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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-028

Medical Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 20-386

Sponsor: Merck

Submission: SE-028 (13 April 2001): a request to approve losartan for the treatment of nephropathy in patients with type II diabetes.

Review date: 3 May 2002

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

Summary: This supplement consists of a single study (RENAAL).

Distribution: NDA 20-386

HFD-110/Project Manager

HFD-710/Hung

HFD-110/Pelayo

This secondary review is based upon the primary medical review of Dr. Pelayo (8 March 2002, amended 1 April 2002) and the primary statistical review of Dr. Hung (1 March 2002, amended 1 and 16 April 2002). Reference is also made to the Cardio-Renal Advisory Committee meeting of 12 April 2002 and to the DSI clinical site audit report of 23 April 2002.

The sponsor has requested a waiver from a requirement to conduct pediatric studies, since nephropathy in type II diabetes is not a pediatric disease. This waiver should be granted.

With regard to financial disclosure, the sponsor categorically denies inappropriate financial arrangements with investigators, as defined in 21CFR 54.2(a). Numerous subinvestigators did not return financial disclosure certification and could not be reached by the sponsor. Fifty-two investigators and sub-investigators reported equity interests or "significant payments of other sorts" in the range of [redacted]
The integrity of RENAAL was largely protected by trial design, particularly blinding, and the large number of participating sites.

The only directly relevant clinical data were obtained in the RENAAL study, thoroughly described and analyzed in the medical and statistical reviews.

At this writing, there are two issues relating to the interpretation of RENAAL data, and then there is the consideration of the strength of evidence.

The Cardio-Renal Advisory Committee expressed some anxiety about regional heterogeneity in the primary end point, recapitulating discussions within the Division. However, when treatment effects by country are considered by enrollment, the expected funnel-shaped pattern appears (see upper left panel of Figure 1 below, which is similar to Figure 7 in the Medical Review), and the US, in particular, is clearly no outlier. Where some discussion arises is with respect to a prospective analysis of results by region (continent), wherein it is seen that the largest effect is seen in Asia, the region with the

smallest enrollment (see figure 6 and table 15 in the Medical Review). The US was also the country with the largest enrollment in IDNT (upper right panel of Figure 1), and likewise, the US is not an outlier in IDNT. These results are in contrast to MERIT-HF (lower panel of Figure 1), where the US results lie substantially outside the 95% confidence limit envelope. The heterogeneity in RENAAL does not merit mention in labeling.

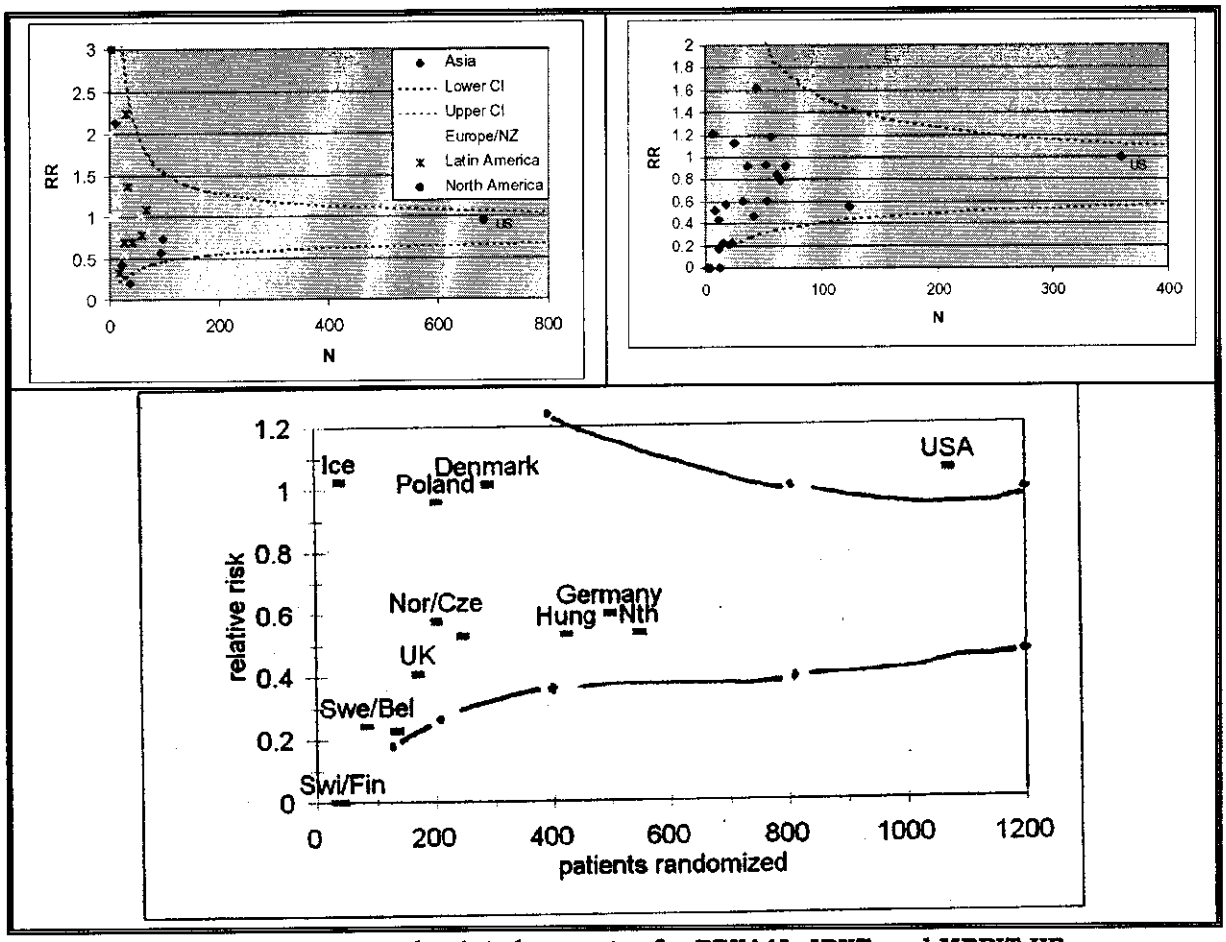

Figure 1. Primary end points by country for RENAAL, IDNT, and MERIT-HF.

All studies had event end points analyzed by time to first event. For RENAAL (upper left) and IDNT (upper right), the end point was death, ESRD, or doubling of serum creatinine. For MERIT (bottom[1]) the end point was all-cause mortality. The predicted funnel boundaries are sketched (literally in the case of MERIT) based on the overall study result and its confidence limits, log-transformed, and scaled by the square root of the sample size.

The other issue of interpretation has arisen from DSI audit of two sites in Hong Kong. The Asian focus of the DSI audit arose because of early and relatively naïve assessment of the regional heterogeneity. Dr. U's visits to sites for investigators Chan and Lam in Hong Kong turned up numerous discrepancies between the site records and the SAS datasets with respect to the time or existence of primary and secondary end point events. In each case, the data concerning the events in question were reviewed by the adjudication committee[2], blinded to treatment, sometimes supplemented by core lab

[1] *Figure, minus confidence limit envelope, can be found in both the primary statistical review (Cui) and secondary review (Fenichel) for MERIT-HF.*

[2] *Steven Haffner, MD (Endpoint Committee Chairman), University of Texas Health Sciences Center, San Antonio, Texas;*

results probably not available to the investigator. One might disagree with the decisions of the adjudication committee, but the decisions made by the adjudication committee are, in these cases, accurately recorded in the SAS dataset, so this is not really an issue of data integrity.

Table 1. Subjects with questioned data integrity

ID	Description	Adjudicated?
3399	2SC date discrepancy	Yes
3402	2SC doubling not confirmed thrice; later confirmed	Yes
3406	CVA not counted; negative CT; event after close out date	No
3408	2SC date discrepancy	Yes
3410	Discrepancy on event of ESRD. Subject probably met need for dialysis, but was DNR; died 3 days later	No
3412	CVA not reported	?
3413	One of 5 CHF hospitalizations not reported; hospitalization in question attributed to anemia.	No
3570	ESRD date discrepancy	Yes
3573	ESRD date discrepancy	Yes
3600	ESRD declaration based on calculated GFR	Yes
3604	ESRD declared at dialysis, not catheter insertion.	Yes
3628	Discrepancy on event of ESRD	Yes
4027	ESRD date discrepancy	Yes
4031	Dialysis event 3 days prior to death not considered chronic	Yes
4152	ESRD event after study closeout date	No
4459	CHF event adjudication discrepancy	Yes

It is useful to consider whether bias appears had primary end point events been adjudicated as suggested in the DSI review. Lengthening the time to an event would increase the treatment effect if it occurred in the losartan group or decrease the treatment effect if it occurred in the placebo group. For the above questioned events, there were 10 related to the primary end point analysis (6 on placebo and 4 on losartan), for which the DSI reviewer would have selected dates other than the ones picked by the Adjudication Committee, but before the study close. There were 4 cases where the effect would have been to decrease the treatment effect (differences of 3, 4, 7, and 140 days) and 6 cases where the effect would have been to increase the treatment effect (by 10, 73, 97, 100, 120, and 160 days). These results do not support the DSI recommendation "requesting the sponsor to provide assurances that these noted discrepancies are not system[at]ic".

