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dose escalation, dose reduction, or discontinuation for high potassium levels required.

- Note the elimination half-life of 4-6 hours compared to those for the active metabolites of spironolactone (10-35 hours). In the hypertension trials eplerenone QD and BID appeared to produce similar patterns of reductions in blood pressure (BP) over 24-hours as measured by ambulatory BP monitoring (ABPM). However, at a total daily dose of 100 mg, eplerenone 50 mg BID produced greater trough cuff (4/3 mm Hg) and ABPM (2/1 mm Hg) BP reductions than 100 mg QD. The BP reductions with 25 mg BID and 50 mg QD were similar. The comparability of QD and BID dosing of eplerenone for hypertension needs further study. The heart failure studies of eplerenone used QD dosing exclusively, so little information is provided by them regarding optimal dosing interval in HF.
- Eplerenone clearance is reduced in renal and hepatic impairment and in the elderly. Because HF patients typically have one or more of these features, one might expect that the drug exposures attained in the heart failure trials would be greater than the drug exposures attained in the hypertension trials for the same administered doses. The PK studies in HF patients described below confirm this expectation.

2. Summary of Pharmacokinetics in Heart Failure Patients

The two studies targeting PK in HF patients were the following:

- Study 058 was a phase 1, single-center, open-label, single- and multiple-dose PK study in 8 HF patients and 8 matched (gender, age, weight) controls. The dosage was 50 mg given singly and daily for 5 days. The HF patients were class II-IV with LVEF ≤ 40 with clinical evidence of HF. After single dosing C_{max} and AUC were 7% and 29% higher respectively than in the matched controls. After multiple dosing C_{max} and AUC were 30% and 38% higher. None of these differences was statistically significant.
- A population PK substudy was conducted as part of EPHEBUS. Blood samples were collected prior to and 1 hour after the first dose and about 1 hour apart at week 1 and month 6. The dosage in EPHEBUS was 25 mg initially increased to 50 mg daily at one month if toxicity was acceptable. While 258 patients were enrolled in this substudy, only data from 113 patients and 324 levels were used. Data were excluded for various reasons including missing sample times, insufficient quantities, aberrant delays in drug absorption. A one-compartment model with first order absorption was used. The effects of various covariates were tested, but only SGOT appeared to have some influence on the model and its effect was small. The model provided an estimate of 4.91 L/hr for CL/F. This compares to 5.36 L/hr in Study 058, 7.33 L/hr in hypertensive patients, 6.60 L/hr

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in the elderly, and 9.63 L/hr in healthy young volunteers. The sponsor also notes that the ages of the HF patients were older than those of the hypertensive patients.

B. Pharmacodynamics

For a complete review, see the biopharmaceutics review of the NDA. The material presented here is reproduced from the sponsor's summary and the hypertension NDA and is included here as background to the review of the clinical data contained in the sNDA. The clinical reviewer did not analyze the primary data from the sNDA for the following summary.

1. Pertinent Pharmacodynamics from the Hypertension Studies

For blood pressure (BP) reduction eplerenone shows a substantial effect within two weeks and maximal or near maximal effect by four weeks of repeated daily dosing. The BP effects appear to be maintained at least for one year and there do not appear to be adverse withdrawal effects.

The dose-response of eplerenone for BP reduction is somewhat unclear. One pivotal study (010) showed greater reductions with eplerenone 400 mg daily vs. 100 mg daily and lower dosages while the second (049) showed no difference between 100 mg daily and 200 mg daily. Similarly, whether eplerenone is equally effective for BP reduction with once daily vs. twice daily dosing is also somewhat unclear. Only one trial (010) addressed QD vs. BID dosing. While the ABPM do not show clear differences in 24 hour control between QD and BID dosing regimens and most dosages did not show differences in trough cuff seated BP, reductions in trough cuff seated BP were significantly lower with 50 mg BID vs. 100 mg QD.

Because one of the studies in this sNDA tested the similar aldosterone antagonist spironolactone, it is relevant to compare eplerenone and spironolactone. Two of the hypertension trials compared eplerenone and spironolactone. In study 010 in essential hypertension, spironolactone 50 mg BID was similar to eplerenone 200 mg BID and 400 mg QD in blood pressure reductions. In study 018 in primary hyperaldosteronism, spironolactone 75-225 mg QD was clearly more efficacious in controlling blood pressure than eplerenone 100-300 mg (mean trough seated cuff DBP reduction -12.5 vs. -5.6, SBP reduction -27.0 vs. -9.9). Spironolactone also produced substantially more sex-hormone related AEs and hyperkalemia. These studies suggest that spironolactone is significantly more potent than eplerenone for BP reduction. Study 010 suggests a four-fold decreased relative potency of eplerenone compared to spironolactone.

For eplerenone effects upon RAAS hormones in the hypertension trials, see the next section.

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2. Pharmacodynamics Pertinent to Dose Selection

The sponsor selected the dosage for the pivotal study (EPHESUS) based on eplerenone's effects upon renin-angiotensin-aldosterone system (RAAS) hormones and BNP: "Dose selection in this study was based on the results of the phase 2 eplerenone HF and hypertension trials, in which eplerenone 25 to 50 mg QD increased plasma renin and aldosterone levels and lowered plasma BNP levels. Eplerenone 50 mg QD was also determined to be similar to spironolactone 25 mg based upon the effect on BNP, renin, and aldosterone levels in a chronic HF population." The study in a chronic HF population is Study 011. Its results are summarized in Section VI.C.1 below and do suggest that eplerenone 50 mg QD is similar to spironolactone 25 mg in effects upon renin and aldosterone.

RAAS hormone levels were also measured in the two hypertension studies having spironolactone arms. In Study 010 in essential hypertension, changes in serum aldosterone, direct and total renin produced by spironolactone 50 mg BID were intermediate between those produced by eplerenone 100 mg and 400 mg daily. Males appeared to have greater RAAS hormone changes with eplerenone. In Study 018 in primary aldosteronism, the median increases with spironolactone titrated 75-225 mg substantially exceeded (0.8 to 2.8 fold) the increases with eplerenone titrated 100-300 mg. The differences were greater for renin than for aldosterone.

COMMENT: These studies appear consistent with approximately a half potency of eplerenone compared to spironolactone in affecting RAAS hormones. Note that for reducing BP eplerenone appeared to be about one-fourth as potent as spironolactone.

3. Sponsor's Summary of Pharmacodynamics for Heart Failure

The following is extracted from the sponsor's summary of pharmacodynamic effects of eplerenone pertinent to the HF indication:

"Similar to the results in the hypertension trials of eplerenone, evidence of blockade of aldosterone at the mineralocorticoid receptor by eplerenone was obtained in all 3 HF clinical studies. Serum or urinary aldosterone levels increased from baseline compared to placebo in both phase 2 studies and in an EPHESUS substudy. Levels of total and active plasma renin increased from baseline compared to placebo in both phase 2 studies; however, no significant increases from baseline were observed in the EPHESUS substudy."

"Substudies were conducted at selected sites in EPHESUS. Included were the assessments of cardiorenal hormones, cytokines, and collagen markers; vascular compliance; fibrinolytic balance; cardiac remodeling; and heart rate variability (HRV). As expected, eplerenone significantly increased serum aldosterone levels compared to placebo. There were no consistent effects of eplerenone on other cardiorenal hormones

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or on cytokines or collagen markers. In the vascular compliance substudy, eplerenone and placebo each had no effect on vascular compliance (carotid/femoral PWV and carotid/radial PWV). Similar effects of eplerenone and placebo on LVM were observed in the cardiac remodeling substudy, with reductions noted with both treatments. In the HRV substudy, indices of HRV were similarly improved in both placebo and eplerenone patients.

“The available EPHEBUS substudy results did not confirm a mechanism by which aldosterone blockade reduces all cause mortality and CV mortality/hospitalization. The effect on the RAAS was confirmed by the increase in serum aldosterone levels in one of the substudies.”

COMMENT:

- The sponsor is ignoring another mechanism that may affect mortality, in particular sudden death: potassium levels.
- Note the absence of a sponsor comment on the fibrinolytic balance results. Some of the eplerenone hypertension studies also examined fibrinolytic balance. The sponsor concluded from them that eplerenone had no significant clinical effect on fibrinolytic activity compared to enalapril or amlodipine. I interpreted the data as suggesting that eplerenone produced a modest increase in PAI-1 and possibly a slight increase in t-PA. The latter changes could promote thrombosis rather than inhibiting it.

C. Toxicity

The eplerenone hypertension studies provide substantial data on the toxicity of eplerenone in humans. They also left partially unanswered some questions regarding possible adverse effects (AEs). The adverse event information from the hypertension label and from the hypertension NDA are summarized below as background for the additional AE data provided by this sNDA.

1. Pertinent AE Information from the Hypertension Label

In the hypertension trials 3,091 patients were treated with eplerenone. A total of 690 patients were treated for over 6 months and 106 patients were treated for over 1 year. In placebo-controlled studies, the overall rates of adverse events were 47% with eplerenone and 45% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 3% of patients treated with eplerenone and 3% of patients given placebo. The most common reasons for discontinuation of eplerenone were headache, dizziness, angina pectoris/myocardial infarction, and increased GGT. The adverse events that were reported at a rate of at least

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1% of patients and at a higher rate in patients treated with eplerenone in daily doses of 25 to 400 mg versus placebo are shown in the table below.

Table 4: Label Rates (%) of AEs Occurring in Placebo-Controlled Studies in =1% of Hypertensive Patients Treated with Eplerenone (INSPIRA) and at a More Frequent Rate than in Placebo-Treated Patients

	INSPIRA (n=945)	Placebo (n=372)
Metabolic		
Hypercholesterolemia	1	0
Hypertriglyceridemia	1	0
Digestive		
Diarrhea	2	1
Abdominal pain	1	0
Urinary		
Albuminuria	1	0
Respiratory		
Coughing	2	1
Central/Peripheral Nervous System		
Dizziness	3	2
Body as a Whole		
Fatigue	2	1
Influenza-like symptoms	2	1

Note: Adverse events that are too general to be informative or are very common in the treated population are excluded.

