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**GENERIC DRUG NAME and/or COMPOUND NUMBER:** Eplerenone / SC-066110

**PROTOCOL NO.**: A6141116

**PROTOCOL TITLE**: A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Early Treatment With Eplerenone in Patients With Acute Myocardial Infarction (Also Known as the Reminder Study)

**Study Centers**: A total of 65 centers in 11 countries took part in the study and enrolled the subjects which included 7 sites in Canada, 4 in Poland, 7 in Spain, 5 in the Czech Republic, 4 in Hungary, 8 in the United Kingdom, 8 in France, 5 in Slovakia, 12 in Germany, 3 in Greece, and 2 in the Netherlands.

**Study Initiation and Final Completion Dates:** 28 September 2010 to 29 October 2012

**Phase of Development**: Phase 4

**Study Objectives:**

Primary objective: To assess the impact of eplerenone on cardiovascular (CV) mortality and morbidity in subjects with acute myocardial infarction (AMI) when initiated within the first 24 hours of onset of symptoms (preferably during the first 12 hours).

Secondary objectives: To investigate the effect of eplerenone on serum biomarkers of collagen metabolism/myocardial fibrosis (eg, procollagen type III N-terminal peptide [PIIINP], carboxyterminal telopeptide of type I collagen [ICTP], procollagen type 1 N-terminal propeptide [PINP]) and CV risk (eg, [ADMA] adult onset diabetes mellitus [DM], adiponectin) and to potentially relate these measures to clinical outcomes.

Safety was also assessed throughout the study by a Data and Safety Monitoring Board (DSMB) reviewing the incidence of nature of adverse events (AEs) reported in each group.

**METHODS**

**Study Design:** This was a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial in subjects with AMI. Following emergency room/ambulance evaluation/diagnosis, eligible subjects were randomized (1:1 ratio) and treated, in addition to standard of care for an AMI, for more details on treatment see Section Study Treatment.

The schedule of study activities is provided in Table 1.

## Table 1. Timetable of Study Procedures/Evaluations

| Protocol Activity | Screening | Treatment | | | | | | | | End of Study/ET |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | Week 1 | Week 4 | 3 Months | 6 Months | 9 Months | 12 Months | 15 Months | 18 Months | Final Visit[a] |
| | Day 1 | Day 1 | Period 2 | Period 3 | Blood Test[b] | Period 4 | Blood Test[b] | Period 5 | Blood Test[b] | Period 6 | Study End |
| Study Days | 1 | 1 | 7 | 28 | 90 | 180 | 270 | 360 | 450 | 540 | |
| Window | | | ±3 | ±5 | ±10 | ±10 | ±10 | ±10 | ±10 | ±10 | |
| Informed consent | X | | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Physical examinations, vitals | X | | | | | | | | | | X |
| Laboratory | | | | | | | | | | | |
| Hematology[c] | X | | | | | | | | | | |
| Blood chemistry[c] | X | | | | | | | | | | |
| Serum potassium and creatinine | | | X | X | X | X | X | X | X | X | X |
| Blood pressure and heart rate | X | | X | X | | X | | X | | X | X |
| Review concomitant medications | X | | X | X | | X | | X | | X | X |
| 12-Lead ECG | X | | | | | X | | | | | X |
| Registration/randomization | | X | | | | | | | | | |
| Study treatment suppy and compliance check | | X | | X | | X | | X | | X | |
| Adverse events assessment | | | X | X | | X | | X | | X | X |

## Table 1. Timetable of Study Procedures/Evaluations

| Protocol Activity | Screening | Treatment | | | | | | | | End of Study/ET |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | Week 1 | Week 4 | 3 Months | 6 Months | 9 Months | 12 Months | 15 Months | 18 Months | Final Visit[a] |
| | Day 1 | Day 1 | Period 2 | Period 3 | Blood Test[b] | Period 4 | Blood Test[b] | Period 5 | Blood Test[b] | Period 6 | Study End |
| Efficacy assessment | | | | | | | | | | | |
| Efficay assessment | | | X | X | | X | | X | | X | X |
| BNP/NTproBNP assessment | | | | X | | X | | X | | X | X |
| Transthoracic echocardiogram | | | | | | X | | | | | X[d] |
| Retained blood sample for biomarker assessment | | X | | | | X[e] | | | | | |

BNP=brain (B-type) natriuretic peptide; ECG=electrocardiogram; ET=Early Termination; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide.

a. End of study for any given subject could vary. Typically, it fell between 3 months and 18 months post-randomization. Subjects followed for greater than 18 months repeated the 15 months and 18 months visits until final study visit.

b. Blood test for serum potassium and creatinine at 3, 9 and 15 months did not require a study visit if it could be facilitated at another surgery/clinic.

c. Additional assessments could have been done at any time during the study at the discretion of the investigator.

d. Echocardiograms were not performed if a subject discontinued before Week 4 visit or after Month 6 visit.

e. Biomarker samples were only drawn from the first 612 randomized subjects.

**Number of Subjects (Planned and Analyzed):** There were 1012 subjects planned for the study. A total of 1025 subjects were screened (48 in Canada, 72 in Poland, 130 in Spain, 84 in Czech Republic, 155 in Hungary, 84 in United Kingdom, 57 in France, 143 in Slovakia, 196 in Germany, 33 in Greece, and 23 in Neatherlands), 1012 subjects were randomized, and 1010 subjects were treated: 505 subjects each received eplerenone or placebo. A total of 422 and 424 subjects in the eplerenone and placebo groups, respectively, completed the study.

**Diagnosis and Main Criteria for Inclusion:** Male and non-pregnant female subjects, ≥18 years old, who experienced an AMI with ST-segment elevation (STEMI) within the previous 24 hours, as confirmed by symptoms and elctrocardigram (ECG) were included.

Excluded were subjects who were scheduled to receive or had received any investigational medication or used any investigational device within 30 days prior to the first dose of study medication; were treated with eplerenone or other aldosterone antagonists within the past 1 month; had known sensitivity or intolerance to eplerenone, spironolactone or tablet excipients; had known low ejection fraction of less than 40% or any previous history of heart failure; had an implanted cardiac defibrillator or awaited cardiac transplant; had hypertrophic cardiomyopathy or uncontrolled hypotension (systolic blood pressure [SBP]<90mm Hg); had concomitant use of or required treatment with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride); had an estimated glomerular filtration rate (eGFR) ≤30ml/min (based on admission serum creatinine and the modification of diet in renal disease formula) or serum creatinine ≥220 µmol/L; had concomitant use of potent cytochrome p450 3A4 (CYP3A4) inhibitors (eg, ketoconazole; itraconazole; nefazodone; troleandomycin; clarithromycin, ritonavir; and nelfinavir) or CYP3A4 inducers(St. John's wort, rifampin; carbamazepine; phenytoin; and phenobarbital); had preexisting significant hepatic disease.

**Study Treatment:** Within 24 hours of the onset of AMI symptoms, screening procedures were completed and subjects were randomized to receive eplerenone 25 mg or placebo once a day (OD). The first dose of study medication was administered as soon as possible following onset of symptoms and randomization. The second dose of drug was administered approximately 24 hours after the first dose but only after serum potassium and creatinine results were available. At Day 2, the dose of study drug could be increased to 50 mg OD (2 tablets) if serum potassium was <5.0 mmol/L and the subject was not taking mild or moderate inhibitors of CYP3A4 (dose not to exceed 25 mg OD). Further dosage adjustments were made in response to measured serum potassium levels as described in Table 2.

All subsequent doses of study drug were taken orally each morning with water (with or without food). At discharge from the hospital, subjects were given enough study drug or placebo to last until the Study Period 3 visit (4 weeks ±5 days after randomization); thereafter, study drug or placebo was dispensed at the Study Period 4 visit (6 months±10 days after randomization) and subsequently every 6 months until completion of the study. Serum potassium was determined within 24 hours of initiation of treatment, again within the first week of treatment, as needed periodically thereafter, at each 3-month interval, and within 1 week following any dose change. Assessment of potassium level could be repeated if the potassium increase was thought to be spurious (ie, due to hemolysis or

recent dosing with a potassium supplement). Dose adjustments were made based on the most recent potassium level as shown in Table 2.

**Table 2. Dose Adjustment After Initiation of Eplerenone Treatment**

| Serum Potassium (mmol/L) | Action | Dose Adjustment |
|---|---|---|
| <5.0 | Increase | 25 mg EOD to 25 mg OD<br>25 mg OD to 50 mg OD |
| 5.0 – 5.4 | Maintain | No dose adjustment |
| 5.5 – 5.9 | Decrease | 50 mg OD to 25 mg OD<br>25 mg OD to 25 mg EOD<br>25 mg EOD to withhold |
| ≥6.0 | Withhold | N/A |

EOD=every other day; OD=once daily; N/A=not applicable.

**Efficacy Endpoints:**

Primary Endpoint:

Composite of time to first event of CV mortality, re-hospitalization or extended initial hospital stay due to diagnosis of heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction ≤40% after 1 month or brain (B-type) natriuretic peptide (BNP) >200 pg/mL or amino-terminal pro-brain (B-type) natriuretic peptide (NT-proBNP) >450 pg/mL (age <50 years); >900 pg/mL (age 50 to 75 years) or >1800 pg/mL (age >75 years) after 1 month.

Secondary Endpoints:

- Time to CV mortality.
- Time to diagnosis of heart failure.
- Time to first and each subsequent episode (after an event-free interval of ≥48 hours) of sustained ventricular tachycardia or ventricular fibrillation.
- Time to first recorded ejection fraction ≤40% (recorded 1 month or later post-randomization).
- Time to BNP >200 pg/mL or NT-proBNP >450, >900 or >1800 pg/mL for ages <50 years, 50 to 75 years, and >75 years, respectively (recorded 1 month or later post-randomization).
- Time to decision to provide an implantable cardiac defibrillator or cardiac resynchronization therapy.
- Time to second or subsequent nonfatal myocardial infarction (MI).
- QRS duration at 6 months post-randomization.
- Left atrial diameter (LAD) recorded each time an echocardiogram was obtained.

- Change in serum levels of biomarkers (ICTP, PINP, PIIINP, interleukins (IL-6), aldosterone, cortisol, and galectin-3) at 6 months post-randomization. Blood samples for biomarkers were stored and analyzed post-completion of the study.

**Safety Evaluations:** Incidence of treatment-emergent adverse events (TEAEs), laboratory evaluations, physical examinations, vital signs (blood pressure [BP] and heart rate [HR]), height, body weight, and 12-lead electrocardiograms were evaluated. Hyperkalemia or hypokalemia, cerebrovascular events, CV events, hepatic events, renal events, and gynecomastia were identified as events of special interest.

**Statistical Methods:**

There were 3 populations that could be included in the analyses mentioned below:

Full Analysis Set (FAS): It was defined as all randomized subjects, regardless of compliance with the study drug and the protocol. Subjects randomized but were not treated were also part of FAS.

Safety Analysis Set: It included all randomized subjects who received at least 1 dose of the study drug (referred to as the treated population). The subject safety data was analyzed under the actual treatment received. Subjects randomized but never treated were excluded from safety analysis set.

Biomarker Analysis Set: It was a subset of FAS subjects with biomarker data (ICTP, PINP, PIIINP, IL-6, aldosterone, cortisol, and galectin-3).

Analysis of Primary Endpoint: The primary statistical analysis for the primary endpoint was performed using the Cox-proportional hazards (PH) regression model with treatment as the factor and adjusting for the following covariates:

- eGFR in mL/min/1.73 $m^2$)
- Previous MI (yes/no)
- Time (in hours) of first dose administered post-onset of symptoms
- Index MI location: (anterior versus all others)

As a secondary analysis of the primary endpoint, other baseline prognostic covariates found to be unbalanced between treatment groups or deemed to be clinically relevant were added to the model above (as an expanded adjusted model) and included:

- Age
- left ventricular ejection fraction (LVEF) ≥ or <30 %
- Body mass index

- Hemoglobin
- HR
- SBP
- Diabetes (yes / no)
- History of hypertension (yes / no)
- Baseline left bundle branch block OR "Baseline QRS >130 msec" (if either 1 was yes versus both were no)
- Atrial fibrillation (AF, yes / no)

Additionally, an unadjusted Cox PH model was also performed for the primary endpoint.