As part of this review, an attempt was made to reconcile dates in the investigator-indicated clinical events dataset (QCE.XPT) with dates in the adjudicated events dataset (QADJEN.XPT). Of the 360 adjudicated creatinine doubling events, 307 have corresponding investigator events. Of the 341 adjudicated ESRD events, 337 have corresponding investigator events. To look for bias, for each event, the difference in dates was computed and assigned a sign depending upon whether the net effect was in favor of a treatment benefit, as was done for the 10 cases reported by DSI. The distribution of such values is shown in Figure 2.

Joseph P. Carrozza, MD, Harvard Medical School, Boston, Massachusetts; Daniel Kolansky, MD, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Leopoldo Raij, MD, University of Minnesota School of Medicine, Minneapolis, Minnesota; Dominic Sica, MD, Medical College of Virginia, Richmond, Virginia; Robert Toto, MD, Director of Clinical Research at Dallas Nephrology Associates, Dallas, Texas. These were 3 nephrologists, 2 cardiologists, and an epidemiologist. There was no sponsor representative.

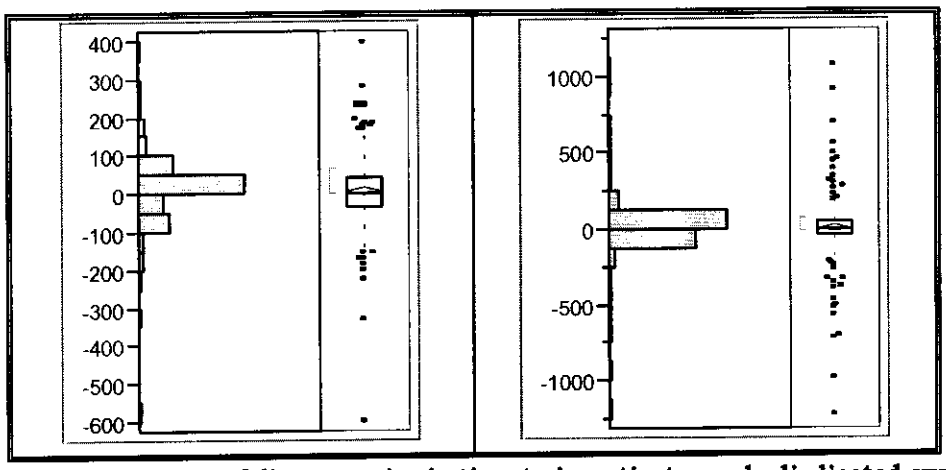

Figure 2. Distribution of discrepancies in time to investigator and adjudicated events.
LEFT: Differences in doubling of serum creatinine. RIGHT: Differences in ESRD. Sign of the difference is based on the effect the choice would have on the treatment effect.

While there are substantial differences in the dates indicated by the investigator and the adjudication committee, the differences were as likely to favor placebo as active treatment, so there is no indication of a systematic discrepancy, nor any need for further explanation by the sponsor or adjudicating committee.

On the issue of strength of evidence, it seems important to note the difference between theoretical and practical implications of, say, two studies with p-values less than 0.05 for their primary end points. The pure or theoretical case is one in which one can say nothing more than the results of the primary analysis. This is the only case for which one knows how to compute the joint probability for both trial results ending up in the same tail of the distribution, the oft-quoted 0.00125. In practice, one always knows somewhat more than this; one just does not know how to compute rigorously the extra information's contribution to the overall strength of evidence.

Everyone would probably agree that robustness analyses, internal consistency, dose-response, understanding of a mechanism of action, expected effects in secondary end points, and analogies of results from drugs of the same pharmacological class all contribute to the sense that a difference in results between treatment groups is a real and reproducible property of treatment. To what no two will agree is the valuation of these additional data. Nevertheless, if one were to decide that a joint probability of 0.00125 represents an adequate level of confidence[3], two real trials 'winning' with $p<0.05$ often produce a ridiculously high level of confidence that a treatment effect exists.

The boundaries of this problem are best tested in development programs with one (relevant) study. Such cases represent opportunities to explore the political and psychological basis of regulatory decision-making by experts, but the questions we ask the Advisory Committee uniformly fail to do so very precisely.

Four of eleven Advisory Committee members, led by Dr. Tom Fleming, found RENAAL a compelling single study, largely on the basis of a robust effect of losartan on the more clinically important primary end point's components—death and ESRD. ESRD is an outcome expected within months of creatinine doubling in this population, so the

[3] *Of course, one could take the position that two studies with $p<0.05$ are adequate only if accompanied by understanding of mechanism, internal consistency, etc.*

observation of treatment effects on the expected natural history of the disease is particularly reassuring[4].

There were no or few other secondary end point analyses that reviewers or Committee members appeared to consider particularly supportive. There was no effect of treatment on a composite end point of cardiovascular morbidity and mortality events (relative risk reduction 95% confidence limits from -8 to +24%)[5]. However, proteinuria decreased on losartan, consistent with the presumed mechanism of action, and the rate of loss of renal function, assessed by the reciprocal of the serum creatinine, also was less on losartan. Apparently these factors played lesser roles than did ESRD and death in Committee members' thinking.

In addition, in an apparent reversal from the previous Advisory Committee meeting, the Committee denied that the data from the ACE inhibitor captopril in type I diabetic nephropathy was relevant to decision-making of an angiotensin receptor antagonist in type II diabetes.

However, the Committee, as it had in considering irbesartan, continued to find relevance in the data from the development program for another angiotensin receptor antagonist in type II diabetes. Supported by those data, 4 additional Committee members (total of 8 out of 11) found adequate support for the approval of losartan for nephropathy of type II diabetes.

As has been discussed at these two Advisory Committees and internally at FDA, there is ample precedent for factoring into decision-making what one knows about other members of a pharmacological class. The novel aspects are, perhaps, that this is being done openly in the case of losartan and irbesartan, and that no drug will have gotten approval for this indication solely on its own merits.

There are some reassuring aspects of the current case that ought to limit the generalizability of any regulatory decision here. First, the primary analysis included event-free follow-up for subjects in whom it was not possible to observe creatinine doubling events. This had less of an impact in RENAAL than it did in IDNT, but it does mean that a better estimate of the effect size is larger and the corresponding p-value is lower than has been reported. Second, both drugs are approved products with similar indications in hypertension (only). Consequently, there are drug-specific, if not indication-specific safety data available beyond the development program in diabetic nephropathy. Third, the available data indicate that both drugs are relatively safe in their indicated use and, so far as one can tell, free from dose-related adverse events. Finally, one can say, again so far as one can tell without comparative studies, that the two drugs are not distinguishable with regard to activity or specificity from other members of their pharmacological class.

It is perilous to believe that one understands mechanism well enough to borrow effectiveness information from a closely related drug. But understanding mechanism and seeing support for it within a development program is surely reassuring. Not seeing support for a presumed mechanism within a development program undermines one's confidence in the results. If this is true within a development program, then it is hard to argue that mechanism does not make a relevant, if somewhat more tenuous, link across programs. Had disparate results been demonstrated in IDNT and RENAAL, one would have worried about the discrepancy.

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[4] The effects of irbesartan on ESRD and death were less persuasive in IDNT, most likely because IDNT had less aggressive follow-up for subjects once they doubled serum creatinine.

[5] Similar analyses in IDNT showed similar results.

Therefore IDNT provides relevant support for the belief that the clinical benefits seen in the losartan development program are reliable, that they can be expected to appear in clinical practice. The support IDNT provides is less good than would have been a similar study with losartan, but it is substantial support.

Approval of losartan for nephropathy in type II diabetes sets no significant regulatory precedents, other than illuminating a common but generally occult decision-making practice.