The major dose-limiting toxicity of eplerenone, not reflected in the data above because it is uncommon at the dosages recommended for treating hypertension, is hyperkalemia. The hypertension label does include a warning about hyperkalemia. The changes in serum potassium recorded in the placebo-controlled, fixed-dose, hypertension studies are shown in the following table.

Table 5: Label Changes in Serum Potassium in the Placebo-Controlled, Fixed-Dose Eplerenone Hypertension Studies

Daily dosage	N	Mean change meq/L	% > 5.5 meq/L
Placebo	194	0	1
25	97	0.08	0
50	245	0.14	0
100	193	0.09	1
200	139	0.19	1
400	104	0.36	8.7

Patients with both type 2 diabetes and micro-albuminuria are at increased risk of developing persistent hyperkalemia. In a study in such patients taking eplerenone 200 mg, the frequencies of maximum serum potassium levels >5.5 meq/L were 33% with

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eplerenone given alone and 38% when eplerenone was given with enalapril. Rates of hyperkalemia increased with decreasing renal function. In all hypertension studies serum potassium elevations >5.5 meq/L were observed in 10.4% of patients treated with eplerenone with baseline calculated creatinine clearance <70 mL/min, 5.6% of patients with baseline creatinine clearance of 70 to 100 mL/min, and 2.6% of patients with baseline creatinine clearance of >100 mL/min.

Gynecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo. The rates of these sex hormone related adverse events are shown in the table below. The rates increased slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in active control arms of the studies with eplerenone.

Table 6: Label Rates of Sex Hormone Related AEs with Eplerenone in the Hypertension Studies

	Rates in males			Rates in females
	Gyneco- mastia	Masto- dynia	Either	Abnormal vaginal bleeding
All controlled studies	0.5%	0.5%	1.0%	0.6%
Controlled studies lasting ≥6 months	0.7%	1.3%	1.6%	0.8%
Open label, long term study	1.0%	0.3%	1.0%	2.1%

2. Unanswered AE Questions from the Hypertension NDA

The hypertension trials did not provide sufficient data to answer all questions regarding the AE profile of eplerenone. (This is typical: The NDA drug data bases typically provide enough data about common and major toxicities but aren't large enough to provide information about rare toxicities or all of the details about uncommon toxicities.) The following are some of the unanswered AE questions from the eplerenone hypertension NDA:

- Eplerenone does appear to cause gynecomastia in males and it may also cause vaginal bleeding in females as noted in the table from the label above. The rates at which it does so appear to be lower than those with spironolactone, but the extent of the difference is unclear because spironolactone was given at more effective dosages in the two studies in which it was used and compared to eplerenone. Furthermore, gynecomastia is an AE that would be expected to manifest itself only with longer durations of exposure, i.e., six months or more. The durations of exposure in the hypertension trials, 283 patients for 180 days or more and 106 patients for more than 360 days, is not adequate to estimate

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precisely the incidence rates for gynecomastia with extended eplerenone exposure.

- Eplerenone appears to affect TSH levels. The data from the three hypertension studies in which TSH levels were measured are consistent but difficult to interpret: TSH levels rose in eplerenone-treated males and in placebo or enalapril-treated females. Whether these are post-hoc, subgroup spurious results or real differences is not clear. Thyroid AE rates were higher in the open-label eplerenone group but not in the monotherapy groups. Thyroid effects, like sex-hormone AEs, may be delayed. There is an animal model for thyroid dysfunction that supposedly is not active in humans, but small effects with other drugs active in the same animal model (e.g., spironolactone) could have been missed.
- Whether eplerenone causes any increase in cerebrovascular or peripheral vascular thrombotic AEs is not clear. The absolute rates in the hypertension trials were low, e.g., 0.2 to 0.7 percent, but they were nominally higher than in the placebo controls. While a low but real increase in these rates might not negate a mortality benefit in treating HF, it could negate the beneficial effects of lowering blood pressure. There is also a potential mechanism, increase in PAI-1 levels, that provides a biological basis for increased thrombotic rates.

COMMENT: This review scrutinizes the HF studies for information on these three possible AEs.

IV. Description of Clinical Data and Sources

A. Overall Data

The NDA is an electronic submission, although the first three summary volumes were also provided in paper versions. The clinical data sections of the NDA (2. Labeling, 3. Summary, 8. Clinical Data, 11. Case Report Tabulations, and 12. Case Report Forms) were the primary information sources used for this review. These files describe the sponsor's experience with eplerenone in heart failure. The Case Report Tabulations were provided as SAS transfer data sets that were used to confirm the sponsor's statistical analyses and to perform other reviewer-defined analyses relevant both to efficacy and to safety.

The NDA submissions used for this review are summarized in the table below:

Table 7: Reviewer's NDA Submissions Used in Review

Submission Date	Description
11/28/01	Original NDA for hypertension for background
04/04/03	Supplemental NDA SE1-002 for HF post-MI

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Submission Date	Description
05/08/03	Amended financial disclosure for SE1-002
07/16/03	Supplemental data set for SE1-002
08/01/03	120-day safety update

During the review process I asked questions and clarifications from the sponsor regarding the data in the NDA submissions. I used the sponsor's responses in this review. I have filed my questions and the sponsor's responses in the Division File System (DFS).

B. Table Listing the Clinical Trials

As the sponsor describes in the Introduction to the NDA, the primary focus of the NDA is one large, international trial of eplerenone in patients with heart failure (HF) after acute myocardial infarction (MI), "A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Eplerenone in Patients With Heart Failure Following Acute Myocardial Infarction (EPHESUS)." This trial is referenced as EPHESUS throughout this review. The clinical development program for eplerenone in HF also included one independent pharmacokinetic (PK) study 058 in HF, a population PK substudy as part of EPHESUS, and two phase 2 dose-ranging studies in HF patients. The PK study results are summarized above in the Pharmacokinetics section and the two dose-ranging studies, 011 and 402, are summarized below in the trials section along with EPHESUS. In addition, the sponsor has included information on a related trial of spironolactone in HF patients, the Randomized Aldactone Evaluation Study (RALES). While RALES did not use eplerenone and the study population is different (class III-IV HF not limited to post-MI), eplerenone is an analog of spironolactone and the RALES data provide additional evidence regarding the effects of aldosterone receptor blockage in heart failure. The clinical trials are summarized in the table below.

Table 8: Reviewer's Table of the Clinical Trials

#	Description	Reference	Drugs	N	Weeks	Endpoint
011	Dose-ranging in HF	011	E 25-200 S 25 Placebo	321	18	Safety; NYHA class
402	Dose-ranging in HF Japan	402	E 25-100 Placebo	161	12	Safety; NYHA class
035	Phase 3 HF Post-MI	EPHESUS	E 25-50 Placebo	6,632	Mean 69	Mortality
IG5-004	Spironolactone class 3-4 HF	RALES	S 25-50 Placebo	1,663	Mean 93	Mortality

All trials were randomized, double-blind, placebo-controlled, parallel-group studies.

HF = heart failure; MI = myocardial infarction

E = eplerenone; S = spironolactone; dosing is in mg orally once daily

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C. Postmarketing Experience

No post marketing data are available for this submission.

D. Literature Review

For the hypertension NDA review I performed extensive Medline and Embase searches regarding eplerenone and spironolactone. I did not find any pertinent information regarding eplerenone not contained in the NDA. I updated the Medline searches for eplerenone for this NDA and again did not find any pertinent information not contained in the NDA. The results from the spironolactone searches are summarized in the background sections above.

V. Clinical Review Methods

A. How the Review was Conducted

This sNDA submission consists of one large, pivotal study (EPHESUS), another large study (RALES) of a related drug (spironolactone), and two small dose-ranging studies (one international, one Japanese.) Because each of these studies is relatively unique, I performed detailed reviews of both safety and efficacy of the two large studies and summary reviews of both safety and efficacy in the two small studies. The detailed individual study reviews of both efficacy and safety are included below in Section VI.C of the Efficacy section. Section VI.D summarizes the HF efficacy data and compares it to the efficacy data for spironolactone. Section VII discusses the HF study safety results compared to both the spironolactone safety data and the data from the hypertension trials.

For the review I relied heavily upon the SAS data sets submitted as the "case report tabulations". I verified the accuracy of the primary analyses performed by the sponsor as well as performed additional subgroup analyses. I also used the SAS data sets for the safety analyses of adverse events.

B. Overview of Materials Consulted in Review

I relied upon the materials submitted for this supplemental NDA and the original NDA submission for the hypertension indication. The IND was not consulted. As noted above, I used the electronic submissions extensively. The review also analyzed Drug Experience Reports submitted by the sponsor in response to reviewer questions as described in the next section.

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C. Overview of Methods Used to Evaluate Data Quality and Integrity

FDA Division of Scientific Investigation (DSI) site audits were not requested because the major pivotal study involves many sites none of which contributed more than a small fraction of the subjects. I evaluated data quality and integrity by the following mechanisms:

- I checked the internal consistency of the sNDA by frequently comparing the text of the NDA and the electronic case report tabulations to the case report forms (provided as electronic copies of the hand-written forms), by reproducing the sponsor's analyses from the electronic case report tabulations, and by comparing the coding of AEs to the investigator's text. I always could reproduce the sponsor's analyses from the electronic case report tabulations with the exception of SAE reports for RALES.
- For SAE reports for RALES the sponsor confirmed that the tables in the sNDA were not generated from the electronic case report tabulations submitted with the sNDA but from Drug Experience Reports (DERs—FDA Medwatch forms) maintained by the sponsor in a separate electronic system. At I's request the sponsor provided copies of the DERs for both RALES and EPHEBUS. From the DERs I could reproduce the sponsor's tables in the sNDA submission.
- In addition to the problem with incomplete SAEs for RALES in the original sNDA submission, I also found that the coding of AEs appeared to be less than optimal. The sponsor used a WHO system for AE coding. While the vast majority of AEs appeared to be coded appropriately and there appeared to be reasonable justification for the coding of all AEs, alternative interpretations for some AEs appeared to be preferable and coding appeared to be inconsistent between RALES and EPHEBUS. For example, in EPHEBUS one AE reported by the investigator as "KARCINOMA IN SITU OF THE PROSTATE GLAND" was coded as CARCINOMA rather than CARCINOMA OF THE PROSTATE. In RALES, two patients reported by the investigators as prostate adenocarcinomas were coded as PROSTATE DISORDER. A third patient who had AEs reported as PROSTATIC EPITHELIOMA was also coded as PROSTATE DISORDER. For this patient the DER form has a statement that malignancy was confirmed.