A Kaplan-Meier curve for the cumulative probability of the primary endpoint event rate was generated by each treatment group based on the log-rank test. The number of total subjects-at-risk was presented together with Kaplan-Meier plots.

Analysis of Secondary Endpoints: All of the time-to-event secondary endpoints were analyzed using the same statistical methods (adjusted and unadjusted Cox PH models, with the exception of the expanded adjusted model) as for the primary endpoint.

Subgroup Analysis: Analyses of the primary efficacy endpoint and secondary efficacy endpoints (time-to-event endpoints) were performed using Cox PH models without any covariate adjustment. The test of the treatment-by-subgroup interaction was also performed using the Cox PH regression model including treatment, subgroup, and treatment-by-subgroup interaction terms. Additionally, a forest plot for subgroup comparison was also presented for the following prespecified subgroups:

- Gender (male and female)
- Baseline SBP and pulse pressure (< median and ≥ median)
- Baseline HR (< median and ≥ median)
- Baseline eGFR (<60 mL/mL/1.73 $m^2$ and ≥60 mL/min/1.73 $m^2$)
- Prior beta blocker plus angiotensin-converting enzyme inhibitors (ACEI) plus angiotensin receptor blocker (ARB) use (yes and no)
- Prior ACEI or ARB use (yes and no)
- AF (yes and no)
- Diabetes mellitus (yes and no)

- Anterior or non-anterior MI
- Previous MI (yes or no)
- Acute reperfusion <6 hours, 6 to 24 hours or not reperfused
- Percutaneous coronary intervention (PCI) or thrombolytics used in those reperfused (primary PCI, thrombolysis, or no reperfusion)
- Age ≤75 years or >75 years (per protocol)
- Age <75 years or ≥75 years (per previous eplerenone studies)
- First dose administered 0-12 or 12-24 hours post-onset of symptoms
- Prior hypertension (yes or no)
- Cardiac enzymes raised (yes or no)

Continous Efficacy Variables: For all of the continuous variables (QRS duration, LAD, and BNP and NT-proBNP levels), the actual value and change from the baseline data (if available) was summarized for each visit.

An analysis of covariance (ANCOVA) model was performed for QRS duration and LAD based on the last observation carried forward method including treatment groups with and without adjustments for the 4 covariates listed below:

- Baseline eGFR (in mL/min/1.73 $m^2$)
- Previous MI (yes / no)
- Time (in hours) of first dose administered post-onset of symptom
- Index MI location: (anterior versus all others)

A mixed model repeated measure analysis was performed on the $\log_2$ transformed BNP and NT-ProBNP values to compare the treatment difference. The model was adjusted with and without the same 4 covariates listed above.

The anti-log and geometric means for each treatment by visit were also presented.

Additionally, for BNP and NT-pro-BNP measurements at each visit, the following analyses were performed:

- Descriptive summary statistics (number of subjects [N], mean, standard deviation [SD], median, 25% and 75% quartiles, geometric mean, minimum and maximum)
- Wilcoxon rank-sum test for between treatment difference

- Signed rank test for change from baseline within treatment difference

Box plots with median, 25% and 75% quartiles, 10th and 90th percentiles (instead of minimum and maximum due to extreme outliers) for each treatment.

Analysis of Biomarker Measurements: For the biomarkers measured in this study (aldosterone, PIIINP, ICTP, Galectin-3, Interleukin-6, PINP, and cortisol), an ANCOVA model was performed with $log_2$ transformed biomarker measurements using treatment as the main effect with and without adjusting the same 4 covariates as applied to the BNP and NT-proBNP biomarker analysis. The anti-log and geometric means for each treatment by visit were also presented.

Additionally, for each biomarker measurement at each visit the following analyses were performed:

- Descriptive summary statistics (N, mean, SD, median, 25% and 75% quartiles, geometric mean, minimum and maximum)
- Wilcoxon rank-sum test for between treatment difference
- Signed rank test for change from baseline within treatment difference

Box plots with median, 25% and 75% quartiles, 10th and 90th percentiles (instead of minimum and maximum due to extreme outliers) for each treatment.

Safety Evaluation: Safety data were summarized descriptively.

## RESULTS

**Subject Disposition and Demography**: Subject disposition and a summary of subject discontinuations from treatment is provided in Table 3 and Table 4 respectively. Demograhics and baseline characteristics are shown in Table 5.

**Table 3. Subject Disposition**

| Number (%) of Subjects | Eplerenone | Placebo |
|---|---|---|
| Screened N=1025 | | |
| Assigned to study treatment | 506 | 506 |
| Treated | 505 | 505 |
| Completed | 422 (83.4) | 424 (83.8) |
| Discontinued | 84 (16.6) | 82 (16.2) |

N=number of subjects

**Table 4. Discontinuations From Treatment (Full Analysis Set)**

| Number (%) of Subjects | Eplerenone | Placebo |
|---|---|---|
| Subject Died[a] | 3 (0.6) | 3 (0.6) |
| Relation to study drug or not defined | 75 (14.8) | 68 (13.4) |
| Adverse event | 3 (0.6) | 0 |
| Insufficient clinical response | 0 | 1 (0.2) |
| Lost to follow-up | 16 (3.2) | 14 (2.8) |
| No longer willing to participate in study | 48 (9.5) | 48 (9.5) |
| Protocol violation | 2 (0.4) | 1 (0.2) |
| Did not meet entrance criteria | 1 (0.2) | 0 |
| Study terminated by sponsor | 0 | 1 (0.2) |
| Other | 5 (1.0) | 3 (0.6) |
| Related to Study Drug | 1 (0.2) | 3 (0.6) |
| Adverse event | 1 (0.2) | 3 (0.6) |
| Not Related to Study Drug | 6 (1.2) | 8 (1.6) |
| Adverse event | 6 (1.2) | 8 (1.6) |
| Total | 84 (16.6) | 82 (16.2) |

Note: End of study summary pages could not be retrieved for 2 subjects at 1 Site. These subjects were considered to be lost to follow-up and counted as discontinued in this summary.
a. The count of deaths was 2 (0.4%) in the eplerenone group due to not counting the non-adjudicated death of a subject.

**Table 5. Demographic and Baseline Characteristics (Full Analysis Set)**

| | Eplerenone | Placebo |
|---|---|---|
| Number of subjects, n (%) | 506 | 506 |
| Male | 420 (83.0) | 403 (79.6) |
| Female | 86 (17.0) | 103 (20.4) |
| Age, years | | |
| Mean (SD) | 58.5 (10.8) | 57.8 (11.0) |
| Range | 23-88 | 30-86 |
| Race, n (%) | | |
| White | 475 (93.9) | 471 (93.1) |
| Black | 1 (0.2) | 1 (0.2) |
| Asian | 0 | 5 (1.0) |
| Other | 30 (5.9) | 29 (5.7) |
| Weight, kg | | |
| Mean (SD) | 83.3 (16.0) | 83.6 (15.1) |
| Range | 42.0-160.0 | 47.0-150.0 |
| Height, cm | | |
| Mean (SD) | 172.4 (8.8) | 172.0 (8.7) |
| Range | 149.0-204.0 | 148.0-199.0 |
| Body mass index, $kg/m^2$ | | |
| Mean (SD) | 27.9 (4.5) | 28.2 (4.2) |
| Range | 16.5-49.4 | 18.8-43.8 |
| Heart rate, bpm | | |
| Number of subjects | 505 | 505 |
| Mean (SD) | 72.945 (12.9072) | 74.087 (12.5466) |
| Range | 28.00, 128.00 | 45.00, 120.00 |
| Serum Potassium (mEq/L) | | |
| Number of subjects | 504 | 505 |
| Mean (SD) | 4.065 (0.4639) | 4.046 (0.4469) |
| Range | 2.65, 6.30 | 2.54, 5.90 |

**Table 5. Demographic and Baseline Characteristics (Full Analysis Set)**

| | Eplerenone | Placebo |
|---|---|---|
| eGFR Classification, n (%) | | |
| ≤30 mL/min/1.73 $m^2$ | 0 | 1 (0.2) |
| >30 to <50 mL/min/1.73 $m^2$ | 6 (1.2) | 13 (2.6) |
| ≥50 mL/min/1.73 $m^2$ | 493 (97.4) | 485 (95.8) |
| First dose administered Post-Primary Diagnosis of ST Segment Elevation Myocardial Infarction (hours) | | |
| Number of subjects | 503 | 501 |
| Mean (SD) | 16.38 (7.24) | 15.40 (6.64) |
| Median | 17.67 | 16.00 |
| Range | 0.5, 73.2 | 0.0, 34.5 |

eGFR=estimated glomerular filtration rate; SD=standard deviation, n=number of subjects in category

**Efficacy Results**:

Primary Efficacy Results:

The primary endpoint was a composite of time to first event of CV mortality, re-hospitalization or extended initial hospital stay due to diagnosis of heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction ≤40% after 1 month or BNP >200 pg/mL or NT-proBNP >450 pg/mL (age <50 years); >900 pg/mL (age 50 to 75 years) or >1800 pg/mL (age >75 years) after 1 month. A summary of all adjudicated clinical endpoints is provided in Table 6.

**A total of 92 (18.2%) subjects in the eplerenone group and 149 (29.4%) subjects in the placebo group met the primary endpoint. This represented a statistically significant 42% relative risk reduction for the eplerenone group compared to the placebo group (p <0.0001). A summary of the survival analysis on the primary endpoint is provided in Table 7, and a Kaplan-Meier plot of time to first event is provided in**

Figure 1. Results from the unadjusted survival analysis and the expanded adjusted model of the primary endpoint were comparable to the primary adjusted survival analysis.

**Table 6. Summary of All Adjudicated Clinical Endpoints (Full Analysis Set)**

| | Eplerenone | Placebo |
|---|---|---|
| Total number of subjects | 506 | 506 |
| Total number of all cases adjudicated | 23 | 30 |
| Total number of adjudicated study endpoints | 23 | 24 |
| Total number of adjudicated non-endpoint cases | 0 | 6 |
| Primary endpoint components | | |
| CV mortality | 2 (0.4) | 2 (0.4) |
| Re-hospitalization or extended initial hospital stay due to diagnosis of heart failure | 7 (1.4) | 11 (2.2) |
| Sustained ventricular tachycardia or ventricular fibrillation | 0 | 3 (0.6) |
| Ejection fraction ≤40% 1 month or more post-randomization | 20 (4.0) | 19 (3.8) |
| BNP or NT-proBNP threshold 1 month or more post-randomization | 81 (16.0) | 131 (25.9) |

**Table 6. Summary of All Adjudicated Clinical Endpoints (Full Analysis Set)**

| | Eplerenone | Placebo |
|---|---|---|
| Secondary endpoint events | | |
| Implantation of cardiac defibrillator or cardiac resynchronization therapy | 3 (0.6) | 3 (0.6) |
| Hospitalization due to stroke | 3 (0.6) | 2 (0.4) |
| Second or subsequent non-fatal MI | 10 (2.0) | 6 (1.2) |

BNP=brain (B-type) natriuretic peptide; CV=cardiovascular; MI=myocardial infarction; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide

**Figure 1. Kaplan-Meier Plot of Time to First Primary Endpoint (Full Analysis Set)**

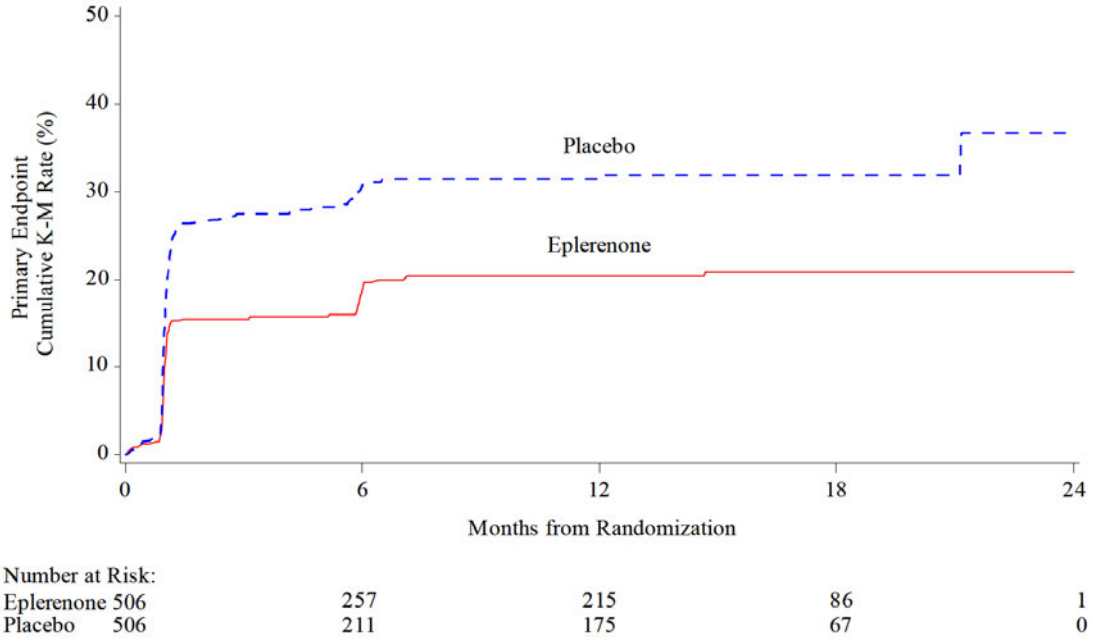



**Table 7. Survival Analysis of the Primary Endpoint (Full Analysis Set)**

| Primary Endpoint | Eplerenone (N=506) | Placebo (N=506) | Between Treatment Comparisons | |
|---|---|---|---|---|
| | | | Hazard Ratio (95% CI) | p-value |
| Event rate: n (%) | 92 (18.2) | 149 (29.4) | | |
| Total person-days at risk[a] | 143245 | 121283 | | |
| Incidence rate (per 100 Person-Days)[b] | 0.064 | 0.123 | | |
| Primary analysis[c] | | | 0.581 (0.446, 0.756) | <0.0001 |
| Secondary analysis[d] | | | 0.579 (0.447, 0.751) | <0.0001 |
| Adjusted model #2[e] | | | 0.587 (0.450, 0.767) | <0.0001 |

**Table 7. Survival Analysis of the Primary Endpoint (Full Analysis Set)**

| Primary Endpoint | Eplerenone (N=506) | Placebo (N=506) | Between Treatment Comparisons | |
|---|---|---|---|---|
| | | | Hazard Ratio (95% CI) | p-value |

CI=confidence interval; eGFR=estimated glomerular filtration rate; MI=myocardial infarction; N=number of subjects in each treatment group; n=number of subjects in category; PH=proportional hazard; QRS=time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization

a. Total person days at risk= the sum of at-risk time, defined as days from randomization to the first event of interest or censoring.

b. Incidence rate (per 100 person-days) = number of subjects with event / total person-days at risk×100.

c. Based on a Cox PH model including treatment as the main effect, adjusting for baseline eGFR, with or without previous MI, time (in hours) of first dose administered post-onset, and location of index MI anterior or non-anterior.

d. Based on a Cox PH model including treatment as the only covariate in the model.

e. Based on a Cox PH model including treatment as the main effect, adjusting for all covariates included in the primary Cox PH model (see note c above), as well as for the following additional covariates: age, body mass index, hemoglobin at baseline, heart rate at baseline, systolic blood pressure at baseline, diabetes (yes/no), hypertension (yes/no), atrial fibrillation (yes/no), and presence of either baseline left bundle branch block or baseline QRS >130 msec (yes/no).

Secondary Efficacy Results:

Survival Analysis of the Secondary Endpoint:

A summary of all adjudicated clinical endpoints is provided in Table 6, a survival analysis is provided in Table 8, and a survival plot of time to first BNP/NT-proBNP component is provided in

Figure 2.

**Table 8. Survival Analysis of the Secondary Endpoints (Adjusted)**

| Secondary Endpoints | Event Rate: n (%) | | Between-Treatment Comparison | |
|---|---|---|---|---|
| | Eplerenone (N=506) | Placebo (N=506) | Hazard Ratio (95% CI)[a] | p-value[a] |
| Cardiovascular mortality | 2 (0.4) | 2 (0.4) | 0.562 (0.050, 6.308) | 0.6406 |
| Re-hospitalization or extended initial hospital stay due to diagnosis of heart failure | 7 (1.4) | 11 (2.2) | 0.726 (0.265, 1.990) | 0.5338 |
| Sustained ventricular tachycardia or ventricular fibrillation | 0 (0.0) | 3 (0.6) | | |
| Ejection fraction ≤40% 1 month or more post-randomization | 20 (4.0) | 19 (3.8) | 1.083 (0.575, 2.040) | 0.8042 |
| BNP or NT-proBNP threshold 1 month or more post-randomization | 81 (16.0) | 131 (25.9) | 0.598 (0.452, 0.791) | 0.0003 |
| Implantation of cardiac defibrillator or cardiac resynchronization therapy | 3 (0.6) | 3 (0.6) | 1.069 (0.213, 5.371) | 0.9353 |
| Second or subsequent non-fatal MI | 10 (2.0) | 6 (1.2) | 1.600 (0.566, 4.525) | 0.3757 |
| All-cause mortality | 3 (0.6) | 3 (0.6) | 0.654 (0.107, 3.999) | 0.6456 |

**Table 8. Survival Analysis of the Secondary Endpoints (Adjusted)**

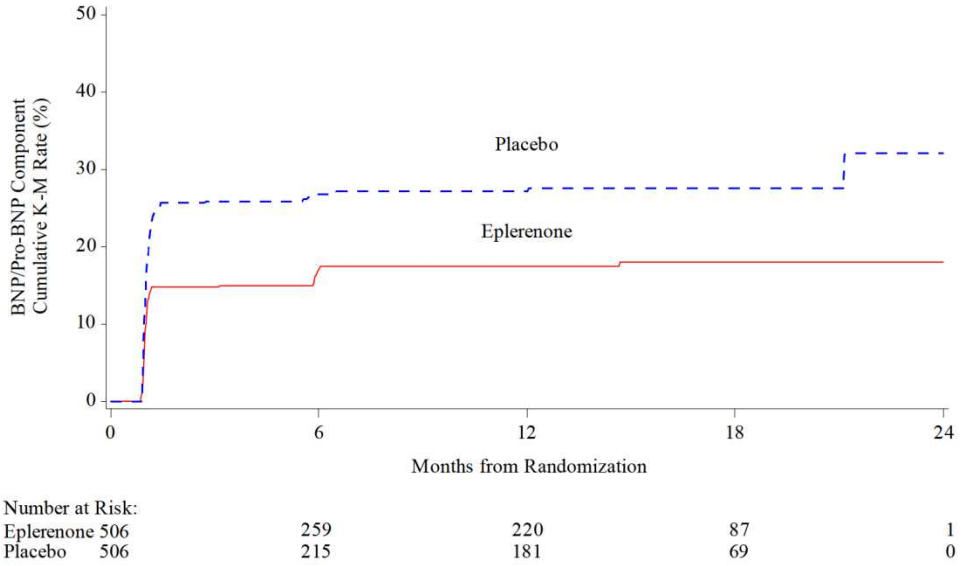
| Secondary Endpoints | Event Rate: n (%) | | Between-Treatment Comparison | |
|---|---|---|---|---|
| | Eplerenone (N=506) | Placebo (N=506) | Hazard Ratio (95% CI)[a] | p-value[a] |

One subject was discontinued from the study due to death of unknown cause. The death was reported in the SAE safety database, but was not adjudicated. This subject's death was included in the event 'All-Cause Mortality.

BNP=brain (B-type) natriuretic peptide; CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; MI=myocardial infarction; N=number of subjects in each treatment group; n=number of subjects in category; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide; PH=proportional hazard; QRS=time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; SAE =serious adverse event

a. Based on a Cox PH model including treatment as the main factor adjusting for baseline eGFR, with or without previous MI, index MI location, and time (in hours) of first dose administered post-onset of index symptom.

**Figure 2. Kaplan-Meier Plot of Time to First BNP/NT-proBNP Component**




BNP=brain (B-type) natriuretic peptide; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide.

BNP and NT-proBNP Levels:

A repeated measure analysis (based on log-transformed data) of the BNP and NT-proBNP levels across visits showed a statistically significant overall treatment effect and visit effect ($p<0.05$), but no statistically significant differences were observed for the treatment-by-visit interactions as represented in Table 9. Summary statistics of BNP and NT-proBNP actual values at baseline and follow-up visits are presented in Table 10.

At Week 4, both mean and median BNP levels were lower for subjects in the eplerenone group (mean of 157.8 pg/mL and median of 87.9 pg/mL) compared with subjects in the placebo group (mean of 199.0 pg/mL and median of 105.0 pg/mL), and between-group differences were statistically significant (p=0.05). At Week 4, both mean and median NT-proBNP levels were lower for subjects in the eplerenone group (mean of 644.1 pg/mL and median of 471.7 pg/mL) compared with subjects in the placebo group (mean of 955.2 pg/mL and median of 498.5 pg/mL); between-group differences were also statistically significant (p=0.02).

**Table 9. Summary of BNP and NT-proBNP (pg/mL) Overall Treatment and Visit Effect Using Repeated Measure Model (Adjusted and Unadjusted( (Full Analysis Set)**

| Model Effect | Testing on the Effects of the Factors/Covariates Listed in the Repeated Models | |
|---|---|---|
| | p-Value (Adjusted Model)[a] | p-Value (Unadjusted Model)[b] |
| BNP (pg/mL) | | |
| Treatment | 0.0085 | 0.0085 |
| Visit | <.0001 | <.0001 |
| Treatment×visit | 0.6749 | 0.744 |
| Baseline eGFR | 0.2531 | |
| Previous MI (yes/no) | 0.4069 | |
| Time from onset of index symptom to first dose (in hours) | 0.0462 | |
| Location of index MI (anterior vs. all other locations) | 0.0435 | |
| Age | <.0001 | |
| Gender | 0.0008 | |
| NT-proBNP (pg/mL) | | |
| Treatment | 0.0181 | 0.1418 |
| Visit | <.0001 | <.0001 |
| Treatment×visit | 0.2149 | 0.1882 |
| Baseline eGFR | 0.0632 | |
| Previous MI (yes/no) | 0.845 | |
| Time from onset of index symptom to first dose (in hours) | 0.0051 | |
| Location of index MI (anterior vs.all other locations) | 0.0726 | |
| Age | <.0001 | |
| Gender | 0.0001 | |

**Table 9. Summary of BNP and NT-proBNP (pg/mL) Overall Treatment and Visit Effect Using Repeated Measure Model (Adjusted and Unadjusted( (Full Analysis Set)**

| Model Effect | Testing on the Effects of the Factors/Covariates Listed in the Repeated Models | |
|---|---|---|
| | p-Value (Adjusted Model)[a] | p-Value (Unadjusted Model)[b] |

Note: For 2 subjects, BNP=0 at 1 visit each. These appear to be data errors, and BNP was defined as missing in these 2 cases. At 1 site, eGFRs for some subjects were entered 'per second' rather than 'per minute'. To correct this problem all eGFRs <2 were multiplied by 60 to convert them to 'per minute'.
BNP=brain (B-type) natriuretic peptide; eGFR=estimated glomerular filtration rate; MI=myocardial infarction; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide
a. The p-value was based on a mixed model repeated measures model with observed value at the given time point as the dependent variable, treatment as the major factor and baseline eGFR, previous MI (yes/no), time (in hours) of first dose administered post onset of index symptom, location of index MI (anterior versus all other locations), age, and gender as the covariates. The data were normalized using the log2 transformation prior to running the model.
b. The p-value was based on a mixed model repeated measures model with observed value at the given time point as the dependent variable, treatment as the major factor and no covariates. The data were normalized using the log2 transformation prior to running the model.