Many of these considerations apply as well to the support of irbesartan's diabetic nephropathy indication by RENAAL.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

MEDICAL REVIEW
ADDENDUM

NDA No.: 20-386/SE1-028
DRUG NAME: COZAAR™ Tablets (Losartan Potassium)
SPONSOR: Merck & Co., Inc.
West Point, Pennsylvania 19486
TYPE OF DOCUMENT: New Drug Application-Efficacy Supplement
DATE RECEIVED: November 13, 2001
DATE REVIEW STARTED: January 10, 2002
DATE REVIEW COMPLETED: March 7, 2002
DATE REVIEW REVISED: April 1, 2002
MEDICAL REVIEWER: Juan Carlos Pelayo, M.D.

ERRATA

1. The statement in page 5:

... Hence, the retrospective nature of the subgroup analysis together with the lack of statistical power for such analysis precludes any valid conclusion on the use of losartan in special populations.

should read:

... **Hence, the lack of statistical power for a subgroup analysis precludes any valid conclusion on the use of losartan in special populations.**

2. The statement in page 7:

... Subgroup analysis of the primary endpoint by demographic variables or baseline factors is of interest, but its retrospective nature together with the lack of statistical power preclude any valid conclusion on the use of losartan in special populations.

should read:

... **Subgroup analysis of the primary endpoint by demographic variables or baseline factors is of interest, but the lack of statistical power precludes any valid conclusion on the use of losartan in special populations.**

3. The statement in page 24:

... The retrospective nature of the analysis in addition to the small number of patients in each category per group precludes a valid commentary on the findings.

should read:

... The small number of patients in each category per group, i.e., the lack of statistical power, precludes a valid commentary on the findings.

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/s/

Juan Carlos Pelayo
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MEDICAL OFFICER

MEDICAL REVIEW

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INTRODUCTION AND BACKGROUND

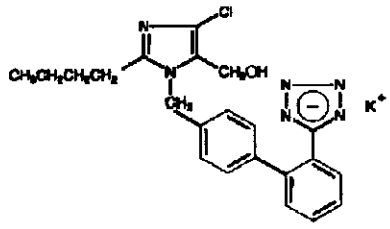
The prevalence of end-stage renal disease continues to increase in the United States; currently it is approximately twice what it was a decade ago. [1] This increase spans all racial and ethnic groups, however Hispanics, Native Americans, and Blacks carry a risk that range from two to more than four times those of whites. Diabetic nephropathy is the leading cause of end-stage renal disease in the United States and is a significant health problem because of the resultant morbidity and mortality. Of note, renal disease due to type 2 diabetes appears to account for almost all of the increasing number of patients with kidney failure. In only 10% to 15% of patients with type 2 diabetes mellitus does end-stage renal disease develop, however type 2 diabetes accounts for approximately 50% of end-stage renal disease cases with diabetic nephropathy since 85% of all patients with diabetes have type 2. Hence, the discovery of therapeutic interventions aim to prevent/attenuate the progression of diabetic nephropathy due to type 2 diabetes to end-stage renal disease is a public health priority. Patients with type 2 diabetes mellitus have a high prevalence of hypertension. In this regard, epidemiological data and results from clinical trials suggest that strict glycemic and blood pressure control blunt its renal complications.

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

Based on the results from pre-clinical as well as clinical studies the sponsor reasoned that losartan, via hemodynamic and non-hemodynamic mechanisms through blockade of the renin-angiotensin system in addition to the antihypertensive action, could effect a treatment benefit to normotensive or hypertensive patients with type 2 diabetes and nephropathy like that observed with captopril in patients with renal disease due to type 1 diabetes mellitus.[2] To test the hypothesis Merck & Co. Inc. sponsored the clinical development of COZAAR™ (Losartan Potassium) in normotensive as well as hypertensive patients with diabetic renal disease due to type 2 diabetes mellitus. In essence, the clinical development program of losartan consists of one pivotal clinical trial.[3] The results from this investigation were published in the *New England Journal of Medicine*[4] and submitted to the FDA by the sponsor as an efficacy supplement (SE1-028) to NDA 20-386.

GENERAL INFORMATION

Drug name: COZAAR™ (Losartan Potassium). Losartan is a non-peptide molecule, chemically described as 2-butyl-4-chloro-1-[*p*-(*o* -1*H*-tetrazol-5-ylphenyl) benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C_{22} H_{22} $ClKN_6$ O, and its structural formula is:



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

[2] Lewis EJ, *et al.* The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. N Engl J Med 1993;329:1456-62.

[3] A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Non-Insulin Dependent Diabetes Mellitus and Nephropathy (RENAAL).

[4] Brenner, BM, *et al.* Effects Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. N Engl J Med 2001;345:861-9.

Drug Class: COZAAR™ is an angiotensin II receptor antagonist with a much greater affinity (more than 1000-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor and its active carboxylic metabolite (E-3174) is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Sponsor's Proposed Indication(s): COZAAR™ is approved "for the treatment of hypertension" regardless etiology. "It may be used alone or in combination with other antihypertensive agents."[5]

The sponsor is now seeking a new indication: *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, and end-stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria."

Dose and Regimens: COZAAR™ is available for oral administration in tablets containing 25 mg, 50 mg or 100 mg of losartan. The current recommended initial dose of COZAAR™ in hypertensive patients is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume and patients with a history of hepatic impairment. COZAAR™ can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

The sponsor recommends in patients with type 2 diabetic renal disease 50 mg once daily as the starting dose, and this dose may be increased to 100 mg once daily based on blood pressure response.

COZAAR™ in Pediatric Population: The study submitted in support of this supplemental NDA did not evaluate patients within the pediatric age groups. Pursuant to 21 CFR 314.55 (c), Merck & Co., Inc requested a full waiver to the pediatric data requirement for the treatment of pediatric patients with type 2 diabetes and nephropathy. "The rationale for this full waiver request is that the proposed indication does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Although type 2 diabetes may develop in adolescents, the complication of diabetic nephropathy develops 5-10 years after the onset of disease. Thus, such patients generally would be young adults by the time nephropathy occurred and treatment with losartan could be started to delay progression of their underlying disease (per the proposed indication)."

Post-Marketing Experience: COZAAR™ was approved in United States of America on April 14, 1995, since then several countries worldwide have approved it for the treatment of hypertension.

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

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

HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

[5] As per the current label for COZAAR™ Tablets (Losartan Potassium).

DESCRIPTION OF CLINICAL DATA AND SOURCES

The clinical development program of losartan consists of one international, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study in normotensive/hypertensive patients with diabetic renal disease due to type 2 diabetes (Protocol No. 147. A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Noninsulin Dependent Diabetes Mellitus and Nephropathy, RENAAL study). Hence, any regulatory action on COZAAR™ (Losartan Potassium) for the new sought indication "*Renal Protection in Type 2 Diabetic Patients with proteinuria*" depends on the interpretation of the results from this study.

The RENAAL study evaluated 1513 normotensive/hypertensive patients with type 2 diabetes and nephropathy, who were randomized from 250 investigative centers in 29 countries from Europe, Asia, Latin and North America. The study investigated whether losartan, either alone or in combination with conventional antihypertensive therapy (diuretics, calcium channel blockers, beta blockers, alpha blockers, and centrally acting agents), reduced the number of patients with type 2 diabetes experiencing a doubling of serum creatinine, ESRD, or death compared to placebo-treated patients (with or without conventional antihypertensive therapy). In addition, the study assessed the effects of losartan (versus placebo) on cardiovascular morbidity and mortality, progression of renal disease measured as the slope of the reciprocal of serum creatinine, and changes in proteinuria. Other parameters measured included quality of life (U.S. patients only) and healthcare resource utilization (U.S. and European patients only). The trial was conducted in accordance with accepted Ethical Standards.

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

DOSING, REGIMEN, AND ADMINISTRATION ISSUES

RENAAL is the only trial submitted by the sponsor where the effect of COZAAR™ (Losartan Potassium), up to 100 mg, on renal and cardiovascular morbidity and all-cause mortality was evaluated in patients with renal disease due to type 2 diabetes mellitus. The percentage of patients who took the designated daily dose of losartan more than 50% of the time is as follows: 1.6% took 25 mg, 26.6% took 50 mg and 71.8% took 100 mg. The results from the RENAAL study indicate that losartan given daily significantly increased the time to doubling of serum creatinine, as compared with placebo. Based on the above results, if COZAAR™ (Losartan Potassium) is approved for the treatment of subjects with diabetic nephropathy due to type 2 diabetes, 100 mg daily should be the recommended dosage regimen. There are no new issues arising from the RENAAL study with regard to the administration of losartan.

