CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #: 21-437/S-002

DRUG NAME: INSPRA (Eplerenone)
INDICATION: Heart Failure
APPLICANT: Pharmacia
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KEY WORDS: Adding a co-primary endpoint, modifying the definition of the added co-primary endpoint, removing or adding secondary endpoints, interim analysis, early trial termination, lack of statistical significance criteria for secondary endpoints

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the EPHESUS results, eplerenone yielded a statistically significant reduction (15%, 95% CI: 4%-25%, p = 0.008) in mortality, mostly CV mortality (17%, 95% CI: 6% - 28%). There was no evidence that eplerenone reduced the incidence of non-CV death. For the other co-primary efficacy endpoint – CV mortality/hospitalization, the final definition of CV hospitalization was established in the late stage of the trial (a few months before the trial end). It is not clear whether the modification of CV hospitalization was ever influenced by examination of the trial data. Dr. Marciniak has concerns with the definition of CV hospitalization. By taking this endpoint as it is, there was a statistically significant reduction in favor of eplerenone (p = 0.002). All cause mortality/hospitalization appeared to reach borderline statistical significance. Numerically, eplerenone seemed to have a favorable effect on mortality in US.

Based on RALES, spironolactone yielded a statistically significant reduction (30%, 95% CI: 18%-40%, p < 0.0001) in mortality, mostly through cardiac death (31% reduction, 95% CI: 18% - 42%, nominal p < 0.0001). Numerically, spironolactone also appeared to have a favorable effect on other mortality. There seemed to be a significant reduction in cardiac death/hospitalization or non-fatal hospitalization with spironolactone (p < 0.0006 for both), though there was no statistical decision rule for assessment of statistical significance of these endpoints in the protocol. Spironolactone appeared to improve NYHA class. In US, spironolactone seemed to have an favorable effect on mortality but numerically the effect seemed to be smaller than that seen in Western Europe.

1.2 Brief Overview of Clinical Studies

This new drug application contains two large clinical studies, EPHESUS and RALES. EPHESUS was a multi-center, randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial designed to compare the safety and efficacy of eplerenone (25 mg qd → 50 mg qd if serum potassium < 5.0 mmol/L with further dose adjustment depending on the most recent potassium level) versus placebo in patients with a diagnosis of acute myocardial infarction with heart failure and left ventricular dysfunction. The standard therapy patients received throughout the study could have included angiotension-converting enzyme inhibitors, diuretics, nitrates, and beta-blockers. Patients could have received anticoagulants, antiplatelet agents, or thrombolytics and might also have had emergency angioplasty or coronary artery bypass graft. The planned sample size was about 6,200. The study was estimated to last approximately 2.5 years.

RALES was a randomized, double-blind, placebo-controlled, parallel group, multi-national trial to evaluate the safety and efficacy of spironolactone 25 mg QD or every other day or 50 mg QD administered compared with placebo in patients with severe heart failure (New York Heart Association [NYHA] III or IV). The background therapy patients received included loop diuretic, ACE-inhibitor, if tolerated, and digoxin. There was no fixed planned sample size specified in the protocol. The sample size was based on total number of deaths which in turn

depends on the postulated treatment effect (20%-25% reduction in mortality rate) and proportion of the patients in NYHA Class IV. The total length of the trial was planned as 57 months and the trial was designed to end in December 1999. The study was terminated on 24 August 1998 because of a statistically significant and clinically meaningful reduction in mortality in the spironolactone-treated group compared to the placebo group, as determined by an independent Data and Safety Monitoring Board (DSMB).

1.3 Statistical Issues and Findings

For EPHESUS, a statistical issue pertains to (slight ?) modification of CV death/hospitalization that was added as a co-primary endpoint. The modification occurred in the late stage of the trial shortly before the end of the trial; thus, it is susceptible to potential bias depending on whether the modification was ever influenced by examination of any part of the trial data (please read Dr. Marciniak's review). This concern also pertains to adding a CV mortality/non-fatal AMI as a secondary endpoint in a protocol amendment. Another issue is that there was no statistical decision rule for assessment of statistical significance of each secondary endpoint.

For RALE, the statistical issue is that there was no statistical decision rule for assessment of statistical significance of each secondary endpoint.

2. INTRODUCTION

2.1 Overview

This new drug application contains two large clinical studies, EPHESUS and RALES. EPHESUS was a multicenter (671 study sites in 37 countries), randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial designed to compare the safety and efficacy of eplerenone (25 mg qd → 50 mg qd if serum potassium < 5.0 mmol/L with further dose adjustment depending on the most recent potassium level) versus placebo in patients with a diagnosis of acute myocardial infarction with heart failure and left ventricular dysfunction. The standard therapy patients received throughout the study could have included angiotension-converting enzyme inhibitors (ACE-I), diuretics, nitrates, and beta-blockers. Patients could have received anticoagulants, antiplatelet agents, or thrombolytics and might also have had emergency angioplasty or coronary artery bypass graft (CABG). The planned sample size was about 6,200. The study was estimated to last approximately 2.5 years.

RALES was a randomized, double-blind, placebo-controlled, parallel group, multinational trial to evaluate the safety and efficacy of spironolactone 25 mg QD or every other day or 50 mg QD administered compared with placebo in patients with severe heart failure (HF; New York Heart Association [NYHA] III or IV). The background therapy patients received included loop diuretic, ACE-inhibitor, if tolerated, and digoxin. There was no fixed planned sample size specified in the protocol. The sample size was based on total number of deaths which in turn depends on the postulated treatment effect (20%-25% reduction in mortality rate) and proportion of the patients in NYHA Class IV. The total length of the trial was planned as 57 months and the trial was designed to end in December 1999. The study was terminated on 24 August 1998 because of a statistically significant and clinically meaningful reduction in mortality in the spironolactone-treated group compared to the placebo group, as determined by an independent Data and Safety Monitoring Board (DSMB).

2.2 Data Sources

The datasets analyzed are in \N21437\S_002\2003_04_04\CRT\datasets in CDER EDR.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 EPHESUS

A total of 6642 patients were randomized but all 10 patients from site 4017 in Romania were excluded from analysis because the accuracy of the data from a subinvestigator associated with this site was suspect and there was evidence that this subinvestigator altered the source documents so that patients appeared to qualify for randomization. The two treatment groups are comparable with respect to loss to follow-up (0.3%) and percent of patients permanently discontinued study medication (about 15%).

Primary Efficacy Endpoints

The original primary efficacy endpoint was all cause mortality. Cardiovascular (CV) mortality/hospitalization was added as a coprimary enpoint in Protocol Amendment 9 (12/20/2000) at which time 69% of the patients had been recruited. According to the review of Dr. Tom Marciniak, medical reviewer, Protocol Amend 10 (04/24/2002) modified the definition of this composite endpoint slightly. The definition of CV hospitalization consisted of hospitalization or prolongation of hospitalization adjudicated as having heart failure, recurrent AMI, stroke, or ventricular arrhythmia. Please read Dr. Marciniak's for his concerns with this definition.

The follow-up rate for all cause mortality was about 99.7%. For hospitalization, some patients in both treatment groups had missing dates of hospitalization which were then imputed according to some kind of pre-determined algorithm (according to the sponsor's response to the reviewer's question) applied to both treatment groups. The quality of the hospitalization data is questionable. Nevertheless, the censoring distributions for CV mortality/hospitalization in the two treatment groups are comparable (Table 1.4, page 20). It should also be noted that the definition of CV hospitalization was modified in the late stage of the trial (close to the trial end). It is not clear whether such modification was ever influenced by examination of the interim trial data. If there is no problem with the modification, then for either of the primary endpoints the incidence rate in the eplerenone group was statistically significantly lower than that in the placebo group (p=0.008 for all cause mortality, p=0.002 for CV mortality/hospitalization; Table E-1 below). Kaplan-Meier survival curves are provided in Figures 1.1, 1.3 (pages 21, 22). The eplerenone effects in terms of hazard ratio on all cause mortality and CV mortality/hospitalization appeared to be approximately constant after two weeks (Figures 1.2, 1.4, pages 21, 22).

Table E-1. Analysis of Primary Endpoints (ITT patients)
[Source: Reviewer's analysis results, identical with the sponsor's results in Table 8 of the study report]

	Placebo N=3313	Eplerenone N=3319	Risk ratio (95%CI)#	p-value*
All cause mortality	554 (16.7%)	478 (14.4%)	0.85 (0.75, 0.96)	0.008
CV mortality/hospitalization	993 (30.0%)	885 (26.7%)	0.87 (0.79, 0.95)	0.002

* based on logrank test stratified by region
# based on Cox proportional hazards model including treatment as the only factor, stratified by region

86% of the deaths are CV deaths, mostly due to sudden cardiac death, recurrent AMI or HF. The eplerenone effect on CV death is almost identical to that on all cause mortality. The eplerenone appeared to have little effect on non-CV death (Table 1.5, page23). 70% of the composite events of CV deaths or hospitalizations were CV hospitalizations as the first event (Table 1.6, page 24).

Secondary Efficacy Endpoints

Originally there were 4 specified secondary variables – CV mortality, CV hospitalization, all cause hospitalization, all cause mortality/hospitalization. According to the study report, CV mortality/nonfatal AMI was added as a secondary endpoint prior to unblinding study data and reflected in the final statistical analysis plan (11/7/2002). The CV hospitalization and all cause hospitalization were removed because competing risks of death make p-values difficult to interpret. Consequently, the secondary efficacy endpoints in the final analysis were CV mortality, all cause mortality/hospitalization, and CV mortality/nonfatal AMI.

The eplerenone group had a lower incidence of each secondary endpoint than the placebo group. However, there was no pre-specified statistical decision rule for the secondary endpoints. It is not clear whether removing or adding the endpoints to result in this final list of the secondary endpoints in the late stage of the trial was ever influenced by the examination of the interim data by the DSMB. By taking the endpoints as they are, CV mortality was statistically significant in favor of eplerenone, even by the most conservative Bonferroni adjustment after both primary endpoints reached statistical significance. CV mortality/non-fatal AMI achieved borderline significance, after the most conservative Bonferroni adjustment. All cause mortality/hospitalization was almost statistically significant.

For hospitalization, some patients in both treatment groups had missing dates of hospitalization which were then imputed according to some kind of pre-determined algorithm (according to the sponsor's response to the reviewer's question) applied to both treatment groups. The quality of the hospitalization data is questionable. The two treatment groups appeared to have comparable distributions on time to follow-up for patients who survived and were not hospitalized for any reason (Table 1.8, page 25).

Table E-2. Analysis of Secondary Endpoints (ITT patients)
[Source: Reviewer's analysis results, identical with the sponsor's results in Table 11 of the study report]

	Placebo N=3313	Eplerenone N=3319	Risk ratio (95%CI)#	p-value*
CV mortality	483 (14.6%)	407 (12.3%)	0.83 (0.72, 0.94)	0.005
All cause mortality/hospitalization	1829 (55.2%)	1730 (52.1%)	0.92 (0.86, 0.98)	0.016
CV mortality/nonfatal AMI	667 (20.1%)	585 (17.6%)	0.86 (0.77, 0.96)	0.009

* based on logrank test stratified by region
# based on Cox proportional hazards model including treatment as the only factor, stratified by region

Summary of hospitalizations (Tables 1.9, 1.10, 1.11, pages 25, 26, 27) appeared to support that eplerenone may have potential benefit to reduce hospitalization but the effect if any is small.

Eplerenone seemed to improve NYHA classification for patients but there was no statistical decision rule pre-specified for assessment of its statistical significance. There was no evidence for a beneficial effect of eplerenone on quality of life.

3.1.2 RALES

A total of 1663 patients were randomized. The spironolactone group appeared to have a greater proportion of patients stopping study medication due to adverse sign or symptom. Overall speaking, the two treatment groups seemed comparable with respect to proportion of patients stopping study medication.

Primary Efficacy Endpoint

All cause mortality was the only primary efficacy endpoint. There were a few deaths whose dates of death were missing. After several robustness analyses, it can be concluded that spironolactone yielded a statistically significant reduction (30% reduction with 95% CI of 18%-40%) in all cause mortality (nominal $p < 0.0001$ versus nominal alpha level of 0.0047 as a result of interim termination of the trial for survival benefit). Though most of the deaths were cardiac related, the reduction of other mortality with spironolactone numerically appeared to be substantial.

Table R-1. Total Mortality
[*Source: Reviewer's analysis of the derived data base provided by the sponsor*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Total mortality	386 (45.9%)	284 (34.5%)	0.70 (0.60, 0.82)	< 0.0001
Cardiac mortality	314 (37.3%)	226 (27.5%)	0.69 (0.58, 0.82)	< 0.0001
Sudden death	110 (13.1%)	82 (10.0%)		
Myocardial infarction	15 (1.8%)	17 (2.1%)		
Progression of CHF	189 (22.5%)	127 (15.5%)		
Other mortality	72 (8.6%)	58 (7.1%)	0.77 (0.54, 1.08)	0.13
Stroke	11 (1.3%)	8 (1.0%)		
Other cardiovascular death	13 (1.5%)	12 (1.5%)		
Noncardiovascular death	41 (4.9%)	29 (3.5%)		
Unknown	7 (0.8%)	9 (1.1%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Secondary Efficacy Endpoint

There was no pre-specified statistical decision rule for assessing statistical significance of each secondary endpoint. However, the nominal p-values for cardiac mortality, cardiac mortality or hospitalization, and non-fatal hospitalization are all very small in favor of spironolactone, as summarized below.

Table R-2. Cardiac death or hospitalization
[*Source: Reviewer's analysis of the derived data base provided by the sponsor*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Cardiac mortality or hospitalization	498 (59.2%)	379 (46.1%)	0.68 (0.59, 0.78)	< .0001
Decomposition of the composite endpoint – cardiac mortality or hospitalization				
Cardiac mortality	314 (37.3%)	226 (27.5%)	0.69 (0.58, 0.82)	< .0001
Sudden death	110 (13.1%)	82 (10.0%)		
Myocardial infarction	15 (1.8%)	17 (2.1%)		
Progression of CHF	189 (22.5%)	127 (15.5%)		
Nonfatal hospitalization	184 (21.9%)	153 (18.6%)		
HF aggravation (definitive)	138 (16.4%)	108 (13.1%)		
HF aggravation (non-specific)	12 (1.4%)	5 (0.6%)		
Ventricular arrhythmia	13 (1.5%)	12 (1.5%)		
Myocardial infarction	6 (0.7%)	5 (0.6%)		
Angina (stable/unstable)	15 (1.8%)	15 (1.8%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Table R-3. Incidence of non-fatal hospitalization
[*Source: Sponsor's Table 9.3; reviewer's analysis produced almost identical results except minor discrepancy marked by @*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Nonfatal hospitalization	481 (57.2%)	421 (51.2%)	0.79 (0.70, 0.90)	0.0005
HF aggravation (definitive)@	289 (34.4%)	209 (25.4%)		
HF aggravation (non-specific)	34 (4.0%)	18 (2.2%)		
AF/AFL or supravent tachy	23 (2.7%)	30 (3.6%)		
Ventricular arrhythmia	24 (2.9%)	23 (2.8%)		
Myocardial infarction	14 (1.7%)	10 (1.2%)		
Angina (stable/unstable)	35 (4.2%)	43 (5.2%)		
Stroke	20 (2.4%)	14 (1.7%)		
Other cardiovascular@	93 (11.1%)	91 (11.1%)		
Non-cardiovascular	233 (27.6%)	223 (27.1%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Nineteen (10 in the placebo group, 9 in the sprionolactone group) of the 1663 patients did not have final visit NYHA class data. Nonetheless, spironolactone seemed to improve NYHA functional class as shown in the following table.

