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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

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INDICATION: Renal Protection

SPONSOR: Merck & Co., Inc.

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0. SUMMARY

This submission contains only one study. The conclusions in Section 4 constitute the summary.

1. INTRODUCTION

This statistical review pertains to the results of the RENAAL trial which is the major component of this submission. Most of the sponsor's main results have been confirmed by this reviewer's analyses. **Only the results of the reviewer's analyses will be presented in this review unless stated otherwise.**

2. OVERVIEW OF RENAAL STUDY RESULTS

The RENAAL study is a multi-center, randomized, parallel group, double-blind trial of losartan versus placebo in patients with type 2 diabetes and nephropathy on a background of conventional antihypertensive therapy (ACE inhibitor or AIIA therapy excluded). For inclusion and exclusion criteria, the readers are referred to the medical reviewer's review.

Following a 6-week of screening period, eligible patients were stratified by baseline level of proteinuria (urine albumin to urine creatinine ratio from a first morning void above or below 2000 mg/gCr), and randomized 1:1 to either losartan 50 mg or placebo. The losartan should be increased to 100 mg daily if at the first month of the study or at any point following trough blood pressure did not reach the goal of 140/90 mmHg. After titration occurred, the study design provided the investigators the flexibility to individualize treatment by adding, increasing, or changing patient's background medication in order to achieve trough goal blood pressure of 140/90 mmHg. Additionally, at the investigator's discretion, patients could begin the study on the lower dose of 25 mg losartan or placebo or be reduced to that dose if necessary during the study.

The primary efficacy endpoint was a composite endpoint of doubling serum creatinine, end-stage renal disease (ESRD), or death for any reason. To be considered an endpoint, doubling of serum creatinine must have been a rise in serum creatinine that was at least twice the baseline serum creatinine value and confirmed by a second serum creatinine measurement, analyzed by the central laboratory, and drawn no earlier than 4 weeks following the initial doubling. ESRD was defined as the need for dialysis or transplantation. The prespecified secondary efficacy endpoint was a composite of cardiovascular morbidity and mortality endpoints, which included cardiovascular death, hospitalization for heart failure, hospitalization for unstable angina, myocardial infarction, stroke, and revascularization. Other secondary measures included progression of renal disease assessed by the slope of the reciprocal of serum creatinine concentration and changes in proteinuria.

Sample Size Planning

Sample size estimation was based on the assumption that the 5-year doubling of serum creatinine/ESRD/death rate in the placebo group would be 58% and that this rate would be reduced to 46.4% (20% reduction) in the losartan group. A total of 1320 to 1400 patients are needed to be able to detect this difference at 4.8% significance level (because of interim analysis described below) and with power 95%, assuming a minimum follow-up period of 3.5 years, 2-year enrollment period, proportional hazards for the treatments, and censoring at discontinuation time for a discontinuation rate of 13% per year. The protocol originally planned for 1520 patients to be enrolled over a 1-year period but was amended 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.

Interim Analysis Plan

The original plan allowed for a single efficacy interim analysis and a series of safety-only analyses. The preplanned interim analysis was to be performed when half of the expected events (284 of 568 events) associated with the sample size and event rate estimates had been observed or the last patient entered had been followed for 2 years, whichever came first. This interim analysis would use the O'Brien-Fleming stopping boundary as a guideline for any recommendation of early termination due to overwhelming efficacy (as measured by the composite for the hard endpoints of ESRD and death only). According to this boundary, the critical p-value at the interim analysis had to be 0.0035 for both the primary endpoint and the composite of the 2 hard endpoints, resulting in the final evaluation α of 0.049. However, at the routine DSMB meetings at which the safety data were unblinded, the committee also considered stopping the study if losartan was superior to placebo with respect to the primary endpoint and also with respect to the composite of the 2 "hard" endpoints, ESRD and death at a two-sided α -level of 0.0001. The DSMB planned 10 unblinded looks at death and ESRD during the course of the study. Each of these looks was provided at a α of 0.0001 to allow the DSMB to stop the study, if losartan was extremely superior to placebo. The total α adjustment for these evaluations was 0.001. This was subtracted from the original α of 0.049, to give the final evaluation α of 0.048, required for the primary hypothesis. For other outcomes, a p-value of <0.05 was considered to indicate statistical significance. All statistical tests were two-sided.

The Steering Committee could, at any point during the study, consider whether external circumstances (e.g., results from other diabetic studies, IRB issues with placebo control, etc.) had occurred that would make it difficult to keep patients in the study. Any decision to end RENAAL for external reasons would be made independently of the unblinded interim data; therefore, for the end-of-study analyses, the only statistical adjustment would be due to the interim analysis by the DSMB.

Randomization

According to the sponsor's response to this reviewer's request, the date of randomization was not specifically collected for RENAAL. The sponsor used the date of the first dose of study drug as the date of the start of the study for the purpose of time to event analysis. The decision to use this date for endpoint analyses was made prior to unblinding the database. The next closest date to date of randomization is date of the "randomization" visit but there is no guarantee that randomization actually took place at that visit.. Among the 1513 randomized patients, the dates differ in only 12 patients, and in 11 of the 12 they differ by only 1 day and in the other case they differ by 12 days.

Analysis methods

The statistical analysis for efficacy and safety will be based on intent-to-treat principle. The primary analysis of the composite endpoint will be based on the time to the first event (i.e., doubling serum creatinine, ERD or death). The components of this endpoint will be analyzed in a similar fashion. For all time to event variables, the relative risk for each event, its confidence interval and the test for treatment difference will be based on the Cox regression model. According to the original protocol, the model will contain treatment group indicator, an indicator variable for the stratification factor of proteinuria at baseline and a factor for country. The treatment by country interaction will also be assessed using Cox regression ($\alpha=0.10$). Life table event rates and mortality curves will be based on the product-limit estimates. In the protocol amendments, country was changed to region (North America [United States + Canada + Puerto Rico], Latin America, Europe [Eastern + Western], and Asia).