USE IN SPECIAL POPULATIONS

The population in the RENAAL study predominantly consisted of white (48.6%) males (63.2%) under the age of 65 years (66.4%). Females, subjects >65 years of age, as well as Hispanics, Native Americans, Blacks, Asians and other races were significantly underrepresented in the clinical trial, and subjects within pediatric age groups were not randomized into the study. Hence, the retrospective nature of the subgroup analysis together with the lack of statistical power for such analysis precludes any valid conclusion on the use of losartan in special populations.

SUMMARY/CONCLUSIONS

The clinical development program of losartan consists of a single pivotal clinical trial, the RENAAL study. Hence, any regulatory action on COZAAR™ (Losartan Potassium) for the new sought indication "*Renal Protection in Type 2 Diabetic Patients with proteinuria*" hinges primarily on the interpretation of the results from that study.

It seems that the regulatory obstacle to overcome before a decision is made is whether and why the RENAAL study, a single clinical trial showing a modest treatment benefit primarily through a surrogate endpoint with a marginal p-value[6] and without confirmatory evidence, is insufficient for approval. What follows is a summary of efficacy highlighting the consistency of the results and design features of the study critical to their interpretation, and ancillary as well as complementary information that together dispel the notion that the results of the RENAAL study are insufficient to warrant approval.

Efficacy: A total of 1513 subjects (losartan n=751 and placebo n=762), with overt nephropathy due to type 2 diabetes mellitus, were randomized into the clinical trial. The population was predominantly white (48.6%), males (63.2%), under the age of 65 years (66.4%) with a mean BMI of 29.7%. 96.6% of the subjects were hypertensive at study entry. The mean baseline seated systolic and diastolic blood pressures were 152.5 mmHg and 82.4 mmHg, respectively. Mean serum creatinine was 1.9 mg/dl and mean proteinuria (UA/Cr) was 1808 mg/gCr. Ninety percent of the patients had diabetes for ≥5 years, and 60.1% and 49.0% had used insulin and oral anti-diabetics prior to study entry, respectively. Mean $HbA1_c$ was 8.5%.

Based on comparison of the means, there were no significant differences/imbalances between the treatment groups in baseline demographic characteristics, blood pressure, prior therapies, and laboratory measures that could potentially obscure the interpretation of the study's results.

The RENAAL study demonstrated a modest treatment benefit for losartan in hypertensive patients[7] with advanced diabetic nephropathy due to type 2 diabetes mellitus. The risk of the primary endpoint, a composite outcome variable of time to first event of doubling serum creatinine, ESRD or death[8], was significantly reduced by losartan treatment, the relative risk reduction was 16.1% with a marginal p-value equal to 0.022. An analysis of the primary endpoint by country indicates that there was not significant regional heterogeneity.

Albeit the study was not powered to detect differences between treatments for the components of the primary endpoint, the treatment benefit is explained entirely by a delay in the time to doubling of serum creatinine. The risk of the component of doubling of serum creatinine was reduced by 25.3% (95.2% CI 0.61, 0.92; p=0.006) in losartan-treated subjects. Losartan treatment had no effect on time to ESRD (p=0.66) or death (p=0.91). This outcome is not unexpected because in the study's inclusion criteria a serum creatinine ≤3.0 mg/dl corresponded to the maximum value for study entry, for both males and females subjects, so a value equal to 6.0 mg/dl albeit means a doubling as a rule does not establish ESRD prompting dialysis or renal transplantation. Therefore, one could have predicted that the treatment effect would be primarily an effect on doubling of serum creatinine. Also the study was not powered to separately assess an effect on mortality. Nevertheless, the risk of the composite endpoint of ESRD or death was reduced by 19.9% in patients receiving losartan (p=0.009, 255 (34.0%) events for losartan and 300 (39.4%) for placebo, hazard ratio 0.8 and CI 0.68, 0.95).[9]

It should be noticed that even though doubling of serum creatinine is a surrogate of clinical benefit, the FDA's perspective on the subject is that of a validated surrogate endpoint. In view of that, the observed differences in

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[6] Currently, the Division of Cardio-Renal Drug Products advises sponsors that approval of a drug, requires two trials with the primary endpoint tested at a p-value = 0.05 or one trial with a p-value = 0.00125. However, at the End-of-Phase II Meeting, dated March 8, 1996, the FDA did not address this subject with the sponsor.

[7] In reality, this clinical investigation evaluated the renal protective effect of losartan almost uniquely in hypertensive patients because >95% of the randomized subjects had hypertension at study entry.

[8] The definition of the primary endpoint had the concordance of the FDA from the inception of the study (End-of-Phase II Meeting, dated March 8, 1996).

[9] This was a pre-specified analysis of the primary endpoint. The results were verified by Dr. Hung (FDA, HFD-710.)

doubling of serum creatinine should weigh in the regulatory decision the same as differences in ESRD events. A retrospective analysis of the total incidence for the morbid and mortal components of the primary composite endpoint lends support to the aforementioned notion. Albeit losartan treatment did not affect mortality (158 *vs.* 155 deaths, p=0.884, 95.2% confidence interval 0.81, 1.27), losartan-treated patients had significantly fewer ESRD events throughout the trial as compared with those subjects in the placebo group, 147 *vs.* 194, respectively (p=0.002, risk reduction of 28.6%, 95.2% confidence interval 0.57, 0.89). The difference in the number of ESRD events between the groups is forty-seven. According to the sponsor, of the subjects who had a doubling of baseline serum creatinine, 51% *vs.* 65% developed ESRD in the losartan and placebo groups, respectively. These analyses significantly strengthen the evidence in support of a renal protective effect of losartan in subjects with type 2 diabetes mellitus and overt nephropathy.

Subgroup analysis of the primary endpoint by demographic variables or baseline factors is of interest, but its retrospective nature together with the lack of statistical power preclude any valid conclusion on the use of losartan in special populations.

In keeping with the results on doubling of serum creatinine and ESRD, losartan-treated patients lost renal function at a rate[10] significantly lower than patients receiving placebo did (estimated reduction in the rate of decline in renal function 12.7%, p=0.0091). Also, losartan treatment reduced proteinuria to a greater extent than placebo, on average 33%, and this effect was statistically significant at month 3 through month 39 (p<0.001) and at month 42 (p<0.01). Of interest, the sponsor conducted a retrospective analysis to ascertain the effect of baseline proteinuria on the progression of renal disease, in comparison to placebo, losartan had a significant beneficial effect only in patients who had proteinuria ≥2000 mg/gCr (p=0.042 for patients with proteinuria between 2000 and 3000 mg/gCr, and p=0.019 for patients with proteinuria ≥3000 mg/gCr).

The results of the intent-to-treat analysis of the secondary composite endpoint of cardiovascular morbidity/mortality, pre-specified as the time to first event of myocardial infarction, stroke, hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or cardiovascular deaths, indicate that losartan administration failed to effect a treatment benefit. The estimated risk reduction (losartan *vs.* placebo) was 9.6% (95% confidence interval -7.5%, 24.0%, p=0.253). Losartan only reduced the risk for hospitalization for heart failure (total incidence) by 31.6% (89 patients with losartan *vs.* 126 with placebo; hazard ratio 0.68, p=0.006). Again it is worth mentioning that the study was not powered to evaluate the effect of losartan on cardiovascular morbidity/mortality.

Treatment with losartan as compared with placebo did not significantly affect the rate of amputation and failed to improve quality of life.

The study was not well controlled in that the groups had statistically significant dissimilar blood pressure levels almost throughout the duration of the trial. Noteworthy, the losartan group had significantly lower mean blood pressure levels than the placebo group did [range -0.89 to -3.55 mmHg, mean (±SD) -2.29 (±0.74) mmHg]. Contrary to the current belief, statistical adjustment(s) for differences in blood pressure control is not plausible because at present a quantitative description of the relationship between blood pressure and progression of renal disease due to diabetes mellitus remains intangible. Thus, the contribution of a greater blood pressure control to the overall renal protective effect of losartan can not be determined.[11]

Glycemic control based on $HbA1_c$ levels was comparable between the groups.