I checked the coding for all cancers and neoplasms and for all prostate, adrenal or suprarenal, breast or gynecomastia, and menstrual disorders. I searched the investigator's text descriptions of the AEs for additional prostate, breast or gynecomastia, and adrenal or suprarenal disorders. I also searched the DER reports for prostate and breast disorders and identified one probable prostate cancer case that was not reported as an AE. I also spot checked other AEs, e.g., liver and renal function abnormalities. The one category of AEs for which I's recordings may provide some differences in interpretations from the sponsor's is neoplasia. I's codings differ from the sponsor's both for prostate cancer (as noted

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in the last paragraph) and for two adrenal adenomas, which the sponsor coded as NEOPLASM.

- I also requested and obtained from the sponsor a small (n=20), random sample (stratified by death and non-death endpoints) of the documentation provided to the Critical Events Committee (CEC) for adjudicating endpoints. This documentation included the case report forms as well as investigator narratives and copies of hospital notes and death certificates. I verified that the data provided in this documentation corresponded to that provided in the NDA. I also verified that the adjudications of the CEC were reasonable.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards. Protocols and informed consent forms were approved by institutional review boards (IRB). The protocols include a Regulatory Requirements Appendix that specifies requirements for IRB approval and references FDA regulations and the Declaration of Helsinki. The risks to the patient in the trials appear to have been minimal and explained adequately in the informed consent documents. Monitoring for patient safety appears to have been adequate.

RALES preceded EPHESUS and provided evidence that an aldosterone antagonist is effective in reducing mortality in HF. While at first glance it might appear that the RALES results preclude doing another placebo-controlled trial of an aldosterone antagonist in HF, the focus in EPHESUS was upon patients immediately post-MI with lesser severity of HF. There is sufficient uncertainty that the RALES results apply to this population such that EPHESUS is ethically justifiable.

E. Evaluation of Financial Disclosure

There were no investigators who participated in financial arrangements with or hold financial interests in Pharmacia.

COMMENT: No financial conflicts of interest were identified.

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VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Eplerenone appears to show solid efficacy in improving survival in HF patients post-MI. In EPHEBUS the mortality risk reduction was about 15% with a p value of 0.008. The follow-up rate for vital status was excellent (99.7%), other aspects of the trial design and conduct appear good, and there are no subgroup variations that suggest major issues with validity. For this vital endpoint the EPHEBUS results alone are adequate to support an indication. RALES, while testing a related but different drug and a different target population (NYHA class III-IV HF) and appearing to be a less well-conducted study, does provide supporting evidence that aldosterone blockers improve survival in HF failure. Both studies suggest that the mechanism of action may be through effects upon potassium metabolism.

[

The sponsor's definition of the CV hospitalization component is peculiar, i.e., many CV causes, such as atrial arrhythmias and angina, are excluded. Using all CV hospitalizations the difference in this combined endpoint is not statistically significant by the sponsor's α allocation. Also, CV death is the major contributor to the combined endpoint, all hospitalizations and combined all cause mortality/hospitalizations were not significantly reduced, and the mortality and hospitalization rates were not consistent by region or gender.

]

While the survival benefits appear solid and, given the survival benefit, there are no major issues regarding safety for the HF post-MI indication, there are remaining questions regarding safety for the hypertension indication as discussed in the Integrated Review of Safety.

B. General Approach to Review of the Efficacy of the Drug

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For efficacy this sNDA provides one pivotal study: EPHESUS. It also provides a second trial (RALES) with a related agent (spironolactone) as supporting evidence. I review both of these trials, as well as the two smaller, dose-ranging studies in HF, individually in Section VI.C. below. To facilitate comparisons between EPHESUS and RALES I usually present specific analyses in the RALES review in the same order as in the EPHESUS review. I present the detailed analyses in the individual study reviews in Section C below. I provide some comparisons of the two trials in the Section C reviews and additional discussion of the relevance of RALES to EPHESUS and comparison of EPHESUS to the hypertension trails in Section D.

C. Detailed Review of Trials by Indication

The following reviews of the trials by indication include both the efficacy results and the safety results.

1. Study 011, Dose Ranging in Heart Failure

1.1. Background

Study IE3-97-02-011 is entitled "A Dose-Ranging Study of Eplerenone Versus Placebo and Spironolactone in Patients with Symptomatic Heart Failure." It tested single or divided daily doses of eplerenone 25-100 mg against spironolactone 25 mg QD and placebo for 12 weeks in patients with HF and then a doubled-dose of eplerenone for an additional four weeks.

1.2. Design and Conduct

This was a randomized, double-blind, multi-center, placebo- and active drug-controlled parallel group trial in patients with an ejection fraction $\leq 40\%$, a history of NYHA class II-IV HF within six months, and class II-IV HF at the time of enrollment stable on an ACEI and a loop diuretic (beta blocker use was allowed but not specified.) Fifty-seven investigators enrolled 321 patients at 57 study sites in six countries, the US (36% of patients), Poland (31%), France, Germany, Belgium, and the Netherlands. The study was conducted from August 4, 1997, to July 12, 1998. The mean age of the patients was 61 (range 31 to 87), 78% were males, 87% were white, 13% were black, and 39% had class II and 59% had class III HF at baseline.

After a 2-week pretreatment period to screen and qualify patients for the study, eligible patients were randomized to receive 12 weeks of double-blind eplerenone 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD; spironolactone 25 mg QD; or placebo. Patients randomized to the eplerenone 100 mg QD group received only 50 mg QD for the first week, then 100 mg QD for 11 weeks. During the last four weeks of the treatment period (weeks 13-16), patients received a doubled dose of eplerenone, whereas the dose of spironolactone remained unchanged.

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Patients returned to the clinic at weeks 2, 4, 8, 12, 14, and 16 for evaluations. Signs and symptoms were assessed by NYHA class and Sodium Retention Score (SRS). Neuro-hormone evaluation included determinations of urinary aldosterone, plasma renin (total and active), N-terminal atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and endothelin. Renal sodium/potassium excretion effect was assessed by urine sodium/potassium ratio and 24-hour urinary sodium. Thyroid function was assessed by thyroxin, free thyroxin, and thyroid stimulating hormone (TSH). Changes in progestational (estradiol, luteinizing hormone [LH], and follicle stimulating hormone [FSH]) and androgenic (testosterone [total and free] and dihydrotestosterone [DHT]) hormones were also measured. QOL was assessed by the following questionnaires: Minnesota Living with Heart Failure Questionnaire (MLHFQ), Short Form-12 Health Survey (SF-12), Patient Utility (EuroQOL), and a Sexual Dysfunction Questionnaire (SDQ). Safety was evaluated by assessment of incidence of hyperkalemia and symptomatic hypotension, all adverse experiences (AEs), and clinical laboratory abnormalities for the first 12 weeks and the last 4 weeks, to determine the effect of dose-doubling during the latter period. Vital signs assessed were systolic and diastolic blood pressure (SBP and DBP), HR, and body weight.

Of the 321 patients randomized, 317 received study medication and returned for at least one post-baseline visit, 275 patients continued in the trial and had their eplerenone dose doubled at week 13, 195 patients were evaluable for weeks 1-12, 172 patients were evaluable for weeks 13-16, and 265 patients completed the 16-week study period. There were numerous deviations from the entry criteria and protocol noncompliance in each group. The evaluable cohort consisted of randomized patients who satisfied all of the following criteria:

A. Exhibit evidence of symptomatic HF at the time of enrollment, defined as:

1. Ejection fraction \leq 40% (based on contrast ventriculography, radionuclide, scan, or echocardiography) within six months prior to the first dose of study medication;
2. NYHA functional class III or IV within six months prior to the first dose of study medication; and
3. NYHA functional class II-IV at time of study enrollment.

B. Continued to receive an ACEI for which the dose was unchanged for one month prior to the first dose of study medication and a loop diuretic for which dose was unchanged for two weeks prior to the first dose of study medication. If on digoxin at study entry, the therapy must have begun at least three months prior to enrollment and the dose must have been unchanged for at least one month prior to the first dose of study medication.

C. Did not have:

1. Hemodynamically significant and uncorrected valvular disease upon entry;
 2. An MI within three months prior to the first dose of study medication;
- and
3. Unstable angina upon entry.

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D. Had not received a potassium-sparing diuretic during the trial or within one month prior to the first dose of study medication.

E. Had not received any of the following at the time of study enrollment or during the interval under consideration:

1. Chronic use of NSAIDs (including chronic aspirin use at a dose > 160 mg/day).

Chronic use was defined as use for greater than three consecutive days;

2. Steroids;

3. Dopamine agonists or antagonists;

4. Insulin;

5. Heparin;

6. Antiarrhythmics (except amiodarone); and

7. Estrogen/progesterone contraceptive or replacement therapy.

F. Had the prestudy cardiac assessments within 14 days prior to the first dose of study medication.

G. Underwent the week 2 visit within 7 ± 3 days, week 4 visit 28 ± 7 days, week 8 visit 56 ± 7 days, and week 12 visit 84 ± 10 days from the date of the first dose of study medication.

H. Took at least 80% of the prescribed doses of study medication for the interval under consideration.

1.3. Efficacy Summary

After 12 and 16 weeks of treatment there was no apparent improvement in signs and symptoms of HF as measured by NYHA class or sodium retention score with eplerenone or spironolactone vs. placebo. All groups showed a trend toward improvement over their baseline state. For the Minnesota Living with Heart Failure Questionnaire (MLHFQ), overall, physical dimension, and emotional dimension scores decreased during the study (decrease is improvement), but the differences among the treatment groups were generally not statistically significant and there were no significant dose responses observed.

At weeks 12 and 16, urinary aldosterone in the eplerenone groups increased in a dose-response fashion to significantly greater levels than placebo ($p = 0.012$) and to comparable levels with spironolactone for eplerenone doses >25 mg QD. Likewise, total and active plasma renin in all eplerenone groups rose to significantly greater levels than placebo ($p = 0.043$).