The renal function measured as the reciprocal of serum creatinine ($1/Cr$) across over time during the trial will be analyzed. The rate of decline in renal function will be assessed by the slope of the observed $1/Cr$ over the quarterly follow-up period. As the primary analysis, a linear random-effects model will be used to compare slopes in renal function. Region, strata of proteinuria at baseline and baseline serum creatinine values will be included in the model as fixed covariates. Supportive analyses include an ANCOVA analysis to compare the treatment effect with the dependent variable of an individual chronic slope. If normality assumption is not appropriate, the same ANCOVA model will be performed with the dependent variable of the rank of an individual chronic slope.

Proteinuria which is the ratio of urine albumin to urine creatinine will be analyzed. The primary analysis will be based on the intention-to-treat approach. All the observed proteinuria values during the quarterly follow-up period from all patients will be included in the analysis according to the treatment group to which they are randomized, regardless of whether patients discontinue double-blind therapy or have the events of doubling of serum creatinine before the study is completed (3.5 years from last patient randomized). Note that the follow-up time for the secondary endpoint is defined as the period from randomization to the last measurement of proteinuria before ESRD during the study. The mixed-effects (longitudinal) model will be used with terms including treatment (losartan/placebo), time, region and baseline proteinuria levels. A

natural logarithm transformation will be applied for the proteinuria data for the mixed model. The mean change profiles over time will be plotted to show the time course of the treatment effect on proteinuria. Interaction between treatment and time for the mean changes of the proteinuria levels will be explored.

Protocol Amendments

There appeared to be six protocol amendments. Only the following amendment may potentially have a substantive effect on statistical evaluation.

Amendment 147-03

Since patient enrollment had been slower than anticipated in the protocol, recruitment of 1520 patients would not be achieved in the projected timeframe. An enrollment period of approximately 2 years was estimated to allow recruitment of at least 1320 patients required to achieve 95% power. In addition, the interim analysis stopping rules were updated. For the purpose of the DSMB review only, an interim analysis ($\alpha=0.0035$) would be performed by the Merck statistician assigned to the DSMB when half of the expected events associated with this sample size and event rate estimates have been observed or the last patient entered has been followed for 1.75 years, whichever came first.

Changes in the Conduct of the Study or Planned Analyses

The study was to be completed in March of 2002, 3.5 years from last patient in. However, the Steering Committee, whose obligation was to keep abreast of current research in the field and continually re-evaluate the ethical context of the trial, voted unanimously to end the study early, while blinded, 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 was and remained blinded until the results of the trial were 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, excluding agents that block the RAAS.”

The “soon-to-be-published information” referred to data from the HOPE diabetic subpopulation, which demonstrated that in over 900 patients with or without renal insufficiency, there appeared to be significantly less cardiovascular events in patients receiving an ACE inhibitor. The endpoint cutoff date for this study was 10-Feb-2001, i.e., any endpoint occurring on or before February 10 was adjudicated. Endpoints occurring after this date were not collected with the exception of any possible silent myocardial infarctions detected by the core lab on the final visit ECGs.

Efficacy results

A total of 1513 patients at 250 centers from 28 countries were randomized. The total number of the primary endpoint events is 686, larger than the planned number of 568, despite the early ending of the trial by about 1-2 months.

Baseline

Two treatment groups were comparable with respect to baseline demographic characteristics, medical history, electrocardiographic changes, and drug therapy, as shown in Table 7 of the sponsor’s study report.

Primary endpoint (doubling serum creatinine, ESRD or death)

The sponsor’s analysis on the primary efficacy endpoint, doubling of serum creatinine, ESRD or death, was based on the Cox regression model using baseline proteinuria as a stratification factor and geographical region (Asia pacific, Europe, Latin America, North America) as the adjustment factor. As noted above, according to the sponsor, the date of randomization was not specifically collected for RENAAL. The sponsor used the date of the first dose of study drug as the date of the start of the study for the purpose of time to event analysis. The next closest date to date of randomization is date of the “randomization” visit but there is no guarantee that randomization actually took place at that visit. Among the 1513 randomized patients, the dates differ in only 12 patients, and in 11 of the 12 they differ by only 1 day and in the other case they differ by 12 days. Using the date of the “randomization” visit for analysis, the results changed little.

The censoring distribution with respect to the primary endpoint was comparable between the two treatment groups (Table A.1 in the Appendix). As shown in Table 1, the rate of the composite endpoint of doubling serum creatinine, ESRD or death was significantly lower in the losartan group than in the placebo group (hazard ratio of 0.84 with 95.2% CI of 0.72 to 0.97, $p = 0.022$). This treatment difference seemed to be largely attributed to the difference in doubling of serum creatinine. The hazard ratio of ESRD was 0.93. The hazard ratio of all cause death was 0.98. ESRD or death constituted approximately 50% of the primary composite events as the first endpoint. However, on a whole, the losartan group had a significantly fewer ESRD events (hazard ratio of 0.71 with 95.2% CI of 0.57 to 0.89, $p = 0.002$). The mortality rate differed little between the two treatment groups.