At this point, commentary on ancillary as well as complementary information to the RENAAL study is in order. To reiterate, hitherto, there is not a drug approved by the FDA for the treatment of the nephropathy associated with type 2 diabetes mellitus. Captopril, an angiotensin converting enzyme inhibitor, is the only drug to gain FDA's approval for the treatment of diabetic nephropathy but only for those patients with overt nephropathy due to type 1 diabetes mellitus. The captopril study, performed over a decade ago, is heralded as the "gold

[10] Determined by the slope of the reciprocal of serum creatinine (1/sCr) across time (year) during the trial.
[11] Of note, the captopril study and the study with another angiotensin II receptor antagonist in patients with nephropathy due to type 2 diabetes had comparable discrepancy in blood pressure control, that is the subjects receiving the test drugs had significantly lower blood pressures than those placebo-treated subjects.

standard" of clinical trials for diabetic nephropathy. And the prevailing view is that new clinical trials investigating treatments for diabetic nephropathy have to measure up to its results. The study had three primary endpoints a) total incidence of doubling of serum creatinine, b) the rate of urine protein excretion and c) total incidence of ESRD or death. The results are as follows: doubling of serum creatinine was reached by 43 of 202 placebo and 25 of 207 captopril subjects (RR=51.1%, p=0.004); ESRD was reached by 31 placebo and 20 captopril subjects (RR=41.9%, p=0.055); deaths occurred to 14 of 202 placebo and 8 of 207 captopril subjects (RR=46.6%, p=0.150); ESRD or death was reached by 42 of 202 placebo subjects and by 23 of 207 captopril subjects (RR=50.5%, p=0.006).[12] Noteworthy, there was a significant imbalance in the rate of urinary protein excretion at baseline, proteinuria was significantly lower in the captopril group than in the placebo group ($p<0.02$). How this major baseline difference may have affected the study's outcome is uncertain. Perusal of the above results indicates that they are qualitatively similar but quantitatively, i.e., the magnitude of the effect, larger as compared to the RENAAL study. However, to draw conclusions from that comparison lacks scientific rigor because among others the captopril study was carried out over a decade ago. Since then the treatment of patients with diabetes mellitus have significantly evolved, namely more strict glycemic and blood pressure control, use of different antihypertensives combination, use of lipid lowering agents, etc., which in and of itself could have alter the responsiveness of the disease to therapeutic interventions. Thus whether one could replicate today the results of the captopril study, in particular as it relates to the magnitude of the effect, in patients with nephropathy due to type 2 diabetes is uncertain at best.

Finally, it is important to mention that the RENAAL study is not the only clinical investigation that had evaluated the effect(s) of an angiotensin II antagonist on the progressive nature of the nephropathy associated with type 2 diabetes mellitus. The IDNT study[13], which its results were published at the same time as the RENAAL study, demonstrated a treatment benefit for another AII antagonist in hypertensive patients with advanced diabetic nephropathy due to type 2 diabetes. The primary composite endpoint was time to first event of doubling of serum creatinine, ESRD, or death, the AII antagonist significantly reduced the risk of the primary composite endpoint (relative risk reduction of 20%, p=0.0234 *vs.* placebo and relative risk reduction of 23%, p=0.0064 *vs.* Amlodipine). Thus the results from the IDNT and RENAAL studies complement each other, lending support to the developing notion of a drug class effect.

Safety: The safety profile of losartan that emerged from the evaluation of the RENAAL study primarily in hypertensive subjects with advanced nephropathy due to type 2 diabetes mellitus is comparable to the safety profile delineated already in patients with hypertension regardless causality. Overall losartan was well tolerated and safe; there are no new safety concerns regarding the use of losartan in this diabetic population.

A risk-benefit analysis based on the available empirical data supports the notion that losartan administration is associated with a treatment benefit, delays the progression of diabetic nephropathy, without significant safety risks.

RECOMMENDATIONS

The recommendation is that COZAAR™ (Losartan Potassium) be approved for the treatment of hypertensive patients with overt nephropathy due to type 2 diabetes mellitus.[14]

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[12] The information was obtained from the FDA's primary medical review of the captopril study, dated October 14, 1993.

[13] Lewis, EJ, *et al.* Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. N Engl J Med 2001;345:851-60. The results of the IDNT study were discussed at the Cardio-Renal Advisory Committee Meeting on January 17, 2002.

[14] The labeling for losartan should be modified to reflect the results of the RENAAL study.

STUDY REVIEW

Protocol No. 147. A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Noninsulin Dependent Diabetes Mellitus and Nephropathy (RENAAL)

INVESTIGATIONAL PLAN

Study Design: This was a double-blind, randomized, placebo (±conventional non-ACE inhibitor, non-AIIA antihypertensive therapy) controlled, multinational, multicenter long-term study to determine the effect of losartan (±conventional non-ACE inhibitor, non-AIIA antihypertensive therapy) on renal and cardiovascular endpoints in normotensive and hypertensive patients with type 2 diabetes and nephropathy. Following a 6-week screening period, eligible patients were stratified by baseline level of proteinuria, i.e., urine albumin to urine creatinine ratio (UA/Cr) from a first morning void above or below 2000 mg/g Cr, and randomized 1:1 to either losartan 50 mg or placebo on a background of conventional antihypertensive therapy (ACE inhibitor or AIIA therapy excluded). After the first month of double-blind therapy if trough blood pressure did not reach the goal of <140/90 mmHg losartan was to be increased to 100 mg daily (2 tablets of study drug).[15] Patients were to receive double-blind therapy for approximately 4.5 years.

As recommended by the American Diabetes Association patients were encouraged to follow a 0.8 mg/kg/day protein and 2,000 mg/day or less sodium diet.

With the exception of ACE inhibitors and angiotensin II antagonists, prior and concomitant use of conventional antihypertensives was permitted. Short-term use of NSAIDs, steroids or immunosuppressives was allowed on a case-by-case basis if medically warranted.

Study Population: Male and female patients between 31 and 70 years of age, with type 2 diabetes and proteinuria (an albumin to creatinine ratio of ≥300 mg/g), with serum creatinine levels between 1.5 to 3.0 mg/dl for males and 1.3 to 3.0 mg/dl for all females and males <60 kg, with or without hypertension (Sitting BP ≤200/110 mmHg) were enrolled in the study.[16]

Efficacy Variables: The primary composite endpoint is time to the first event of doubling of serum creatinine, ESRD, or death due to any cause. Doubling of serum creatinine is defined as a twofold increase from baseline (average of the last two prerandomization values); the first value which defines this doubling must be confirmed (i.e., remain doubled) by a repeat measurement taken approximately 4 weeks after the first doubling has been observed. ESRD is defined as the need for chronic dialysis or renal transplantation.

The time to first event of the composite endpoint of cardiovascular morbidity/mortality is the secondary endpoint. Cardiovascular morbidity/ mortality is defined as: death due to cardiovascular disease, nonfatal MI, nonfatal stroke, unstable angina requiring hospitalization, heart failure requiring hospitalization, and need for coronary or peripheral revascularization. Changes from baseline (average of last two prerandomization values) in the ratio of urine albumin to urine creatinine is the other secondary endpoint. Progression of renal disease as measured by the reciprocal of serum creatinine is also a secondary endpoint.

Tertiary endpoints are quality of life (U.S. only), healthcare resource utilization (U.S. and Europe), and incidence of amputations.

A pre-specified interim analysis of the primary composite endpoint was performed for review by the DSMB

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[15] If necessary, the patient's usual antihypertensive drug therapy should 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, a beta-blocker, a calcium channel blocker, an alpha-blocker or a centrally acting agent. Of note, angiotensin converting enzyme inhibitors and other angiotensin II antagonists were excluded from the trial.

[16] For a complete description of this study's protocol the reader is referred to NDA20-386/SE1-028, Protocol No. 147.

only when one-half of the expected number of endpoints was reached.

Safety: Clinical and laboratory data were collected every 3 months.[17] Patients who discontinued early from study therapy continued to be followed in the clinic every 3 months, or by telephone contact if they could not visit the clinic, until the end of the study.

Treatment Compliance: Drug dispensing information was recorded on a drug accountability worksheet at each visit. A tablet count was also performed when study drug was returned at each visit and recorded on the drug accountability worksheet. The patient was questioned about compliance if the tablet count was not consistent with the number of days between visits. The sponsor defined compliance "as taking study drug >80% of the time during the double-blind treatment."

