is consistent with what has been previously reported in numerous clinical studies [33]. In addition, no differences were observed in HBA<sub>1c</sub> between the losartan and placebo groups. No reports of adverse experiences demonstrating an interaction of losartan with commonly used oral hypoglycemic agents or insulin were observed.

In order to more specifically assess the safety of losartan in diabetic patients with proteinuria, several adverse experiences most likely to occur in this patient population were pre-specified for statistical analysis: acute renal failure, anemia, hyperglycemia, hypoglycemia, hyperkalemia, and hypokalemia. With the exceptions of hyperkalemia and hypokalemia, there were no significant differences in the incidence of these events between treatment groups. The findings of this analysis support the fact that diabetic patients with renal disease are at higher risk for potassium imbalances. It is also known that drugs that block the RAAS are associated with increases in serum potassium. Therefore, it is not surprising that the number of patients reporting hyperkalemia was ~2-fold higher in the losartan group (24.2%), compared to patients taking placebo (12.3%), in whom the risk also was elevated, reflecting characteristics of the underlying disease state. Conversely, hypokalemia was ~2-fold higher in the placebo group (4.7%) compared to the losartan group (2.5%). The concurrent use of diuretics, necessary for the treatment of hypertension and edema in patients with nephropathy, is most likely accountable for the increased incidence of hypokalemia in this group. As would be expected, diuretic use was similar in both groups; however, the effect of diuretics on potassium excretion may have been counteracted by the addition of losartan.

Despite the observed effects on potassium in this patient population, the study shows that these electrolyte imbalances are manageable, evidenced by the very low proportion of patients discontinuing due to hyperkalemia, and no discontinuations due to hypokalemia. There were no deaths attributed to hyperkalemia or hypokalemia. Hyperkalemia and hypokalemia can be treated using dietary and/or pharmacologic means. In general, these findings further substantiate what is already known by physicians: that potassium levels should be evaluated in patients with nephropathy if they are treated with agents that block the RAAS.

The safety findings of this study accord well with the overall summary of spontaneous postmarketing adverse experiences in diabetic patients with renal disease reported to Merck & Co., Inc. Similar to the RENAAL findings, there were no unexpected adverse experiences reported by the general public, in that the reports appeared to be a consequence of the underlying disease. Given that a relatively limited number of spontaneous adverse events were reported in diabetic patients with renal disease, and that millions of patients worldwide with various disease histories have been exposed to

losartan, the summary of the spontaneous postmarketing adverse experiences supports the drug's favorable tolerability profile.

The risks of losartan in this type 2 diabetic population were clearly defined in RENAAL and are considered manageable, as evidenced by the type and number of adverse event reports in the losartan versus placebo groups.

Given the strong renal protective effects and documented tolerability profile of losartan in patients with type 2 diabetes and proteinuria, the benefits of losartan therapy in this population clearly outweigh the risks.

#### **4. Overall Conclusions**

1. The results of the RENAAL study provide convincing evidence that losartan delays the progression of renal disease in type 2 diabetic patients with proteinuria. The consistent and significant effects of losartan across multiple endpoints in the large multi-center RENAAL trial promote confidence in its findings and provide confirmatory evidence that the study results are scientifically sound. Additionally, the pre-specified supportive analyses (6-month lagged censoring and per protocol) and the post hoc adjustment using baseline proteinuria as a continuous covariate all support the renal protective effects of losartan in this patient population.
2. Additional confirmatory evidence for the findings of RENAAL come from:
  - a. Several clinical studies of losartan in diabetic and non-diabetic patients with renal disease that demonstrated reductions in proteinuria. [34; 35; 26; 8; 27; 29; 30; 31].
  - b. Long-term preclinical studies that have demonstrated the renal protective benefits of losartan treatment in preventing glomerulosclerosis and reducing proteinuria in animal models of diabetic nephropathy [24; 25].
3. The results of RENAAL confirm that the safety profile of losartan in type 2 diabetic patients with proteinuria is consistent with that presented in the currently approved U.S. prescribing information for losartan.
4. Given the strong renal protective effects and documented safety and tolerability profile of losartan in this population, the benefits of losartan clearly outweigh the risks.

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## Appendix 1

### COZAAR™ Prescribing Information

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 **MERCK & CO., INC.**  
Whitehouse Station, NJ 08889, USA

#### **COZAAR®** **(LOSARTAN POTASSIUM TABLETS)**

##### **USE IN PREGNANCY**

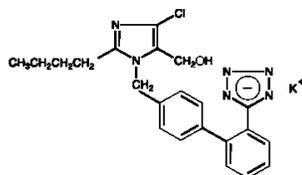
**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.** When pregnancy is detected, COZAAR should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

##### **DESCRIPTION**

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT<sub>1</sub>) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl)phenyl]benzylimidazole-5-methanol monopotassium salt.