Table 1. Incidence of adjudicated primary events (Reviewer's Analysis)

	Losartan (N=751)	Placebo (N=762)	Hazard ratio (95.2% CI)	p-value ^{\$}
Primary event				
Doubling serum creatinine, ESRD or death	327 (43.5%) Median time = 1303 days	359 (47.1%) Median time =1373 days	0.84 (0.72, 0.97)	0.022
Decomposition of the 1st primary event				
Doubling of SC	162 (21.6%)	198 (26.0%)	0.75 (0.61, 0.92)	0.006
ESRD	64 (8.5%)	65 (8.5%)	0.93 (0.65, 1.31)	0.66
Death	101 (13.5%)	96 (12.6%)	0.98 (0.74, 1.30)	0.91
1st component endpoint				
Doubling of SC	162 (21.6%)	198 (26.2%)	0.75 (0.61, 0.92)	0.006
ESRD	147 (19.5%)	194 (25.5%)	0.71 (0.57, 0.89)	0.002
Death	158 (21.0%)	155 (20.3%)	1.02 (0.81, 1.27)	0.88
ESRD or death	255 (34.0%)	300 (39.4%)	0.80 (0.68, 0.95)	0.009

^{\$} nominal p-value, pre-specified primary analysis (Cox model using geographical region as covariate and baseline proteinuria as a stratification variable)

Time between components of primary endpoint

From Table 2, the proportion of patients with ESRD who subsequently died seemed to be higher in the losartan group than in the placebo group. However, none of the comparisons in this table is a randomized comparison.

Table 2. Time from Doubling of Serum Creatinine to ESRD and From ESRD to death (Sponsor's analysis, not confirmed by Reviewer)

	Losartan		Placebo	
	events/sample size (%)	Mean follow-up (days)	events/sample size (%)	Mean follow-up (days)
DSC to ESRD	83/162 (51.2%)	279.5	129/198 (65.2%)	252.5
ESRD to death	50/147 (34.0%)	363.4	49/194 (25.3%)	400.3

Losartan effect on primary endpoint over time

The effect of losartan relative to placebo in terms of the hazard of the primary endpoint did not appear to be constant over the duration of the trial (see Figure 1, in the Appendix). The hazard curves appeared to be converging.

Subgroup results

There was no noticeable inconsistency in the results over the subgroups by demographic variables or baseline factors (Table 3).

Table 3. Subgroup results on primary endpoint (Reviewer's analysis)

	Losartan (N=751)	Placebo (N=762)	Hazard ratio (95% CI)
Female	138 / 289 (47.8 %)	145 / 268 (54.1 %)	0.80 (0.64 , 1.01)
Male	189 / 462 (40.9 %)	214 / 494 (43.3 %)	0.90 (0.74 , 1.09)
Age			
< 65 yrs	222 / 503 (44.1 %)	246 / 502 (49.0 %)	0.83 (0.69 , 1.00)
≥ 65 yrs	105 / 248 (42.3 %)	113 / 260 (43.5 %)	0.95 (0.73 , 1.23)
Asian	49 / 117 (41.9 %)	74 / 135 (54.8 %)	0.69 (0.48 , 0.99)
Hispanic	77 / 140 (55.0 %)	74 / 137 (54.0 %)	1.01 (0.74 , 1.39)
black	50 / 125 (40.0 %)	41 / 105 (39.0 %)	0.97 (0.64 , 1.47)
white	145 / 358 (40.5 %)	163 / 377 (43.2 %)	0.87 (0.69 , 1.09)
Proteinuria			
< 2000 mg/g	150 / 501 (29.9 %)	161 / 511 (31.5 %)	0.91 (0.73 , 1.14)
≥ 2000 mg/g	177 / 250 (70.8 %)	198 / 251 (78.9 %)	0.78 (0.64 , 0.96)
BMI			
< 30 kg/m ²	195 / 437 (44.6 %)	226 / 471 (48.0 %)	0.87 (0.72 , 1.06)
≥ 30 kg/m ²	132 / 314 (42.0 %)	133 / 291 (45.7 %)	0.88 (0.69 , 1.11)
Duration of hypertension			
< 10 yrs	178 / 387 (46.0 %)	204 / 409 (49.9 %)	0.88 (0.72 , 1.08)
≥ 10 yrs	149 / 364 (40.9 %)	155 / 353 (43.9 %)	0.86 (0.69 , 1.08)
Total Cholesterol			
< 240 mg/dL	187 / 496 (37.7 %)	205 / 489 (41.9 %)	0.84 (0.69 , 1.03)
≥ 240 mg/dL	140 / 255 (54.9 %)	154 / 273 (56.4 %)	0.93 (0.74 , 1.17)
Serum Creatinine			
< 2 mg/dL	174 / 482 (36.1 %)	173 / 483 (35.8 %)	0.97 (0.78 , 1.20)
≥ 2 mg/dL	153 / 269 (56.9 %)	186 / 279 (66.7 %)	0.77 (0.62 , 0.95)
Serum Albumin			
< 3.6 mg/dL	143 / 207 (69.1 %)	145 / 202 (71.8 %)	0.87 (0.69 , 1.10)
≥ 3.6 mg/dL	184 / 544 (33.8 %)	214 / 560 (38.2 %)	0.84 (0.69 , 1.02)
Serum Uric Acid			
< 7 mg/dL	197 / 459 (42.9 %)	203 / 448 (45.3 %)	0.90 (0.74 , 1.09)
≥ 7 mg/dL	130 / 292 (44.5 %)	156 / 314 (49.7 %)	0.83 (0.66 , 1.05)
HbA1c			
< 10%	5 / 9 (55.6 %)	2 / 8 (25.0 %)	2.73 (0.53 , 14.1)
≥ 10%	322 / 742 (43.4 %)	357 / 754 (47.3 %)	0.86 (0.74 , 1.00)
Hemoglobin			
< 12 mg/dL	163 / 315 (51.7 %)	178 / 310 (57.4 %)	0.81 (0.66 , 1.01)
≥ 12 mg/dL	164 / 436 (37.6 %)	181 / 452 (40.0 %)	0.90 (0.73 , 1.11)
Nonsmoker	69 / 147 (46.9 %)	61 / 130 (46.9 %)	0.98 (0.70 , 1.39)
Smoker	258 / 604 (42.7 %)	298 / 632 (47.2 %)	0.84 (0.71 , 0.99)
Sitting SBP			
< 140 mmHg	60 / 191 (31.4 %)	66 / 187 (35.3 %)	0.86 (0.61 , 1.22)
≥ 140 mmHg	267 / 560 (47.7 %)	293 / 575 (51.0 %)	0.87 (0.74 , 1.03)
Insulin Use			
No	113 / 290 (39.0 %)	128 / 313 (40.9 %)	0.92 (0.71 , 1.18)
Yes	214 / 461 (46.4 %)	231 / 449 (51.4 %)	0.83 (0.69 , 1.00)