Table R-4. Change from baseline to Final Visit in NYHA Functional Class
[*Source: Table 5 of the study report; reviewer's analysis produced almost identical results*]

	Placebo (N=841)	Spironolactone (N=822)	p-value
Baseline NYHA Class III			
N	575	586	
Final NYHA			0.001
I	33 (5.7%)	51 (8.7%)	
II	154 (26.8%)	180 (30.7%)	
III	134 (23.3%)	148 (25.3%)	
IV	14 (2.4%)	21 (3.64%)	
Death	240 (41.7%)	186 (31.7%)	
Worsening	254 (44.2%)	207 (35.3%)	0.002*
No change	134 (23.3%)	148 (25.3%)	
Improvement	187 (32.5%)	231 (39.4%)	
Baseline NYHA Class IV			
N	254	223	
Final NYHA			0.003
I	9 (3.5%)	18 (8.1%)	
II	38 (15.0%)	41 (18.4%)	
III	43 (16.9%)	45 (20.2%)	
IV	19 (7.5%)	21 (9.4%)	
Death	145 (57.1%)	98 (43.9%)	
Worsening	145 (57.1%)	98 (43.9%)	0.005**
No change	19 (7.5%)	21 (9.4%)	
Improvement	90 (35.4%)	104 (46.6%)	

p-value generated from Wilcoxon rank-sum test
* worsening (IV or death at final visit), no change (III at final visit), improvement (I or II at final visit)
** worsening (death at final visit), no change (IV at final visit), improvement (I, II, or III at final visit)

3.2 Evaluation of Safety

Please read Dr. Marciniak's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 EPHESUS

The eplerenone effects on all cause mortality and CV mortality/hospitalization appeared to be consistent across subgroups, except possibly in small subgroups.

Table E-3. All cause mortality by subgroups
[Source: excerpted from the Sponsor's Tables T11.1, confirmed by the reviewer's analysis]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
Race			
Black	10/44 (22.7%)	4/30 (13.3%)	0.47 (0.15, 1.51)
Other	544/3269 (16.6%)	474/3289 (14.4%)	0.85 (0.75, 0.96)
Gender			
Female	194/979 (19.8%)	152/939 (16.2%)	0.79 (0.64, 0.98)
Male	360/2334 (15.4%)	326/2380 (13.7%)	0.88 (0.76, 1.02)
Age			
< 65	180/1614 (11.2%)	146/1678 (8.7%)	0.77 (0.62, 0.96)
65 +	374/1699 (22.0%)	332/1641 (20.2%)	0.90 (0.78, 1.05)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

Table E-4. CV mortality/hospitalization by subgroups
[Source: excerpted from the Sponsor's Tables T11.3, confirmed by the reviewer's analysis]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
Race			
Black	24/44 (54.5%)	9/30 (30.0%)	0.42 (0.20, 0.91)
Other	969/3269 (29.6%)	876/3289 (26.6%)	0.88 (0.80, 0.96)
Gender			
Female	317/979 (32.4%)	302/939 (32.2%)	0.98 (0.83, 1.14)
Male	676/2334 (29.0%)	583/2380 (24.5%)	0.82 (0.74, 0.92)
Age			
< 65	375/1614 (23.2%)	317/1678 (18.9%)	0.79 (0.68, 0.92)
65 +	618/1699 (36.4%)	568/1641 (34.6%)	0.94 (0.83, 1.05)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

4.1.2 RALES

The spironolactone effect on all cause mortality appeared to be consistent across subgroups, except possibly in small subgroups.

Table R-5. All cause mortality by subgroups (RALES)
[Source: Reviewer's analysis]

	Placebo (N=841)	Spironolatone (N=822)	Hazard ratio* (95% CI)
Race			
Black	27/64 (42.2%)	22/56 (39.3%)	0.92 (0.53, 1.62)
Caucasian	339/728 (46.6%)	243/712 (34.1%)	0.68 (0.58, 0.80)
Asian	9/17 (52.9%)	7/15 (46.7%)	0.78 (0.29, 2.10)
Other	11/32 (34.4%)	12/39 (30.8%)	0.93 (0.41, 2.10)
Gender			
Female	95/227 (41.9%)	68/219 (31.1%)	0.72 (0.53, 0.98)
Male	291/614 (47.4%)	216/603 (35.8%)	0.70 (0.59, 0.84)

Age			
< 65	126/343 (36.7%)	100/333 (30.0%)	0.80 (0.62, 1.05)
65 +	260/498 (52.2%)	184/489 (37.6%)	0.66 (0.55, 0.80)

* analysis based on PH model containing treatment variable only

4.2 Other Special/Subgroup Populations

4.2.1 EPHESUS

The results of other subgroups are summarized in Tables 1.15-1.16 (pages 32-35).

4.2.2 RALES

The results of other subgroups are summarized in Tables 2.11 (pages 51).

4.3 Regional Analysis

4.3.1 EPHESUS

The hazard ratios of US/CANADA (contributing 13% of the patients) were closer to one than those of other regions for both primary endpoints. However, this was driven by the apparent detrimental effect in CANADA. US had a trend favoring eplerenone in both of the primary endpoints (hazard ratio of 0.90 in all cause mortality and 0.86 in CV mortality/hospitalization, Table E-5 below). Based on the funnel plots (Figures 1.5 and 1.6, page 30) for the eplerenone effect in terms of log hazard ratio among countries, US/CANADA did not appear to be an outlier.

Table E-5. Two primary endpoints by geographical region
[*Source: Reviewer's analysis*]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
All cause mortality			
US & Canada	69/427 (16.2%)	71/431 (16.5%)	1.04 (0.75, 1.45)
US	53/307 (17.3%)	48/307 (15.6%)	0.90 (0.61, 1.33)
Canada	16/120 (13.3%)	23/124 (18.6%)	1.53 (0.80, 2.90)
Western Europe	151/870 (17.4%)	110/859 (12.8%)	0.71 (0.56, 0.91)
Eastern Europe	221/1453 (15.2%)	206/1464 (14.1%)	0.92 (0.76, 1.11)
Latin America	74/284 (26.1%)	54/287 (18.8%)	0.69 (0.49, 0.98)
Rest of World	39/279 (14.0%)	37/278 (13.3%)	0.94 (0.60, 1.47)
CV mortality/hospitalization			
US & Canada	148/427 (34.7%)	135/431 (31.3%)	0.94 (0.74, 1.18)
US	107/307 (34.9%)	93/307 (30.3%)	0.86 (0.65, 1.13)
Canada	41/120 (34.2%)	42/124 (33.9%)	1.22 (0.79, 1.88)

Western Europe	274/870 (31.5%)	241/859 (28.1%)	0.83 (0.70, 0.99)
Eastern Europe	381/1453 (26.2%)	343/1464 (23.4%)	0.88 (0.76, 1.02)
Latin America	104/284 (36.6%)	86/287 (30.0%)	0.78 (0.58, 1.03)
Rest of World	86/279 (30.8%)	80/278 (28.8%)	0.90 (0.66, 1.22)

*analysis based on PH model containing treatment variable only

In US, the differences in hospitalization as the first event between eplerenone and placebo are very small. So the favorable trend in the two mortality/hospitalization composite endpoints in US appeared to be mostly attributed to the eplerenone benefit on CV mortality.

Table E-6. Decomposition of CV mortality/hospitalization and of all cause mortality/hospitalization for US
[*Source: Reviewer's analysis*]

	Placebo (N=307)	Eplerenone (N=307)
CV mortality	19 (6.2%)	12 (3.9%)
CV hospitalization	88 (28.7%)	81 (26.4%)
All cause mortality	17 (5.5%)	8 (2.6%)
All cause hospitalization	183 (59.6%)	182 (59.3%)

4.3.2 RALES

The spironolactone effect on all cause mortality appeared to be consistent across geographical regions. Contributing only 3% patients, US showed a smaller effect than West Europe that contributed 64% patients.

Table R-6. All cause mortality by geographical region
[*Source: Reviewer's analysis*]

	Placebo (N=841)	Eplerenone (N=822)	Hazard ratio* (95% CI)
US & Canada	27/58 (46.6%)	23/56 (41.1%)	0.84 (0.48, 1.46)
US	11/26 (42.3%)	9/24 (37.5%)	0.82 (0.39, 1.97)
Western Europe	251/540 (46.5%)	183/526 (34.8%)	0.70 (0.58, 0.85)
Latin America	97/217 (44.7%)	69/216 (31.9%)	0.65 (0.48, 0.88)
Rest of World	11/26 (42.3%)	9/24 (37.5%)	0.98 (0.40, 2.37)

* analysis based on PH model containing treatment variable only

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For EPHESUS, a statistical issue pertains to (slight ?) modification of the definition of CV death/hospitalization that was added as a co-primary endpoint. The modification was done in the late stage of the trial shortly before the end of the trial; thus, it is susceptible to potential bias depending on whether the modification was ever influenced by examination of any part of the trial data (please read Dr. Marciniak's review). This concern also pertains to adding a CV mortality/non-fatal AMI as a secondary endpoint in a protocol amendment. Another issue is that there was no statistical decision rule for assessment of statistical significance of each secondary endpoint.

For RALE, the statistical issue is that there was no statistical decision rule for assessment of statistical significance of each secondary endpoint.

5.2 Conclusions and Recommendations

Based on the EPHESUS results, eplerenone yielded a statistically significant reduction (15%, 95% CI: 4%-25%, $p = 0.008$) in mortality, mostly CV mortality (17%, 95% CI: 6% - 28%). There was no evidence that eplerenone reduced the incidence of non-CV death. For the other co-primary efficacy endpoint – CV mortality/hospitalization, the final definition of CV hospitalization was established in the late stage of the trial (a few months before the trial end). It is not clear whether the modification of CV hospitalization was ever influenced by examination of the trial data. Dr. Marciniak has concerns with the definition of CV hospitalization. By taking this endpoint as it is, there was a statistically significant reduction in favor of eplerenone ($p = 0.002$). All cause mortality/hospitalization appeared to reach borderline statistical significance. Numerically, eplerenone seemed to have a favorable effect on mortality in US.

Based on RALES, spironolactone yielded a statistically significant reduction (30%, 95% CI: 18%-40%, $p < 0.0001$) in mortality, mostly through cardiac death (31% reduction, 95% CI: 18% - 42%, nominal $p < 0.0001$). Numerically, spironolactone also appeared to have a favorable effect on other mortality. There seemed to be a significant reduction in cardiac death/hospitalization or non-fatal hospitalization with spironolactone ($p < 0.0006$ for both), though there was no statistical decision rule for assessment of statistical significance of these endpoints in the protocol. Spironolactone appeared to improve NYHA class. In US, spironolactone seemed to have an favorable effect on mortality but numerically the effect seemed to be smaller than that seen in Western Europe.

APPENDICES

1. EPHESUS Trial (#IE3-99-02-035)

This was a multicenter (671 study sites in 37 countries), randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial designed to compare the safety and efficacy of eplerenone versus placebo in patients with a diagnosis of acute myocardial infarction (AMI) with heart failure and left ventricular dysfunction. Patients were to be screened within 14 days after the index AMI and randomized to received eplerenone 25 mg qd or placebo between > 48 hours and up to 14 days after the index AMI. At 4 weeks, the dose of study drug was increased to 50 mg qd if serum potassium < 5.0 mmol/L. Further dose adjustment depended on the most recent potassium level. The treatment period was to last until 1,012 deaths occurred. It was estimated that this would require 6,200 randomized patients and that the study would last approximately 2.5 years.

The standard therapy patients received throughout the study could have included angiotension-converting enzyme inhibitors (ACE-I), diuretics, nitrates, and beta-blockers. Patients could have received anticoagulants, antiplatelet agents, or thrombolytics and might also have had emergency angioplasty or coronary artery bypass graft (CABG).

1.1. Efficacy Variables

The original primary efficacy endpoint was all cause mortality. Cardiovascular (CV) mortality/hospitalization was added as a coprimary enpoint by Protocol Amendment 9 (12/20/2000). According to the study report, 4267 patients (69% of the planned sample size) had been recruited by the time of this amendment. According to the review of Dr. Tom Marciniak, medical reviewer, Protocol Amend 10 (04/24/2002) modified the definitions of this composite endpoint slightly. The definition of CV hospitalization consisted of hospitalization or prolongation of hospitalization adjudicated as having heart failure, recurrent AMI, stroke, or ventricular arrhythmia.

Secondary efficacy endpoints were CV mortality, all cause mortality/hospitalization, and CV mortality/nonfatal AMI. According to the study report, the decision to analyze the CV mortality/nonfatal AMI was made prior to unblinding study data and is reflected in the final statistical analysis plan (11/7/2002). The CV hospitalization and all cause hospitalization listed as secondary efficacy variables in the protocol were removed because competing risks of death make p-values difficult to interpret.

Additional efficacy variables were new diagnosis of atrial fribrillation or atrial flutter, fatal or nonfatal recurrent AMI, fatal or nonfatal stroke, early revascularization (>14 days and <60 days after the index AMI), and late revascularization (>60 days after the index AMI).

1.2. Interim Analyses

An independent DSMB monitored data for evidence of differential mortality or morbidity between the two treatment groups and evaluated data for safety using tables constructed from partially audited serious adverse event data. The decision on early study closure for efficacy was based on a Haybittle-Peto-type rule as specified in the DSMB charter. Throughout the trial, four interim analyses were performed and the overall alpha level allocated to these interim analyses was 0.002. To maintain the blind at Searle and among other study participants, an external statistical group will prepare all aspects of the interim reports and communicate directly with the DSMB.