Statistical Methods: The sample size calculation for this trial is based upon the assumption that the 5-year doubling of serum creatinine/ESRD/death rate in the placebo group will be 58% and that this rate will be reduced by 20% (absolute proportion of 46.4%) in the losartan group. The predicted doubling of serum creatinine, ESRD and death event rates in the placebo group are based upon unpublished data from two NIDDM cohorts. Ninety-five percent (95%) lower confidence bounds of the first-event rates were used for sample size estimation to account for variability of the estimates and improvement in disease management (e.g., better glucose control, higher use of lipid-lowering agents). An additional adjustment (increase) was made to the doubling and ESRD event rates to account for the inclusion of higher risk patients that were not represented in the cohorts. Based upon the assumed event rate and treatment effect, in order to have at least 95% power at the 4.9% significance level (two-sided, adjusted for interim analysis), the trial should enroll at least 1520 patients and continue until the last enrolled patient has been followed for 4 years. The sample size estimate has also assumed the following: patients will be entered at a uniform rate during a 1-year enrollment period, the treatments will have proportional hazards, and that 50% of the patients will discontinue double-blind study therapy during the course of the trial (13% per year) for reasons other than the primary endpoints.

The primary approach that will be used for all efficacy and safety analyses is the "intent-to-treat" approach.

Study Administrative Structure: The study was overseen by an independent Steering Committee, who were blinded to the data throughout the duration of the study. An independent, blinded Endpoint Committee adjudicated all endpoints and an independent Data Safety Monitoring Board (DSMB), who were unblinded, monitored the safety of the study on a regular basis. The DSMB was responsible for identifying safety issues and interpreting emerging study data at the interim analyses.

RESULTS

Interim monitoring and Analysis: "The study was planned to be completed in Mar-2002, 4.5 years from last patient in. However, the Steering Committee, whose obligation was to stay abreast of current research in the field and continually re-evaluate the ethical context of the trial, voted unanimously to end the study early, for reasons unrelated to the study data. The reason for this decision was documented in the minutes of the Steering Committee meeting on 10-Feb-2001 and is described in the following paragraph taken from a letter that was sent to all investigators: "At its meeting on 10-Feb-2001, the RENAAL Steering Committee took this action due to increasing evidence that ACE inhibitors are effective in reducing cardiovascular events in patients with characteristics similar to RENAAL patients. This decision to discontinue was in part due to soon-to-be published information showing that cardiovascular events are reduced by ACE inhibitors in diabetic patients with renal impairment. The action of the Steering Committee was taken on the basis of external evidence only and was therefore independent of any knowledge of the results of the trial. The Steering Committee has been and will remain blinded until the results of the trial are analyzed and presented. The Committee further recommended that physicians caring for patients in the RENAAL trial make this information available to their patients and strongly consider addition of therapy aimed at blockade of the renin-angiotensin-aldosterone system (RAAS). In the usual care arm of the RENAAL Study, patients were receiving antihypertensive therapy,

[17] See attached tables (Appendix, pages 32 and 33): Schedule of Clinical Observations and Laboratory Measurements.

excluding agents that block the RAAS. The "soon-to-be published information" referred to the renal insufficiency sup-population of the Heart Outcomes Prevention Evaluation (HOPE) study (with or without diabetes) which demonstrated that use of an ACE inhibitor reduced cardiovascular events."

The endpoint cutoff date for this study was 10-Feb-2001, i.e., any endpoint occurring on or before 10-Feb-2001 was adjudicated.

Amendments: The original protocol was amended 6 times.[18] Significant amendments to the design of the study included:

Amendment No.: 03

1. A new secondary hypothesis and objective is added to assess the effect of losartan on progression of renal disease as measured by the reciprocal of serum creatinine.
2. Data Analysis
    a. Sample size: The originally approved protocol was designed to enroll 1520 patients giving at least 95% power (actual power is 97%) for the primary endpoint. Since patient enrollment has been slower than anticipated in the protocol, recruitment of 1520 patients will not be achieved in the projected timeframe. An enrollment period of approximately 2 years is estimated to allow recruitment of at least 1320 patients, the sample size required to achieve 95% power. Therefore, using a 2-year enrollment cutoff, 1320 to 1400 patients will be enrolled which will provide at least 95% power.
    b. Duration of follow-up: The original study was planned to have a 1-year enrollment period, with a follow-up period of 4 years from the time the last patient is randomized (an average follow-up of 4.5 years assuming a uniform enrollment pattern). Since the actual enrollment period has been extended to 2 years, the duration of follow-up is reduced to 3.5 years in order to maintain the average follow-tip of 4.5 years, while the study's power is preserved at 95%.
    c. The interim analysis stopping rules are updated.

Amendment No.: 04

1. Clarification of the definition of doubling of serum creatinine and time frame for confirmatory value.
    a. The initial doubling of serum creatinine measurement may be obtained from the local laboratory or the central laboratory. However, the confirmatory value must be obtained from the central laboratory (Smith Kline Beecham Laboratories).
    b. The time period for the confirmatory value should be no earlier than 4 weeks after the initial doubling value was obtained.
2. Definition of ESRD
    a. To include patients requiring chronic dialysis but refusing initiation of dialysis and or dialysis is not readily available.
    b. The need for dialysis refers to patients with a need for chronic dialysis.
3. Definition of patient follow-up:

Because this is a long-term study, some patients will inevitably discontinue study therapy or become lost to follow-up for various reasons. Because the protocol utilizes the intent-to-treat analysis, endpoint information for patients who have discontinued is imperative. Therefore, telephone follow-up, whenever possible, will be used for patients who discontinued from study drug and are unable/refuse to come to the clinic for protocol scheduled visits. For those patients who refuse telephone follow-up or appear lost to follow-up, public records may be used to obtain primary endpoint information (i.e., ESRD or death).

Telephone Follow-Up: Patients who have discontinued study drug and will not be followed at regular clinic visits will he asked if they agree to phone contact every 3 months. Calls will be based from the date of randomization in an attempt to maintain the patient's visit schedule per protocol. Abbreviated information on the primary endpoints and date of dialysis, transplantation, or death will be obtained.

Lost to Follow-Up: For patients who refuse phone contact or are lost to follow-up, public database searches, i.e., governmental databases such as Healthcare Financing Administration (HCFA) and the National Death Index (NDI) in the United States, will be necessary to determine the status of patients. Therefore, investigators

[18] For a summary of amendments see NDA 20-386/SE1-028, Protocol No. 147, Appendix 3.3.3.

will need to acquire patient information such as full name, social security number, address, and contact number for a relative in order to access public records. Each subsidiary will work with the investigator to obtain this information through their respective governments as well.

4. Patients who have discontinued study drug may be restarted at any time on a case-by-case basis. Prior to reinitiating study therapy the investigator must receive approval from the sponsor if the time period for discontinuation of study drug has been >1 month. The investigator will call the sponsor with date of last dose of study therapy and reason for discontinuation to receive approval.

5. The Steering Committee has developed an algorithm for treatment of hypertension, especially for those patients with elevated systolic pressures. The algorithm is a recommended guideline, not a mandatory procedure, to assist the investigator in reaching the goal blood pressure of <140/90 mmHg.

Protocol Violations: Protocol violations were documented pre- and post randomization in 11 patients, 5 subjects received placebo and the remaining 6 were losartan-treated subjects. All randomized subjects were included in the intent to treat efficacy analysis dataset, whether or not a subject had a significant protocol violation. The type of protocol violation in each subject is provided in Table 1. In the losartan group one subject had insulin-dependent diabetes mellitus, three subjects had study therapy compliance <65%, and three subjects received ACE inhibitor or AIIA for >6 months during the study. Three subjects receiving placebo were also treated with an ACE inhibitor or AIIA for >6 months during the study, and two subjects had study therapy compliance <65%.

Table 1. Protocol Violation

Study Site	Allocation #	Treatment	Protocol Violation
147-004	2080	Losartan	Study therapy compliance <65%.
147-039	2390	Losartan	Patient with Insulin-Dependent Diabetes Mellitus.
147-199	3316	Losartan	Use of ACE inhibitor or AIIA >6 months during the study.
147-172	3936	Losartan	Study therapy compliance <65%.
147-163	4243	Losartan	Study therapy compliance <65% and ACEI/AIIA >6 months.
147-295	5056	Losartan	Use of ACE inhibitor or AIIA >6 months during the study.
147-101	1822	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-041	1872	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-371	2458	Placebo	Study therapy compliance <65%.
147-335	3067	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-290	5082	Placebo	Study therapy compliance <65%.

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 6.]