Its empirical formula is C<sub>22</sub>H<sub>22</sub>ClKN<sub>6</sub>O, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.

##### **CLINICAL PHARMACOLOGY**

###### *Mechanism of Action*

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active

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metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT<sub>1</sub> receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

*Pharmacokinetics*

*General*

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C<sub>max</sub> but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of <sup>14</sup>C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral <sup>14</sup>C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of <sup>14</sup>C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

*Special Populations*

*Pediatric:* Losartan pharmacokinetics have not been investigated in patients <18 years of age.

*Geriatric and Gender:* Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as

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high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

*Race:* Pharmacokinetic differences due to race have not been studied.

*Renal Insufficiency:* Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, *Hypotension — Volume-Depleted Patients* and DOSAGE AND ADMINISTRATION).

*Hepatic Insufficiency:* Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

*Drug Interactions*

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

*Pharmacodynamics and Clinical Effects*

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose

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giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. COZAAR was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

**INDICATIONS AND USAGE**

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**CONTRAINDICATIONS**

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

**WARNINGS**

*Fetal/Neonatal Morbidity and Mortality*

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and

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physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m<sup>2</sup> basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

*Hypotension — Volume-Depleted Patients*

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

**PRECAUTIONS**

*General*

*Hypersensitivity:* Angioedema. See ADVERSE REACTIONS, *Post-Marketing Experience*.

*Impaired Hepatic Function*

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

*Impaired Renal Function*

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with COZAAR; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with COZAAR; in some patients, these effects were reversible upon discontinuation of therapy.

*Information for Patients*

*Pregnancy:* Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

*Potassium Supplements:* A patient receiving COZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, *Drug Interactions*).

*Drug Interactions*

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL

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PHARMACOLOGY, *Drug Interactions.*) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ( $p < 0.05$ ) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

*Pregnancy*

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

*Nursing Mothers*

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

*Pediatric Use*

Safety and effectiveness in pediatric patients have not been established.

*Use in the Elderly*

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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**ADVERSE REACTIONS**

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well-tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
<i>Digestive</i>		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
<i>Musculoskeletal</i>		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
<i>Nervous System/Psychiatric</i>		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
<i>Respiratory</i>		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan: *Body as a Whole*: facial edema, fever, orthostatic effects, syncope; *Cardiovascular*: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive*: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic*: anemia; *Metabolic*: gout; *Musculoskeletal*: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric*: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory

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impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory*: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin*: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses*: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital*: impotence, nocturia, urinary frequency, urinary tract infection.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1†	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2††	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

† Demographics = (89% caucasian, 64% female)  
 †† Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

*Post-Marketing Experience*

The following additional adverse reactions have been reported in post-marketing experience:

*Hypersensitivity*: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

*Digestive*: Hepatitis (reported rarely).

*Respiratory*: Dry cough (see above).

Hyperkalemia and hyponatremia have been reported.

*Laboratory Test Findings*

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

*Creatinine, Blood Urea Nitrogen*: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone (see PRECAUTIONS, *Impaired Renal Function*).

*Hemoglobin and Hematocrit*: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

*Liver Function Tests*: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

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**OVERDOSAGE**

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m<sup>2</sup> basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

**DOSAGE AND ADMINISTRATION**

Dosing must be individualized. The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension — Volume-Depleted Patients*) and patients with a history of hepatic impairment (see PRECAUTIONS, *General*). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

**HOW SUPPLIED**

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

**NDC** 0006-0951-54 unit of use bottles of 90

**NDC** 0006-0951-58 unit of use bottles of 100

**NDC** 0006-0951-28 unit dose packages of 100.

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

**NDC** 0006-0952-31 unit of use bottles of 30

**NDC** 0006-0952-54 unit of use bottles of 90

**NDC** 0006-0952-58 unit of use bottles of 100

**NDC** 0006-0952-28 unit dose packages of 100

**NDC** 0006-0952-82 bottles of 1,000.

No. 6536 — Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code 960 on one side and MRK on the other. They are supplied as follows:

**NDC** 0006-0960-31 unit of use bottles of 30

**NDC** 0006-0960-58 unit of use bottles of 100

**NDC** 0006-0960-28 unit dose packages of 100.

**Storage**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

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Dist. by:  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Issued November 2001  
Printed in USA