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Table 9: Sponsor's Changes in NYHA Class, Sodium Retention Score, and RAAS Hormones From Baseline to Week 12 in Study 011

Change from Baseline to Week 12 Endpoint (ITT Cohort)	Placebo	Eplerenone 25 mg QD	Eplerenone 25 mg BID	Eplerenone 50 mg QD	Eplerenone 100 mg QD	Spironolactone 25 mg QD
NYHA Classification	-0.4 (n=54)	-0.3 (n=62)	-0.2 (n=52)	-0.2* (n=55)	-0.2 (n=49)	-0.3 (n=45)
Sodium Retention Score	-0.5 (n=53)	-0.4 (n=61)	-0.6 (n=52)	-0.5 (n=54)	-0.4 (n=48)	-0.4 (n=45)
Urinary Aldosterone (nmol/24hr) ††	0.1† (n=51)	7.8† (n=55)	29.9* (n=47)	30.5* (n=46)	23.4* (n=46)	24.3* (n=42)
Plasma Renin Total (mIU/L)**	46.6 (n=52)	519.8* (n=58)	442.5* (n=46)	649.4* (n=49)	770.4* (n=48)	485.3* (n=42)
Plasma Renin Active (IU/L)**	9.2 (n=52)	275.1 (n=58)	169.0 (n=46)	323.2* (n=49)	236.3* (n=48)	200.4* (n=42)

*Pairwise comparison significantly different from placebo.
 †Pairwise comparison significantly different from spironolactone.
 **Statistically significant dose response.
 ††Statistically significant difference among all treatment groups and dose response.

For the dose response analysis, treatment groups analyzed were placebo, eplerenone 25 mg QD, eplerenone 50 mg (25 mg BID and 50 mg QD combined), and eplerenone 100 mg QD. Dose response was tested using the Spearman rank correlation test (using Cochran-Mantel-Haenszel correlation test). Statistically significant positive dose responses were observed for urinary aldosterone, plasma renin (total and active), estradiol (females), LH (males), and urine sodium/potassium ratio and negative dose responses for BNP and endothelin.

1.4. Safety Summary

Total exposure was 61.2 patient-exposure years to eplerenone, 12.7 PEY to spironolactone, and 15.7 PEY to placebo. Of the 321 patients in the study during weeks 1-12, 217 (67.6%) experienced at least one AE. Of the 275 patients in the study during weeks 13-16, 113 (41.4%) experienced at least one AE. Patients who received eplerenone and spironolactone had a higher incidence of hyperkalemia and renal function abnormalities than patients who received placebo.

Ten patients died during the study, seven (3%) of the eplerenone, two (4%) of the spironolactone, and one (2%) of the placebo patients. The causes of death were lung cancer, renal failure and terminal HF in one each eplerenone patients, stroke in one spironolactone patient, and sudden death in the rest.

Thirty-six patients withdrew because of AEs, 27 (12%) of the eplerenone, six (13%) of the spironolactone, and three (5%) of the placebo patients. Reasons for withdrawal of the eplerenone patients included three sudden deaths, two arrhythmias, two myocardial

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infarctions and one angina, three HF, five dyspnea, two CPK increased, three renal insufficiency, three hyperkalemia, and two hepatic function abnormalities.

Forty patients experienced serious AEs, 30 (14%) of the eplerenone, six (13%) of the spironolactone, and four (7%) of the placebo patients. The types of SAEs for eplerenone patients were similar to those causing withdrawal.

For an easier comparison of rates of important types of AEs the rates of deaths, withdrawals, SAEs, hyperkalemia, and renal function abnormalities are listed in the following table.

Table 10: Reviewer's Rates of Important Types of AEs in Study 011

	Deaths	AE Withdrawals	SAEs	Hyperkalemia	Renal Ab
Placebo	2%	5%	7%	4%	2%
Eplerenone	3%	12%	14%	9%	12%
Spironolactone	4%	13%	13%	13%	10%

Renal Ab = renal function abnormality, i.e., increased BUN or creatinine or renal insufficiency

The rates of hyperkalemia and renal function were lower in the eplerenone 50 mg BID group but rates of withdrawals and SAEs were not different in that group. Otherwise variations by eplerenone dosage were not obvious.

Changes in vital signs (heart, SBP, DBP, and body weight) did not vary significantly among the treatment groups.

Eplerenone and spironolactone did produce a few sex-hormone related AEs. Two females on eplerenone experienced breast pain, two males on eplerenone experienced gynecomastia and an additional male on eplerenone experienced breast tenderness, and one male on spironolactone experienced gynecomastia. The breast tenderness occurred at days 20-40 in a patient receiving eplerenone 50 mg QD patient while the gynecomastia occurred in patients receiving 100 mg or more daily after 12 weeks. The case of gynecomastia on spironolactone was early (day 16) and another eplerenone patient was reported to have gynecomastia at baseline. No placebo patients reported these symptoms.

Hypothyroidism was reported in one placebo patient, and one each elevated TSH and hyperthyroidism in eplerenone patients.

Eplerenone produced some significant changes in hormone levels. In males the mean changes in estradiol from week 12-16 were significantly different from placebo in the eplerenone 50 mg BID and 100 mg QD groups (but not in the 200 mg QD group) and the dose response was statistically significant for both males and females. There were no significant differences by group in changes in free and total testosterone or dihydrotestosterone except a significant increase in dihydrotestosterone in males and decrease in females in week 12-16 change of the eplerenone 50 mg BID group compared with spironolactone.

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In males there was a statistically significant mean increase in LH from week 1-12 in the spironolactone compared to other groups and a significant dose response. The mean differences from week 1-16 were also significantly different with greater increases in the eplerenone 100 mg QD and 200 mg QD groups and the spironolactone group. There were no significant differences in LH among groups in females. There were baseline differences by group in FSH levels but no significant differences in FSH changes.

The difference among all groups in mean thyroxin levels and mean free thyroxin levels were statistically significant at week 16, with thyroxin levels in the eplerenone 200 mg group significantly lower than those in the spironolactone group. TSH levels did not vary significantly among groups at baseline or the two endpoints.

1.5. Conclusions

This study does not provide evidence that eplerenone is effective in patients with HF but neither was it powered to do so. The overall safety of eplerenone in this population appears comparable to that of spironolactone. Both drugs have greater rates of SAEs than placebo and both drugs appear to cause hormonal changes and hormone-related AEs. With regard to RAAS hormones, changes in renin levels were seen with the lowest eplerenone dosage 25 mg daily comparable to higher dosages while changes in urinary aldosterone comparable to the higher dosages were seen starting with the 50 mg daily dosage. The RAAS changes provide justification for the 25-50 mg daily dosage used in EPHEBUS.

2. Study 402, Dose Ranging in Heart Failure in Japan

2.1. Background

Study JE3-00-02-402 is entitled "Dose-Response Study of Eplerenone in Symptomatic Patients With Heart Failure." It is a Japanese study comparing eplerenone 25-100 mg daily to placebo in HF patients.

Per the sponsor, [

] Comparison of the Japan and ex-Japan phase 1 data show similarity in the pharmacokinetic profile for eplerenone in the 2 populations. Data from the Japan Study 403 (not reviewed) and the two pivotal studies for the US NDA for hypertension (Studies 010 and 049) confirmed that the antihypertensive efficacy and dose-response relationship of eplerenone are similar between Japanese and non-Japanese hypertensive patients. Although Japanese and non-Japanese patients differed with respect to baseline characteristics of weight, body mass index (BMI), active plasma renin, and aldosterone: renin ratio, antihypertensive efficacy was similar in the two populations. In addition, the safety profile was similar in Japanese and non-Japanese patients.

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Per the sponsor, this study was conducted to verify that eplerenone would have similar efficacy and safety in Japanese HF patients as demonstrated in Study 011 in non-Japanese patients. The differences from 011 are the following: (1) eplerenone dosing in 402 was limited to once daily (based on the sponsor's claim that once and twice daily dosing were shown to be equivalent in Study 011—I would argue that Study 011 was underpowered and had conduct problems that do not support such a claim); (2) sex-hormone and TSH levels were not assessed in Study 402; (3) an active comparator was not used in Study 402; and (4) like Study 011, patients in Study 402 were to receive ACEI and loop diuretics but they received ACEI and/or loop diuretics.

2.2. Design and Conduct

This was a Japanese, multi-center, randomized, double-blind, placebo-controlled, parallel group trial in patients with an ejection fraction $\leq 40\%$, a history of NYHA class II-IV HF within six months, and class II-IV HF at the time of enrollment stable on an ACEI and/or a loop diuretic. Thirty-seven investigators enrolled 161 patients at 36 sites in Japan. The study was conducted from November 1, 2000, to September 11, 2002. The mean age of the patients was 64 (range 29 to 88), 84% were male, and 63% were NYHA class II.

After a 2-week pretreatment period to screen and qualify patients for the study, eligible patients were randomized to receive 12 weeks of double-blind eplerenone 25 mg, 50 mg, 100 mg, or placebo QD. Follow-up visits were scheduled for 2, 4, 8 and 12 weeks with an additional potassium level measured at 1 week. Assessments included RAAS hormone (plasma renin and serum aldosterone) and cardiorenal hormone (serum nt-BNP, plasma BNP, and plasma nt-ANP) levels, NYHA functional classification, HR, BP, body weight, serum potassium, and 24-hour urine collection for sodium, potassium, and urinary aldosterone (selected sites). Safety was assessed by routine clinical laboratory evaluations, vital signs, physical examinations, ECGs, concomitant medications, and monitoring of adverse events.

Of the 161 patients randomized, 152 received study drug, and 135 completed the study. The most common reason for discontinuation was an adverse event (15 patients.) Twenty-two patients had inclusion or exclusion criteria violations.

2.3. Efficacy Summary

There were no statistically significant differences between placebo and any of the eplerenone treatment groups in change from baseline in NYHA functional classification.

The percent changes in geometric mean values for the RAAS and HF-related hormones are shown in the following table.