Unblinding: According to the sponsor, "a total of 6 patients were prematurely unblinded. Patient 2135 (Site 147-0013) experienced CHF, underwent a cardiac catheterization that revealed multiple coronary artery occlusions, and was unblinded at the request of the attending physician for medical management reasons. Patient 3329 (Site 147-0219) was inadvertently unblinded by the local monitor for regulatory adverse experience reporting purposes. This patient had been admitted with worsening renal function and uncontrolled hypertension. Patient 3334 (Site 147-0198) was admitted to the hospital with a myocardial infarction and left cardiac heart failure. The attending cardiologist requested to be unblinded for medical management reasons without the investigator's knowledge. Patient 3368 (Site 147-0218) was unblinded by the attending hospital physician when the patient was admitted with acute myocardial infarction and acute chronic renal failure. The unblinding occurred without the investigator's knowledge. Patient 3552 (Site 147-0193) was also unblinded for medical management reasons by the attending cardiologist. This patient had been admitted with angina pectoris, atrial fibrillation, and acute pulmonary edema. Patient 5024 (Site 147-0258) experienced unstable angina and acute heart failure and was unblinded at the primary investigator's request for medical management reasons."

Disposition of Subjects: 250 investigative sites in 29 countries from North and Latin America, Asia and Europe, randomized a total of 1513 subjects.

The number of patients randomized into the study by country and treatment group are summarized in Table 2. Of note, investigative sites in the United States enrolled forty-five percent of the patients.

Table 2. Number (%) of Patients Randomized by Country and Treatment Group.

Country	Losartan N=751 n	Placebo N=762 n	Total N=1513 n (%)
Argentina	9	8	17 (1.12)
Austria	8	7	15 (0.99)
Brazil	28	30	58 (3.83)
Canada	0	1	1 (0.06)
Chile	13	13	26 (1.71)
Costa Rica	17	16	33 (2.18)
Czech Republic	17	16	33 (2.18)
Denmark	8	8	16 (1.05)
France	5	7	12 (0.79)
Germany	6	6	12 (0.79)
Hong Kong	46	46	92 (6.08)
Hungary	5	5	10 (0.66)
Israel	19	18	37 (2.44)
Italy	13	13	26 (1.71)
Japan	44	52	96 (6.34)
Malaysia	11	10	21 (1.38)
Mexico	33	34	67 (4.42)
Netherlands	4	3	7 (0.46)
New Zealand	1	2	3 (0.19)
Peru	21	21	42 (2.77)
Portugal	5	5	10 (0.66)
Puerto Rico	2	3	5 (0.33)
Russian Federation	14	12	26 (1.71)
Singapore	5	6	11 (0.72)
Slovakia	1	1	2 (0.13)
Spain	36	31	67 (4.42)
United Kingdom	28	28	56 (3.70)
United States	336	345	681 (45.0)
Venezuela	16	15	31 (2.04)

[FDA's analysis. Source NDA 20-386/SE1-028, Protocol No. 147, Dataset: DEMOG.xpt.]

Table 3 summarizes the number of patients randomized into the study by region and treatment group. North America randomized 45.4% of the research subjects while Asia, Europe and Latin America randomized 17.0%, 19.5% and 18.1% of the subjects, respectively.

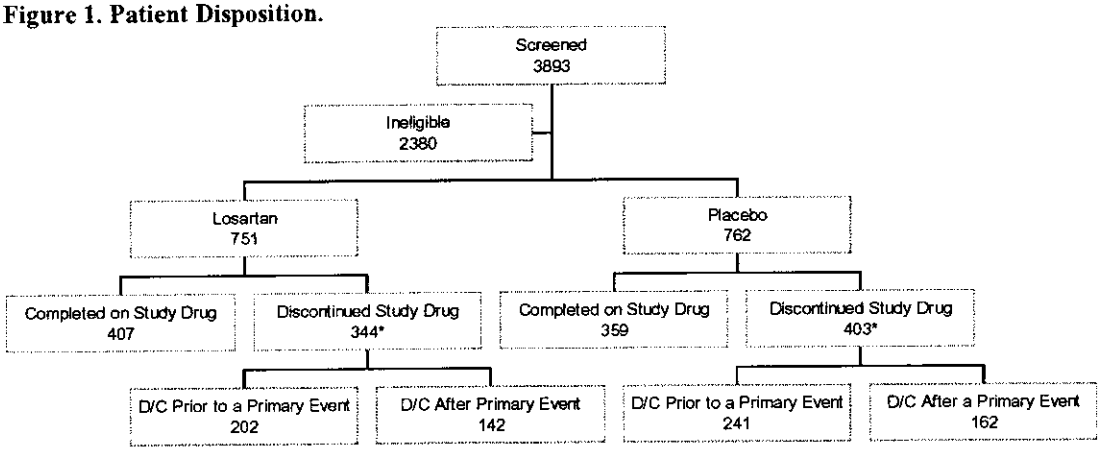
Table 3. Number (%) of Patients Randomized by Region and Treatment Group.

Region	Losartan N=751 n	Placebo N=762 n	Total N=1513 n (%)
Asia	125	132	257 (17.0)
Europe	151	144	295 (19.5)
Latin America	137	137	274 (18.1)
North America	338	349	687 (45.4)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 5.]

As summarized in Figure 1, of the 751 and 762 patients randomized to losartan or placebo, 344 (45.8%) and 403 (52.9%) discontinued study therapy, respectively. This high rate of discontinuation is in accordance with the sponsor's prediction of 13% incidence per year. With respect to discontinuation from study drug prior to experiencing a primary endpoint, 202 (26.9%) losartan and 241 (31.6%) placebo treated patients discontinued study therapy.

Figure 1. Patient Disposition.



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002. *Includes patients who died while on study drug.].

The protocol required that patients who discontinued study therapy be followed in the clinic every 3 months until the end of the study to allow for continued collection of primary and secondary endpoint information. Regular telephone contact was performed, if patients could no longer visit the clinic, in order to capture ESRD or death information; doubling of serum creatinine and cardiovascular outcomes could not be collected from patients in telephone follow-up. According to the sponsor no patient was lost to follow-up; outcomes of ESRD or death information were available in all randomized patients.

Table 4 displays the number of patients who were discontinued, for any reason (excluding those who died while on study therapy) and had a serum creatinine measurement done during the follow-up period. Approximately one-third of the patients had no measurement of serum creatinine and approximately two-thirds had at least one or more serum creatinine measurements after they were discontinued from study therapy.

Table 4. Summary of Serum Creatinine Measurements During the Off-therapy Follow-Up Period in Patients Discontinued for Any Reason

Treatment	Serum Creatinine Measurements	Count (%)
Losartan	0 Scr measurement	93 (33.3)
	1-3 Scr measurements	98 (35.1)
	>3 Scr measurements	88 (31.5)
	Total Patients	279
Placebo	0 Scr measurement	104 (31.2)
	1-3 Scr measurements	115 (34.5)
	>3 Scr measurements	114 (34.2)
	Total Patients	333

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002.]

Table 5 displays the number of patients who were discontinued prior to a primary endpoint and had a serum creatinine measurement done during the follow-up period. Again, approximately one-third of the patients had

no measurement of serum creatinine and approximately two-thirds had at least one or more serum creatinine measurements.

Table 5. Summary of Serum Creatinine Measurements During the Off-therapy Follow-up Period For Patients Who Discontinued Prior to Reaching the Endpoint

Treatment	Serum Creatinine Measurements	Count (%)
Losartan	0 Scr measurement	69 (34.5)
	1-3 Scr measurements	63 (31.5)
	>3 Scr measurements	68 (34.0)
	Total Patients	200
Placebo	0 Scr measurement	69 (28.8)
	1-3 Scr measurements	83 (34.6)
	>3 Scr measurements	88 (36.7)
	Total Patients	240

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002. Scr = Serum creatinine. 3 patients died while on therapy and are therefore not included in these counts, two on losartan (ANs 3905, 4591) and one on placebo (AN 3500).]

Table 6 shows the number (%) of patients randomized into the study and their disposition, i.e., whether they completed or discontinued the trial and the reason for discontinuation, by treatment group.[19] Noteworthy, overall 49.3% of the randomized subjects discontinued study drug, 45.8% of the subjects randomized to losartan and 52.8% subjects receiving placebo discontinued study drug prematurely. Slightly more patients receiving placebo (31.7%) than those treated with losartan (26.4%) were prematurely discontinued because of clinical adverse events. Laboratory adverse experiences were responsible for discontinuations in 2.6% and 2.1% of the patients receiving losartan and placebo, respectively.