**Table 10. Summary Statistics of BNP and NT-proBNP (pg/mL) Over Time - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | Eplerenone (N=506) | Placebo (N=506) | Total (N=1012) |
|---|---|---|---|---|
| BNP (pg/mL) | | | | |
| Week 4 | N | 179 | 175 | 354 |
| | Mean | 157.8 | 199.0 | 178.1 |
| | SD | 225.2 | 293.1 | 261.4 |
| | Range (Min, Max) | (5, 1950) | (8, 2625) | (5, 2625) |
| | Median | 87.9 | 105.0 | 96.0 |
| | 1st Quartile | 45.0 | 56.0 | 49.9 |
| | 3rd Quartile | 173.0 | 212.5 | 188.0 |
| | Geometric Mean | 87.2 | 109.9 | 97.7 |
| | p-value, between groups[a] | | | 0.0511 |
| Month 6 | N | 114 | 106 | 220 |
| | Mean | 95.3 | 88.7 | 92.1 |
| | SD | 227.8 | 115.0 | 182.0 |
| | Range (Min, Max) | (5, 2366) | (2, 783) | (2, 2366) |
| | Median | 52.5 | 54.4 | 53.7 |
| | 1st Quartile | 23.5 | 32.1 | 27.4 |
| | 3rd Quartile | 98.0 | 111.0 | 100.0 |
| | Geometric Mean | 49.6 | 55.4 | 52.3 |
| | p-value, between groups[a] | | | 0.3461 |
| Month 12 | N | 90 | 87 | 177 |
| | Mean | 61.8 | 72.8 | 67.2 |
| | SD | 73.3 | 122.5 | 100.4 |
| | Range (Min, Max) | (2, 530) | (5, 1043) | (2, 1043) |
| | Median | 37.6 | 42.2 | 40.7 |
| | 1st Quartile | 23.3 | 22.7 | 23.3 |
| | 3rd Quartile | 75.5 | 91.7 | 78.2 |
| | Geometric Mean | 39.3 | 43.5 | 41.3 |
| | p-value, between groups[a] | | | 0.5224 |

**Table 10. Summary Statistics of BNP and NT-proBNP (pg/mL) Over Time - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | Eplerenone (N=506) | Placebo (N=506) | Total (N=1012) |
|---|---|---|---|---|
| Month 18 | N | 44 | 43 | 87 |
| | Mean | 49.4 | 80.3 | 64.6 |
| | SD | 40.5 | 107.8 | 82.1 |
| | Range (Min, Max) | (10, 159) | (5, 610) | (5, 610) |
| | Median | 36.5 | 44.0 | 37.7 |
| | 1st Quartile | 17.2 | 20.8 | 17.6 |
| | 3rd Quartile | 71.7 | 92.7 | 89 |
| | Geometric Mean | 35.3 | 46 | 40.2 |
| | p-value, between groups[a] | | | 0.2181 |
| End of Treatment | N | 176 | 173 | 349 |
| | Mean | 64.1 | 102.7 | 83.3 |
| | SD | 87.5 | 276.4 | 204.9 |
| | Range (Min, Max) | (4, 880) | (2, 3151) | (2, 3151) |
| | Median | 39 | 49.8 | 44 |
| | 1st Quartile | 18 | 26 | 22.3 |
| | 3rd Quartile | 76.2 | 90.2 | 85 |
| | Geometric Mean | 39.2 | 49.6 | 44.1 |
| | p-value, between groups[a] | | | 0.0419 |
| NT-proBNP (pg/mL) | | | | |
| Week 4 | N | 253 | 254 | 507 |
| | Mean | 644.1 | 955.2 | 800 |
| | SD | 712.2 | 1348 | 1088.7 |
| | Range (Min, Max) | (5, 5655) | (16, 11430) | (5, 11430) |
| | Median | 471.7 | 498.5 | 482 |
| | 1st Quartile | 164.1 | 222 | 190.8 |
| | 3rd Quartile | 779 | 1196 | 985.5 |
| | Geometric Mean | 374.1 | 489.6 | 428.1 |
| | p-value, between groups[a] | | | 0.0221 |
| Month 6 | N | 170 | 158 | 328 |
| | Mean | 262.1 | 358.6 | 308.6 |
| | SD | 520.8 | 616.3 | 570 |
| | Range (Min, Max) | (5, 5612) | (9, 3810) | (5, 5612) |
| | Median | 128.2 | 154.5 | 140 |
| | 1st Quartile | 71 | 66 | 68.9 |
| | 3rd Quartile | 296 | 357 | 323.5 |
| | Geometric Mean | 135.1 | 157.4 | 145.4 |
| | p-value, between groups[a] | | | 0.4332 |
| Month 12 | N | 130 | 122 | 252 |
| | Mean | 239.1 | 328 | 282.2 |
| | SD | 503.6 | 553.6 | 529.2 |
| | Range (Min, Max) | (5, 4874) | (10, 3895) | (5, 4874) |
| | Median | 107.7 | 133.2 | 117.5 |
| | 1st Quartile | 49 | 77.5 | 57.9 |
| | 3rd Quartile | 222 | 330 | 258 |
| | Geometric Mean | 110.3 | 151 | 128.4 |
| | p-value, between groups[a] | | | 0.0516 |
| Month 18 | N | 51 | 50 | 101 |
| | Mean | 227.5 | 318.8 | 272.7 |
| | SD | 339.8 | 606.6 | 490 |
| | Range (Min, Max) | (18, 1609) | (15, 3431) | (15, 3431) |
| | Median | 99 | 129.5 | 105 |
| | 1st Quartile | 46 | 52.2 | 52.2 |
| | 3rd Quartile | 198 | 231 | 222.3 |
| | Geometric Mean | 115.6 | 130.4 | 122.7 |
| | p-value, between groups[a] | | | 0.7573 |

**Table 10. Summary Statistics of BNP and NT-proBNP (pg/mL) Over Time - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | Eplerenone (N=506) | Placebo (N=506) | Total (N=1012) |
|---|---|---|---|---|
| End of Treatment | N | 230 | 233 | 463 |
| | Mean | 257.4 | 370.6 | 314.4 |
| | SD | 465.1 | 694.9 | 594.1 |
| | Range (Min, Max) | (2, 4383) | (5, 6932) | (2, 6932) |
| | Median | 125.5 | 146.6 | 133 |
| | 1st Quartile | 57.3 | 60 | 58 |
| | 3rd Quartile | 276.6 | 376 | 321.9 |
| | Geometric Mean | 128.3 | 155.7 | 141.4 |
| | p-value, between groups[a] | | | 0.139 |

NOTE: Only the values of BNP >0 were included.
BNP=brain (B-type) natriuretic peptide; max=maximum; min=minimum; NT-proBNP=amino-terminal pro-brain (B-type) natriuretic peptide; SD=standard deviation.
a. Wilcoxon rank-sum test.

QRS Duration:

A summary of observed QRS durations over time and changes from baseline is provided in Table 11 within and between-treatment comparisons of QRS duration at Month 6 and final visit adjusting for baseline QRS duration and other covariates are provided in Table 12, and the same comparison adjusting for baseline QRS duration only is provided in Table 13. Overall, QRS durations were comparable at Month 6 and between-group differences were not statistically significant using either adjustment model. At the final visit, subjects in the eplerenone group had a slightly lower mean QRS duration (93.73 msec, SD=14.84) compared with subjects in the placebo group (95.34 msec, SD=17.34); differences were statistically significant (p=0.0361) when adjusting for Baseline QRS duration and the 4 covariates, and when adjusting for Baseline QRS duration alone (p=0.0402).

**Table 11. Summary Statistics of QRS Duration (msec) Over Time: Observed Value and Change From Baseline Values - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | QRS Duration (msec) | | |
|---|---|---|---|---|
| | | Eplerenone(N=506) | Placebo (N=506) | Total (N=1012) |
| BL | N[a] | 497 | 494 | 991 |
| | Mean | 94.93 | 94.10 | 94.52 |
| | SD | 21.08 | 17.27 | 19.27 |
| | Range (min, max) | (56.0, 400.0) | (41.0, 166.0) | (41.0, 400.0) |
| | Median | 94.00 | 94.00 | 94.00 |
| | 1st Quartile | 81.00 | 82.00 | 82.00 |
| | 3rd Quartile | 102.00 | 100.00 | 102.00 |
| Month 6 | | | | |
| Observed value | N[a] | 347 | 343 | 690 |
| | Mean | 93.31 | 94.62 | 93.96 |
| | SD | 15.04 | 16.00 | 15.52 |
| | Range (min, max) | (40.0, 184.0) | (60.0, 165.0) | (40.0, 184.0) |
| | Median | 93.00 | 92.00 | 92.00 |
| | 1st Quartile | 84.00 | 84.00 | 84.00 |
| | 3rd Quartile | 100.00 | 100.00 | 100.00 |

**Table 11. Summary Statistics of QRS Duration (msec) Over Time: Observed Value and Change From Baseline Values - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | QRS Duration (msec) | | |
|---|---|---|---|---|
| | | Eplerenone(N=506) | Placebo (N=506) | Total (N=1012) |
| Change from BL | N[a] | 344 | 337 | 681 |
| | Mean | -1.53 | 0.10 | -0.73 |
| | SD | 21.50 | 15.60 | 18.81 |
| | Range (min, max) | (-274.0, 92.0) | (-54.0, 63.0) | (-274.0, 92.0) |
| | Median | 0.00 | 0.00 | 0.00 |
| | 1st Quartile | -10.00 | -8.00 | -8.00 |
| | 3rd Quartile | 7.50 | 8.00 | 8.00 |
| Final visit | | | | |
| Observed value | N[a] | 424 | 418 | 842 |
| | Mean | 93.73 | 95.34 | 94.53 |
| | SD | 14.84 | 17.34 | 16.14 |
| | Range (min, max) | (40.0, 184.0) | (60.0, 200.0) | (40.0, 200.0) |
| | Median | 92.00 | 92.00 | 92.00 |
| | 1st Quartile | 84.00 | 84.00 | 84.00 |
| | 3rd Quartile | 100.00 | 101.00 | 100.00 |
| Change from BL | N[a] | 420 | 412 | 832 |
| | Mean | -1.50 | 1.13 | -0.20 |
| | SD | 20.34 | 17.23 | 18.90 |
| | Range (min, max) | (-274.0, 92.0) | (-68.0, 76.0) | (-274.0, 92.0) |
| | Median | 0.00 | 0.00 | 0.00 |
| | 1st Quartile | -10.00 | -8.00 | -9.00 |
| | 3rd Quartile | 8.00 | 10.00 | 8.50 |

BL=baseline; max=maximum; min=minimum; N=number of subjects; QRS=time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; SD=standard deviation.
a. n denotes the number of subjects without missing QRS duration measurement. Final Visit was the last valid measurement after the study medication.