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Table 11: Reviewer's Percent Changes in Geometric Mean Values for RAAS and HF-Related Hormones in Study 402

	Eplerenone mg/day			
	Placebo	25	50	100
Serum aldosterone	9%	43%	73%	138%
Total plasma renin	-12%	15%	35%	28%
Active plasma renin	-14%	55%	80%	54%
nt-BNP	4%	-6%	2%	-16%
BNP	4%	-13%	5%	-5%
nt-ANP	4%	-10%	-5%	-4%

The increases from baseline in serum aldosterone in the eplerenone 50 mg QD and 100 mg QD treatment groups were statistically significant compared to placebo (p 0.002). There was a significant dose-dependent relationship across all treatment groups with respect to the increase in serum aldosterone. All three eplerenone treatment groups significantly increased total and active plasma renin levels from baseline compared to placebo (p 0.007). Urinary aldosterone changes were not significantly different among the groups but numbers of measurements were small. The decrease from baseline in nt-BNP in the eplerenone 100 mg QD treatment group was statistically significant compared to placebo (p=0.001).

2.4. Safety Summary

There were 287 AEs reported in 108 of the 152 patients receiving study drug with the greatest number of AEs (89) reported in the placebo group. The rates by treatment group of patients with AEs, SAEs, and AEs causing discontinuation are shown in the following table.

Table 12: Sponsor's Summary of Patients with Adverse Events in Study 402

	Placebo N=38	Eplerenone		
		25 mg QD N=37	50 mg QD N=39	100 mg QD N=38
Any Adverse Event	29 (76.3%)	25 (67.6%)	28 (71.8%)	26 (68.4%)
Serious Adverse Event(s)	2 (5.3%)	2 (5.4%)	4 (10.3%)	2 (5.3%)
Permanent Discontinuation of Study Medication Due to Adverse Event	3 (7.9%)	6 (16.2%)	7 (17.9%)	3 (7.9%)

The eplerenone SAEs included a death from unknown cause, one each ventricular tachycardia (and worsening HF) and ventricular fibrillation, another worsening HF, a stroke, nausea and vomiting, and hematemesis. Four eplerenone and one placebo patients were withdrawn because of hyperkalemia. Other causes for withdrawal in eplerenone patients (besides the SAEs listed above) were (one each) hypokalemia and prolonged QTc (a second patient had hypokalemia and prolonged QTc as an ordinary AE and

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continued on treatment) , hypothyroidism, CPK increased, “congestive liver”, and liver enzyme elevations.

Two patients (1 placebo, 1 eplerenone 100 mg QD) died within 30 days of the last dose of study medication of a pulmonary embolism and unknown causes, respectively. The eplerenone patient died 18 days after completing the study.

No patient in the study reported female breast pain, menstrual disorder, gynecomastia, decreased libido, or impotence.

Mean baseline SBP and SDP were within normal limits in all groups. Mean changes at week 12 were small and not significant except for DBP in the 50 mg group as shown in the following table.

Table 13: Sponsor’s Change from Baseline to Week 12 in SBP/DBP for Study 402

	Placebo (N=38)	Eplerenone		
		25 mg QD (N=36)	50 mg QD (N=38)	100 mg QD (N=38)
Baseline Mean	121.4/73.2	124.8/74.0	121.1/74.0	123.4/74.4
Adjusted Mean Change (mmHg)	2.5/1.7	-0.7/0.4	-2.8/-4.1	-1.8/-0.1
Standard Error	2.10/1.34	2.15/1.37	2.09/1.33	2.11/1.35
p-values vs placebo (2-sided) [†]		0.288/0.500	0.075/0.002	0.149/0.346

Source: Table T8.1

[†] Based on ANCOVA with baseline value as the covariate and treatment and center as factors. P-values are based on pairwise contrasts of each treatment group versus placebo.

2.5. Conclusions

This study, like Study 011, does not provide evidence that eplerenone is effective in patients with HF but neither was it powered to do so. The RAAS hormone changes suggest that eplerenone 25-50 mg is reasonable to test for efficacy in HF assuming that the mechanism of action is related to RAAS hormone changes. However, even for RAAS hormone changes the dose-response relationship is not well defined. The AE profile in these Japanese patients does not appear to be dramatically different than in the US population, although the effects of cultural and trial conduct differences are difficult to estimate.

3. EPHESUS, Study 035

Study 035 is entitled “Evaluating the Safety and Efficacy of Eplerenone in Patients with Heart Failure Following Acute Myocardial Infarction (EPHESUS)” and is referenced in this review as EPHESUS. (EPHESUS is the acronym for “Eplerenone Post-AMI Heart Failure Efficacy and Survival Study”.) It was an international, randomized, double-blind, placebo-controlled, parallel-group study of eplerenone 25-50 mg in patients with heart

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failure (HF) post acute myocardial infarction (MI) with an original primary endpoint of all-cause mortality. It is the pivotal study supporting the new indication.

3.1. Sites and Investigators

Six hundred sixty-five investigators enrolled 6,642 patients at 671 study sites in 37 countries (Canada, US, Argentina, Brazil, Chile, Columbia, Mexico, Venezuela, Bulgaria, Czech Republic, Estonia, Hungary, Poland, Romania, Russia, Slovakia, Ukraine, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK, Australia, Israel, New Zealand, South Africa, South Korea, and Taiwan). The sponsor excluded ten patients from one subinvestigator at site 4017 in Romania because of evidence of alteration of source documents, leaving 6,632 included in the analyses of the study.

The US contributed 9.3% of the these patients, second only to the 9.6% of patients contributed by Russia. The patients were widely distributed among the countries, with a range from 6 in Korea to 637 in Russia, a mean of 179 patients per country and a median of 119.

The sponsor originally defined in the protocol four regions to be used in analyses: the US and Canada, Eastern Europe, Latin American, and the rest of the world, including Western Europe. The sponsor changed the definitions of the regions in the Statistical Analysis Plan submitted in November 2002 to the US and Canada, Western Europe, Eastern Europe, Latin America, and the rest of the world. The distribution of patients by these regions is shown in the following table.

Table 14: Reviewer's Patients by Region in EPHEBUS

Region	N	Percent
US & Canada	858	13%
US	614	9.3%
Canada	244	3.7%
Western Europe	1,729	26%
Eastern Europe	2,917	44%
Latin America	571	9%
Rest of world	557	8%
Total	6,632	100%

Patients were also widely distributed by site. The range of patients by site was 1 to 90, with a mean of 10 and median of six patients per site. The three sites with the most patients were located in Bulgaria and the top 25 sites were also located in Eastern Europe with the exception of two sites in South Africa and one site in Spain.

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3.2. Background

3.2.1. Initial Protocol

The initial protocol was IE3-99-02-035, dated October 7, 1999. It was amended 10 times prior to completion of the study as itemized in the next section. The initial protocol specified a single primary endpoint of all-cause mortality. Amendment A9, dated December 20, 2000, added a second primary endpoint.

3.2.2. Protocol Amendments

The protocol was amended ten times by the following amendments:

- A1, dated 13 December 1999, defined the population pharmacokinetics substudy.
- A2, dated 30 March 2000, modified the inclusion criteria for documentation of MI (also allowing CPK-MB > 2 x ULN and/or lactate dehydrogenase cardiac isoenzymes > 2 x ULN) and heart failure, specified entrance criteria for diabetic patients, modified the secondary objectives of the study, clarified quality of life assessments, and clarified reporting of serious adverse events and study medication dosing.
- A3, dated 18 April 2000, defined the cardiorenal hormones, cytokines, and collagen markers substudy.
- A4, dated 18 April 2000, defined the vascular compliance substudy.
- A5, dated 18 April 2000, defined the fibrinolytic balance substudy.
- A6, dated 18 April 2000, defined the cardiac remodeling substudy.
- A7, dated 22 May 2000, defined the heart rate variability substudy.
- A8, dated 9 August 2000, modified the inclusion criteria for documentation of MI (also allowing troponin T > 3 x ULN or troponin I = the value considered diagnostic of a MI by the laboratory performing the assay); modified the exclusion criteria for CABG, specified the conditions under which PTCR is allowed prior to randomization, modified the statistical methods for interim analyses, and clarified the conditions for permanent discontinuation of study medication.
- A9, dated 20 December 2000, allowed patients to be randomized up to 14 days following the index MI, modified the inclusion criterion for evidence of HF, deleted the exclusion criterion for planned CABG, specified that diagnostic

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arteriography, CABG, and PTCR are allowed following randomization, added a second primary endpoint, added pharmacoeconomic information, corrected a reference and revised case report forms.

- PA10, dated 24 April 2002, provided the opportunity for patients who have not permanently discontinued study medication to continue in an open-label extension if the results for either of the two primary endpoints showed a significant difference favoring eplerenone over placebo, clarified the definitions for cardiovascular mortality and for cardiovascular morbidity leading to hospitalization, added osteopontin is added as an analyte in the cardiorenal hormones, cytokines and collagen markers sub-study, and designated a medical monitor.

COMMENT: Note that the second primary endpoint was added in Amendment A9, dated 20 December 2000, after the first very promising trial results had been reported to the DSMB. The sponsor solicited approval of the primary endpoint change as discussed below in Section 3.3.6.2. Note also that the criteria for the second primary endpoint were not finalized until Amendment PA10, dated 24 April 2002.

3.2.3. Study Dates

The first patient was enrolled on December 27, 1999, and the last patient was enrolled on December 31, 2001. Enrollment did not start to escalate until March 2000, built up steadily, and then dropped to about a fourth of the peak levels for the last three months of 2001. The last patient completed the study on November 30, 2002, but the majority of patients had last follow-up in early September 2002. The cutoff date for the analyses is August 30, 2002.

3.3. Study Design

EPHESUS was an international, randomized, double-blind, placebo-controlled, parallel-group study of eplerenone 25-50 mg in patients with heart failure (HF) post acute myocardial infarction (MI). Patients were to be screened within 14 days after the index MI and randomized between >48 hours and up to 14 days after the index AMI. 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.

Throughout the study, patients received standard therapy, which could have included angiotensin-converting enzyme inhibitors (ACEI), diuretics, nitrates, and β -blockers, and could have received anticoagulants, antiplatelet agents, or thrombolytics. The patients may also have had emergency angioplasty or coronary artery bypass graft (CABG).