Dihydropyridine			
No	128 / 345 (37.1 %)	148 / 351 (42.2 %)	0.84 (0.66 , 1.06)
Yes	199 / 406 (49.0 %)	211 / 411 (51.3 %)	0.89 (0.74 , 1.08)
ACEI or AIIA Use			
No	146 / 351 (41.6 %)	180 / 386 (46.6 %)	0.85 (0.68 , 1.06)
Yes	181 / 400 (45.3 %)	179 / 376 (47.6 %)	0.88 (0.72 , 1.08)
Beta Blocker Use			
No	265 / 614 (43.2 %)	298 / 622 (47.9 %)	0.84 (0.72 , 1.00)
Yes	62 / 137 (45.3 %)	61 / 140 (43.6 %)	0.99 (0.69 , 1.41)
Calcium Blocker Use			
No	82 / 219 (37.4 %)	89 / 216 (41.2 %)	0.84 (0.62 , 1.14)
Yes	245 / 532 (46.1 %)	270 / 546 (49.5 %)	0.88 (0.74 , 1.05)

Results of primary endpoint by geographical region

As suggested in the sponsor's Figure 9, the hazard ratio for the primary endpoint appeared to be quite different between Asia and other regions. The Asia region appeared to show a big effect with losartan (45% reduction in hazard) but other regions showed little or no effect; see Table 4.

Table 4. Primary endpoint by geographical region (Reviewer's analysis)

	Losartan	Placebo	Hazard ratio (95% CI)
All regions	327/751 (43.5%)	359/762 (47.1%)	0.84 (0.72, 0.98)
Asia	49/125 (39.2%)	78/132 (59.1%)	0.55 (0.39, 0.79)
Europe	58/151 (38.4%)	51/144 (35.4%)	1.05 (0.72, 1.53)
Latin America	78/137 (56.9%)	80/137 (58.4%)	0.93 (0.68, 1.27)
North America	142/338 (42.0%)	150/349 (43.0%)	0.94 (0.75, 1.19)

Table 5 summarizes by-country results of the primary endpoint. In Asia, four countries showed a big effect with losartan (hazard reduction ranging from 17% to 78%); Singapore having very small and the smallest sample size in the region showed a reversed trend. In Europe, Spain had the largest sample size and gave a hazard reduction of 19%; United Kingdom having the next largest sample size showed no effect or a bit reversed trend. Other countries had very small sample size and showed mixed trends. In Latin America, Mexico and Brazil having the largest sample size showed different trends; the former showed a bit opposite trend but the latter gave a hazard reduction of 22%. Other countries also showed mixed trends. In North America, United States showed little effect with losartan; other countries contributed few events. Overall, only Asia seemed to show a consistent favorable effect with losartan. However, Israel contributed a small number of patients and gave the biggest effect with losartan. By putting Israel in Europe, the hazard ratio changed to 0.64 with 95% CI of 0.44 to 0.93 for Asia and to 0.87 with 95% CI of 0.61 to 1.24 for Europe. A substantial numerical difference in hazard ratio between Asia and non-Asia remained.

Table 5. Primary endpoint by country (Reviewer's analysis)

	Losartan	Placebo	Hazard ratio (95% CI)
All regions	327/751 (43.5%)	359/762 (47.1%)	0.84 (0.72, 0.98)