**Table 12. Within- & Between-Treatment Comparison of QRS Duration (msec) at Month 6 and Final Visit: Adjusting for Baseline QRS Duration and Other Covariates (Full Analysis Set)**

| Visit | Statistics | QRS Duration (msec) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI | p-value |
| Baseline | N[a] | 497 | 494 | | 0.4946 |
| | Mean (SD) | 94.93 (21.08) | 94.10 (17.27) | | |
| Month 6 | | | | | |
| Observed Value | N[a] | 347 | 343 | | |
| | Mean (SD) | 93.31 (15.04) | 94.62 (16.00) | | |
| | LS mean (95% CI)[b] | 93.45 (90.84, 96.07) | 94.91 (92.20, 97.61) | -1.45 (-3.55, 0.65) | 0.1744 |

**Table 12. Within- & Between-Treatment Comparison of QRS Duration (msec) at Month 6 and Final Visit: Adjusting for Baseline QRS Duration and Other Covariates (Full Analysis Set)**

| Visit | Statistics | QRS Duration (msec) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI | p-value |
| Change from baseline | N[a] | 344 | 337 | | |
| | Mean (SD) | -1.53 (21.50) | 0.10 (15.60) | | |
| | LS mean (95% CI)[c] | -1.23 (-3.85, 1.38) | 0.22 (-2.49, 2.93) | -1.45 (-3.55, 0.65) | 0.1744 |
| Within treatment comparison | p-value[c] | 0.3545 | 0.8729 | | |
| Final visit | | | | | |
| Observed Value | N[a] | 424 | 418 | | |
| | Mean (SD) | 93.73 (14.84) | 95.34 (17.34) | | |
| | LS mean (95% CI)[b] | 92.67 (90.10, 95.24) | 94.79 (92.17, 97.41) | -2.12 (-4.10, -0.14) | 0.0361 |
| Change from baseline | N[a] | 420 | 412 | | |
| | Mean (SD) | -1.50 (20.34) | 1.13 (17.23) | | |
| | LS mean (95% CI)[c] | -2.06 (-4.63, 0.51) | 0.06 (-2.56, 2.68) | -2.12 (-4.10, -0.14) | 0.0361 |
| Within treatment comparison | p-value[c] | 0.1158 | 0.9641 | | |

Note: Final visit was the valid measurement after the study medication start date. At one site, eGFRs for some subjects were entered "per second" rather than "per minute". To correct this problem all eGFRs <2 were multiplied by 60 to convert them to "per minute".
CI=confidence interval; LS=least square; max=maximum; min=minimum; N=number of subjects; QRS=time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; SD=standard deviation
a. n denotes the number of subjects with no missing data for baseline visit, and no missing data at both baseline and the post-baseline visit for all post-baseline visits.
b. For observed values at each post-baseline time point, the LS means, LS means difference, 95% confidence intervals and p-values were based on an analysis of covariance model with observed values as the dependent variable, treatment as the major factor, and baseline QRS duration, baseline eGFR, with or without previous MI, time (in hours) of first dose administered post onset of index symptom, and location of index MI (anterior versus all other locations)as covariates.
c. For change from baseline at each post-baseline time point, the LS means, LS mean difference, 95% confidence intervals and p-value were based on the same model as in (b), except that the dependent variable was change from baseline rather observed value.

**Table 13. Within- & Between-Treatment Comparison of QRS Duration (msec) at Month 6 and Final Visit: Adjusting for Baseline QRS Duration Only (Full Analysis Set)**

| Visit | Statistics | QRS Duration (msec) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI | p-value |
| Baseline | N[a] | 497 | 494 | | 0.4946 |
| | Mean (SD) | 94.93 (21.08) | 94.10 (17.27) | | |
| Month 6 | | | | | |
| Observed value | N[a] | 347 | 343 | | |
| | Mean (SD) | 93.31 (15.04) | 94.62 (16.00) | | |
| | LS mean (95% CI)[b] | 93.24 (91.78, 94.69) | 94.71 (93.24, 96.19) | -1.48 (-3.55, 0.59) | 0.1615 |
| Change from baseline | N[a] | 344 | 337 | | |
| | Mean (SD) | -1.53 (21.50) | 0.10 (15.60) | | |
| | LS mean (95% CI)[b] | -1.46 (-2.91, -0.00) | 0.02 (-1.45, 1.49) | -1.48 (-3.55, 0.59) | 0.1615 |
| Within-treatment comparison | p-value[c] | 0.0500 | 0.9772 | | |
| Final visit | | | | | |
| Observed value | N[a] | 424 | 418 | | |
| | Mean (SD) | 93.73 (14.84) | 95.34 (17.34) | | |
| | LS mean (95% CI)[b] | 93.52 (92.14, 94.90) | 95.57 (94.18, 96.97) | -2.05 (-4.01, -0.09) | 0.0402 |
| Change from baseline | N[a] | 420 | 412 | | |
| | Mean (SD) | -1.50 (20.34) | 1.13 (17.23) | | |
| | LS mean (95% CI)[b] | -1.21 (-2.59, 0.16) | 0.84 (-0.55, 2.23) | -2.05 (-4.01, -0.09) | 0.0402 |
| Within treatment comparison | p-value[c] | 0.0843 | 0.2381 | | |

Final visit was the last valid measurement after the study medication start date.
CI=confidence interval; LS=least square; max=maximum; min=minimum; N=number of subjects; QRS=time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; SD=standard deviation.
a. denotes the number of subjects with no missing data for baseline visit, and no missing data at both baseline and the post-baseline visit for all post-baseline visits.
b. For observed values at each post-baseline time point, the LS means, LS means difference, 95% confidence intervals and p-values were based on an analysis of covariance model with observed values as the dependent variable, treatment as the major factor, and baseline QRS duration as covariates.
c. For change from baseline at each post-baseline time point, the LS means, LS mean difference, 95% confidence intervals and p-value were based on the same model as in (b), except that the dependent variable was change from baseline rather observed value.

Left Arterial Diameter:

Within- and between-treatment comparisons of LAD (adjusted model) is provided in Table 14, a summary of observed LAD at Month 6 and the final visit is provided in, Table 15, and using an unadjusted model is provided in Table 16. Overall, group mean LAD were comparable at both time points and there were no statistically significant between-group differences.

**Table 14. Within- & Between-Treatment Comparison of Left Atrial Diameter (cm) at Month 6 and Final Visit (Adjusted) (Full Analysis Set)**

| Visit | Statistics | Left Atrial Diameter (cm) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI[a] | p-value[a] |
| Month 6 Observed Value | N[b] | 268 | 243 | | |
| | Mean (SD) | 3.92 (0.654) | 3.90 (0.703) | | |
| | LS mean (95% CI) | 3.97 (3.84, 4.10) | 3.95 (3.81, 4.09) | 0.02 (-0.10, 0.14) | 0.7123 |
| Final visit Observed Value | N[b] | 393 | 378 | | |
| | Mean (SD) | 3.91 (0.641) | 3.87 (0.658) | | |
| | LS mean (95% CI) | 3.96 (3.85, 4.07) | 3.92 (3.81, 4.04) | 0.04 (-0.05, 0.13) | 0.4105 |

Note: Final visit is the last valid measurement after the study medication start date. To correct errors in units, left atrial diameters (LADs) below 0.8 were multiplied by 10, and values greater than 8 were divided by 10. At one site, eGFRs for some subjects were entered 'per second' rather than 'per minute'. To correct this problem all eGFRs <2 were multiplied by 60 to convert them to 'per minute'.
CI=confidence interval; LS=least square; N=number of subjects.
a. Between-treatment comparisons: for each time point, the LSMeans, 95% CI of LSMeans, LSMeans difference, 95% CI of LSMeans difference, and p-value were based on an analysis of covariance model with observed value at the given time point as the variable, treatment as the major factor and baseline eGFR, previous MI (yes/no), time (in hours) of first dose administered post onset of index symptom, and location of index MI (anterior versus all other locations) as the covariates.
b. N denotes the number of subjects with no missing data at the given time point.

**Table 15. Summary Statistics of Left Atrial Diameter (cm) Over Time: Observed Value - By Treatment Groups and Overall (Full Analysis Set)**

| Visit | Statistics | Eplerenone (N=506) | Placebo (N=506) | Total (N=1012) |
|---|---|---|---|---|
| Month 6 | | | | |
| Observed value | N[a] | 268 | 243 | 511 |
| | Mean | 3.92 | 3.90 | 3.91 |
| | SD | 0.654 | 0.703 | 0.677 |
| | Range (Min, Max) | (1.4, 5.8) | (1.2, 7.5) | (1.2, 7.5) |
| | Median | 3.90 | 3.90 | 3.90 |
| | First Quartile | 3.50 | 3.50 | 3.50 |
| | Third Quartile | 4.30 | 4.30 | 4.30 |
| Final visit | | | | |
| Observed value | N[a] | 393 | 378 | 771 |
| | Mean | 3.91 | 3.87 | 3.89 |
| | SD | 0.641 | 0.658 | 0.650 |
| | Range (Min, Max) | (1.3, 6.3) | (1.0, 7.5) | (1.0, 7.5) |
| | Median | 3.90 | 3.90 | 3.90 |
| | First Quartile | 3.50 | 3.50 | 3.50 |
| | Third Quartile | 4.30 | 4.20 | 4.30 |

a. denotes the number of subjects with non-missing measurement of left atrial diameter at the given time point.
Final visit was the last valid measurement after the study medication start date.
To correct errors in units, left atrial diameters (LADs) below 0.8 were multiplied by 10, and values >8 were divided by 10.
max=maximum; min=minimum; N=number of subjects in each treatment group; SD=standard deviation.

**Table 16. Within- & Between-Treatment Comparison of Left Atrial Diameter (cm) at Month 6 and Final Visit (Unadjusted) (Full Analysis Set)**

| Visit | Statistics | Left Atrial Diameter (cm) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI[a] | p-value |
| Month 6 | | | | | |
| Observed value | N[b] | 268 | 243 | | |
| | Mean (SD) | 3.92 (0.654) | 3.90 (0.703) | | |
| | LS mean (95% CI) | 3.93 (3.84, 4.01) | 3.90(3.81, 3.98) | 0.03 (-0.09, 0.15) | 0.6177 |
| Final visit | | | | | |
| Observed value | N[b] | 393 | 378 | | |
| | Mean (SD) | 3.91 (0.641) | 3.87 (0.658) | | |
| | LS mean (95% CI) | 3.91 (3.84, 3.97) | 3.87 (3.80, 3.93) | 0.04 (-0.05, 0.13) | 0.3931 |

**Table 16. Within- & Between-Treatment Comparison of Left Atrial Diameter (cm) at Month 6 and Final Visit (Unadjusted) (Full Analysis Set)**

| Visit | Statistics | Left Atrial Diameter (cm) | | Between-Treatment Difference Eplerenone-Placebo | |
|---|---|---|---|---|---|
| | | Eplerenone (N=506) | Placebo (N=506) | LS Mean Difference 95% CI[a] | p-value |

Final visit was the last valid measurement after the study medication start date.
CI=confidence interval; LS=least square; N=number of subjects.
a. Between-treatment comparisons: for each time point, the LS Means, 95% CI of LS Means, LS Means difference, 95% CI of LS Means difference, and p-value were based on an analysis of covariance model with observed value at the given time point as the dependent variable, treatment as the major factor and no covariates.
b. N denotes the number of subjects with no missing data at the given time point.

Serum Biomarkers:

Summary statistics of biomarker values at Baseline and Month 6, and the nonparametric test results for between and within treatment differences are presented in Table 17.