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Patients were randomized to receive eplerenone 25 mg QD (once daily) or placebo. At 4 weeks, the dose of study drug was increased to 50 mg QD if serum potassium was < 5.0 mmol/L. Further dose adjustments depended upon the most recent potassium level, with upward or downward adjustments among 0, 25, and 50 mg.

Study visits occurred at screening, baseline (randomization), one week, and four weeks, three months, and every three months thereafter until the study was terminated. Medical history, cardiac enzymes, Killip class, time to reperfusion (if applicable), documentation of MI and of HF, determination of left ventricular ejection fraction (LVEF), and a serum pregnancy test for women of childbearing potential were done at screening. A physical examination and 12-lead electrocardiogram (ECG) were performed at screening and at the final visit (permanent discontinuation of study drug). Safety laboratory evaluations (hematology, biochemistry, and urinalysis) were performed at screening, week 4, months 3 and 6, and every 6 months thereafter until the study was terminated. For sites in the US, Canada, and Brazil, a urine sample was collected at week 4 and at months 6, 12, and 18 for determination of urinary albumin/creatinine ratio (UACR). An optional additional blood sample for DNA analysis was collected during screening. In addition, optional blood samples for future biochemical analyses were collected at screening, at week 4, month 9, and at the final visit. Vital signs (seated heart rate and blood pressure [BP]), weight, and NYHA functional classification were assessed at weeks 1 and 4, at month 3, and every 3 months thereafter. Adverse events and concurrent medications were recorded at every visit. All randomized patients were followed for endpoints every 3 months until the study was terminated. At selected sites, substudies were conducted to assess QoL; population pharmacokinetics; cardiorenal hormones, cytokines, and collagen markers; vascular compliance; plasma fibrinolytic balance; cardiac remodeling; and heart rate variability (HRV).

3.3.1. Objectives

The primary objective of this study were to compare the effect of eplerenone plus standard therapy vs. placebo plus standard therapy on the rate of all cause mortality in patients with HF after MI. A second primary objective was added during the course of the study: to compare the effect on the time to first occurrence of CV mortality or CV hospitalization.

Secondary objectives were to compare the two treatment groups for the following:

- CV mortality
- CV hospitalizations
- All cause hospitalizations
- CV mortality and CV hospitalizations (elevated to primary objective)
- All cause mortality and all cause hospitalizations

Additional objectives were to compare the two treatment groups for the following:

- New diagnosis of atrial fibrillation or flutter

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- NYHA functional class
- Quality of life

3.3.2. Number of Subjects, Randomization, and Blinding

The study randomized 6,642 patients but 10 patients from a subinvestigator at one site were excluded from analyses because of evidence of alterations of source documents. The eplerenone group had 3,319 patients and the placebo group 3,313 patients.

The sponsor's clinical database administrator generated the patient randomization schedule using sponsor's standard randomization program. The sponsor's statistician prepared a program to generate a randomization schedule for medication kit identification numbers, separate from the patient randomization schedule. The database administrator executed the program to obtain identification numbers. The randomizations were provided to a drug packaging contractor and to the interactive voice response system (IVRS) center for drug assignments. Site personnel called the 24-hour IVRS center to randomize each patient. The investigator provided the IVRS center with various identifiers for each patient and confirmed that inclusion/exclusion criteria had been met. The IVRS center assigned the patient to a treatment according to the patient randomization schedule described above. The IVRS system then selected a blinded medication identification number appropriate to the patient's treatment assignment from those available at the study site.

Double-blind eplerenone or matching placebo was supplied in bottles pre-labeled with appropriate kit numbers for each treatment arm. Two-part labels were computer-generated for this blinded study. One part of the label, containing study and patient information, was attached to the container; the other part was a tear-off portion that contained the same information plus a sealed pouch containing the identity of the assigned treatment. This tear-off tab was to be removed at the time of dispensing, attached to the patient's appropriate CRF, and retained in the investigator's study file.

3.3.3. Inclusion and Exclusion Criteria

Subjects were supposed to meet all of the following inclusion and exclusion criteria 48 hours to 14 days after an acute myocardial infarction (MI).

Inclusion criteria:

1. The patient had an MI, as documented by the following:
 - a. cardiac enzyme rise, as shown by one or more of the following:
 - total CPK > 2x ULN
 - CPK-MB > 2x ULN or > 10% of total CPK

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- LDH cardiac isoenzymes > 2x ULN
- troponin T > 3 x ULN or troponin I = the value considered diagnostic of an AMI by the laboratory performing the assay
- b. evolving ECG diagnostic of MI
- 2. LV dysfunction documented by LVEF = 40% following MI and before randomization (but not necessarily at time of randomization)
- 3. Diabetic (on treatment or hemoglobin A_{1c} > ULN)
or
clinical evidence of HF demonstrated by one of the following:
 - a. pulmonary congestion
 - b. chest x-ray showing pulmonary venous congestion
 - c. third heart sound (S₃)
- 4. Stable clinical status at time of randomization
- 5. Male or nonpregnant female = 21 years of age
- 6. If female, post-menopausal or using adequate contraception
- 7. If female, negative serum pregnancy test
- 8. No abnormal lab values which the investigator judges to preclude safe participation
- 9. Willing and able to participate
- 10. Informed consent

Exclusion criteria:

1. HF of primary valvular or congenital etiology.
2. Current evidence of clinical instability
3. Post-infarct angina likely to lead to acute coronary arteriography
4. (Criterion 4 deleted—numbering left unchanged to match CRFs)
5. Implanted cardiac defibrillator (ICD)
6. Uncontrolled hypotension (SBP < 90 mmHg)
7. Required use of potassium-sparing diuretics or spironolactone
8. Serum creatinine level > 2.5 mg/dL
9. Serum potassium level > 5.0 mEq/L
10. Planned cardiac transplantation
11. Current alcohol or drug abuse problems
12. Any condition which, in the investigator's opinion, makes participation in this study not in the best interest of the patient
13. Known hypersensitivity to eplerenone or spironolactone
14. Severe organic disorder or has had surgery or disease of the gastrointestinal tract which, in the opinion of the investigator, may interfere with the absorption, pharmacokinetics, or elimination of the study medication
15. Chronic psychoses or behavioral conditions
16. Comorbid condition that would be expected to result in death during the next three years
17. Any investigational medication or within 30 days
18. Previously admitted to the study

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COMMENT: Note that diabetics originally didn't have to meet any HF entrance criteria. An early amendment (A2, dated 30 March 2000) added the requirement that they meet the LVEF criterion. They never had to meet the requirement for other clinical signs of HF.

3.3.4. Dosage and Administration

The first dose of study medication (25 mg for eplerenone) was to be taken as soon as possible after randomization and no more than 24 hours after randomization. The second dose of study medication was to be taken the following morning and was to follow the first dose by at least 12 hours. All other doses of study medication were to be taken each morning with water or as otherwise directed by the investigator.

3.3.5. Duration and Adjustment of Therapy

Treatment was continued while the patient was on-study. Patients received either eplerenone 25 mg QD or placebo (1 tablet QD) for the first four weeks of treatment. At four weeks, the dose of study drug was increased to 50 mg QD (2 tablets once daily) if serum potassium < 5.0 mmol/L. If serum potassium was =5.0 mmol/L at week 4 but < 5.0 mmol/L at week 5, the dose of study drug was increased to 50 mg QD. In this case, serum potassium was to be checked at week 6. At any time during the study, the dose of study medication was to be adjusted according to the patient's serum potassium level, as detailed in the table below.

Table 15: Sponsor's Study Medication Dosing Adjustment for Serum Potassium Levels in EPHEBUS

Serum Potassium Level (mmol/L)	Current Dosing Schedule	Action	New Dosing Schedule
< 5.0	Withhold	Increase	1 tablet QOD
< 5.0	1 tablet QOD	Increase	1 tablet QD
< 5.0	1 tablet QD	Increase	2 tablets QD
< 5.0	2 tablets QD	No change	2 tablets QD
≥ 5.0 and < 5.5	Withhold	Increase	1 tablet QOD
≥ 5.0 and < 5.5	1 tablet QOD	No change	1 tablet QOD
≥ 5.0 and < 5.5	1 tablet QD	No change	1 tablet QD
≥ 5.0 and < 5.5	2 tablets QD	No change	2 tablets QD
≥ 5.5 and < 6.0	Withhold	No change	None
≥ 5.5 and < 6.0	1 tablet QOD	Decrease	None
≥ 5.5 and < 6.0	1 tablet QD	Decrease	1 tablet QOD
≥ 5.5 and < 6.0	2 tablets QD	Decrease	1 tablet QD
≥ 6.0	Any dose	*	None

*Potassium supplements, if any, were to be stopped and the patient was to continue to receive study medication. If persistent elevation, study medication was to be discontinued. If single elevation, dosing was to be withheld.

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3.3.6. Safety and Efficacy Endpoints

3.3.6.1. Original Primary Efficacy Endpoint

The primary efficacy endpoint as defined in the original protocol was time to occurrence of all cause mortality. In addition to capturing mortality through hospitalizations, notifications, and missed appointments, the sponsor also had investigators perform mortality "sweeps". The investigators were instructed to contact patients and other sources and ascertain the vital status of the patients. The first sweep began in September 2001 and lasted 3 months. The second sweep was done from January 31 to 15-February 15, 2002.

COMMENT: The primary endpoint of all cause mortality is the preferred endpoint for a HF study of this type. The sponsor's procedures for insuring complete mortality ascertainment, e.g., mortality sweeps, appear to be good.

3.3.6.2. Added Primary Efficacy Endpoint

Amendment A9, dated 20 December 2000, added a second primary endpoint of time to first occurrence of either cardiovascular (CV) mortality or CV hospitalization. Mortality was allocated 0.04 of alpha and this new primary endpoint was allocated 0.01.