1.3. Statistical Decision Criteria

The alpha level of 0.04 was allocated to all cause mortality and 0.01 to CV mortality/hospitalization. Because of the four interim analyses using the total alpha of 0.002, the final analysis of all cause mortality used a significance level of 0.038. Since CV mortality/hospitalization was not a basis for stopping in the interim analyses, no adjustment was made to the significance level for this endpoint. A positive outcome for this trial was a statistically significant decrease in all cause mortality for eplerenone relative to placebo, or a statistically significant decrease in CV mortality/hospitalization relative to placebo with no significant increase in all cause mortality.

All secondary efficacy endpoints would be tested at the 0.05 alpha level. There was no method proposed to make statistical adjustments for testing multiple secondary endpoints.

1.4. Statistical Analysis Methods

For each of the coprimary endpoints, the logrank test stratified by region was used to compare treatment groups. There were five geographical groupings: (1) Canada/US, (2) Latin America, including Argentina, Brazil, Chile, Columbia, Mexico, and Venezuela, (3) Eastern Europe, including Bulgaria, Czech Republic, Estonia, Hungary, Poland, Romania, Russia, Slovakia, and Ukraine, (4) Western Europe, including Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and UK, and (5) Rest of the World (ROW), including Australia, Israel, New Zealand, South Africa, South Korea, and Taiwan. Time to the first occurrence of the event for each patient was measured from the date of randomization. For living patients not lost to follow-up, the mortality endpoint events were censored at the study close-out date. For CV mortality/hospitalization, if a patient died from a non-CV cause and did not experience a CV hospitalization prior to death, the censoring time was the date of death. Otherwise, censoring dates were as for all cause mortality. The similar methods were used to analyze the secondary endpoints.

1.5. Sample Size Estimation

The sample size was based on the all-cause mortality endpoint. A total of Randomized patients 1,012 deaths were thought to provide a 90% power to detect an 18.5% reduction in the rate of death compared to the placebo group at 0.05 alpha level and 88.3% power at 0.04 alpha level,

based on the information provided in the external studies (AIRE, TRACE, GISSI-III). When the first-year placebo mortality rate in the placebo group is 15% or greater and up to 6,200 patients are enrolled over an 18-month period, the target number of 1,012 deaths should occur within the first 30 months of the trial (18 month enrollment plus 12 months follow-up after the last patient is enrolled). It is also assumed that the hazard ratio between the two treatment arms is constant over time (proportional hazards) and that a greater rate of recruitment will occur in the final 12 months of the enrollment period than in the initial six months.

The second co-primary endpoint is the occurrence of CV death or CV morbidity leading to hospitalization. Power to detect a risk reduction due to eplerenone for this endpoint depends on the number of events that will occur in the trial. Based on the number of composite endpoints, the power to detect a 18.5% risk reduction is above 90%.

Sample size estimates have not been adjusted for loss-to-follow-up, because study management procedures are expected to keep the loss below 1%.

1.6. Subgroup Analyses

Subgroup analyses of the primary and secondary endpoints will be performed.
The prespecified subgroups are based on baseline recordings of race (black, non-black), sex, age, presence of diabetes, ejection fraction, serum potassium, serum creatinine, use of ?-blockers, use of digoxin, use of potassium supplements, use of lipid lowering agents, first versus subsequent AMI, Killip class, reperfusion status, history of hypertension, history of HF, history of smoking, history of angina, time from index AMI to randomization, heart rate at randomization, systolic blood pressure at randomization, pulse pressure at randomization, and geographic region. Subgroups based on continuous measures such as age, ejection fraction, serum potassium, and serum creatinine will be dichotomized at the median value. No statistical significance criterion was specified.

1.7. Study Patients Information

According to the study report, all 10 patients from site 4017 in Romania were excluded from analysis because the accuracy of the data from a subinvestigator associated with this site was suspect and there was evidence that this subinvestigator altered the source documents so that patients appeared to qualify for randomization. The disposition of the intent-to-treat (ITT) population is given in Table 1.1. The two treatment groups are comparable with respect to percent of loss to follow-up (0.3%) and percent of the patients permanently discontinued study medication (about 15%). The percent of the patients requested to discontinue treatment seemed a bit higher in the eplerenone group.

Table 1.1. Disposition of ITT Patients
[Sources: Table 5 in the sponsor's study report]

	Placebo N=3313	Eplerenone 25-50 mg QD N=3319
Not treated	12 (0.4%)	12 (0.4%)
Died	5 (0.2%)	4 (0.1%)
Alive	7 (0.2%)	8 (0.2%)
Treated	3301 (99.6%)	3307 (99.6%)
Died	550 (16.6%)	476 (14.3%)
Alive	2744 (82.8%)	2821 (85.0%)
Lost to follow-up	7 (0.2%)	10 (0.3%)
Permanently discontinued study medication	493 (14.9%)	528 (16.0%)
Discovery of pre-existing violation of entry criteria	3 (0.1%)	1 (0.0%)
Protocol noncompliance	53 (1.6%)	65 (2.0%)
Treatment with spironolactone	44 (1.3%)	32 (1.0%)
Adverse sign or symptom[+]	142 (4.3%)	144 (4.4%)
Pre-existing adverse event	1 (0.0%)	0 (0.0%)
Adverse event occurred 7 days after last dose	6 (0.2%)	3 (0.1%)
Increased potassium level	23 (0.7%)	35 (1.1%)
Administrative reasons	17 (0.5%)	17 (0.5%)
Patient request to discontinue treatment	204 (6.2%)	231 (7.0%)

1.8. Demographic and Baseline Characteristics

The two treatment groups appeared to be comparable with respect to demographic and baseline characteristics, except that the mean BMI seemed to be a little larger in the eplerenone group in female patients (Table 1.2).

Table 1.2. Demographic and Baseline Characteristics
[Source: Table 6 of the sponsor's study report, confirmed by reviewer's analysis]

	Placebo N=3313	Eplerenone 25-50 mg QD N=3319	p-value[†]
Age (years)			0.135
<35	19 (0.6%)	8 (0.2%)	
35-44	157 (4.7%)	154 (4.6%)	
45-54	566 (17.1%)	600 (18.1%)	
55-64	872 (26.3%)	916 (27.6%)	
65-74	989 (29.9%)	1025 (30.9%)	
>74	710 (21.4%)	616 (18.6%)	
Mean (SD)	64.2 (11.71)	63.7 (11.33)	
Range	22-93	31-94	
Ethnicity			0.541
Caucasian	2989 (90.2%)	2995 (90.2%)	
Black	44 (1.3%)	30 (0.9%)	
Asian	32 (1.0%)	36 (1.1%)	
Hispanic/Latin American	188 (5.7%)	197 (5.9%)	
Other	60 (1.8%)	61 (1.8%)	
Gender			0.258
Male	2334 (70.4%)	2380 (71.7%)	
Female	979 (29.6%)	939 (28.3%)	
Weight (kg)			
Female	N=979	N=938	0.063
Mean (SD)	70.1 (14.5)	71.3 (13.9)	
Range	38.0-155.7	40.0-126.6	
Male	N=2331	N=2380	0.483
Mean (SD)	81.0 (14.1)	81.3 (14.4)	
Range	42.0-154.0	44.5-163.0	
Height (cm)			
Female	N=974	N=935	0.247
Mean (SD)	159.7 (7.1)	159.3 (6.5)	
Range	132.0-193.0	136.0-177.8	
Male	N=2329	N=2374	0.772
Mean (SD)	172.4 (7.3)	172.5 (7.4)	
Range	124.0-210.8	128.0-198.0	
Body Mass Index (kg/m^2)			
Female	N=974	N=935	0.007*
Mean (SD)	27.4 (5.3)	28.1 (5.1)	
Range	16.0-52.7	16.0-49.3	
Male	N=2328	N=2374	0.462
Mean (SD)	27.2 (4.1)	27.3 (4.3)	
Range	15.4-55.3	16.4-53.8	

1.9. Efficacy Results

1.9.1. Primary efficacy variables

There were two primary efficacy endpoints – all cause mortality and CV mortality/hospitalization. For the mortality endpoint, the follow-up rate was about 99.7%. For hospitalization, some patients in both treatment groups had missing dates of hospitalization which were then imputed according to some kind of pre-determined algorithm (according to the sponsor's response to the reviewer's question) applied to both treatment groups. The quality of the hospitalization data is questionable. Nevertheless, the eplerenone group appeared to have a bit longer mean or median time to follow-up for patients who survived and were not hospitalized for any CV reason (Table 1.4); otherwise, the distributions were comparable. It should also be noted that the sponsor's definition of CV hospitalization was established in the late stage of the trial (close to the trial end).

For both endpoints, the incidence rate in the eplerenone group was statistically significantly lower than that in the placebo group (p=0.008 for all cause mortality, p=0.002 for CV mortality/hospitalization).

Table 1.3. Analysis of Primary Endpoints (ITT patients)
[Source: Reviewer's analysis results, identical with the sponsor's results in Table 8 of the study report]

	Placebo N=3313	Eplerenone N=3319	Risk ratio (95%CI)#	p-value*
All cause mortality	554 (16.7%)	478 (14.4%)	0.85 (0.75, 0.96)	0.008
CV mortality/hospitalization	993 (30.0%)	885 (26.7%)	0.87 (0.79, 0.95)	0.002

* based on logrank test stratified by region
# based on Cox proportional hazards model including treatment as the only factor, stratified by region

Table 1.4. Summary statistics on time (in days) to follow-up for patients who survived and were not hospitalized for any CV reason
[Source: Reviewer's analysis]

	N	mean	max	99%	95%	75%	50%	25%	5%	1%	min
Eper	2434	522	911	872	806	633	513	400	281	182	4
plbo	2320	518	978	873	801	632	508	395	282	135	16

Figures 1.1 and 1.3 give the Kaplan-Meier plots for the two endpoints, respectively. Figures 1.2 and 1.4 give log minus log Kaplan-Meier estimates versus log time, which suggest that the eplerenone effects on mortality and CV mortality/hospitalization in terms of hazard ratio appeared to be approximately constant after passing the first two weeks.

Figure 1.1. Cumulative incidence of all cause mortality
[Source: Figure 2 of the sponsor's report, confirmed by the reviewer's analysis]

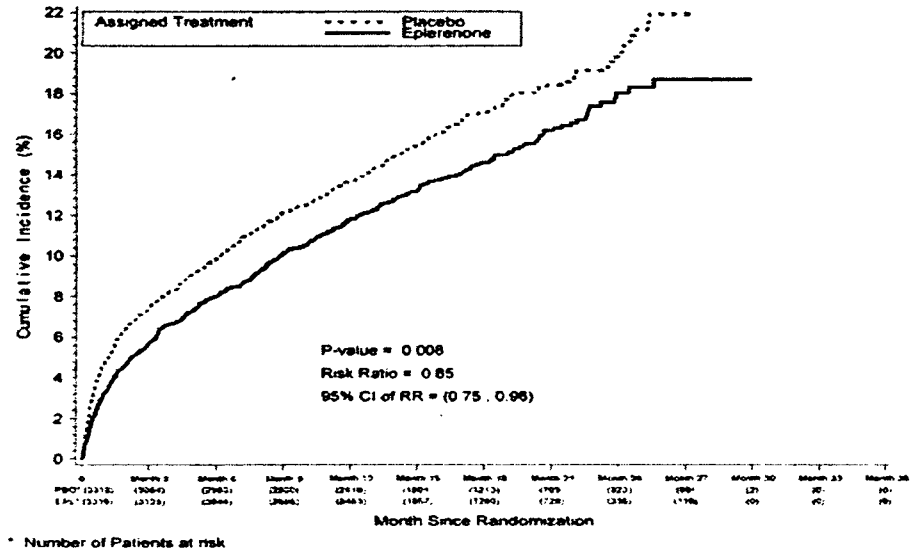


Figure 1.2. Log(-log(surival)) plot for all cause mortality
[Source: Reviewer's analysis]

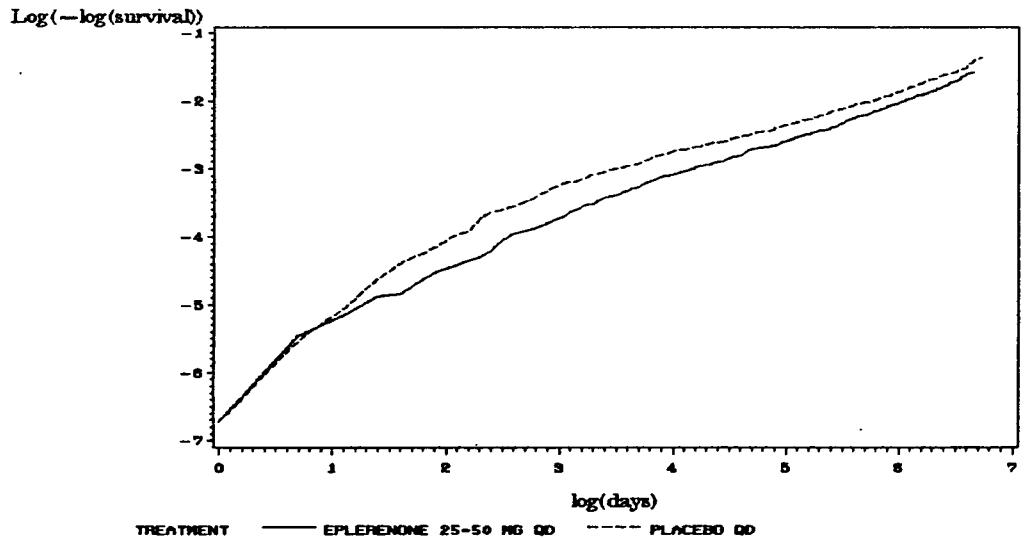


Figure 1.3. Cumulative incidence of CV death/hospitalization
[Source: Figure 3 of the sponsor's report, confirmed by the reviewer's analysis]