**Table 17. Summary Statistics of Biomarker Measurements: Actual Value and Change From Baseline - By Treatment Group and Overall**

| Biomarker (Unit) Visit | Statistic | Biomarker Value | |
|---|---|---|---|
| | | Eplerenone | Placebo |
| Aldosterone (nmol/L) | | | |
| Baseline | N | 265 | 260 |
| | Mean (SD) | 0.250 (0.2162) | 0.255 (0.2004) |
| | Median (range) | 0.190 (0.06, 1.90) | 0.200 (0.06, 1.58) |
| | Geometric mean | 0.199 | 0.206 |
| | p-value, between groups[a] | - | 0.3782 |
| Month 6 | N | 266 | 259 |
| | Mean (SD) | 0.472 (0.9881) | 0.246 (0.1484) |
| | Median (range) | 0.355 (0.09, 15.90) | 0.210 (0.06, 1.13) |
| | Geometric mean | 0.344 | 0.211 |
| | p-value, within group change from baseline[b] | <0.0001 | 0.5552 |
| | p-value, between groups[a] | - | <0.0001 |
| PIIINP (ng/mL) | | | |
| Baseline | N | 266 | 260 |
| | Mean (SD) | 3.97 (1.423) | 4.00 (1.301) |
| | Median (range) | 3.90 (0.4, 11.6) | 4.00 (0.4, 10.1) |
| | Geometric mean | 3.71 | 3.76 |
| | p-value, between groups[a] | - | 0.6368 |
| Month 6 | N | 266 | 259 |
| | Mean (SD) | 4.21 (1.237) | 4.48 (1.570) |
| | Median (range) | 4.20 (1.0, 10.8) | 4.30 (1.2, 11.6) |
| | Geometric mean | 4.01 | 4.22 |
| | p-value, within group change from baseline[b] | 0.0005 | <0.0001 |
| | p-value, between groups[a] | - | 0.1558 |

**Table 17. Summary Statistics of Biomarker Measurements: Actual Value and Change From Baseline - By Treatment Group and Overall**

| Biomarker (Unit) / Visit | Statistic | Biomarker Value | |
|---|---|---|---|
| | | Eplerenone | Placebo |
| ICTP (µg/L) | | | |
| Baseline | N | 266 | 260 |
| | Mean (SD) | 3.89 (1.415) | 3.90 (1.395) |
| | Median (range) | 3.70 (0.2, 11.3) | 3.80 (1.4, 12.7) |
| | Geometric mean | 3.65 | 3.69 |
| | p-value, between groups[a] | - | 0.8307 |
| Month 6 | N | 266 | 259 |
| | Mean (SD) | 4.02 (1.465) | 4.10 (1.545) |
| | Median (range) | 3.70 (0.2, 11.7) | 3.70 (1.8, 15.3) |
| | Geometric mean | 3.78 | 3.87 |
| | p-value, within group change from baseline[b] | 0.0944 | 0.0360 |
| | p-value, between groups[a] | - | 0.6459 |
| Galectin 3 (ng/mL) | | | |
| Baseline | N | 266 | 257 |
| | Mean (SD) | 13.54 (6.927) | 13.62 (7.571) |
| | Median (range) | 11.90 (4.4, 78.0) | 11.80 (4.9, 90.7) |
| | Geometric mean | 12.40 | 12.45 |
| | p-value, between groups[a] | - | 0.9889 |
| Month 6 | N | 265 | 258 |
| | Mean (SD) | 11.88 (3.958) | 11.20 (3.525) |
| | Median (range) | 11.20 (4.1, 39.1) | 10.60 (5.7, 35.4) |
| | Geometric mean | 11.33 | 10.74 |
| | p-value, within group change from baseline[b] | 0.0008 | <0.0001 |
| | p-value, between groups[a] | - | 0.0293 |
| Interleukin-6 (pg/mL) | | | |
| Baseline | N | 265 | 257 |
| | Mean (SD) | 13.541 (14.5310) | 13.746 (14.1808) |
| | Median (range) | 7.900 (1.35, 138.51) | 8.500 (0.88, 129.20) |
| | Geometric mean | 9.289 | 9.301 |
| | p-value, between groups[a] | - | 0.7797 |
| Month 6 | N | 264 | 254 |
| | Mean (SD) | 2.822 (4.1828) | 2.488 (3.8403) |
| | Median (range) | 1.845 (0.58, 47.61) | 1.755 (0.44, 45.22) |
| | Geometric mean | 2.027 | 1.823 |
| | p-value, within group change from baseline[b] | <0.0001 | <0.0001 |
| | p-value, between groups[a] | - | 0.0801 |
| PINP (ng/mL) | | | |
| Baseline | N | 266 | 260 |
| | Mean (SD) | 34.6 (16.13) | 33.4 (16.64) |
| | Median (range) | 32.0 (4, 98) | 29.0 (6, 113) |
| | Geometric mean | 31.1 | 29.9 |
| | p-value, between groups[a] | - | 0.2175 |
| Month 6 | N | 266 | 259 |
| | Mean (SD) | 33.1 (14.96) | 35.4 (15.98) |
| | Median (range) | 30.0 (7, 104) | 32.0 (5, 110) |
| | Geometric mean | 30.1 | 32.2 |
| | p-value, within group change from baseline[b] | 0.1723 | 0.0295 |
| | p-value, between groups[a] | - | 0.0865 |

**Table 17. Summary Statistics of Biomarker Measurements: Actual Value and Change From Baseline - By Treatment Group and Overall**

| Biomarker (Unit) Visit | Statistic | Biomarker Value | |
|---|---|---|---|
| | | Eplerenone | Placebo |
| Serum cortisol (nmol/L) | | | |
| Baseline | N | 266 | 260 |
| | Mean (SD) | 510.8 (387.20) | 536.5 (414.17) |
| | Median (range) | 449.0 (29, 3976) | 450.0 (22, 4876) |
| | Geometric mean | 421.5 | 436.8 |
| | p-value, between groups[a] | | 0.5825 |
| Month 6 | N | 266 | 259 |
| | Mean (SD) | 399.4 (156.16) | 387.2 (157.96) |
| | Median (range) | 379.0 (5, 958) | 366.0 (79, 1103) |
| | Geometric mean | 366.0 | 355.9 |
| | p-value, within group change from baseline[b] | <0.0001 | <0.0001 |
| | p-value, between groups[a] | | 0.3347 |

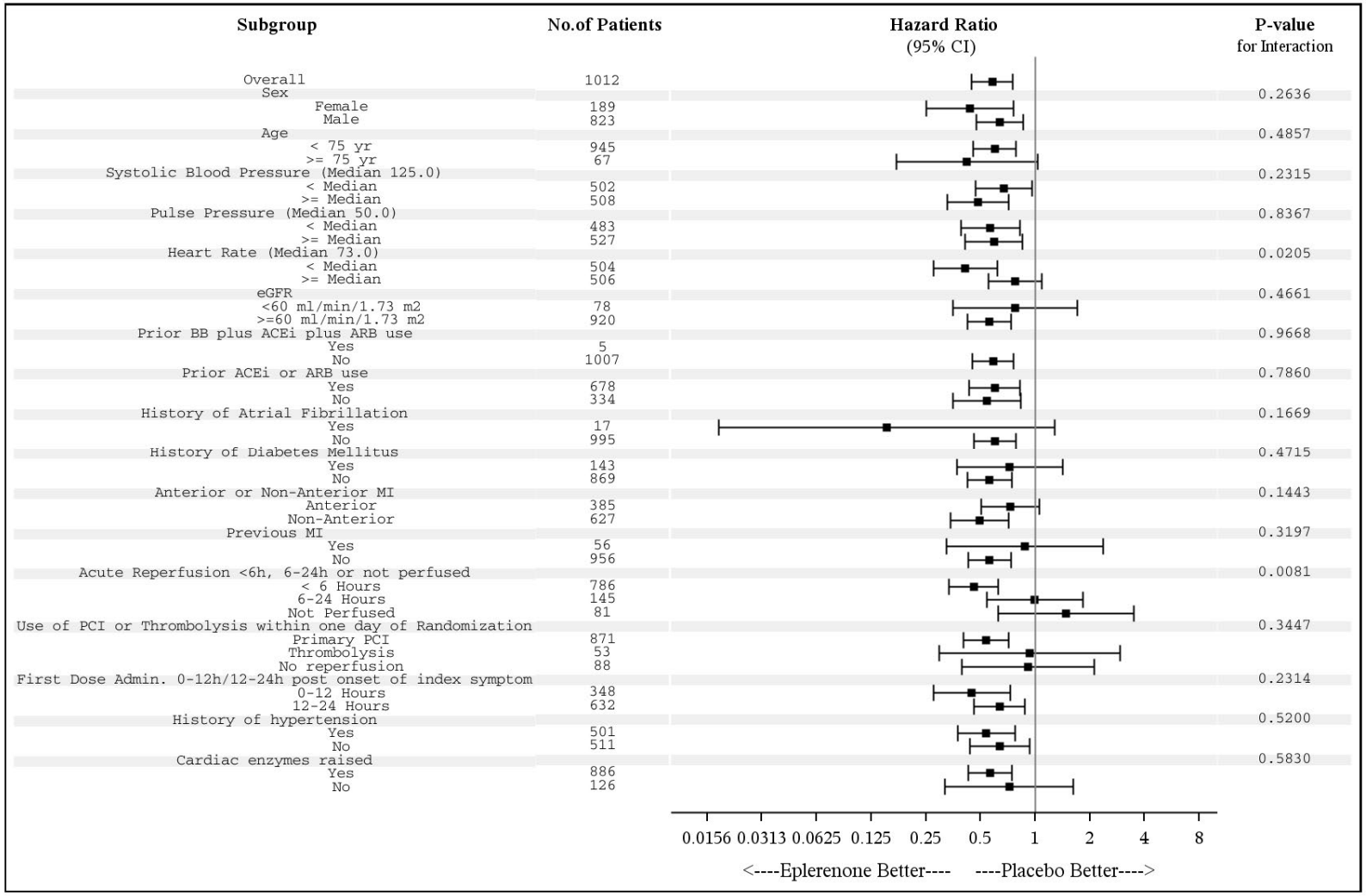
ICTP=carboxyterminal telopeptide of type I collagen; LS=least square; N=number of subjects; PIIINP=procollagen Type III N-terminal peptide; PINP=procollagen Type 1 N-terminal propeptide; SD=standard deviation.

a. Wilcoxon rank-sum test.
b. Signed rank test.

Subgroup Analyses:

Hazard ratios by subgroups on the primary endpoint are summarized in Figure 3. Significant treatment-by-subgroup interactions were observed for the primary endpoint survival analysis on the following subgroups: baseline HR (p=0.0205) and acute reperfusion (p=0.0081). Based on the 95% CI hazard ratios, results on the primary endpoint by subgroup were in general favorable to those subjects who received eplerenone compared with placebo. There were no significant treatment-by-subgroup interactions for the primary endpoint survival analysis using the Wald test for all other subgroups analyzed.

**Figure 3. Forest Plot on Primary Endpoint for All Subjects and Prespecified Sub-groups**




ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; eGFR=estimated glomerular filtration rate; MI=myocardial infarction; PCI=percutaneous coronary intervention

**Safety Results:**

AE/SAE results are not separated out. An overview of the number and percentage of subjects with AEs (all causality and treatment-related) in each treatment group is presented in Table 18. The percentages of subjects with AEs were 59.0% and 58.6% in the eplerenone and placebo groups, respectively. The majority of AEs were considered to be unrelated to study treatment and mild or moderate in severity.

**Table 18. Overview of Treatment-Emergent Adverse Events (All Causalities and Treatment-Related) – Safety Population**

| Number (%) of Subjects | Eplerenone | Placebo |
|---|---|---|
| | All Causalities | |
| Subjects evaluable for AEs | 505 | 505 |
| Number of AEs | 978 | 1012 |
| Subjects with AEs | 298 (59.0) | 296 (58.6) |
| Subjects with SAEs | 100 (19.8) | 101 (20.0) |
| Subjects with severe AEs | 41 (8.1) | 44 (8.7) |
| Subjects discontinued due to AEs | 28 (5.5) | 24 (4.8) |
| Subjects with dose reduced or temporary discontinuation due to AEs | 31 (6.1) | 38 (7.5) |
| | Treatment-Related | |
| Subjects evaluable for AEs | 505 | 505 |
| Number of AEs | 70 | 82 |
| Subjects with AEs | 44 (8.7) | 53 (10.5) |
| Subjects with SAEs | 0 | 0 |
| Subjects with severe AEs | 2 (0.4) | 0 |
| Subjects discontinued due to AEs | 5 (1.0) | 7 (1.4) |
| Subjects with dose reduced or temporary discontinuation due to AEs | 12 (2.4) | 13 (2.6) |

Except for number of AEs, subjects were counted only once per treatment in each row. Based on investigator assessment Medical Dictionary for Regulatory Activities (version 15.1) coding dictionary applied.
AE=adverse event; SAE=serious adverse event.