Asia	Hong Kong	19/46 (41.3%)	27/46 (58.7%)	0.57 (0.32, 1.04)
	Israel	4/19 (21.1%)	12/18 (66.7%)	0.22 (0.07, 0.70)
	Japan	22/44 (50.0%)	34/52 (65.4%)	0.73 (0.43, 1.26)
	Malaysia	2/11 (18.2%)	4/10 (40.0%)	0.42 (0.08, 2.31)
	Singapore	2/5 (40.0%)	1/6 (16.7%)	2.12 (0.19, 23.51)
Europe	Austria	5/8 (62.5%)	4/7 (57.1%)	1.17 (0.31, 4.38)
	Czech Republic	9/17 (52.9%)	6/16 (37.5%)	1.63 (0.58, 4.59)
	Denmark	3/8 (37.5%)	3/8 (37.5%)	0.76 (0.15, 3.83)
	France	5/5 (100%)	7/7 (100%)	1
	Germany	3/6 (50.0%)	2/6 (33.3%)	1.15 (0.19, 6.97)
	Hungary	3/5 (60.0%)	2/5 (40.0%)	1.43 (0.24, 8.61)
	Italy	2/13 (15.4%)	3/13 (23.1%)	0.55 (0.09, 3.33)
	Netherlands	4/4 (100%)	3/3 (100%)	1
	New Zealand	1/1 (100%)	1/2 (50.0%)	2
	Portugal	3/5 (60.0%)	2/5 (40.0%)	1.23 (0.20, 7.40)
	Russian Federation	6/14 (42.9%)	4/12 (33.3%)	1.34 (0.38, 4.77)
	Slovakia	1/1 (100%)	1/1 (100%)	1
	Spain	14/36 (38.9%)	14/31 (45.2%)	0.81 (0.38, 1.69)
	United Kingdom	10/28 (35.7%)	10/28 (35.7%)	1.02 (0.42, 2.45)
Latin America	Argentina	2/9 (22.2%)	5/8 (62.5%)	0.32 (0.06, 1.65)
	Brazil	17/28 (60.7%)	20/30 (66.7%)	0.78 (0.41, 1.49)
	Chile	7/13 (53.8%)	8/13 (61.5%)	0.69 (0.25, 1.91)
	Costa Rica	12/17 (70.6%)	8/16 (50.0%)	1.36 (0.55, 3.34)
	Mexico	19/33 (57.6%)	18/34 (52.9%)	1.08 (0.57, 2.07)
	Peru	10/21 (47.6%)	13/21 (61.9%)	0.69 (0.30, 1.58)
	Venezuela	11/16 (68.8%)	8/15 (53.3%)	2.24 (0.82, 6.08)
North America	Canada	.	1/1 (100%)	.
	Puerto Rico	2/2 (100%)	1/3 (33.3%)	3
	United States	142/336 (42.3%)	148/345 (42.9%)	0.95 (0.76, 1.20)

The differences in hazard ratio of the primary endpoint between Asia and non-Asia regions seemed to appear in most of the subgroups by baseline characteristics (Tables A.2 and A.3 in the Appendix). The incidence of the primary composite endpoint in the placebo group appeared to be higher in Asia than in non-Asia region whereas the incidence in the losartan group appeared to be in the same ballpark between the regions. Table A.4 in the Appendix exhibits the potential differences in baseline characteristics between Asia and Non-Asia regions. The two regions appeared to be comparable with respect to most of the baseline characteristics, except possibly on BMI, Dihydropyridine use, and proteinuria. Asia region seemed to have a larger proportion of the patients with proteinuria ≥ 2000 mg/g. In this study, proteinuria seemed to be a strong predictor of the primary composite endpoint, as reported by the sponsor and in Table 9 of this review. Thus, the apparent difference in hazard ratio between Asia and non-Asia regions might be attributed, at least partly, to a higher baseline proteinuria level (Table A.5 in the Appendix), or to a higher incidence rate of the primary endpoint in the placebo group in Asia region.

Secondary endpoints

Losartan seemed to be associated with a larger reduction of hospitalization for HF. There was no clear suggestion for beneficial effect on any of other secondary endpoints with losartan (Table 6).

Table 6. Incidence of secondary endpoints (Reviewer's analysis)

	Losartan (N=751)	Placebo (N=762)	Hazard ratio (95% CI)	p-value ^{\$}
Cardiovascular mortality/morbidity	247 (32.9%)	268 (35.2%)	0.90 (0.76, 1.08)	0.25
Hospitalized for HF	89 (11.9%)	126 (16.5%)	0.68 (0.52, 0.90)	0.006
MI	50 (6.7%)	68 (8.9%)	0.72 (0.50, 1.04)	0.079
Stroke	47 (6.3%)	50 (6.6%)	0.85 (0.64, 1.41)	0.78
Cardiovascular death	90 (12.0%)	79 (10.4%)	1.12 (0.83, 1.52)	0.45
Revascularization	69 (9.2%)	60 (7.9%)	1.19 (0.84, 1.68)	0.34
Hospitalized for Unstable angina	42 (5.6%)	41 (5.4%)	1.03 (0.67, 1.59)	0.89

^{\$} using the same Cox regression model as for the primary endpoint

Progression of Renal Disease

The rate of decline in renal function was smaller in the losartan group than in the placebo group

Table 7. Summary of slopes of reciprocal of serum creatinine at quartiles (Sponsor's results confirmed by Reviewer's analysis)

	Losartan (N=751)	Placebo (N=762)	Est. renal loss reduction	p-value ^{\$}
Chronic slope (dL/mg/yr) (Month 3 and after) Quartiles: 25 th 50 th 75 th	N = 693 -0.10 -0.052 -0.020	N=678 -0.13 -0.070 -0.028	25.5%	< 0.0001
Overall slope (dL/mg/yr) (all phases) Quartiles: 25 th 50 th 75 th	N = 745 -0.11 -0.057 -0.025	N=754 -0.14 -0.070 -0.025	18.5%	0.011

Negative slope indicates a loss of renal function

Est. loss reduction is estimated using a linear random effects model adjusted for region, startum, and baseline serum creatinine

^{\$} based on two-sample median score nonparametric test

Table 8. Comparison of mean slopes for renal progression

Analysis of slope (dL/mg/yr)	Losartan (N=751)	Placebo (N=762)	Est. renal loss reduction	p-value\$
Chronic phase	-0.060	-0.070	13.9%	0.0033
All phases	-0.067	-0.077	12.7%	0.0091

Negative slope indicates a loss of renal function

Est. loss reduction is estimated using a linear random effects model adjusted for region, startum, and baseline serum creatinine

\$ based on two-sample median score nonparametric test

Change in Proteinuria over Time

Table 14, Figures 6 and 7 of the sponsor's results (not yet confirmed by reviewer's analysis) appeared to indicate that the Losartan group had a much greater percent decrease in proteinuria in terms of geometric mean and median than the placebo group.