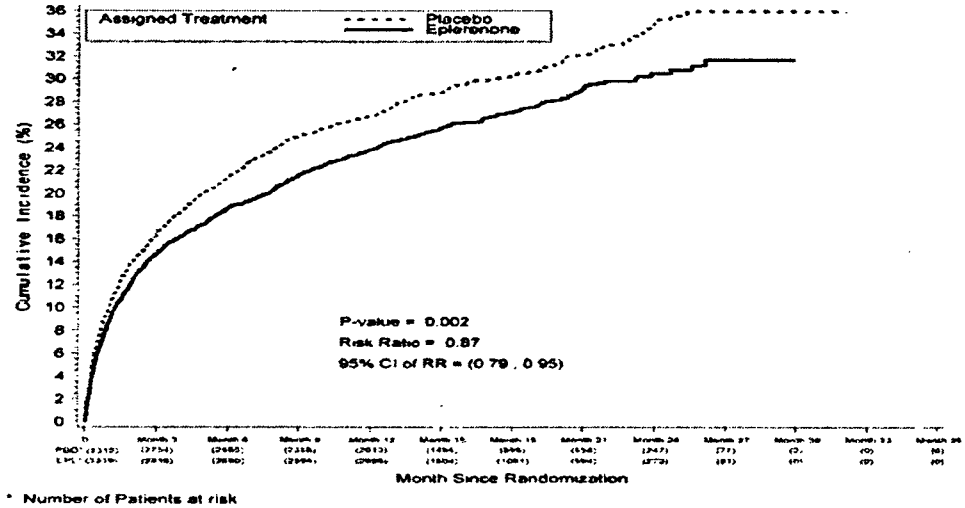
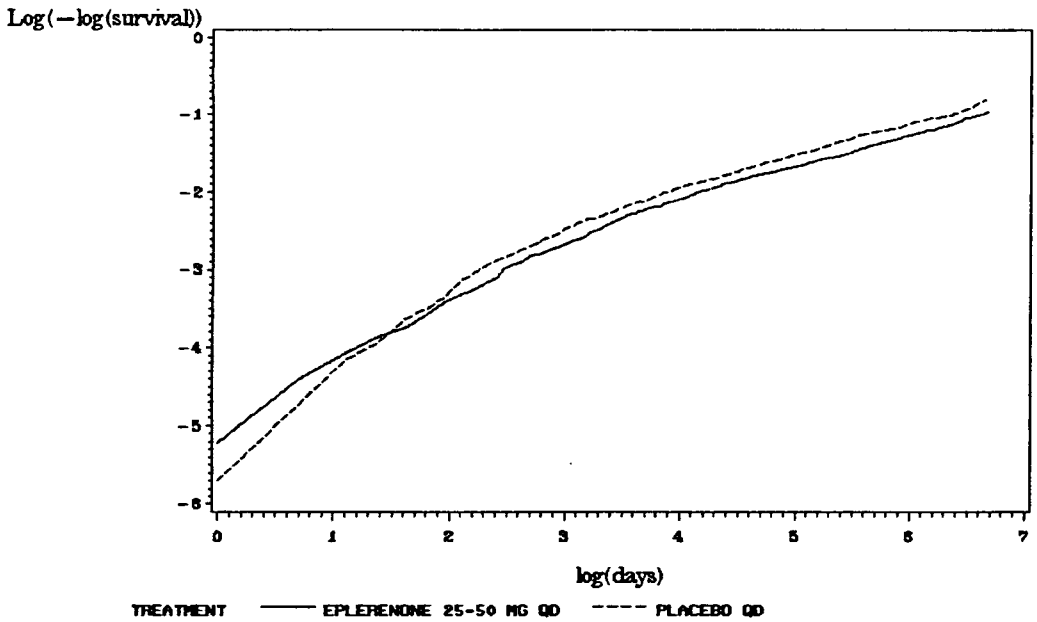


Figure 1.4. Log(-log(surival)) plot for CV death/hospitalization
[Source: Reviewer's analysis]



As shown in Table 1.5, most of the deaths were CV deaths according to adjudication. The risk ratio of CV death was 0.83 (95% CI: 0.72-0.94) which is similar to 0.85 (95% CI: 0.75-0.96) for all cause mortality. The CV deaths are due to sudden cardiac death, recurrent AMI or HF, according to the adjudication.

Table 1.5. Summary of Events Contributing to All Cause Mortality (ITT patients)
[Source: Reviewer's analysis results, identical to the sponsor's results in Table 9 of the study report]

	Placebo N=3313	Eplerenone N=3319
All cause mortality	554 (16.7%)	478 (14.4%)
CV death	483 (14.6%)	407 (12.3%)
Sudden cardiac death	201 (6.1%)	162 (4.9%)
Recurrent AMI	94 (2.8%)	78 (2.4%)
HF	127 (3.8%)	104 (3.1%)
Stroke	28 (0.8%)	26 (0.8%)
Aneurysm	1 (0.0%)	1 (0.0%)
Pulmonary embolism	4 (0.1%)	4 (0.1%)
Other CV death	28 (0.8%)	32 (1.0%)
Non-CV death	54 (1.6%)	60 (1.8%)
Sepsis	7 (0.2%)	9 (0.3%)
Pneumonia	8 (0.2%)	10 (0.3%)
Cancer	19 (0.6%)	20 (0.6%)
Other non-CV death	20 (0.6%)	21 (0.6%)
Unwitnessed death	1 (0.0%)	0
Unknown cause of death	16 (0.5%)	11 (0.3%)

As shown in Table 1.6, approximately seventy percents of the CV composite endpoints were CV hospitalizations as the first event. The eplerenone group had a lower incidence rate of CV hospitalization than the placebo group. Even in the death as the first event, the eplerenone group had a lower incidence than the placebo group; this result is consistent with that of all cause mortality.

Table 1.6. Summary of Events Contributing to CV Mortality/Hospitalization (ITT patients)
[Source: Table 10 of the study report; Reviewer's analysis yields very similar results]

	Placebo N=3313	Eplerenone N=3319
CV mortality/hospitalization	993 (30.0%)	885 (26.7%)
CV mortality	253 (7.6%)	197 (5.9%)
Sudden cardiac death	148 (4.5%)	123 (3.7%)
Recurrent AMI	42 (1.3%)	29 (0.9%)
HF	36 (1.1%)	19 (0.6%)
Stroke	4 (0.1%)	3 (0.1%)
Aneurysm	1 (0.0%)	1 (0.0%)
Pulmonary embolism	2 (0.1%)	1 (0.0%)
Other CV death	20 (0.6%)	21 (0.6%)
CV hospitalization	740 (22.3%)	688 (20.7%)
HF	395 (11.9%)	334 (10.1%)
Ventricular arrhymias	44 (1.3%)	38 (1.1%)
Recurrent AMI	239 (7.2%)	230 (6.9%)
Stroke	56 (1.7%)	75 (2.3%)
HF/Ventricular arrhythmias	1 (0.0%)	3 (0.1%)
HF/Recurrent AMI	1 (0.0%)	3 (0.1%)
HF/Stroke	2 (0.1%)	1 (0.0%)
Ventricular arrhythmias/Recurrent AMI	1 (0.0%)	4 (0.1%)
Recurrent AMI/Stroke	1 (0.0%)	0 (0.0%)

1.9.2. Secondary Efficacy Variables

Originally there were 4 specified secondary variables – CV mortality, CV hospitalization, all cause hospitalization, all cause mortality/hospitalization. According to the study report, CV mortality/nonfatal AMI was added as a secondary endpoint prior to unblinding study data and reflected in the final statistical analysis plan (11/7/2002). The CV hospitalization and all cause hospitalization were removed because competing risks of death make p-values difficult to interpret. Consequently, the secondary efficacy endpoints in the final analysis were CV mortality, all cause mortality/hospitalization, and CV mortality/nonfatal AMI.

As shown in Table 1.7, the eplerenone group had a lower incidence of each secondary endpoint than the placebo group. However, there was no pre-specified statistical decision rule for the secondary endpoints. It is not clear whether removing or adding the endpoints to result in this final list of the secondary endpoints in the late stage of the trial was ever influenced by the examination of the interim data by the DSMB. However, CV mortality was statistically significant in favor of eplerenone, even by the most conservative Bonferroni adjustment after both primary endpoints reached statistical significance. CV mortality/non-fatal AMI achieved borderline significance, after the most conservative Bonferroni adjustment. All cause mortality/hospitalization was almost statistically significant.

For hospitalization, some patients in both treatment groups had missing dates of hospitalization which were then imputed according to some kind of pre-determined algorithm (according to the sponsor's response to the reviewer's question) applied to both treatment groups. The quality of the hospitalization data is questionable. The two treatment groups appeared to have comparable distributions for time to follow-up for patients who survived and were not hospitalized for any reason (Table 1.8).

Table 1.7. Analysis of Secondary Endpoints (ITT patients)
[Source: Reviewer's analysis results, identical with the sponsor's results in Table 11 of the study report]

	Placebo N=3313	Eplerenone N=3319	Risk ratio (95%CI)#	p-value*
CV mortality	483 (14.6%)	407 (12.3%)	0.83 (0.72, 0.94)	0.005
All cause mortality/hospitalization	1829 (55.2%)	1730 (52.1%)	0.92 (0.86, 0.98)	0.016
CV mortality/nonfatal AMI	667 (20.1%)	585 (17.6%)	0.86 (0.77, 0.96)	0.009

* based on logrank test stratified by region
# based on Cox proportional hazards model including treatment as the only factor, stratified by region

Table 1.8. Summary statistics on time (in days) to follow-up for patients who survived and were not hospitalized for any reason

	N	mean	max	99%	95%	75%	50%	25%	5%	1%	min
Eper	1589	520	911	873	799	630	507	395	289	247	40
plbo	1484	518	906	878	799	628	506	389	289	247	37

1.9.3. Summary of Hospitalizations

The hospitalization data were analyzed by the sponsor to capture deaths during hospitalization (Table 1.10) and non-fatal events causing or prolonging hospitalization (Table 1.11). The sponsor's results are mostly confirmed by the reviewer's analyses. Numerically, there were trends in favor of eplerenone with respect to CV related events.

Table 1.9. Summary of Hospitalizations (ITT population)
[Source: Table 12 of the study report; reviewer's analysis yields similar results]

	Placebo N=3313	Eplerenone N=3319
CV hospitalizations	740 (22.3%)	688 (20.7%)
All hospitalizations	1684 (50.8%)	1624 (48.9%)

Table 1.10. Deaths During Hospitalization (ITT population)
[Source: Reviewer's analysis results, identical with the sponsor's results in Table 14 of the study report]

	Placebo N=3313	Eplerenone N=3319
Death During Hospitalization – All causes	300 (9.1%)	272 (8.2%)
CV death	254 (7.7%)	275 (6.8%)
Sudden cardiac death	27 (0.8%)	32 (1.0%)
Recurrent AMI	82 (2.5%)	71 (2.1%)
HF	91 (2.7%)	73 (2.2%)
Stroke	26 (0.8%)	20 (0.6%)
Aneurysm	1 (0.0%)	0 (0.0%)
Pulmonary embolism	3 (0.1%)	3 (0.1%)
Other CV death	24 (0.7%)	26 (0.8%)
Non-CV death	44 (1.3%)	45 (1.4%)
Sepsis	7 (0.2%)	9 (0.3%)
Pneumonia	8 (0.2%)	9 (0.3%)
Cancer	12 (0.4%)	10 (0.3%)
Other non-CV death	17 (0.5%)	17 (0.5%)
Unknown cause of death	2 (0.1%)	2 (0.1%)

Table 1.11. Adjudicated Nonfatal Events Causing or Prolonging Hospitalization (ITT population)
*[Source: Table 14 of the study report; reviewer's results are identical to the sponsor's results in most of the items except for the items marked with * where there are some minor differences]*

	Placebo N=3313	Eplerenone N=3319
All hositalizations*	1525 (46.0%)	1493 (45.0%)
CV hospitalization – primary	649 (19.6%)	606 (18.3%)
HF	391 (11.8%)	345 (10.4%)
Ventricular arrhythmias	54 (1.6%)	52 (1.6%)
Recurrent AMI	229 (6.9%)	224 (6.7%)
Stroke	51 (1.5%)	70 (2.1%)
CV hospitalization – other*	925 (27.9%)	917 (27.6%)
AF/AFL	95 (2.9%)	86 (2.6%)
Stable angina	87 (2.6%)	89 (2.7%)
Unstable angina	307 (9.3%)	321 (9.7%)
PVD	32 (1.0%)	38 (1.1%)
Hypotension	29 (0.9%)	31 (0.9%)
CV surgery*	301 (9.1%)	321 (9.6%)
Other*	368 (11.1%)	318 (9.6%)
Non-CV hospitalization*	559 (16.9%)	539 (16.2%)
Pneumonia*	70 (2.1%)	35 (1.1%)
COPD/COLD	19 (0.6%)	17 (0.5%)
Other pulmonary disease	26 (0.8%)	28 (0.8%)
Diabetes	38 (1.1%)	28 (0.8%)
Elective surgery	44 (1.3%)	65 (2.0%)
Other*	420 (12.7%)	422 (12.7%)

1.10. Additional Efficacy Variables

The study report also included the results for the additional efficacy endpoints in Table 1.12. No statistical decision rule was given in the protocol; nor was in the final statistical analysis plan. Nonetheless, the nominal p-value failed to suggest a statistically significant difference between the placebo and eplerenone.

Table 1.12. Analysis of Additional Efficacy Endpoints (ITT population)
[Source: Table 15 of the study report]

	Placebo N=3313	Eplerenone N=3319	Risk ratio (95%CI)#	p-value*
New diagonosis of AF/AFL	100 (3.0%)	87 (2.6%)	0.85 (0.64, 1.14)	0.27
Recurrent AMI (fatal or nonfatal)	313 (9.4%)	293 (8.8%)	0.92 (0.79, 1.08)	0.33
Stroke	77 (2.3%)	91 (2.7%)	1.16 (0.85, 1.57)	0.34
Early revascularization	47 (1.4%)	34 (1.0%)	0.71 (0.46, 1.11)	0.13
Late revascularization	103 (3.1%)	91 (2.7%)	0.86 (0.65, 1.14)	0.30

* based on logrank test stratified by region
# based on Cox proportional hazards model including treatment as the only factor, stratified by region

Eplerenone seemed to improve NYHA classification for patients (95% of the patients had NYHA data). No statistical decision rule was specified in the protocol to assess statistical significance of this variable.