In either treatment group, TEAEs occurred in ≥2% of subjects. The most common system organ class (SOC) for treatment-related AEs included gastrointestinal disorders (10 [2.0%] and 16 [3.2%] subjects in the eplerenone and placebo groups, respectively), nervous system disorders (6 [1.2%] and 11 [2.2%] subjects in the eplerenone and placebo groups, respectively), and skin and subcutaneous tissue disorders (10 [2.0%] and 5 [1.0%] subjects in the eplerenone and placebo groups, respectively). There were no treatment-related AEs that occurred in ≥2% of subjects in either treatment group. The majority of AEs reported in this study were mild or moderate in intensity. Severe AEs occurred in no more than 4 subjects in either group across all body systems. No subjects in the eplerenone group and 3 subjects in the placebo group experienced ventricular fibrillation, all of which were assessed as severe. An analysis of AEs by a pre-specified tier model was performed. As summarized in Table 19 and provided as a graph in

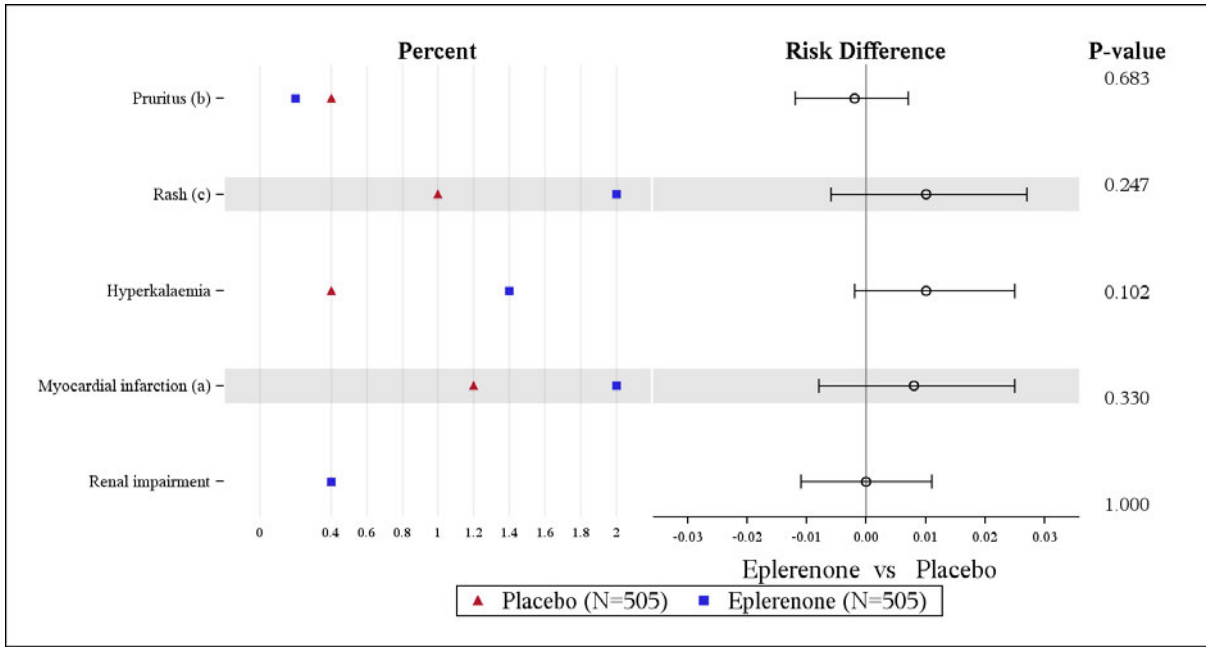
Figure 4, the percentage of subjects with Tier-1 AEs were comparable between treatment groups, no event occurred more than 2.0% in either group, and there were no statistically significant differences between treatment groups.

**Table 19. Summary of Tier-1 Treatment-Emergent Adverse Events (All Causalities, Safety Population)**

| SOC<br>Preferred Term | Number (%) of Subjects<br>Eplerenone | Placebo | Risk Difference (95% CI) | p-value |
|---|---|---|---|---|
| Cardiac disorders | | | | |
| Myocardial infarction[a] | 10 (2.0) | 6 (1.2) | 0.008 (-0.008, 0.025) | 0.330 |
| Metabolism and nutrition disorders | | | | |
| Hyperkalaemia | 7 (1.4) | 2 (0.4) | 0.010 (-0.002, 0.025) | 0.102 |
| Renal and urinary disorders | | | | |
| Renal impairment | 2 (0.4) | 2 (0.4) | 0.000 (-0.011, 0.011) | 1.000 |
| Skin and subcutaneous tissue disorders | | | | |
| Pruritus[b] | 1 (0.2) | 2 (0.4) | -0.002 (-0.012, 0.007) | 0.683 |
| Rash[c] | 10 (2.0) | 5 (1.0) | 0.010 (-0.006, 0.027) | 0.247 |

P-values and confidence intervals are not adjusted for multiplicity and should be used for screening purpose only. Confidence intervals (95% ) were provided to help gauge the precision of the estimates for treatment difference (Risk Difference). Risk Difference is computed as eplerenone versus placebo.
CI=confidence intervals; MedDRA=Medical Dictionary for Regulatory Activities; MI=myocardial infarction; SOC=system organ class.
a. Counts for myocardial infarction include subjects who experienced at least one post-index MI event with preferred term=MI or acute MI (each subject counted only once).
b. Counts for pruritus include subjects who experienced at least 1 event with preferred term=pruritus or pruritus generalized (each subject counted only once).
c. Counts for rash included subjects who experienced at least 1 event with preferred term=rash, rash maculo-papular, rash popular, or rash pruritic (each subject counted only once).

**Figure 4. Graph of Tier 1 Treatment-Emergent Adverse Events (All Causalities)**




N=number of subjects in each treatment group; vs=versus

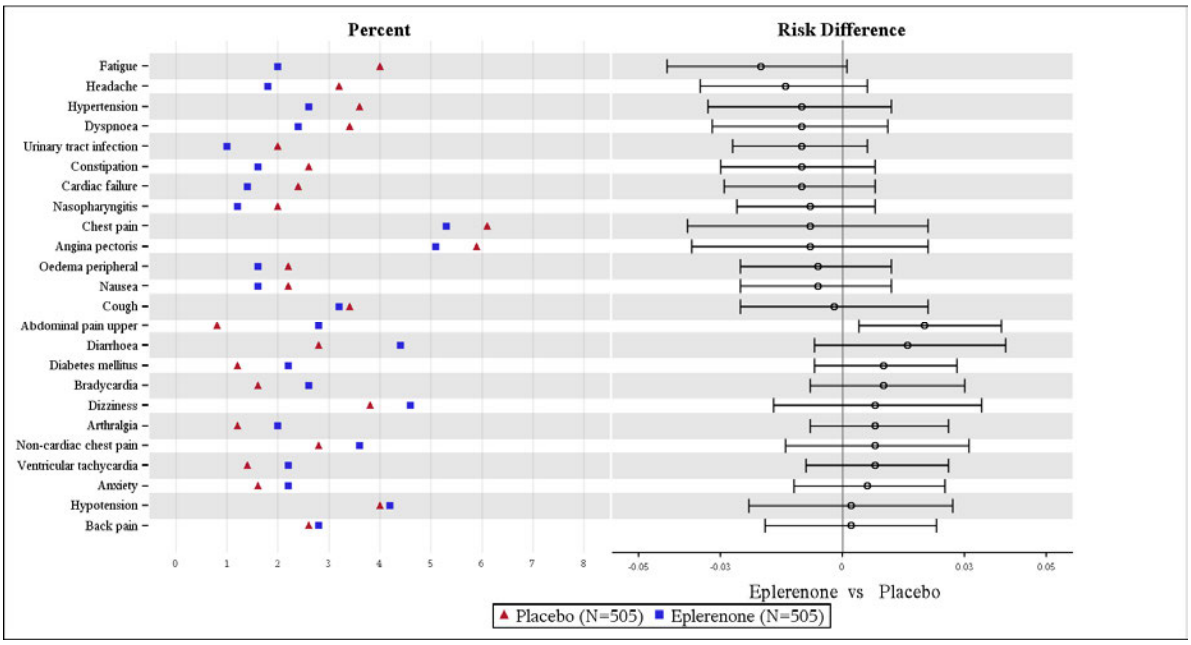
As summarized in Table 20 and provided as a graph in Figure 5, the percentage of subjects with Tier-2 AEs was comparable between treatment groups, and no event occurred more than 6.1% in either group. The most common events reported were angina pectoris, chest pain, diarrhea, hypotension, fatigue, dizziness, non-cardiac chest pain, cough, and hypertension. Statistical testing was not performed on Tier-2 AEs. Risk differences were numerically minor with little variance in the 95% CIs.

**Table 20. Summary of Treatment-Emergent Adverse Events (All Causalities) in ≥2% of Subjects in Either Treatment Group – Safety Population**

| SOC | Number (%) of Subjects | |
|---|---|---|
| Preferred Term | Eplerenone | Placebo |
| Cardiac disorders | | |
| Angina pectoris | 26 (5.1) | 30 (5.9) |
| Bradycardia | 13 (2.6) | 8 (1.6) |
| Cardiac failure | 7 (1.4) | 12 (2.4) |
| Ventricular tachycardia | 11 (2.2) | 7 (1.4) |
| Gastrointestinal disorders | | |
| Abdominal pain upper | 14 (2.8) | 4 (0.8) |
| Constipation | 8 (1.6) | 13 (2.6) |
| Diarrhoea | 22 (4.4) | 14 (2.8) |
| Nausea | 8 (1.6) | 11 (2.2) |
| General disorders and administration site conditions | | |
| Chest pain | 27 (5.3) | 31 (6.1) |
| Fatigue | 10 (2.0) | 20 (4.0) |
| Non-cardiac chest pain | 18 (3.6) | 14 (2.8) |
| Oedema peripheral | 8 (1.6) | 11 (2.2) |
| Infections and infestations | | |
| Nasopharyngitis | 6 (1.2) | 10 (2.0) |
| Urinary tract infection | 5 (1.0) | 10 (2.0) |
| Metabolism and nutrition disorders | | |
| Diabetes mellitus | 11 (2.2) | 6 (1.2) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | 10 (2.0) | 6 (1.2) |
| Back pain | 14 (2.8) | 13 (2.6) |
| Nervous system disorders | | |
| Dizziness | 23 (4.6) | 19 (3.8) |
| Headache | 9 (1.8) | 16 (3.2) |
| Psychiatric disorders | | |
| Anxiety | 11 (2.2) | 8 (1.6) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 16 (3.2) | 17 (3.4) |
| Dyspnoea | 12 (2.4) | 17 (3.4) |
| Vascular disorders | | |
| Hypertension | 13 (2.6) | 18 (3.6) |
| Hypotension | 21 (4.2) | 20 (4.0) |

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. MedDRA (version 15.1) coding applied.
MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class.

**Figure 5. Graph of Tier 2 Treatment-Emergent Adverse Events (≥2% in Either Treatment Group, All Causalities)**




N=number of subjects in each treatment group; vs=versus

A total of 28 (5.5%) and 24 (4.8%) subjects in the eplerenone and placebo groups, respectively, discontinued the study due to AEs and a total of 31 (6.1%) and 38 (7.5%) subjects in the eplerenone and placebo groups, respectively, had temporary discontinuations or dose reductions of the study drug due to AEs as indicated in Table 18.

Treatment related adverse events are presented below in Table 21.