The endpoint addition was discussed at an open meeting of the DSMB on the morning of December 4, 2000, at which time 1,833 patients were enrolled. Prior to this meeting the DSMB was provided with EPHEBUS Interim Analysis Report #1, dated November 22, 2000, that provided partially unblinded results on the first 1,564 subjects. The report provides detailed tabulations of the SAEs, including deaths. Its Table 5 lists 51 deaths in the "Leto" group and 29 deaths in the "Zeus" group. There were 20 deaths due to HF and 30 deaths due to arrhythmias in the Leto group compared to 10 HF and 14 arrhythmia deaths in the Zeus group.

The DSMB minutes record the following for the December 4, 2000, meeting:

"Dr. Roniker [sponsor's medical monitor] discussed the proposed change in primary endpoint from all-cause mortality to a co-primary endpoint of (a) all-cause mortality or (b) cardiovascular hospitalization and all-cause mortality. The Board was reluctant to agree to a co-primary endpoint because it preferred the single primary endpoint of all-cause mortality. The DSMB expressed concern about the credibility of changing the primary endpoint this far into the study. The Board discussed the difficulty of defining 'heart failure,' 'worsening heart failure,' or 'morbidity due to heart failure' and discussed how best to define cardiovascular hospitalizations for the second component of the new co-primary endpoint. After extensive discussion, the board reluctantly agreed to accept

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the proposed co-primary endpoint but recommended changing the wording of the second component of the co-primary endpoint to 'cardiovascular morbidity leading to hospitalization.'"

At the closed session that followed the DSMB reviewed unblinded data summarizing about 10 percent of the deaths. The report also examined non-fatal hospitalizations. Early striking separation of the two survival curves was noted. Following this closed session the DSMB convened for a second open session. The DSMB minutes record the following:

"Dr. Julian [DSMB chair] passed to Dr. Pitt [chair of the Steering Committee] the DSMB's recommendations regarding the proposed protocol amendment 9 as discussed during the open session. Dr. Pitt then explained the reason Pharmacia is considering a new co-primary endpoint. Dr. Pitt referred to the VAL-HeFT trial which had co-primary endpoints. The trial did not meet the co-primary endpoint of all-cause mortality, but did meet its secondary endpoint of hospitalization for heart failure. Dr. Pitt discussed the merits of a co-primary endpoint with Dr. Ray Lipicky at the FDA and understood that Dr. Lipicky thought a co-primary endpoint generally has merits and would be appropriate for this study."

Amendment PA10, dated 24 April 2002, modified the definitions of the second primary endpoint slightly. CV mortality was redefined in this amendment as any mortality adjudicated as:

1. Sudden cardiac death
2. Myocardial infarction
3. Progression of heart failure
4. Stroke
5. Other CV mortality, including aneurysm or pulmonary embolism

CV hospitalization was redefined as any hospitalization adjudicated as:

1. Progression of heart failure
2. Myocardial infarction
3. Stroke
4. Ventricular arrhythmia

COMMENT: While it is preferable to define all endpoints, particularly primary endpoints, prior to initiation of the study, modifying the primary endpoint prior to the unblinding of the data is acceptable. Discussion of the endpoint change with the DSMB, however, appears inappropriate for two reasons:

- Reviewing or approving endpoint changes is not within the mission of the DSMB to "review accumulating data on a periodic basis to ensure patient safety and recommend continuation of the study" (as stated in the protocol and consistent with

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draft FDA guidelines.) As the EPHESUS DSMB Charter also notes, "The Board must remain as independent a possible of interactions with persons involved with the conduct of the trial who might in any way influence decisions relating to the study."

- The DSMB prior to the time the decision to add a secondary endpoint was discussed had been provided with preliminary study results including information on deaths, the original primary endpoint.

There seems to be a lack of parallelism between the sponsor's definitions of CV mortality and of CV hospitalizations. The definition of CV mortality includes most CV events that commonly cause deaths, particularly if the "other CV mortality category" is interpreted liberally. The definition of CV hospitalization does not include atrial arrhythmias, pulmonary embolism, and peripheral vascular disorders. Atrial arrhythmias are common in heart failure patients and particularly ones with more severe HF. If they are not included as causes of CV hospitalizations, then one may have a difficult judgment call to classify a hospitalization for an atrial arrhythmia as non-CV or CV. Regarding pulmonary embolism and peripheral vascular disease, eplerenone showed some effects upon fibrinolytic status, e.g., plasminogen activator inhibitor-1, in the hypertension studies. Because the effects on fibrinolytic status and thromboembolic events were not elucidated fully in those studies, it is possible that eplerenone alters rates of thromboembolic events. They should be included as causes of CV hospitalizations.

3.3.6.3. Secondary Efficacy Endpoints

The secondary objectives listed in the original protocol are the following:

1. CV mortality
2. CV hospitalizations
3. All cause hospitalizations
4. CV mortality and CV hospitalizations (elevated to primary objective)
5. All cause mortality and all cause hospitalizations

The secondary efficacy endpoints first listed in the NDA are the following:

1. CV mortality
2. All cause mortality/hospitalization
3. CV mortality/nonfatal MI (added to the Statistical Analysis Plan prior to unblinding the data)

The NDA notes the following additional endpoints:

1. New diagnosis of atrial fibrillation or atrial flutter
2. NYHA functional classification

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The Statistical Analysis Plan, submitted in November 2002, also lists recurrent MI (fatal or nonfatal), stroke (fatal or nonfatal), early revascularization (>14 days and <60 days after the index MI), and late revascularization (60 days after the index MI).

3.3.6.4. Critical Events Committee

The sponsor employed a blinded Critical Event Committee to adjudicate some of the secondary endpoints (and the second primary endpoint of CV mortality/CV hospitalization after it was added.) The CEC consisted of two subcommittees of physicians, each with its own co-chairman. Each event was distributed to two members of a subcommittee and to the respective co-chairman for evaluation. The CEC members received a cover letter, narrative, copies of source documents such as the SAE worksheet, discharge summary, ECG strips, lab reports, progress notes and death certificates, the concomitant medications case report form (CRF), and the medical history CRF for each event. The investigators did not record on the CRFs their or the admitting physicians' reasons for hospitalization. The details of the hospitalizations are not included in the CRFs, other than in some text fields on the SAE Worksheet that are not included in the NDA case report tabulations.

Consensus had to be reached between the three CEC members before adjudication of the event was finalized. If the assigned cause of death or hospitalization on initial review was not unanimous, the chairman reviewed the case and attempted to reach consensus. If there was still not a consensus the event was reviewed at the a CEC meeting in order to reach consensus. Agreement rates were not kept as most of the cases were reviewed during CEC meetings.

The CEC adjudicated events into the following categories: For death the categories were sudden cardiac death, MI, progression of HF, stroke, other cardiovascular events (aneurysm, pulmonary embolism, or other), non-cardiovascular causes (sepsis, pneumonia, cancer, or other), unwitnessed death, and unknown. For non-fatal hospitalizations the categories were progression of HF, atrial flutter/fibrillation or supraventricular tachycardia, ventricular arrhythmias, myocardial infarction (including definite MI, probable MI, cardiac procedure related MI), angina (stable or unstable), stroke, other cardiovascular causes (PVD, hypotension, elective surgery, or other), non-cardiovascular causes (pneumonia, COPD, other pulmonary disease, diabetes, elective surgery, or other), and non-event. "Non-events" were not defined in the original CEC charter but were added by the CEC and documented in its minutes from August 25, 2000, as "a hospitalization for 'social reasons', 'check-ups', 'physiological testing', 'respite care', etc." Those minutes also state that a MI occurring within 28 days of a previous MI was not to be considered a new event. New diagnosis of atrial fibrillation was adjudicated even if not considered an SAE (by ICH definition).

COMMENT: Adjudication of endpoints by this blinded CEC should help to increase the objectivity of these somewhat subjective endpoints. However, the failure to record the

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assignments of the admitting physicians or investigators or the initial assignments of the CEC members regarding the reasons for hospitalizations and the lack of information on reasons for hospitalization in the CRFs and CRTs makes verification of these data difficult. I checked a small random sample of these endpoints using copies of the material provided to the CEC and did not find any problems. The changing nature of the criteria for some of these endpoints also makes their interpretation difficult. Note also the problems with non-events discussed in Section 3.4.2.1. A benefit of reducing CV hospitalizations will be convincing only if associated with a reduction in all cause hospitalizations.

3.3.6.5. Safety Endpoints

Safety monitoring in this study included recording of adverse events and periodic vital signs and selected laboratory tests. The schedule of observations is shown in the following table. Particular attention was paid to serum potassium, with appropriate dosage adjustments as noted above.

Table 16: Sponsor's Schedule of Observations for EPEHESUS

Week or Month	Screening (0-14 days post-AMI)	Baseline 3 (> 48 hrs)-14 days post-AMI	Treatment Period														Early Cessa- tion of Final Visit
			Weeks (±3 days)					Months (±10 days)								Every 3 months	
			0 48 hours	1 2	4 3	8 5	3 4	6 5	9 8	12 7	16 6	18 9	21 10	24 11	n + 1 (n)		
Observations/Procedures																	
Informed Consent (b)	X																
Medical history	X																
Physical examination (including height)	X																X
12-lead ECG	X																X
Cardiac enzymes	X																
Kalip Class	X																
Documentation of AMI (c)	X																
Documentation of LV dysfunction (d)	X																
Documentation HF (e)	X																
Vital Signs (hearted HR and BP) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DNA analysis (optional)	X																
Blood sample for potential future analyses (optional) (f)	X			X				X									X
Serum pregnancy test (g)	X																
Clinical safety lab and urinalysis (h)	X			X			X	X			X			X		X	X
Randomization (i)		X															
Serum potassium level (j)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA Functional Class			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QoL assessments (k)	X																
Assessment of endpoints			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication (l)		X															
Medication compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of concurrent medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The safety lab tests measured are listed in the following table.