Table 1.13. Analysis of Change from Baseline to Final in NYHA Functional Classification (ITT population) *[Source: Table 16 of the study report]*

	Placebo N=3313	Eplerenone N=3319	p-value*
Missing	169	168	
Baseline NYHA Class			
I	940 (29.9%)	924 (29.3%)	
II	1629 (51.8%)	1650 (52.4%)	
III	529 (16.8%)	520 (16.5%)	
IV	46 (1.5%)	57 (1.8%)	
Change from baseline			< 0.001
Worsened	902 (28.7%)	779 (24.7%)	
No change	1527 (48.6%)	1582 (50.2%)	
Improved	715 (22.7%)	790 (25.1%)	

* based on CMH row-mean score test, stratified by region

Quality of Life

Quality of life (QOL) assessments were conducted in selected countries (Argentina, Belgium, Brazil, Canada, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States) at Screening, at Week 4, at Months 3, 6, 12, 18, and 24, at transition and at study termination. The primary objective of the QOL substudy assessed the effect of eplerenone on change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score over the first 12 months of follow-up, and was evaluated using a repeated measures analysis. Higher scores on the KCCQ indicate better function, fewer symptoms and higher QOL. According to the

sponsor's analysis, KCCQ Overall Summary scores in the placebo group at baseline, 1, 3, 6, and 12 months were 61.5 ± 25, 69.1 ± 22, 73.8 ± 21, 75.6 ± 22 and 77.6 ± 20. The absolute differences (mean (95% confidence intervals)) between eplerenone-treated and placebo patients in KCCQ Overall Summary change scores at months 1, 3, 6, and 12 were 1.0 (95% CI: -1.6, 3.5), 2 (95% CI: -0.8, 4.7), 1.1 (95% CI: -1.8, 4.1), and 1.7(95% CI: -1.3, 4.6). There was no significant difference in improvement in QOL between patients randomized to placebo or eplerenone (p = 0.43).

1.11. Analysis by Region, Subgroup, and Baseline Covariates

Analysis by Region

US/CANADA that contributed 13% of the patients appeared to trend in favor of placebo in all-cause mortality but trend in favor of eplerenone in CV mortality/hospitalization. The sponsor's analysis by region included region and treatment by region interaction in the PH model. The reviewer performed an analysis excluding region and treatment by region interaction from the PH model to examine the discrepancies that may be caused by the inclusion of these two factors in the model. The reviewer's results (given in Table 1.14) are virtually consistent with the sponsor's results. The hazard ratios of US/CANADA were closer to one than those of other regions in both primary endpoints. However, this was driven by the apparent detrimental effect in CANADA. US had a trend favoring eplerenone in both of the primary endpoints (hazard ratio of 0.90 in all cause mortality and 0.86 in CV mortality/hospitalization).

Table 1.14. Two primary endpoints by geographical region
[*Source: Reviewer's analysis*]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
All cause mortality			
US & Canada	69/427 (16.2%)	71/431 (16.5%)	1.04 (0.75, 1.45)
US	53/307 (17.3%)	48/307 (15.6%)	0.90 (0.61, 1.33)
Canada	16/120 (13.3%)	23/124 (18.6%)	1.53 (0.80, 2.90)
Western Europe	151/870 (17.4%)	110/859 (12.8%)	0.71 (0.56, 0.91)
Eastern Europe	221/1453 (15.2%)	206/1464 (14.1%)	0.92 (0.76, 1.11)
Latin America	74/284 (26.1%)	54/287 (18.8%)	0.69 (0.49, 0.98)
Rest of World	39/279 (14.0%)	37/278 (13.3%)	0.94 (0.60, 1.47)
CV mortality/hospitalization			
US & Canada	148/427 (34.7%)	135/431 (31.3%)	0.94 (0.74, 1.18)
US	107/307 (34.9%)	93/307 (30.3%)	0.86 (0.65, 1.13)
Canada	41/120 (34.2%)	42/124 (33.9%)	1.22 (0.79, 1.88)
Western Europe	274/870 (31.5%)	241/859 (28.1%)	0.83 (0.70, 0.99)
Eastern Europe	381/1453 (26.2%)	343/1464 (23.4%)	0.88 (0.76, 1.02)
Latin America	104/284 (36.6%)	86/287 (30.0%)	0.78 (0.58, 1.03)
Rest of World	86/279 (30.8%)	80/278 (28.8%)	0.90 (0.66, 1.22)

*analysis based on PH model containing treatment variable only

The funnel plots for the eplerenone effect in terms of log hazard ratio among countries are given in Figures 1.5 and 1.6. US/CANADA did not appear to be an outlier, based on the plots.

Figure 1.5. Log harzard ratio (LHR) of all cause mortality by country

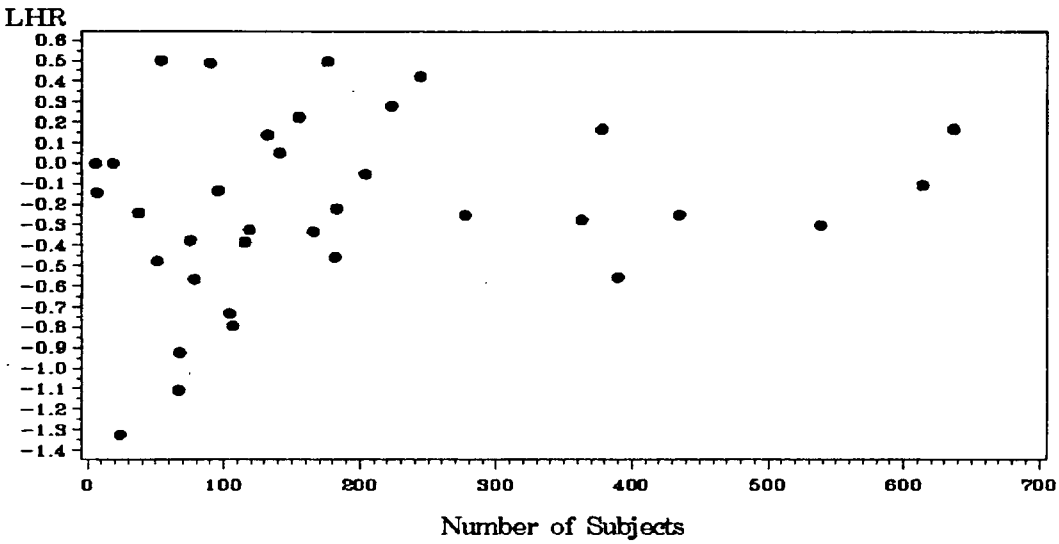


Figure 1.6. Log harzard ratio (LHR) of CV mortality/hospitalization by country

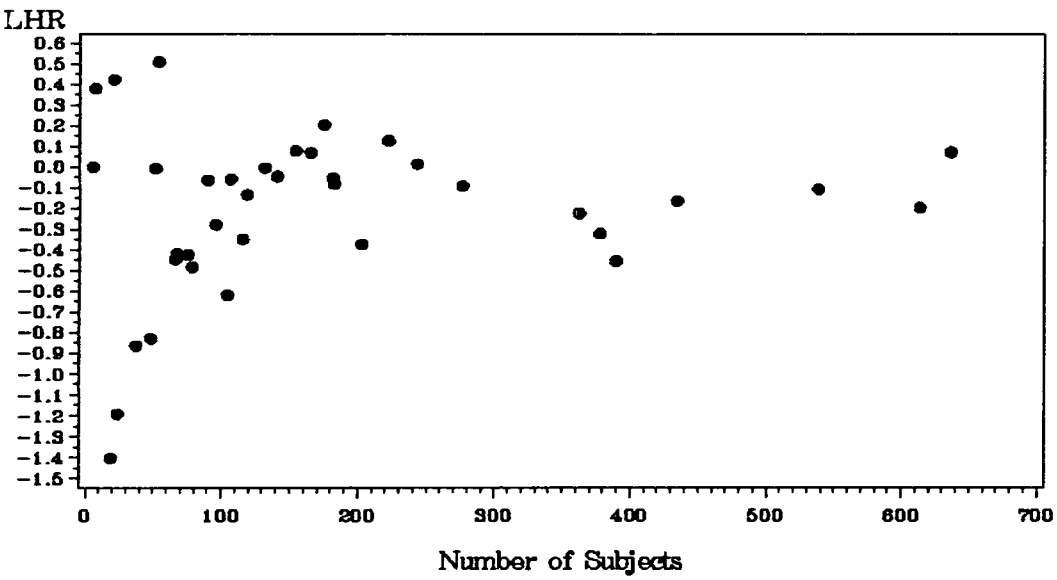


Table 1.14.1 gives the decomposition of CV mortality/hospitalization and of all cause mortality/hospitalization for US. The differences in hospitalization as the first event between eplerenone and placebo are very small. So the favorable trend in the two mortality/hospitalization composite endpoints for US appeared to be mostly attributed to the eplerenone benefit on CV mortality.

Table 1.14.1. Decomposition of CV mortality/hospitalization and of all cause mortality/hospitalization for US
[*Source: Reviewer's analysis*]

	Placebo (N=307)	Eplerenone (N=307)
CV mortality	19 (6.2%)	12 (3.9%)
CV hospitalization	88 (28.7%)	81 (26.4%)
All cause mortality	17 (5.5%)	8 (2.6%)
All cause hospitalization	183 (59.6%)	182 (59.3%)

Analysis by Subgroup and Baseline Covariates

There was no evidence of large inconsistency in the eplerenone effect across subgroups (Tables 1.15 and 1.16), except in small subgroups.

Table 1.15. All cause mortality by subgroups
[*Source: excerpted from the Sponsor's Tables T11.1, confirmed by the reviewer's analysis*]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
Race			
Black	10/44 (22.7%)	4/30 (13.3%)	0.47 (0.15, 1.51)
Other	544/3269 (16.6%)	474/3289 (14.4%)	0.85 (0.75, 0.96)
Gender			
Female	194/979 (19.8%)	152/939 (16.2%)	0.79 (0.64, 0.98)
Male	360/2334 (15.4%)	326/2380 (13.7%)	0.88 (0.76, 1.02)
Age			
< 65	180/1614 (11.2%)	146/1678 (8.7%)	0.77 (0.62, 0.96)
65 +	374/1699 (22.0%)	332/1641 (20.2%)	0.90 (0.78, 1.05)
History of diabetes			
No history	335/2244 (14.9%)	276/2246 (12.3%)	0.81 (0.69, 0.95)
Type I	24/78 (30.8%)	11/65 (16.9%)	0.55 (0.27, 1.12)
Type II	195/991 (19.7%)	191/1008 (18.9%)	0.95 (0.78, 1.16)
History of heart failure before index AMI			
No	410/2810 (14.6%)	346/2847 (12.2%)	0.82 (0.71, 0.94)
Yes	144/503 (28.6%)	132/472 (28.0%)	0.96 (0.76, 1.22)
History of hospitalization for heart failure before index AMI			
No	468/3044 (15.4%)	405/3076 (13.2%)	0.85 (0.74, 0.97)
Yes	86/269 (32.0%)	73/243 (30.0%)	0.88 (0.64, 1.20)
History of hypertension			
No	186/1289 (14.4%)	191/1336 (14.3%)	1.00 (0.81, 1.22)
Yes	368/2024 (18.2%)	287/1983 (14.5%)	0.77 (0.66, 0.90)
History of angina			
No	290/1966 (14.8%)	231/1931 (12.0%)	0.80 (0.67, 0.95)
Yes	264/1347 (19.6%)	247/1388 (17.8%)	0.89 (0.75, 1.06)
Smoking history			
Current smoker	136/1010 (13.5%)	120/1033 (11.6%)	0.86 (0.67, 1.10)
Former smoker	170/996 (17.1%)	168/1001 (16.8%)	0.97 (0.78, 1.20)
Never smoked	248/1304 (19.0%)	189/1283 (14.7%)	0.75 (0.62, 0.91)
Previous AMI			
No	344/2424 (14.2%)	287/2405 (11.9%)	0.83 (0.71, 0.97)
Yes	210/889 (23.6%)	191/914 (20.9%)	0.86 (0.71, 1.04)
Time from AMI to randomization			
Median (=7 days) or less	293/1803 (16.3%)	229/1793 (12.8%)	0.78 (0.65, 0.92)
Above median	261/1509 (17.3%)	249/1526 (16.3%)	0.92 (0.78, 1.10)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

Table 1.15 (Cont'd). All cause mortality by subgroups
[Source: excerpted from the Sponsor's Tables T11.1, confirmed by the reviewer's analysis]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
PTCR within 14 days of index AMI			
No	483/2532 (19.1%)	421/2520 (16.7%)	0.86 (0.75, 0.98)
Yes	71/781 (9.1%)	57/799 (7.1%)	0.78 (0.55, 1.11)
CABG within 14 days of index AMI			
No	552/3282 (16.8%)	475/3280 (14.5%)	0.85 (0.75, 0.96)
Yes	2/31 (6.5%)	3/39 (7.7%)	1.16 (0.19, 6.93)
Killip Class			
Class I	53/505 (10.5%)	57/507 (11.2%)	1.06 (0.73, 1.54)
Class II	325/2134 (15.2%)	270/2143 (12.6%)	0.81 (0.69, 0.95)
Class III	152/551 (27.6%)	125/544 (23.0%)	0.82 (0.65, 1.04)
Class IV	23/101 (22.8%)	22/106 (20.8%)	0.88 (0.49, 1.58)
Ejection fraction before randomization			
Median (=35%) or less	406/1984 (20.5%)	334/1975 (16.9%)	0.81 (0.70, 0.93)
Above median	146/1320 (11.1%)	141/1338 (10.5%)	0.95 (0.75, 1.19)
ACE inhibitors			
No	82/492 (16.7%)	81/524 (15.5%)	0.93 (0.68, 1.26)
Yes	472/2821 (16.7%)	397/2795 (14.2%)	0.83 (0.73, 0.95)
Beta blockers			
No	190/835 (22.8%)	201/836 (24.0%)	1.04 (0.86, 1.27)
Yes	364/2478 (14.7%)	277/2483 (11.2%)	0.75 (0.64, 0.87)
Angiotension-II antagoists			
No	534/3198 (16.7%)	462/3218 (14.4%)	0.85 (0.75, 0.96)
Yes	20/115 (17.4%)	16/101 (15.8%)	0.92 (0.48, 1.78)
Receptor antagonist & beta blocker			
No A and no B	28/142 (19.7%)	28/137 (20.4%)	1.01 (0.60, 1.71)
B only	42/281 (14.9%)	40/321 (12.5%)	0.83 (0.54, 1.28)
A only	162/693 (23.4%)	173/699 (24.7%)	1.05 (0.84, 1.30)
A and B	322/2197 (14.7%)	237/2162 (11.0%)	0.73 (0.62, 0.87)
Alpha blockers			
No	545/3253 (16.8%)	467/3255 (14.3%)	0.84 (0.74, 0.95)
Yes	9/60 (15.0%)	11/64 (17.2%)	1.09 (0.45, 2.63)
Calcium channel blockers			
No	458/2783 (16.5%)	386/2784 (13.9%)	0.83 (0.72, 0.95)
Yes	96/530 (18.1%)	92/535 (17.2%)	0.94 (0.70, 1.25)
Diuretics			
No diuretics	126/1304 (9.7%)	123/1344 (9.2%)	0.94 (0.74, 1.21)
Loop diuretics	405/1855 (21.8%)	332/1806 (18.4%)	0.82 (0.71, 0.95)
Other diuretics	23/154 (14.9%)	23/169 (13.6%)	0.91 (0.51, 1.62)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