Table 6. Discontinuation

	Losartan N=751 n (%)	Placebo N=762 n (%)	Total N=1513 n (%)
Completed Trial	407 (54.1)	359 (47.1)	766 (50.6)
Discontinued Trial	344 (45.8)	403 (52.8)	747 (49.3)
Clinical adverse experience	199 (26.4)	242 (31.7)	441 (29.1)
Laboratory adverse experience	20 (2.6)	16 (2.1)	36 (2.3)
Other reasonH	61 (8.1)	81 (10.6)	142 (9.3)
Patient moved	5 (0.6)	1 (0.1)	6 (0.3)
Patient withdrew consent	57 (7.5)	60 (7.8)	117 (7.7)
Protocol deviation	2 (0.3)	3 (0.3)	5 (0.3)
Patient was lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 4. HIncludes miscellaneous reasons, e.g., patient unable to return for visits, or patient discontinued by personal physician.]

The number (%) of patients who withdrew from the trial, regardless causality, is presented by region in Table 7. It is worth mentioning that except for Asia, the discontinuation rates were similar between groups in the other regions. In Asia 26.4% of the subjects receiving losartan discontinued study drug prematurely versus 45.5% of the placebo-treated subjects.

[19] Table 1A (Appendix) summarizes reasons for discontinuation by region.

Table 7. All-Cause Discontinuation Summary by Region

Region	Losartan N/n (%)	Placebo N/n (%)	Total N/n (%)
Asia	125/33 (26.4)	132/60 (45.5)	257/93 (36.2)
Europe	151/69 (45.7)	144/71 (49.3)	295/140 (47.5)
Latin America	137/61 (44.5)	137/63 (46.0)	274/124 (45.3)
North America	338/181 (53.6)	349/209 (59.9)	687/390 (56.8)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 5.]

Study Population: Table 8 provides a partial summary of patients' demographic and other baseline characteristics. A total of 1513 subjects were randomized into the clinical trial. The study population was predominantly composed of white (48.6%) males (63.2%) under the age of 65 years (66.4%) with a mean BMI of 29.7%. Noteworthy, even though normotensive as well as hypertensive patients could be enrolled into the trial, 96.6% of the randomized subjects were hypertensive at study entry. The mean baseline seated systolic and diastolic blood pressures were 152.5 mmHg and 82.4 mmHg, respectively.

The mean serum creatinine was 1.9 mg/dl and the mean proteinuria level (UA/Cr) was 1808 mg/gCr.

In ninety percent of the patients the duration of diabetes was ≥5 years, and 60.1% and 49.0% of the subjects had used insulin and oral anti-diabetics prior to study entry, respectively. In this regard, the mean glycosylated hemoglobin ($HbA1_c$) level for the entire population was 8.5%.

A history of cardiovascular disease, i.e., prior angina was present in only 9.3% of the randomized subjects, and 12.8% had a history of prior myocardial infarction. Besides a history of nephropathy, which was one of the study entry criteria, retinopathy (63.9%) and neuropathy (50.0%) were among the most common diabetic-related conditions reported at randomization. Only, 8.9% of the subjects did have a history of prior amputation.

While 48.7% of the subjects received ACE inhibitors prior to randomization only 3.2% of the patients reported prior use of AII receptor antagonists. Most commonly use antihypertensive drugs reported by the subjects were calcium channel blockers (71.2%) and diuretics (58.0%), whereas beta-blockers use was reported by 24.1% of the patients.

Thirty three percent and 36.3% of the patients reported use of aspirin and lipid-lowering agents prior to randomization, respectively.

Overall, based on comparison of the means, there were no significant differences/imbalances between the treatment groups in baseline demographic characteristics, blood pressure, prior therapies, and laboratory measures (Table 8).

Table 8. Patient Demographic and Other Baseline Characteristics

Variable		Losartan N=751 n (%)	Placebo N=762 n (%)	Total N=1513 n (%)
Gender:	Female	289 (38.5%)	268 (35.2%)	557 (36.8%)
	Male	462 (61.5%)	494 (64.8%)	956 (63.2%)
Age (yr)H:	<65	503 (66.9%)	502 (65.8%)	1005 (66.4%)
	≥65	248 (33.0%)	260 (34.1%)	508 (33.5%)
Race:	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%)
Hypertensive*		720 (95.8%)	743 (97.5%)	1463 (96.6%)
Body Mass Index (Mean (SD), kg/M^2)		30.0 (6.4)	29.4 (6.2)	29.7 (6.3)

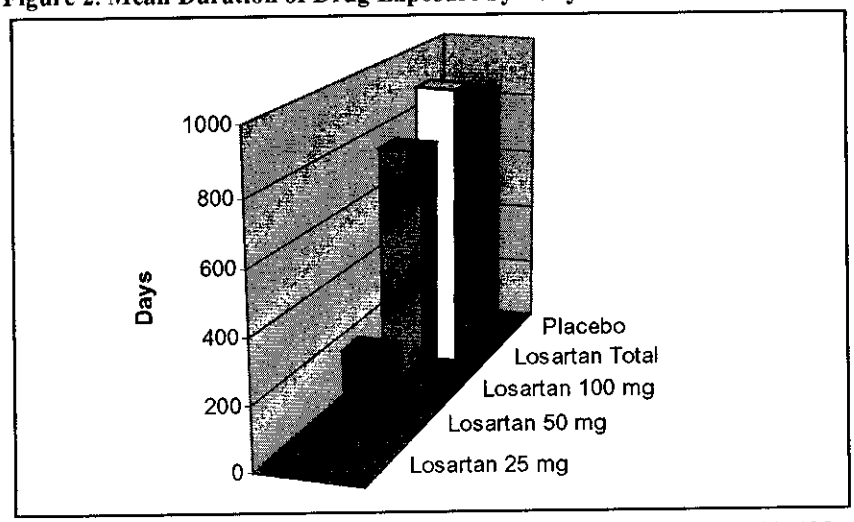
Table 8. Cont'd

Serum Creatinine (Mean (SD), mg/dL)H	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)
Proteinuria (Mean (SD),UA/Cr in mg/g)	1873 (1831)	1743 (1543)	1808 (1693)
HbA1c (Mean (SD) %)	8.5 (1.7)	8.4 (1.6)	8.5 (1.6)
Sitting Systolic BP (Mean (SD)mm Hg)	151.8 (18.7)	153.2 (19.9)	152.5 (19.3)
Sitting Diastolic BP (Mean (SD)mm Hg)	82.4 (10.3)	82.4 (10.6)	82.4 (10.4)
Duration of Diabetes ≥5 yr	676 (90.0%)	686 (90.0%)	1362 (90.0%)
Prior Amputation	65 (8.7%)	70 (9.2%)	135 (8.9%)
Prior Angina	66 (8.8%)	75 (9.8%)	141 (9.3%)
Prior MI	88 (11.7%)	105 (13.8%)	193 (12.8%)
Prior Neuropathy	377 (50.2%)	380 (49.4%)	757 (50.0%)
Prior Retinopathy	495 (65.9%)	472 (61.9%)	967 (63.9%)
Insulin Use	461 (61.4%)	449 (58.9%)	910 (60.1%)
Oral Antidiabetics Use	361 (48.1%)	381 (50.0%)	742 (49.0%)
Prior ACE Inhibitor Use	376 (50.1%)	361 (47.4%)	737 (48.7%)
Prior AIIA Use	29 (3.9%)	20 (2.6%)	49 (3.2%)
Beta Blocker Use	137 (18.2%)	140 (18.4%)	277 (18.3%)
Calcium Channel Blocker (CCB) Use	532 (70.8%)	546 (71.7%)	1078 (71.2%)
Diuretic Use	442 (58.9%)	436 (57.2%)	878 (58.0%)
Aspirin Use	255 (34.0%)	244 (32.0%)	499 (33.0%)
Lipid-Lowering Agents Use	274 (36.5%)	275 (36.1%)	549 (36.3%)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 7. *Hypertensive: on antihypertensive drugs or SiDBP >90 mmHg and SiSBP >140 mmHg. HSome patients who did not meet entry criteria for serum creatinine, or age were randomized. SD denotes standard deviation.]

Extent of Exposure: The study lasted 3.4 years. The mean duration of exposure to placebo or losartan by daily dose is depicted in Figure 2. Overall, patients in the losartan group (regardless of dosage), as compared with placebo-treated patients, had a slightly longer mean duration of exposure to study drug, 913.4 days *vs.* 845.3 days, respectively.

Figure 2. Mean Duration of Drug Exposure by Daily Dose.



[Sponsor's analysis. Adapted from: NDA 20-386/SE1-028, Protocol No. 147, Table 45.]

Table 9 shows the extent of exposure to losartan and placebo and summarizes the number and percent of patients who took 25, 50, 100 mg of losartan daily more than 50% of the time during double-blind treatment.