Predictability of Proteinuria for Treatment Effect on Primary Endpoint

When proteinuria (on the log scale) was adjusted based on the Month 6 or on the values over the entire study, prior to the primary composite endpoint, the treatment effect of losartan diminished. This seems to suggest that proteinuria is a strong predictor for the primary composite endpoint in this study.

Table 9. Adjustment of the Primary endpoint for proteinuria at Month 6 and as a time-varying covariate (Sponsor's results confirmed by reviewer's analysis)

	Losartan (N=751)	Placebo (N=762)	Est. risk reduction	p-value\$
Primary endpoint				
Adj. for Month-6 Proteinuria	43.3%	46.1%	-2.9%	0.73
Adj. for overall proteinuria changes	43.5%	47.1%	1.7%	0.83
ESRD				
Adj. for overall proteinuria changes	19.6%	25.5%	14.1%	0.17
ESRD or death				
Adj. for overall proteinuria changes	34.0%	39.4%	9.5%	0.25

Est. risk reduction using a proportional hazards regression model with adjustment for region and stratum

4. CONCLUSIONS

There was some evidence that losartan might reduce the incidence of the primary composite endpoint, doubling of serum creatinine, ESRD or death, (reduction of risk = 16% with 95% CI of 3% to 28%, $p = 0.022$). The strength of evidence did not meet the usual standard of statistical evidence, at least lower by an order of magnitude in p -value. The effect of losartan in terms of the hazard of the primary endpoint did not appear to be constant over the duration of the trial (Figure 1, the hazard curves appeared to be converging). Approximately a half of the primary events were ESRD or death. The treatment difference seemed to be largely attributed to the difference in doubling of serum creatinine. However, in the patients with doubling serum creatinine, 51% developed ESRD in the losartan group and 65% in the placebo group; mean time from doubling serum creatinine to ESRD was about 30 days longer in the losartan group. In addition, 19.5% of the losartan patients and 25.5% of the placebo patients developed ESRD; thus, losartan seemed to be associated with a 29% reduction in risk of having an ESRD ($p = 0.002$). There is little difference in death rate between the losartan group and the placebo group.

Proteinuria seemed to be a strong predictor of the primary composite event in this study. When proteinuria was adjusted based on the Month 6 value or on the values over time, prior to the primary composite endpoint, the effect of losartan diminished (Table 9).

The data seemed to suggest that there might be a difference in the effect of losartan in terms of hazard reduction of the primary endpoint between Asia and other regions. The Asia region appeared to show a big effect with losartan whereas other regions as a whole showed little effect (Table 4). Further exploration seemed to suggest that this apparent difference, if real, might be attributed to a higher incidence rate of the primary endpoint in the placebo group in Asia, or to a higher baseline proteinuria level in Asia (Table A.5).

The rate of decline in renal function appeared to be smaller in the losartan group than in the placebo group. Losartan seemed to be associated with a reduction of hospitalizations for heart failure. No beneficial effect was found with losartan on cardiovascular mortality or morbidity, myocardial infarction, stroke, revascularization, or hospitalization for unstable angina. This seemed to make it difficult to interpret the apparent benefit with losartan in reduction of hospitalization for heart failure.

5. APPENDIX

Table A.1 Distribution of time (days) to non-event censoring (Reviewer's analysis)

	Event=doubling serum creatinine, ESRD, or death	
	Losartan (N=751)	Placebo (N=762)
# of censored cases	327 (43.5%)	359 (47.1%)
Max	1615	1613
99th %tile	1580	1579
95th	1522	1504
90th	1475	1445
75th	1376	1376
50th	1199	1196
Mean	1212	1201
25th	1040	1026
10th	949	940
5th	914	906
1st	878	885
Min	865	873

Table A.2. Primary endpoint by subgroups in Asia region excluding Israel (Reviewer's analysis)