Table 1.16. CV mortality/hospitalization by subgroups
[Source: excerpted from the Sponsor's Tables T11.3, confirmed by the reviewer's analysis]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
Race			
Black	24/44 (54.5%)	9/30 (30.0%)	0.42 (0.20, 0.91)
Other	969/3269 (29.6%)	876/3289 (26.6%)	0.88 (0.80, 0.96)
Gender			
Female	317/979 (32.4%)	302/939 (32.2%)	0.98 (0.83, 1.14)
Male	676/2334 (29.0%)	583/2380 (24.5%)	0.82 (0.74, 0.92)
Age			
< 65	375/1614 (23.2%)	317/1678 (18.9%)	0.79 (0.68, 0.92)
65 +	618/1699 (36.4%)	568/1641 (34.6%)	0.94 (0.83, 1.05)
History of diabetes			
No history	600/2244 (26.7%)	520/2246 (23.2%)	0.85 (0.75, 0.95)
Type I	29/78 (37.2%)	24/65 (36.9%)	1.03 (0.60, 1.76)
Type II	364/991 (36.7%)	341/1008 (33.8%)	0.88 (0.76, 1.02)
History of heart failure before index AMI			
No	765/2810 (27.2%)	668/2847 (23.5%)	0.84 (0.76, 0.93)
Yes	228/503 (45.3%)	217/472 (46.0%)	0.99 (0.83, 1.20)
History of hospitalization for heart failure before index AMI			
No	851/3044 (28.0%)	762/3076 (24.8%)	0.87 (0.79, 0.96)
Yes	142/269 (52.8%)	123/243 (50.6%)	0.87 (0.69, 1.11)
History of hypertension			
No	322/1289 (25.0%)	312/1336 (23.4%)	0.93 (0.80, 1.09)
Yes	671/2024 (33.2%)	573/1983 (28.9%)	0.84 (0.75, 0.94)
History of angina			
No	526/1966 (26.8%)	458/1931 (23.7%)	0.87 (0.76, 0.98)
Yes	467/1347 (34.7%)	427/1388 (30.8%)	0.86 (0.75, 0.98)
Smoking history			
Current smoker	254/1010 (25.1%)	215/1033 (20.8%)	0.82 (0.68, 0.98)
Former smoker	326/996 (32.7%)	301/1001 (30.1%)	0.89 (0.76, 1.04)
Never smoked	412/1304 (31.6%)	368/1283 (28.7%)	0.88 (0.76, 1.01)
Previous AMI			
No	632/2424 (26.1%)	540/2405 (22.5%)	0.84 (0.75, 0.95)
Yes	361/889 (40.6%)	345/914 (37.7%)	0.89 (0.77, 1.03)
Time from AMI to randomization			
Median (=7 days) or less	529/1803 (29.3%)	457/1793 (25.5%)	0.85 (0.75, 0.96)
Above median	464/1509 (30.7%)	428/1526 (28.0%)	0.89 (0.78, 1.01)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

Table 1.16 (Cont'd). CV mortality/hospitalization by subgroups
[Source: excerpted from the Sponsor's Tables T11.3, confirmed by the reviewer's analysis]

	Placebo (N=3313)	Eplerenone (N=3319)	Hazard ratio* (95% CI)
PTCR within 14 days of index AMI			
No	811/2532 (32.0%)	742/2520 (29.4%)	0.90 (0.81, 0.99)
Yes	182/781 (23.3%)	143/799 (17.9%)	0.75 (0.60, 0.93)
CABG within 14 days of index AMI			
No	986/3282 (30.0%)	875/3280 (26.7%)	0.87 (0.79, 0.95)
Yes	7/31 (22.6%)	10/39 (25.6%)	1.17 (0.44, 3.07)
Killip Class			
Class I	121/505 (24.0%)	113/507 (22.3%)	0.91 (0.70, 1.17)
Class II	590/2134 (27.6%)	512/2143 (23.9%)	0.84 (0.75, 0.95)
Class III	227/551 (41.2%)	209/544 (38.4%)	0.92 (0.76, 1.11)
Class IV	51/101 (50.5%)	46/106 (43.4%)	0.80 (0.54, 1.20)
Ejection fraction before randomization			
Median (=35%) or less	702/1984 (35.4%)	598/1975 (30.3%)	0.82 (0.73, 0.91)
Above median	287/1320 (21.7%)	284/1338 (21.2%)	0.98 (0.83, 1.16)
ACE inhibitors			
No	141/492 (28.7%)	123/524 (23.5%)	0.81 (0.63, 1.03)
Yes	852/2821 (30.2%)	762/2795 (27.3%)	0.88 (0.80, 0.97)
Beta blockers			
No	297/835 (35.6%)	290/836 (34.7%)	0.97 (0.82, 1.14)
Yes	696/2478 (28.1%)	595/2483 (24.0%)	0.83 (0.74, 0.92)
Angiotension-II antagoists			
No	946/3198 (29.6%)	848/3218 (26.4%)	0.87 (0.79, 0.95)
Yes	47/115 (40.9%)	37/101 (36.6%)	0.83 (0.54, 1.28)
Receptor antagonist & beta blocker			
No A and no B	44/142 (31.0%)	39/137 (28.5%)	0.92 (0.60, 1.41)
B only	68/281 (24.2%)	59/321 (18.4%)	0.74 (0.52, 1.05)
A only	253/693 (36.5%)	251/699 (35.9%)	0.97 (0.82, 1.16)
A and B	628/2197 (28.6%)	536/2162 (24.8%)	0.84 (0.75, 0.94)
Alpha blockers			
No	975/3253 (30.0%)	864/3255 (26.5%)	0.86 (0.79, 0.95)
Yes	18/60 (30.0%)	21/64 (32.8%)	1.03 (0.55, 1.93)
Calcium channel blockers			
No	838/2783 (30.1%)	731/2784 (26.3%)	0.85 (0.77, 0.94)
Yes	155/530 (29.2%)	154/535 (28.8%)	0.95 (0.76, 1.18)
Diuretics			
No diuretics	249/1304 (19.1%)	240/1344 (17.9%)	0.93 (0.78, 1.11)
Loop diuretics	701/1855 (37.8%)	609/1806 (33.7%)	0.86 (0.77, 0.96)
Other diuretics	43/154 (27.9%)	36/169 (21.3%)	0.75 (0.48, 1.16)

*analysis based on PH model containing treatment, subgroup, treatment by subgroup interaction, stratified by region

1.12. Conclusions

EPHESUS had two primary efficacy endpoints – all cause mortality and CV mortality/hospitalization. For all cause mortality, the incidence rate in the eplerenone group was statistically significantly lower than in the placebo group ($p = 0.008$). Most of the deaths were CV deaths. The risk reduction of CV death was 17% (95% CI: 6% - 28%) and was very similar to the risk reduction of 15% (95% CI: 4% - 25%) in all-cause mortality. There was no evidence that eplerenone reduced the incidence of non-CV death (Table 1.5, page 23).

The eplerenone group seemed to have a statistically significantly lower incidence rate of CV mortality/hospitalization than the placebo group ($p = 0.002$). The events contributing to CV mortality/hospitalization, deaths during hospitalizations, nonfatal events causing or prolonging hospitalization all seemed to show a trend supporting the potential benefit of eplerenone on CV mortality/hospitalization. However, it should be noted that the sponsor's definition of CV hospitalization was established in the late stage of the trial (close to the trial end). It is not clear whether such modification was ever influenced by the examination of the interim data by the DSMB. In addition, the quality of the hospitalization data is questionable in that some patients in both treatment groups had missing dates of hospitalization which were then imputed according to some kind of pre-determined algorithm (according to the sponsor's response to the reviewer's question) applied to both treatment groups, though the two treatment groups had similar distributions on time to follow-up for patients who survived and were not hospitalized for any CV reason.

Eplerenone also seemed to reduce the incidence of CV mortality/nonfatal AMI (nominal $p = 0.009$) -- the added secondary endpoints during the trial, and possibly all-cause mortality/hospitalization (nominal $p = 0.016$) – an original listed secondary endpoint. The CV mortality/nonfatal AMI was added as a secondary endpoint in a protocol amendment (late stage of the trial) and two of the original listed secondary endpoints were removed. It is not clear whether removing or adding in the late stage of the trial was ever influenced by the examination of the interim data by the DSMB. In addition, there was no prespecified statistical decision rule for the secondary endpoints. If the influence did occur, then the nominal p-values will be difficult to interpret.

For the additional endpoints, there was also no statistical significance criterion pre-specified in the protocol. Eplerenone appeared to improve the NYHA status (nominal p-value < 0.001) but it should be interpreted in the context with other related endpoints. There was no evidence that eplerenone has a beneficial effect on any of other additional endpoints including quality of life.

Numerically, the eplerenone effects on the primary endpoints in US/Canada appeared to be smaller than other regions but did not appear to be an outlier. This was driven by the apparent detrimental mortality effect in Canada. Numerically, eplerenone seemed to have a favorable effect on the two primary endpoints in US. The differences in hospitalization as the first event between eplerenone and placebo were very small (Table 1.14.1, page 31). So the favorable trend in the mortality/hospitalization composite endpoints in US appeared to be mostly attributed to the eplerenone benefit on CV mortality.

There was no evidence of large inconsistency in the eplerenone effect across subgroups, except in small subgroups.

APPEARS THIS WAY
ON ORIGINAL

2. RALES

This was a randomized, double-blind, placebo-controlled, parallel group, multinational trial to evaluate the safety and efficacy of spironolactone 25 mg QD or every other day or 50 mg QD administered in addition to standard treatment (loop diuretic, ACE-inhibitor, if tolerated, and ±digoxin) compared with placebo in patients with severe heart failure (HF; New York Heart Association [NYHA] III or IV). After randomization, patients returned for evaluation every four weeks for the first three months, every three months for the remainder of the first year, and every six months thereafter. Following a one- to four-week stabilization period, patients who were tolerant of the initial dosage regimen continued on the initial dose (one 25 mg tablet of spironolactone or placebo QD). Patients who were intolerant of the initial dosage regimen had their dose decreased to one tablet every other day (QOD; spironolactone 25 mg or placebo). Patients who were tolerant of one tablet QD at Week 8 may have had their dose increased to two tablets QD (spironolactone 50 mg or placebo) at the discretion of the investigator.

According to the study report, the study was terminated on 24 August 1998 because of a statistically significant and clinically meaningful reduction in mortality in the spironolactone-treated group compared to the placebo group, as determined by an independent Data and Safety Monitoring Board (DSMB).

2.1. Efficacy Variables

The primary efficacy endpoint was total mortality. Secondary endpoints included (1) cardiac mortality; (2) incidence of cardiac mortality plus hospitalization for cardiac reasons, defined as hospitalizations for HF aggravation (definitive/nonspecific), atrial flutter/fibrillation or supraventricular tachycardia, ventricular arrhythmias, myocardial infarction, angina (stable or unstable), and stroke; (3) incidence of hospitalization for cardiac reasons; (4) changes in NYHA functional classification; and (5) Quality of Life (for sites in Brazil and Canada only). A Sodium Retention substudy was done for sites in Brazil only. Safety was assessed by adverse events and by results of physical examinations and clinical laboratory tests.

2.2. Sample Size Planning

The extensive sample size plan provided in the original protocol (July 10, 1995) was modified in the protocol amendment #7, March 22, 1996. According to the amended plan, mortality rates are based on experience from SOLVD and CONCENSUS. The control group for the RALES trial is primarily characterized as patients currently taking ACE inhibitors, and having NYHA class III or IV. The active treatment groups for both the SOLVD and CONSENSUS trials were assigned enalapril. Sample size calculations are based on the following assumptions.

1. Conditional mortality rates for the control group are based on the following table of predicted conditional mortality rate for RALES.

	SOLVD/CONSENSUS		Enrollment in RALES in Class III/IV				
Month	III	IV	100/0	75/25	50/50	25/75	0/100
3	21	57	21	30	39	48	57
6	14	38	14	20	26	32	38
12	14	35	14	19	25	30	35
24	14	32	14	18	23	28	32
36	14	25	14	17	20	22	25

2. The treatment effect sizes are 20.0, 22.5, and 25.0 percent so that the conditional mortality rates will be 80.0, 77.5, and 75.0 percent of those derived in the above table.

3. The total length of the trial will be 57 months (from March 1995 through December 1999).

4. Recruitment will take place over 21 months (March 1995 through December 1996). Recruitment usually takes some time before patients are being enrolled at the maximum rate. At the time of this amendment, the actual recruitment rates were observed for 8 months, and these observed rates were used in the calculations. In terms of percentage of the maximum recruitment rate, the assumed percent of patients recruited each month is as follows: 5%, 3%, 8%, 39% for months 1-4 respectively, 50% for months 5-10, 100% for months 11-19, and 50% for months 20 and 21 respectively.

5. Noncompliance is assumed to be about 10% the first year, 5% each additional year.

6. Dropin is assumed to be about 5% per year.

7. Loss to follow-up for mortality will be essentially nonexistent.

8. Patients allocated to active treatment and control in equal proportions.

9. The 1-sided significance level is 0.0225 or 2-sided 0.045. This reduction in the nominal 0.05 significance level is to adjust for interim analyses if a conservative boundary, such as the O'Brien-Fleming, is used.

10. The estimates are based on methods developed by Lakatos' approach.

The following table presents the number of deaths and corresponding sample size needed to detect various treatment effects and proportions of patients in NYHA Class IV.

Total sample size for RALES

Treatment Effect	% in Class IV	Deaths	Patients
20.0%	25	1037	2092
20.0%	50	936	1606
20.0%	75	836	1286
20.0%	100	738	1036
22.5%	25	800	1631
22.5%	50	723	1253
22.5%	75	648	1006
22.5%	100	573	812
25.0%	25	632	1304
25.0%	50	572	1002
25.0%	75	514	806
25.0%	100	456	652

Note that the number of deaths required depends on proportion of patients in Class IV. Since this trial is designed to end in December 1999 rather than after a fixed number of deaths, to have adequate power, this proportion.

2.3. Interim Analysis Plan

The extensive interim analysis plan provided in the original protocol was deleted in the protocol amendment, March 22, 1996. According to the amendment, there will be no interim analyses performed by the sponsor. An external Data and Safety Monitoring Board will meet regularly to review safety and efficacy data. They will establish rules for interim analyses and potential early termination. Per the reviewer's request, the sponsor provided the detailed statistical monitoring plan. Statistical monitoring of accruing data from RALES will have three components: efficacy, safety, and futility. The DSMB will interpret the statistical calculations in the light of the totality of data from the trial as well as information available external to the trial.