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Table 17: Sponsor's Safety Lab Tests in EPHEBUS

Hematology	Serum Chemistry	
Hemoglobin	Sodium	Alkaline Phosphatase
Hematocrit	Potassium	SGOT (AST)
White Blood Cell (WBC) Count with Differential	Chloride	SGPT (ALT)
Platelet Count (estimate not acceptable)	Calcium	Creatine Phosphokinase (CPK)
Red Blood Cell (RBC) Count	Inorganic Phosphate	Magnesium
Hemoglobin A _{1c} *	Blood Urea Nitrogen (BUN)	Total Cholesterol
Urinalysis	Creatinine	Low Density Lipoprotein (LDL) Cholesterol
pH	Total Protein	High Density Lipoprotein (HDL) Cholesterol
Ketones	Total Bilirubin (direct and indirect)	Triglycerides
Glucose	Albumin	γ-GT
Specific Gravity	Uric Acid	Lactate Dehydrogenase (LDH)
Protein	Glucose	
Blood		

*Performed at screening only for diabetic patients who were not receiving an oral hypoglycemic agent or insulin at time of randomization.

The sample size was event driven. Randomized patients were to be followed until 1,012 deaths were reported. Assuming the first-year placebo mortality rate to be 15% or greater and up to 6,200 patients to be enrolled over an 18-month period, the target number of 1,012 deaths was expected to occur within the first 30 months of the trial. For testing of all cause mortality endpoint at the 0.05 level of significance, this number of deaths provided 90% power to detect an 18.5% reduction in the rate of death compared with the placebo treatment group. An amendment added a second primary endpoint, with a 0.04 level of significance allocated to all cause mortality and a 0.01 level of significance allocated to CV mortality/hospitalization. The 1,012 deaths provided 88% power to detect the hypothesized 18.5% risk reduction in all cause mortality at a 0.04 level of significance. These calculations assumed a decreasing hazard of mortality, proportional hazards between the 2 treatment groups, and a greater rate of recruitment in the final 12 months of the enrollment period than in the initial 6 months. The sample size calculations were not adjusted for loss-to-follow-up because the percent of patients with unknown vital status at end of study was expected to be below 1%.

3.3.7.2. Analysis Cohorts and Missing Data

The efficacy analyses were performed on data from all randomized patients regardless of whether or not the patients received study medication. The safety analyses were performed on all randomized patients who received at least one dose of double-blind study medication. The one exception to these analysis cohorts is the exclusion of 10 patients of one subinvestigator from site 4017 in Romania. For this subinvestigator the sponsor had evidence of alteration of source documents so that patients appeared to qualify for randomization.

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For the analyses of the primary endpoints patients lost to follow-up were censored as of the date of last follow-up if an endpoint event had not occurred prior to that date. For most other analyses missing data were excluded. If date of last study drug dose was missing, it was imputed to be the date of the last visit at which the patient was known to be off study medication.

3.3.7.3. Pre-specified Analyses

For each of the primary endpoints, treatment groups were compared using the log-rank test stratified by region. For living patients not lost to follow-up, the mortality endpoint events were censored at the study closeout date, August 30, 2002.

Four interim analyses were performed for the DSMB based on a Haybittle-Peto-type rule. The overall alpha level allocated to these interim analyses was 0.002.

3.4. Results

3.4.1. Study Implementation

3.4.1.1. Disposition of Subjects

The disposition of the subjects, excluding the ten patients from the investigator excluded because of source document alteration, is shown in the following table.

Table 18: Sponsor's Disposition of Patients in EPHEBUS

	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%)

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COMMENT: The follow-up rate for the mortality endpoint, about 99.7%, appears to have been excellent. A large majority of eplerenone patients (84%) continued on treatment throughout the study.

3.4.1.2. Subject Demographics and Baseline Characteristics

Subject demographics were balanced between the two groups as shown in the following table.

Table 19: Reviewer's Subject Demographics in EPHESUS

	Placebo	Eplerenone
Mean age	64.2	63.7
Median age	65	64
Age range	22-93	31-94
Age = 65	51%	49%
Age = 75	21%	19%
Male	71%	72%
White	90%	90%
Black	1%	1%
Hispanic	6%	6%

Baseline demographics varied by region, with the majority of Hispanics enrolled in Latin America. Mean age was slightly higher in Canada and Western Europe. Demographics were well balanced between groups within a country or region. A higher percentage of patients were classified as NYHA class I in Latin America (54%) than in the other regions (27%). A higher percentage of patients were diabetic in the US (22%) than in the other countries (10%).

COMMENT: Note that the study population has a wide age distribution including substantial representation of the elderly but is predominantly white males. The placebo group is slightly but not significantly older than the eplerenone group.

Other baseline characteristics were also balanced between the two groups as shown in the following table.

Table 20: Reviewer's Other Baseline Characteristics in EPHESUS

	Placebo	Eplerenone
Current smoker	31%	31%
Diabetic	32%	32%
Hypertensive	53%	51%
Mean SBP	119	119

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	Placebo	Eplerenone
Mean DBP	72	72
Mean pulse	75	75
Q-wave MI	70%	72%
Location of MI (e.g., anterior, etc.)	NA	NA
Days from MI to randomization	7.3	7.3
Reperfusion	45%	45%
First MI	73%	73%
Killip class 1	15%	15%
Killip class 2	65%	65%
Killip class 3	17%	16%
Killip class 4	3%	3%
Prior heart failure	15%	14%
Mean ejection fraction	0.33	0.33

NA = not available

COMMENT: The two groups appear to be well balanced for most cardiac risk factors.

3.4.1.3. Conduct

3.4.1.3.1. Monitoring

The sponsor's quality assurance group audited 68 of the investigator sites. Note that a subinvestigator's patients at one Romanian site were excluded because of evidence of source document alteration. It is the policy of the sponsor to conduct clinical studies (including study conduct and the archiving of essential documents) in compliance with company standard operating procedures and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

3.4.1.3.2. Protocol Changes and Violations

One hundred thirty-eight patients (59 placebo, 79 eplerenone) violated inclusion and/or exclusion criteria. The most common (>10 patients in either treatment group) violations were documentation of the index MI (8 placebo, 18 eplerenone), stable clinical status at randomization (14 placebo, 7 eplerenone), and acceptable serum potassium level (9 placebo, 14 eplerenone).

Overall 2,858 protocol violations were reported. The majority of the violations were late or missed dates, e.g., the most frequent violation was a schedule visit not occurring during the protocol-specified time window (1,494 occurrences). Other than the ten patients of the Romanian subinvestigator excluded because of evidence of alteration of source documents, no other patients were excluded from the safety or efficacy analyses.

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3.4.1.3.3. Dosing

3.4.1.3.3.1. Study Drug

For all randomized patients, the mean duration of follow-up (time from randomization to either death, last study contact, or 30 August 2002) was 471 days in the placebo group and 482 days in the eplerenone group. The majority of patients (68% placebo, 64% eplerenone) were maintained on the target dose of two tablets (eplerenone 50 mg) daily. The sponsor's summary of exposure is shown in the following table.

Table 21: Sponsor's Summary of Exposure (Treated Patients)

	Placebo N=3301	Eplerenone 25-50 mg QD N=3307
Exposure including gap† (days)		
Mean (SD)	422.1 (225.76)	425.3 (223.31)
Median	441.0	440.0
Range	1-982	1-902
Exposure excluding gap (days)		
Mean (SD)	418.4 (225.54)	422.0 (223.28)
Median	435.0	436.0
Range	1-982	1-894
Patient-years of exposure		
Total (including gap)	3817.8	3853.1
Excluding gap		
Total	3783.9	3823.5
25 mg‡	479.6	619.6
50 mg	3304.3	3203.9
Average daily dose per patient (mg)*		
Mean (SD)	43.5 (8.81)	42.6 (9.60)
Median	47.9	47.7

* Statistically significant

† H Gap = Days when medication was temporarily suspended

‡ Including every other day

3.4.1.3.3.2. Concomitant Therapy

Concomitant medication use was similar between the two groups. To avoid counting temporary medication use during the original hospitalization and for comparison with the development of hyperkalemia, I tabulated medication use at any time after 27 days, shown in the following table.

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Table 22: Reviewer's Selected Medication Use after 27 Days in EPHESUS

	Placebo	Eplerenone
Aspirin	90%	89%
ACE inhibitors	88%	86%
ARB	9%	9%
Beta blockers	82%	81%
Digoxin	23%	21%
Nitrates	67%	67%
Loop diuretics	60%	58%
Other diuretics	16%	14%
Statins	60%	60%
CCB	25%	23%
Antiarrhythmics	16%	17%
Spironolactone	5.3%	3.7%
Spironolactone, n	166	118

ARB = angiotensin receptor blocker

CCB = calcium channel blocker

COMMENT: Note that in this post-MI population beta blocker use, as well as ACE inhibitor use, was substantial. Note also that spironolactone use was not uncommon and significantly more frequent in the placebo group. Spironolactone use in the above table includes use after study medication was discontinued. Because a wide range of drugs, including ones not marketed in the US, were used, I was not able to analyze dosages. While start and stop dates were recorded, there is sufficient variability in the recording to make estimation of duration of therapy extremely difficult.

3.4.2. Efficacy

3.4.2.1. Primary Endpoints

The rates of both primary endpoints, all cause mortality and combined cardiovascular (CV) mortality and CV hospitalizations, were lower in the eplerenone group. The rates of the primary endpoints are shown in the following table.

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Table 23: Sponsor's Analysis of Primary Endpoints in EPHEBUS

	Placebo N=3313	Eplerenone 25-50 mg QD N=3319	p-value [†]	Risk Ratio [‡]	95% CI for Risk Ratio [‡]
All cause mortality	554 (16.7%)	478 (14.4%)	0.008	0.85	(0.75, 0.95)
CV mortality/hospitalization [#]	993 (30.0%)	885 (26.7%)	0.002	0.87	(0.79, 0.95)

Source: Table T8.1

Note: Patients may be counted in both endpoints. The analysis is based on the time to the first occurrence of the event.

† From a log-rank test for equality of time-to-event distribution stratified by region.

‡ Based on a proportional hazards model including treatment as the only factor stratified by region. 95% confidence interval is based on the Wald test.

CV hospitalizations included in endpoint are hospitalizations due to HF, recurrent AMI, stroke, or ventricular arrhythmia.

The first primary endpoint, all-cause mortality, was allocated 0.04 of a, adjusted down to 0.038 for the interim analyses. The second primary endpoint was allocated 0.01 of a.

A Kaplan-Meier plot of cumulative mortality is shown in the following figure.

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