	Losartan (N=106)	Placebo (N=114)	HR
Female	12 / 29 (41.4 %)	28 / 39 (71.8 %)	0.38
Male	33 / 77 (42.9 %)	38 / 75 (50.7 %)	0.82
Age < 65 yrs	32 / 69 (46.4 %)	45 / 79 (57.0 %)	0.70
Age ≥ 65 yrs	13 / 37 (35.1 %)	21 / 35 (60.0 %)	0.51
Asian	45 / 106 (42.5 %)	66 / 114 (57.9 %)	0.64
BMI < 30 kg/m ²	41 / 98 (41.8 %)	64 / 109 (58.7 %)	0.62
BMI ≥ 30 kg/m ²	4 / 8 (50.0 %)	2 / 5 (40.0 %)	1.04
Duration of hypertension < 10 yrs	31 / 69 (44.9 %)	45 / 78 (57.7 %)	0.70
Duration of hypertension ≥ 10 yrs	14 / 37 (37.8 %)	21 / 36 (58.3 %)	0.52
Total Cholesterol < 240 mg/dL	27 / 70 (38.6 %)	38 / 75 (50.7 %)	0.71
Total Cholesterol ≥ 240 mg/dL	18 / 36 (50.0 %)	28 / 39 (71.8 %)	0.55
Serum Creatinine < 2 mg/dL	19 / 60 (31.7 %)	32 / 63 (50.8 %)	0.52
Serum Creatinine ≥ 2 mg/dL	26 / 46 (56.5 %)	34 / 51 (66.7 %)	0.79
Serum Albumin < 3.6 mg/dL	20 / 29 (69.0 %)	29 / 34 (85.3 %)	0.63
Serum Albumin ≥ 3.6 mg/dL	25 / 77 (32.5 %)	37 / 80 (46.3 %)	0.62
Serum Uric Acid < 7 mg/dL	28 / 73 (38.4 %)	36 / 60 (60.0 %)	0.55
Serum Uric Acid ≥ 7 mg/dL	17 / 33 (51.5 %)	30 / 54 (55.6 %)	0.81
HbA1c < 10%	1 / 1 (100 %)	1 / 1 (100 %)	
HbA1c ≥ 10%	44 / 105 (41.9 %)	65 / 113 (57.5 %)	0.63
Hemoglobin < 12 mg/dL	28 / 50 (56.0 %)	43 / 60 (71.7 %)	0.61
Hemoglobin ≥ 12 mg/dL	17 / 56 (30.4 %)	23 / 54 (42.6 %)	0.69
Nonsmoker	12 / 29 (41.4 %)	14 / 23 (60.9 %)	0.59
Smoker	33 / 77 (42.9 %)	52 / 91 (57.1 %)	0.64
Sitting SBP < 140 mmHg	5 / 23 (21.7 %)	12 / 34 (35.3 %)	0.61
Sitting SBP ≥ 140 mmHg	40 / 83 (48.2 %)	54 / 80 (67.5 %)	0.57
Insulin Use No	19 / 48 (39.6 %)	29 / 56 (51.8 %)	0.71
Insulin Use Yes	26 / 58 (44.8 %)	37 / 58 (63.8 %)	0.56
Dihydropyridine No	7 / 24 (29.2 %)	11 / 23 (47.8 %)	0.61
Dihydropyridine Yes	38 / 82 (46.3 %)	55 / 91 (60.4 %)	0.65
ACEI or AIIA Use No	13 / 42 (31.0 %)	25 / 53 (47.2 %)	0.59
ACEI or AIIA Use Yes	32 / 64 (50.0 %)	41 / 61 (67.2 %)	0.61
Beta Blocker Use No	39 / 88 (44.3 %)	60 / 99 (60.6 %)	0.64
Beta Blocker Use Yes	6 / 18 (33.3 %)	6 / 15 (40.0 %)	0.71
Calcium Blocker Use No	6 / 22 (27.3 %)	11 / 23 (47.8 %)	0.56
Calcium Blocker Use Yes	39 / 84 (46.4 %)	55 / 91 (60.4 %)	0.65
Proteinuria < 2000 mg/g	15 / 62 (24.2 %)	22 / 64 (34.4 %)	0.66
Proteinuria ≥ 2000 mg/g	30 / 44 (68.2 %)	44 / 50 (88.0 %)	0.58

Table A.3. Primary endpoint by subgroups in non-Asia region including Israel (Reviewer's analysis)

	Losartan (N=645)	Placebo (N=648)	HR
Female	126 / 260 (48.5 %)	117 / 229 (51.1 %)	0.90
Male	156 / 385 (40.5 %)	176 / 419 (42.0 %)	0.91
Age < 65 yrs	190 / 434 (43.8 %)	201 / 423 (47.5 %)	0.86
Age >= 65 yrs	92 / 211 (43.6 %)	92 / 225 (40.9 %)	1.04
Asian	4 / 11 (36.4 %)	8 / 21 (38.1 %)	1.21
Hispanic	77 / 140 (55.0 %)	74 / 137 (54.0 %)	1.01
black	50 / 125 (40.0 %)	41 / 105 (39.0 %)	0.97
white	145 / 358 (40.5 %)	163 / 377 (43.2 %)	0.87
BMI < 30 kg/m2	154 / 339 (45.4 %)	162 / 362 (44.8 %)	0.97
BMI >= 30 kg/m2	128 / 306 (41.8 %)	131 / 286 (45.8 %)	0.87
Duration of hypertension < 10 yrs	147 / 318 (46.2 %)	159 / 331 (48.0 %)	0.94
Duration of hypertension >= 10 yrs	135 / 327 (41.3 %)	134 / 317 (42.3 %)	0.91
Total Cholesterol < 240 mg/dL	160 / 426 (37.6 %)	167 / 414 (40.3 %)	0.87
Total Cholesterol >= 240 mg/dL	122 / 219 (55.7 %)	126 / 234 (53.8 %)	1.02
Serum Creatinine < 2 mg/dL	155 / 422 (36.7 %)	141 / 420 (33.6 %)	1.07
Serum Creatinine >= 2 mg/dL	127 / 223 (57.0 %)	152 / 228 (66.7 %)	0.76
Serum Albumin < 3.6 mg/dL	123 / 178 (69.1 %)	116 / 168 (69.0 %)	0.93
Serum Albumin >= 3.6 mg/dL	159 / 467 (34.0 %)	177 / 480 (36.9 %)	0.88
Serum Uric Acid < 7 mg/dL	169 / 386 (43.8 %)	167 / 388 (43.0 %)	0.98
Serum Uric Acid >= 7 mg/dL	113 / 259 (43.6 %)	126 / 260 (48.5 %)	0.85
HbA1c < 10%	4 / 8 (50.0 %)	1 / 7 (14.3 %)	4.15
HbA1c >= 10%	278 / 637 (43.6 %)	292 / 641 (45.6 %)	0.91
Hemoglobin < 12 mg/dL	135 / 265 (50.9 %)	135 / 250 (54.0 %)	0.88
Hemoglobin >= 12 mg/dL	147 / 380 (38.7 %)	158 / 398 (39.7 %)	0.93
Nonsmoker	57 / 118 (48.3 %)	47 / 107 (43.9 %)	1.10
Smoker	225 / 527 (42.7 %)	246 / 541 (45.5 %)	0.88
Sitting SBP < 140 mmHg	55 / 168 (32.7 %)	54 / 153 (35.3 %)	0.90
Sitting SBP >=140 mmHg	227 / 477 (47.6 %)	239 / 495 (48.3 %)	0.93
Insulin Use No	94 / 242 (38.8 %)	99 / 257 (38.5 %)	0.98
Insulin Use Yes	188 / 403 (46.7 %)	194 / 391 (49.6 %)	0.88
Dihydropyridine No	121 / 321 (37.7 %)	137 / 328 (41.8 %)	0.86
Dihydropyridine Yes	161 / 324 (49.7 %)	156 / 320 (48.8 %)	0.98
ACEI or AIIA Use No	133 / 309 (43.0 %)	155 / 333 (46.5 %)	0.89
ACEI or AIIA Use Yes	149 / 336 (44.3 %)	138 / 315 (43.8 %)	0.96
Beta Blocker Use No	226 / 526 (43.0 %)	238 / 523 (45.5 %)	0.9
Beta Blocker Use Yes	56 / 119 (47.1 %)	55 / 125 (44.0 %)	1.03
Calcium Blocker Use No	76 / 197 (38.6 %)	78 / 193 (40.4 %)	0.88
Calcium Blocker Use Yes	206 / 448 (46.0 %)	215 / 455 (47.3 %)	0.94
Proteinuria < 2000 mg/g	135 / 439 (30.8 %)	139 / 447 (31.1 %)	0.95
Proteinuria >=2000 mg/g	147 / 206 (71.4 %)	154 / 201 (76.6 %)	0.84