Efficacy RALES will use a group sequential monitoring plan for formal assessment of efficacy of spironalactone. The first interim analysis for efficacy will occur at the DSMB meeting to be held during the summer of 1996, that is, roughly 18 months after the start of recruitment. A formal analysis for efficacy will be performed at each subsequent DSMB meeting. The cumulative α spent for efficacy will be calculated using a Lan-DeMets α-spending function with an upper-tail Type I error of 2.5%. The O'Brien-Fleming spending function will be used. The

last interim analysis will be held in the spring of 1999. Calculation of the cumulative α spent at each interim analysis and at the final analysis requires computation of information time at each interim analysis. The precise information time cannot be known during the course of a trial that uses time-to-event as the outcome measure; instead the information time at each interim analysis must be estimated to calculate appropriate boundaries. Prior to the first interim analysis, —— will prepare a formal analytic plan describing in detail the calculations to be used to construct the monitoring boundaries. The computations for group sequential monitoring of mortality and for calculation of indices of futility will be based on Lakatos' method that uses Markov models to project event rates. At the time of each interim analysis, data from the literature and from the trial itself will be used to project the total mortality rate for the remainder of the trial. The projected total information, and hence the sequential boundaries and the amount of α "spent," will be recalculated at each interim analysis.
The following table shows the dates of the planned meetings along with an example of projected values for information time at each of the planned meetings, the critical z-value for declaring significant benefit at each of the meetings, and the cumulative α used.

Projected cumulatve α spent at each interim analysis - example

Date of meeting	Projected information time	Projected critical z-value	Projected cumulative α spent
Mar '96	-	-	0
Aug '96	.20	4.89	0.00000
Mar '97	.30	3.93	0.00004
Aug '97	.40	3.37	0.00039
Mar '98	.55	2.82	0.0025
Aug '98	.65	2.60	0.0054
Mar '99	.80	2.31	0.012
Dec '99	1.00	2.02	0.025

If the DSMB opts to recommend continuation of the trial even if the formal boundary is crossed, then the amount of α allocated to the interim analysis at that meeting will not have been "spent" and will be applied to the subsequent interim analyses. The DSMB shall not terminate the trial to declare efficacy unless the results of the trial cross the formal boundary for efficacy.
Safety No formal boundary will be set for detection of adverse effects of spironalactone. Instead, the DSMB will use its collective judgment to recommend early termination if the data suggest a net adverse effect of therapy.
Futility If the DSMB so requests, — will review calculations concerning the likelihood that the study has the power to detect an effect of spironalactone consistent with the observed trends. To that end, the DSMB will be presented confidence intervals showing the minimal true effectiveness consistent with the current data and graphs of conditional power under a variety of projected reasonable trends. If the DSMB judges that the probability that the trial will show efficacy is unacceptably low, it may recommend early termination of the trial.

So, if the trial failed to stop in the interim analysis, the critical z value required to establish that treatment with spironolactone in the final analysis was efficacious was 2.02, corresponding to a p-value of 0.043. At the fifth planned interim analysis, the observed effect of spironolactone on the risk of death from all causes exceeded the prespecified critical z value of 2.60 (corresponding to a nominal α-value of 0.0047). Hence, the trial was stopped on 24 August 1998 at the recommendation of the DSMB.

2.4. Statistical Methods

All patients randomized to study medication were to be followed for deaths and hospitalizations for the duration of the trial and were to be included in the Intent-to-Treat cohort. Efficacy analyses were done only for randomized (intent-to-treat) patients. The logrank statistic was to be used to compare mortality between the active and control groups. Kaplan-Meier estimates of mortality were to be presented.

A secondary efficacy measurement for this study is cardiac mortality. In addition, combined endpoints of cardiac mortality and hospitalization, and of hospitalization alone, for HF aggravation (definitive/nonspecific), atrial flutter/fibrillation or supraventricular tachycardia, ventricular arrhythmias, myocardial infarction, angina (stable or unstable), and stroke are to be assessed using a log-rank statistic.

Quality of Life was a substudy done at sites in Canada and Brazil. Differences between groups in Quality of Life were to be analyzed with multivariate analysis of variance (MANOVA) using the subscales as the dependent variables. If the overall MANOVA test was significant, follow-up univariate analysis was to be performed on each subscale. Changes from baseline scores were compared between groups using non-directional independent groups t-tests. An alpha level of 0.05 was considered to be statistically significant.

Changes in NYHA functional classification were to be compared.

2.5. Subgroup Analyses

Subgroup analyses of cardiac mortality and morbidity were also to be performed. These subgroups were to be analyzed according to baseline: EF, etiology of HF, creatinine levels, patient age, ACE-inhibitor type and dose, digoxin use, gender, NYHA class, history of cardiovascular disease other than HF, presence of diabetes, potassium levels.

2.6. Study Patient Information

A total of 1658 (99.7%) of the 1663 randomized patients received at least one dose of study medication: 819 (99.6%) spironolactone patients and 839 (99.8%) placebo patients. Three patients who were randomized to the spironolactone group (patients 0031, 3844, and 4317) and two patients who were randomized to the placebo group (patients 2301 and 2801) did not receive study medication.

Table 2.1. Disposition of ITT patients
[*Source: Sponsor's Table 2.1*]

	Placebo (N=841)	Spironolactone (N=822)
Patients with at least one dose	839 (99.8%)	819 (99.6%)
Alive at end of study	455 (54.1%)	538 (65.5%)
Not on study medication at end of study	100 (11.9%)	114 (13.9%)
Reason for stopping study medication		
Adverse sign or symptom	22 (2.6%)	36 (4.4%)
Noncompliance	52 (6.2%)	48 (5.8%)
Pre-existing violation	3 (0.4%)	3 (0.4%)
Treatment failure	14 (1.7%)	11 (1.3%)
Unknown	9 (1.1%)	16 (1.9%)
On study medication at end of study	337 (40.1%)	411 (50.0%)
Unknown	18 (2.1%)	13 (1.6%)
Dead at end of study	386 (45.9%)	284 (34.5%)
Died while not on study medication	111 (13.2%)	110 (13.4%)
Reason for stopping study medication		
Adverse sign or symptom	20 (2.4%)	27 (3.3%)
Noncompliance	24 (2.9%)	23 (2.8%)
Pre-existing violation	3 (0.4%)	2 (0.2%)
Treatment failure	6 (0.7%)	4 (0.5%)
Unknown	58 (6.9%)	54 (6.6%)
Died while on study medication	275 (32.7%)	172 (20.9%)
Unknown	0	2 (0.2%)
Heart transplants	11 (1.3%)	8 (1.0%)

2.7. Demographic and Baseline Characteristics

The two treatment groups appeared to be comparable with respect to demographic and baseline characteristics and medical history, as seen in Table 2.2.

Table 2.2. Demograhics and baseline characteristics and medical history
[*Source: Tables 4-7 of the study report*]

	Placebo (N=841)	Spironolactone (N=822)	p-value
Race			0.73
Caucasian	728 (86.6%)	712 (86.6%)	
Black	64 (7.6%)	56 (6.8%)	
Oriental	17 (2.0%)	15 (1.8%)	
Other	32 (3.8%)	39 (4.7%)	
Gender			0.91
Female	227 (27.0%)	219 (26.6%)	
Male	614 (73.0%)	603 (73.4%)	
Age			0.90
< 65	343 (40.8%)	333 (40.5%)	
>= 65	498 (59.2%)	489 (59.5%)	
NYHA functional class			0.34
Class I and II	3 (0.4%)	4 (0.5%)	
Class III	581 (69.1%)	592 (72.0%)	
Class IV	257 (30.6%)	226 (27.5%)	
Ejection fraction (%)			0.22
Mean (sd)	25.2 (6.8)	25.6 (6.7)	
Mdian	25.0	26.0	
Range	4 -50	5 - 45	
Etiology of heart failure			0.59
Ischemic	453 (53.9%)	455 (55.4%)	
Non-ischemic	387 (46.0%)	367 (44.6%)	
Systolic blood pressure (mmHg)			0.23
Mean (sd)	121.6 (19.6)	122.8 (20.6)	
Diastolic blood pressure (mmHg)			0.70
Mean (sd)	74.5 (11.3)	74.7 (11.9)	
Heart rate (bpm)			0.74
Mean (sd)	81.0 (14.5)	80.8 (13.86)	
Weight (kg)			0.28
Mean (sd)	71.5 (15.7)	70.7 (14.1)	
Abnormality/disease			
None	119 (14.1%)	131 (15.9%)	
Neutrological	158 (18.8%)	139 (16.9%)	
Cardiovascular	569 (67.7%)	538 (65.5%)	
Respiratory	236 (28.1%)	246 (29.9%)	
Gastrointestinal	253 (30.1%)	233 (28.3%)	
Urogenital	174 (20.7%)	192 (23.4%)	
Musculoskeletal	189 (22.5%)	178 (21.7%)	
Dermatological	60 (7.1%)	68 (8.3%)	
Endocrine	242 (28.8%)	231 (28.1%)	
Hematological	150 (17.8%)	123 (15.0%)	
Hepatic	35 (4.2%)	33 (4.0%)	
reticuloendothelial	16 (1.9%)	17 (2.1%)	

2.8. Efficacy Results

2.8.1. Primary Efficacy Endpoint – Total Mortality

A total of 1658 (99.7%) of the 1663 randomized patients received at least one dose of study medication: 819 (99.6%) spironolactone patients and 839 (99.8%) placebo patients. According to the study report, at the end of the study, a total of 993 patients (538 [65.5%] spironolactone vs 455 [54.1%] placebo) were alive and 670 (284 [34.5%] spironolactone vs 386 [45.9%] placebo) had died. This difference was statistically significant in favor of spironolactone (log-rank $p < 0.001$).

Based on the data base submitted to the EDR by the sponsor, the reviewer was able to confirm the number of deaths in each group but found that the dates of death were missing in eight deaths. If these deaths were excluded, the log-rank test gave a p-value < 0.0001. In response to the reviewer's query, the sponsor clarified that some of the information cannot be obtained from the data base they provided to the EDR. Their analysis was based on a derived data set, which incorporated the data they provided to the EDR as well as additional information based on pre-specified imputation rules and data from MedWatch DER narratives or information from the investigator that they sent to the adjudication committee. The following table summaries the sponsor's clarification on the missing information.

Table 2.3. Supplementary information on mortality

Patient #	Date of death	Date of last follow-up	Cause of death
31	02OCT97		Noncardiovascular death
637	15May98 (a)		Unknown
859	15APR97 (a)		Unknown
880	30JUN97 (b)		Progression of CHF
973	07OCT97 (b)		Unknown
2301	25MAY97		Noncardiovascular death
2801	22SEP96		Sudden cardiac death
3844	05JAN96		Myocardial infarction
50	ALIVE	17SEP98	
53	ALIVE	24SEP98	
1901	ALIVE	24AUG98	
4317	ALIVE	25SEP98	

(a) Data include only month and year. Day 15 of month was imputed per convention
(b) Data were not in the clinical data base and were hard coded into a derived data set, based on other information

Based on the derived data base provided by the sponsor, the results of the time to event analyses are summarized in Table 2.4. The two treatment groups had similar distributions on time to follow up for the survivors (Table 2.5). Spironolactone yielded a statistically significant reduction in all cause deaths and cardiac deaths which accounted for 81% of total deaths ($p < 0.0001$ for both endpoints). Numerically, spironolactone appeared to reduce other deaths, though not statistically significant ($p = 0.13$).

Table 2.4. Total Mortality
[*Source: Reviewer's analysis of the derived data base provided by the sponsor*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Total mortality	386 (45.9%)	284 (34.5%)	0.70 (0.60, 0.82)	< 0.0001
Cardiac mortality	314 (37.3%)	226 (27.5%)	0.69 (0.58, 0.82)	< 0.0001
Sudden death	110 (13.1%)	82 (10.0%)		
Myocardial infarction	15 (1.8%)	17 (2.1%)		
Progression of CHF	189 (22.5%)	127 (15.5%)		
Other mortality	72 (8.6%)	58 (7.1%)	0.77 (0.54, 1.08)	0.13
Stroke	11 (1.3%)	8 (1.0%)		
Other cardiovascular death	13 (1.5%)	12 (1.5%)		
Noncardiovascular death	41 (4.9%)	29 (3.5%)		
Unknown	7 (0.8%)	9 (1.1%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Table 2.5. Summary statistics on time (in days) to follow-up for patients who survived

	N	mean	max	99%	95%	75%	50%	25%	5%	1%	min
Spiro	538	845	1252	1221	1155	987	863	720	539	30	1
plbo	455	843	1242	1221	1157	994	859	718	541	57	1

Figure 2.1. Survival probability plot for all cause mortality
[*Source: Sponsor's figure, confirmed by reviewer's analysis*]

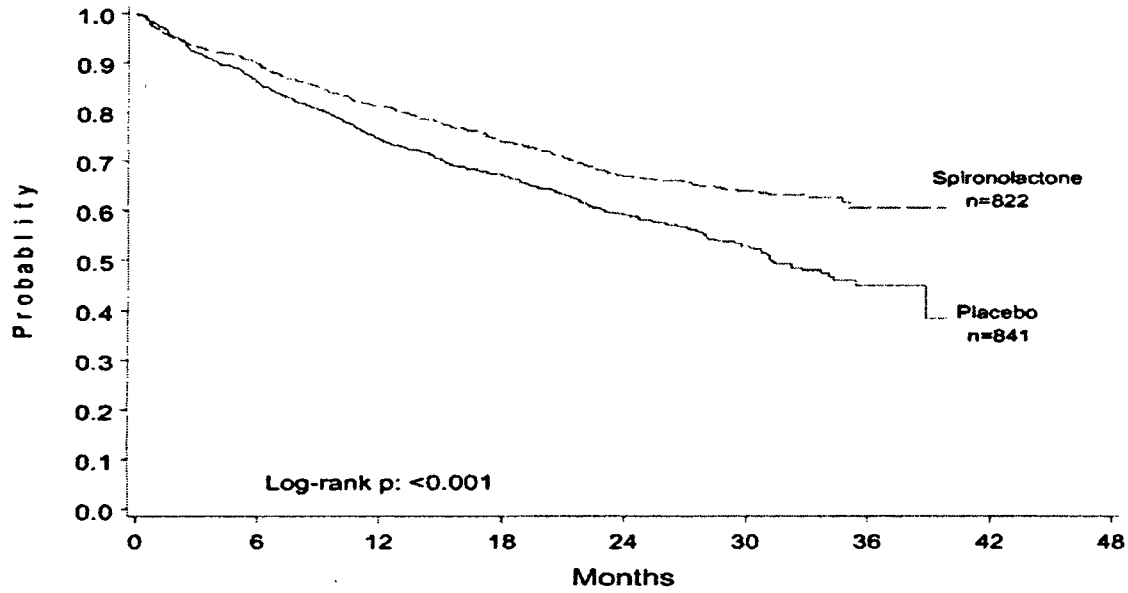
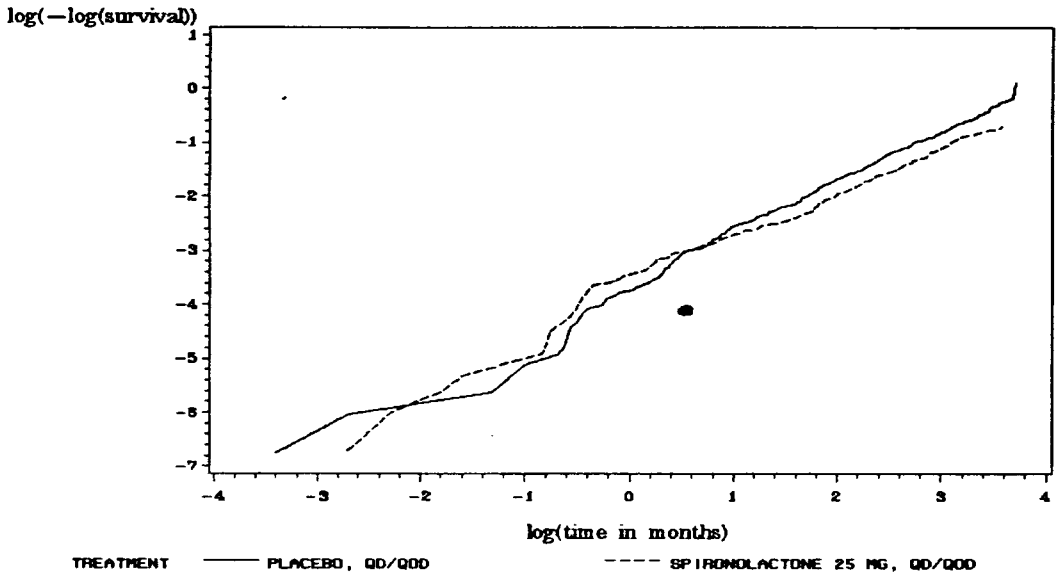


Figure 2.2. log minus log survival probability plot for all cause mortality
[*Source: Reviewer's analysis*]



2.8.2. Secondary Efficacy Endpoints

There was no pre-specified statistical decision rule for assessing statistical significance of each secondary endpoint. However, the nominal p-values for cardiac mortality, cardiac mortality or hospitalization, non-fatal hospitalization, and change of NYHA class are all very small, as summarized below.

Cardiac death

As shown in Table 2.5, cardiac deaths comprised 81% of the total mortality. The spironolactone group had a 31% reduction in the risk of cardiac death compared to the placebo group, which was statistically significant (logrank p-value < 0.0001, 95% CI: 18% - 42%).

Cardiac death or hospitalization

Spironolactone also yielded a statistically significant reduction in cardiac death or hospitalization (Table 2.6) and nonfatal hospitalizations (Table 2.7).

Table 2.6. Cardiac death or hospitalization
[*Source: Reviewer's analysis of the derived data base provided by the sponsor*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Cardiac mortality or hospitalization	498 (59.2%)	379 (46.1%)	0.68 (0.59, 0.78)	< .0001
Decomposition of the composite endpoint – cardiac mortality or hospitalization				
Cardiac mortality	314 (37.3%)	226 (27.5%)	0.69 (0.58, 0.82)	< .0001
Sudden death	110 (13.1%)	82 (10.0%)		
Myocardial infarction	15 (1.8%)	17 (2.1%)		
Progression of CHF	189 (22.5%)	127 (15.5%)		
Nonfatal hospitalization	184 (21.9%)	153 (18.6%)		
HF aggravation (definitive)	138 (16.4%)	108 (13.1%)		
HF aggravation (non-specific)	12 (1.4%)	5 (0.6%)		
Ventricular arrhythmia	13 (1.5%)	12 (1.5%)		
Myocardial infarction	6 (0.7%)	5 (0.6%)		
Angina (stable/unstable)	15 (1.8%)	15 (1.8%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Table 2.7. Incidence of non-fatal hospitalization
[*Source: Sponsor's Table 9.3; reviewer's analysis produced almost identical results except minor discrepancy marked by @*]

	Placebo N=841	Spironolactone N=822	Risk ratio (95%CI)#	p-value*
Nonfatal hospitalization	481 (57.2%)	421 (51.2%)	0.79 (0.70, 0.90)	0.0005
HF aggravation (definitive)@	289 (34.4%)	209 (25.4%)		
HF aggravation (non-specific)	34 (4.0%)	18 (2.2%)		
AF/AFL or supravent tachy	23 (2.7%)	30 (3.6%)		
Ventricular arrhythmia	24 (2.9%)	23 (2.8%)		
Myocardial infarction	14 (1.7%)	10 (1.2%)		
Angina (stable/unstable)	35 (4.2%)	43 (5.2%)		
Stroke	20 (2.4%)	14 (1.7%)		
Other cardiovascular@	93 (11.1%)	91 (11.1%)		
Non-cardiovascular	233 (27.6%)	223 (27.1%)		

* based on logrank test
# based on Cox proportional hazards model including treatment as the only factor

Change of NYHA Functional Class

Nineteen (10 in the placebo group, 9 in the sprionolactone group) of the 1663 patients did not have final visit NYHA class data. Nonetheless, spironolactone seemed to improve NYHA functional class as shown in the following table.

Table 2.8. Change from baseline to Final Visit in NYHA Functional Class
[*Source: Table 5 of the study report; reviewer's analysis produced almost identical results*]

	Placebo (N=841)	Spironolactone (N=822)	p-value
Baseline NYHA Class III			
N	575	586	
Final NYHA			0.001
I	33 (5.7%)	51 (8.7%)	
II	154 (26.8%)	180 (30.7%)	
III	134 (23.3%)	148 (25.3%)	
IV	14 (2.4%)	21 (3.64%)	
Death	240 (41.7%)	186 (31.7%)	
Worsening	254 (44.2%)	207 (35.3%)	0.002*
No change	134 (23.3%)	148 (25.3%)	
Improvement	187 (32.5%)	231 (39.4%)	
Baseline NYHA Class IV			
N	254	223	
Final NYHA			0.003
I	9 (3.5%)	18 (8.1%)	
II	38 (15.0%)	41 (18.4%)	
III	43 (16.9%)	45 (20.2%)	
IV	19 (7.5%)	21 (9.4%)	
Death	145 (57.1%)	98 (43.9%)	
Worsening	145 (57.1%)	98 (43.9%)	0.005**
No change	19 (7.5%)	21 (9.4%)	
Improvement	90 (35.4%)	104 (46.6%)	

p-value generated from Wilcoxon rank-sum test
* worsening (IV or death at final visit), no change (III at final visit), improvement (I or II at final visit)
** worsening (death at final visit), no change (IV at final visit), improvement (I, II, or III at final visit)

Quality of Life

Quality of life was assessed in a subsample of 88 patients in Brazil and Canada only. Sixty patients had complete data for the six months of follow-up. The sponsor concluded that the spironolactone group had statistically significantly greater improvements in Mental Health (p=0.004) and Mental Composite Summary (p=0.016) subscale scores compared to placebo. In my view, given that there were so many dimensions of scores as in Table 2.9, the three spotty nominal significant treatment differences are not conclusive.

Table 2.9. Changes from baseline to Month 3 and Month 6 in SF-36 scores (mean±se)

[*Source: Table 6 of study report*]

	Baseline		Month 3		Month 6	
	Spironolactone (n=32)	Placebo (n=28)	Spironolactone (n=32)	Placebo (n=28)	Spironolactone (n=32)	Placebo (n=28)
SF-36 Dimension						
Physical Functioning	27.0±3.7	33.3±3.6	7.9±3.6*	12.1±4.0*	11.4±3.8*	13.5±4.4*
Role Limitations - Physical	14.1±3.7	23.2±4.0	23.3±7.4*	16.4±7.3*	14.8±5.7*	18.5±7.3*
Bodily Pain	57.7±5.1	65.5±5.1	19.6±5.5*	8.9±5.0*	15.9±5.4*	8.4±6.3
General Health	38.4±3.9	48.2±3.7	9.7±3.7*	9.3±3.6*	12.0±4.0*	10.4±3.8*
Vitality	28.9±4.1	38.0±3.8	16.7±4.4*	18.2±4.7*	19.0±4.5*	16.5±4.4*
Role Limitations - Emotional	25.0±6.2	25.9±5.4	37.8±8.4*	24.4±9.4*	24.0±7.1*	35.8±8.9*
Social Functioning	45.7±5.0	54.6±4.9	24.6±6.1*	18.1±6.1*	23.1±5.7*	18.1±6.1*
Mental Health	44.3±4.3	56.2±4.2	19.9±3.9*†	3.1±4.0	17.5±4.1*†	4.5±5.0
SF-36 Summary Scores						
Physical Composite Summary	32.5±1.1	35.5±1.2	3.0±1.5*	4.4±1.2*	3.9±1.6*	4.4±1.5*
Mental Composite Summary	35.4±2.1	39.5±1.8	13.2±2.2*†	5.3±2.3*	10.3±2.3*	4.5±2.7*

* Statistically significant ($p<0.05$) within group change from baseline
† Statistically significant ($p<0.05$) between group comparison of change from baseline.

2.9. Analysis by Region and by Subgroup

Analysis by Region

The spironolactone effect on all cause mortality appeared to be consistent across geographical regions. Contributing only 3% patients, US showed a smaller effect than West Europe that contributed 64% patients.

Table 2.10. All cause mortality by geographical region
[*Source: Reviewer's analysis*]

	Placebo (N=841)	Eplerenone (N=822)	Hazard ratio* (95% CI)
US & Canada	27/58 (46.6%)	23/56 (41.1%)	0.84 (0.48, 1.46)
US	11/26 (42.3%)	9/24 (37.5%)	0.82 (0.39, 1.97)
Western Europe	251/540 (46.5%)	183/526 (34.8%)	0.70 (0.58, 0.85)
Latin America	97/217 (44.7%)	69/216 (31.9%)	0.65 (0.48, 0.88)
Rest of World	11/26 (42.3%)	9/24 (37.5%)	0.98 (0.40, 2.37)

* analysis based on PH model containing treatment variable only

Analysis by Subgroup and Baseline Covariates

The spironolactone effect on all cause mortality appeared to be consistent across subgroups, except possibly in small subgroups.

Table 2.11. All cause mortality by subgroups (RALES)
[*Source: Reviewer's analysis*]

	Placebo (N=841)	Spironolatone (N=822)	Hazard ratio* (95% CI)
Race			
Black	27/64 (42.2%)	22/56 (39.3%)	0.92 (0.53, 1.62)
Caucasian	339/728 (46.6%)	243/712 (34.1%)	0.68 (0.58, 0.80)
Asian	9/17 (52.9%)	7/15 (46.7%)	0.78 (0.29, 2.10)
Other	11/32 (34.4%)	12/39 (30.8%)	0.93 (0.41, 2.10)
Gender			
Female	95/227 (41.9%)	68/219 (31.1%)	0.72 (0.53, 0.98)
Male	291/614 (47.4%)	216/603 (35.8%)	0.70 (0.59, 0.84)
Age			
< 65	126/343 (36.7%)	100/333 (30.0%)	0.80 (0.62, 1.05)
65 +	260/498 (52.2%)	184/489 (37.6%)	0.66 (0.55, 0.80)
Etiology of heart failure			
Ischemic	222/453 (49.0%)	171/455 (37.6%)	0.72 (0.59, 0.88)
Non-ischemic	164/387 (42.4%)	113/367 (30.8%)	0.68 (0.54, 0.87)
NYHA			
Class III	240/581 (41.3%)	186/592 (31.4%)	0.72 (0.60, 0.87)
Class IV	145/257 (56.4%)	98/226 (43.4%)	0.72 (0.56, 0.93)
History of cardiovascular disease			
No	121/272 (44.5%)	82/284 (28.9%)	0.58 (0.44, 0.77)
Yes	265/569 (46.6%)	202/538 (37.6%)	0.78 (0.65, 0.94)
History of diabetes			
No	280/636 (44.0%)	211/638 (33.1%)	0.71 (0.59, 0.85)
Yes	106/205 (51.7%)	73/184 (39.7%)	0.71 (0.53, 0.95)
Use of beta blockers			
No	354/753 (47.0%)	270/733 (36.8%)	0.74 (0.63, 0.87)
Yes	32/88 (36.4%)	14/89 (15.7%)	0.39 (0.21, 0.73)
Use of captopril			
No	210/439 (47.8%)	160/443 (36.1%)	0.70 (0.57, 0.86)
Yes	176/402 (43.8%)	124/379 (32.7%)	0.71 (0.56, 0.89)
Use of ACE inhibitors			
No	19/37 (51.4%)	13/31 (41.9%)	0.74 (0.37, 1.51)
Yes	367/804 (45.7%)	271/791 (34.3%)	0.71 (0.60, 0.83)
Use of calcium channel blockers			
No	350/753 (46.5%)	258/736 (35.1%)	0.71 (0.61, 0.83)
Yes	36/88 (40.9%)	26/86 (30.2%)	0.68 (0.41, 1.13)

* analysis based on PH model containing treatment variable only

2.10. Conclusion

Spironolactone yielded a statistically significant reduction (30% reduction with 95% CI of 18%-40%) in all cause mortality – the primary endpoint (nominal $p < 0.0001$ versus nominal significance level of 0.0047, because of interim termination of the trial for survival benefit). Though most of the deaths were cardiac related, the reduction of other mortality with spironolactone numerically appeared to be substantial.

The spironolactone effect on all cause mortality appeared to be consistent across geographical regions. Contributing only 3% patients, US showed a smaller effect than West Europe that contributed 64% patients. There was no evidence of substantial inconsistency in the spironolactone effect on all cause mortality across subgroups, except possibly in small subgroups.

There was no statistical decision rule pre-specified for assessing the statistical significance of each secondary endpoint. However, the nominal p-values for cardiac death and cardiac death/hospitalization were very small and statistically significant (Table 2.6, p. 48 and Table 2.8, page 49). Non-fatal hospitalization appeared to be favorably affected by spironolactone but the adjudicated non-cardiovascular hospitalization did not appear to be affected (Table 2.7, page 48). Spironolactone appeared to improve NYHA class. There was no conclusive evidence for the potential quality of life benefit with spironolactone.

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