Table A.4 Baseline characteristics for Asia versus Non-Asia regions (Reviewer's analysis)

	Asia* (N=220)	Non-Asia* (N=1293)
Female	68 (30.9 %)	489 (37.8 %)
Male	152 (69.1 %)	804 (62.2 %)
Age < 65 yrs	148 (67.3 %)	857 (66.3 %)
Age ≥ 65 yrs	72 (32.7 %)	436 (33.7 %)
BMI < 30 kg/m ²	207 (94.1 %)	701 (54.2 %)
BMI ≥ 30 kg/m ²	13 (5.9 %)	592 (45.8 %)
Duration of hypertension < 10 yrs	147 (66.8 %)	649 (50.2 %)
Duration of hypertension ≥ 10 yrs	73 (33.2 %)	644 (49.8 %)
Total Cholesterol < 240 mg/dL	145 (65.9 %)	840 (65.0 %)
Total Cholesterol ≥ 240 mg/dL	75 (34.1 %)	453 (35.0 %)
Serum Creatinine < 2 mg/dL	123 (55.9 %)	842 (65.1 %)
Serum Creatinine ≥ 2 mg/dL	97 (44.1 %)	451 (34.9 %)
Serum Albumin < 3.6 mg/dL	63 (28.6 %)	346 (26.8 %)
Serum Albumin ≥ 3.6 mg/dL	157 (71.4 %)	947 (73.2 %)
Serum Uric Acid < 7 mg/dL	133 (60.5 %)	774 (59.9 %)
Serum Uric Acid ≥ 7 mg/dL	87 (39.5 %)	519 (40.1 %)
HbA1c < 10%	2 (0.9 %)	15 (1.2 %)
HbA1c ≥ 10%	218 (99.1 %)	1278 (98.8 %)
Hemoglobin < 12 mg/dL	110 (50.0 %)	515 (39.8 %)
Hemoglobin ≥ 12 mg/dL	110 (50.0 %)	778 (60.2 %)
Nonsmoker	52 (23.6 %)	225 (17.4 %)
Smoker	168 (76.4 %)	1068 (82.6 %)
Sitting SBP < 140 mmHg	57 (25.9 %)	321 (24.8 %)
Sitting SBP ≥ 140 mmHg	163 (74.1 %)	972 (75.2 %)
Insulin Use No	104 (47.3 %)	499 (38.6 %)
Insulin Use Yes	116 (52.7 %)	794 (61.4 %)
Dihydropyridine No	47 (21.4 %)	649 (50.2 %)
Dihydropyridine Yes	173 (78.6 %)	644 (49.8 %)
ACEI or AIIA Use No	95 (43.2 %)	642 (49.7 %)
ACEI or AIIA Use Yes	125 (56.8 %)	651 (50.3 %)
Beta Blocker Use No	187 (85.0 %)	1049 (81.1 %)
Beta Blocker Use Yes	33 (15.0 %)	244 (18.9 %)
Calcium Blocker Use No	45 (20.5 %)	390 (30.2 %)
Calcium Blocker Use Yes	175 (79.5 %)	903 (69.8 %)
Proteinuria < 2000 mg/g	126 (57.3 %)	886 (68.5 %)
Proteinuria ≥ 2000 mg/g	94 (42.7 %)	407 (31.5 %)

* Israel is put in Non-Asia region

Table A.5 Distribution of proteinuria level (mg/g) [Reviewer's analysis]

	Asia	Other ^{\$}
Max	10150	12208
99th %tile	7670	7537
95th	5248	5102
90th	4602	4045
75th	2976	2433
50th	1672	1161
Mean	2151	1749
25th	767	538
10th	422	294
5th	319	203
1st	122	75
Min	45	31

^{\$} North America, Latin America, Europe

Figure 1. $\log(-\log(\text{survival}))$ versus $\log(\text{days})$ for the primary endpoint, doubling serum creatinine, ESRD, or death