**Table 21. Incidence of Treatment Emergent Adverse Events (Treatment Related) in Safety Population**

| Number of Subjects Evaluable for Adverse Events | Eplerenone (N=505) | Placebo (N=505) |
|---|---|---|
| **Number of subjects with adverse events** | **n (%)** | **n (%)** |
| SOC<br>Preferred Term | | |
| Blood and lymphatic system disorders | 1 (0.2) | 1(0.2) |
| Thrombocytosis | 1 (0.2) | 1 (0.2) |
| Cardiac disorders | 1 (0.2) | 1 (0.2) |
| Bradycardia | 1 (0.2) | 0 |
| Hypertensive heart disease | 0 | 1 (0.2) |
| Eye disorder | 0 | 1 (0.2) |
| Visual impairment | 0 | 1 (0.2) |
| Gastrointestinal disorders | 10 (2.0) | 16 (3.2) |
| Abdominal distension | 1 (0.2) | 2 (0.4) |
| Abdominal pain | 1 (0.2) | 2 (0.4) |
| Abdominal pain upper | 0 | 1 (0.2) |
| Breath odour | 2 (0.4) | 0 |
| Colitis ulcerative | 0 | 1 (0.2) |
| Constipation | 1 (0.2) | 2 (0.4) |

## Table 21. Incidence of Treatment Emergent Adverse Events (Treatment Related) in Safety Population

| Number of Subjects Evaluable for Adverse Events | Eplerenone (N=505) | Placebo (N=505) |
|---|---|---|
| **Number of subjects with adverse events** | **n (%)** | **n (%)** |
| SOC | | |
| Preferred Term | | |
| Diarrhoea | 5 (1.0) | 4 (0.8) |
| Flatulence | 2 (0.4) | 3 (0.6) |
| Lip disorder | 0 | 1 (0.2) |
| Nausea | 2 (0.4) | 1 (0.2) |
| Tooth loss | 0 | 1 (0.2) |
| General disorders and administration site condition | 5 (1.0) | 10 (2.0) |
| Asthenia | 1 (0.2) | 0 |
| Chest discomfort | 2 (0.4) | 0 |
| Chest pain | 2 (0.4) | 1 (0.2) |
| Chills | 0 | 1 (0.2) |
| Fatigue | 1 (0.2) | 8 (1.6) |
| Malaise | 0 | 1 (0.2) |
| Hepatobilliary disorders | 1 (0.2) | 0 |
| Cholecystitis acute | 1 (0.2) | 0 |
| Infection and infestations | 2 (0.4) | 1 (0.2) |
| Gastroenteritis | 1 (0.2) | 0 |
| Gingival infection | 1 (0.2) | 0 |
| Nail infection | 0 | 1 (0.2) |
| Injury, poisoning and procedural complications | 1 (0.2) | 2 (0.4) |
| Fall | 0 | 1 (0.2) |
| Road traffic accident | 0 | 1 (0.2) |
| Subcutaneous hematoma | 1 (0.2) | 0 |
| Investigations | 1 (0.2) | 7 (1.4) |
| Alanine aminotransferase increased | 0 | 1 (0.2) |
| Blood creartinine increased | 0 | 1 (0.2) |
| Blood potassium increased | 1 (0.2) | 1 (0.2) |
| Epidermal growth factor receptor decreased | 0 | 2 (0.4) |
| Glomerular filtration rate decreased | 0 | 2 (0.4) |
| Weight increased | 0 | 1 (0.2) |
| Metabolism and nutrition disorders | 8 (1.6) | 4 (0.8) |
| Decreased appetite | 1 (0.2) | 0 |
| Hypercalcaemia | 1 (0.2) | 0 |
| Hyperkalaemia | 6 (1.2) | 2 (0.4) |
| Hypertriglyceridaemia | 0 | 1 (0.2) |
| Hyperuricaemia | 1 (0.2) | 0 |
| Hypokalaemia | 0 | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 4 (0.8) | 3 (0.6) |
| Back pain | 1 (0.2) | 1 (0.2) |
| Muscle spasms | 1 (0.2) | 0 |
| Musculoskeletal pain | 0 | 1 (0.2) |
| Myalgia | 0 | 1 (0.2) |
| Pain in extremity | 2 (0.4) | 1 (0.2) |
| Sensation of heaviness | 0 | 1 (0.2) |
| Nervous system disorders | 6 (1.2) | 11 (2.2) |
| Dizziness | 5 (1.0) | 4(0.8) |
| Dysgeusia | 0 | 1 (0.2) |
| Headache | 1 (0.2) | 3 (0.6) |
| Hypotonia | 0 | 1 (0.2) |

**Table 21. Incidence of Treatment Emergent Adverse Events (Treatment Related) in Safety Population**

| Number of Subjects Evaluable for Adverse Events | Eplerenone (N=505) | Placebo (N=505) |
|---|---|---|
| **Number of subjects with adverse events** | **n (%)** | **n (%)** |
| SOC | | |
| Preferred Term | | |
| Lethargy | 0 | 1 (0.2) |
| Loss of consciousness | 1 (0.2) | 0 |
| Paraesthesia | 0 | 1 (0.2) |
| Psychiatric disorders | 2 (0.4) | 0 |
| Insomnia | 1 (0.2) | 0 |
| Sleep disorder | 1 (0.2) | 0 |
| Renal and urinary disorders | 2 (0.4) | 4 (0.8) |
| Nocturia | 0 | 1 (0.2) |
| Pollakiuria | 0 | 1 (0.2) |
| Proteinuria | 0 | 1 (0.2) |
| Renal disorder | 1 (0.2) | 0 |
| Renal impairment | 1 (0.2) | 1 (0.2) |
| Reproductive system and breast disorders | 1 (0.2) | 0 |
| Breast discomfort | 1 (0.2) | 0 |
| Respiaratory, thoracic and mediastinal disorders | 2 (0.4) | 4 0.8 |
| Cough | 2 (0.4) | 0 |
| Dyspnoea | 0 | 3 (0.6) |
| Epistaxis | 0 | 1 (0.2) |
| Skin and subcutaneous tissue disorders | 10 (2.0) | 5 (1.0) |
| Acne | 1 (0.2) | 0 |
| Dermatitis allergic | 1 (0.2) | 1 (0.2) |
| Eczema | 1 (0.2) | 0 |
| Erythema | 0 | 1 (0.2) |
| Erythema multiforme | 1 (0.2) | 0 |
| Pruritus | 0 | 1 (0.2) |
| Pruritus generalised | 1 (0.2) | 0 |
| Rash | 3 (0.6) | 2 (0.4) |
| Skin exfoliation | 2 (0.4) | 0 |
| Vascular disorders | 5 (1.0) | 6 (1.2) |
| Circulatory collapse | 1 (0.2) | 0 |
| Hypertension | 0 | 1 (0.2) |
| Hypotension | 5 (1.0) | 5 (1.0) |
| Total preferred term events | 70 | 82 |

Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities had been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild. Included data up to 9999 days after last dose of study drug. When a dictionary other than MedDRA was used, percentages of gender specific events were calculated using the corresponding gender count as denominator. MedDRA (version 15.1) coding dictionary applied.
MedDRA=medical dictionary of regulatory activities; N=number of subjects in each treatment group; n=number of subjects experienced adverse events; SOC=system organ class.

A total of 100 (19.8%) and 101 (20.0%) subjects in the eplerenone and placebo groups reported 141 and 138 serious adverse events (SAEs), respectively (Table 18). No SAEs were considered treatment-related in either treatment group (Table 18). The most frequently occurring SAEs by SOC are listed in Table 22. Events in the cardiac disorders SOC were the most frequently occurring SAEs, with 9.1% of eplerenone-treated subjects and 9.7% of

placebo subjects reporting at least 1 SAE in this class. The only SAE to occur in more than 2% of subjects in either treatment group was angina pectoris (12 [2.4%] subjects in the eplerenone group and 10 [2.0%] in the placebo group). A total of 3 subjects in the eplerenone and 3 subjects in the placebo group died during the conduct of this study.

**Table 22. Treatment-Emergent Serious Adverse Events Occurring in ≥2% of Subjects in Either Treatment Group by System Organ Class, All Causality – Safety Population**

| System Organ Class | Number (%) of Subjects | |
|---|---|---|
| | Eplerenone | Placebo |
| Cardiac disorders | 46 (9.1) | 49 (9.7) |
| General disorders and administration site conditions | 8 (1.6) | 15 (3.0) |
| Nervous system disorders | 14 (2.8) | 11 (2.2) |

Medical Dictionary for Regulatory Activities (version 15.1) coding dictionary applied.

In general, median changes from baseline in laboratory parameters were minimal and similar between treatment groups. There were differences between treatment groups in the change from baseline in serum potassium levels at the final follow-up assessment. The mean (SD) change from baseline in serum potassium was 0.37 (0.571) mEq/L for the eplerenone group and 0.29 (0.520) mEq/L for the placebo group ($p<0.0001$). A summary of mean serum creatinine and potassium values at each visit is provided in Table 23. Changes from baseline in eGFR were minimal and not clinically significant.

A summary of the incidence of laboratory abnormalities without regard to baseline abnormality is provided in Table 24. A total of 215 (43%) subjects in the eplerenone group and 224 (45%) subjects in the placebo group had laboratory abnormalities. The most common abnormalities were eGRF <60 mL/min/1.73 $m^2$, BNP >200 pg/mL, and NT-proBNP >900 pg/mL (Table 24).

**Table 23. Summary of Mean Serum Creatinine and Potassium at Each Visit-Safety Population**

| | Eplerenone | | Placebo | |
|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) |
| Serum creatinine (mg/dL) | | | | |
| Baseline | 505 | 0.911 (0.2021) | 505 | 0.911 (0.2125) |
| Week 1 | 480 | 0.964 (0.1980) | 481 | 0.963 (0.2340) |
| Week 4 | 469 | 0.963 (0.1965) | 467 | 0.956 (0.2117) |
| Month 3 | 405 | 0.968 (0.2025) | 393 | 0.958 (0.2169) |
| Month 6 | 295 | 0.963 (0.2078) | 275 | 0.940 (0.2030) |
| Month 9 | 256 | 0.982 (0.2049) | 247 | 0.966 (0.2150) |
| Month 12 | 247 | 0.966 (0.1917) | 236 | 0.951 (0.2117) |
| Month 15 | 183 | 0.996 (0.2018) | 176 | 0.973 (0.2882) |
| Month 18 | 99 | 0.967 (0.2317) | 93 | 0.936 (0.2323) |
| Month 21 | 23 | 1.026 (0.2212) | 20 | 0.927 (0.2162) |
| Final Visit | 498 | 0.951 (0.2216) | 495 | 0.960 (0.2725) |

**Table 23. Summary of Mean Serum Creatinine and Potassium at Each Visit-Safety Population**

| | Eplerenone | | Placebo | |
|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) |
| Change from baseline P-value | | | | 0.5284 |
| Serum potassium (mEq/L) | | | | |
| Baseline | 504 | 4.065 (0.4639) | 505 | 4.046 (0.4469) |
| Week 1 | 483 | 4.403 (0.4012) | 484 | 4.328 (0.4255) |
| Week 4 | 469 | 4.471 (0.4049) | 470 | 4.358 (0.3897) |
| Month 3 | 404 | 4.498 (0.4165) | 389 | 4.378 (0.3952) |
| Month 6 | 297 | 4.448 (0.3531) | 276 | 4.329 (0.3927) |
| Month 9 | 255 | 4.475 (0.3734) | 248 | 4.346 (0.3448) |
| Month 12 | 248 | 4.461 (0.4011) | 235 | 4.351 (0.4085) |
| Month 15 | 184 | 4.507 (0.4217) | 177 | 4.402 (0.3901) |
| Month 18 | 99 | 4.506 (0.4665) | 92 | 4.367 (0.3603) |
| Month 21 | 23 | 4.505 (0.4184) | 20 | 4.366 (0.3014) |
| Final visit | 498 | 4.441 (0.4282) | 496 | 4.333 (0.3937) |
| Change from baseline P-value[a] | | | | <0.0001 |

Baseline is the last measurement prior to or on the study medication starting date.
Final Visit is the last valid measurement after the study medication start date.
N=number of subjects; SD=standard deviation.
a. The treatment comparison p-values were based on analysis of covariance models with change from baseline as the dependent variable, treatment as the main factor, and the corresponding baseline value as a covariate.

**Table 24. Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) With >50 Subjects Evaluable (Safety Population)**

| Parameter | Criteria | Eplerenone | | Placebo | |
|---|---|---|---|---|---|
| | | N | n (%) | N | n (%) |
| Liver function | | | | | |
| Albumin | <0.8 x LLN | 351 | 4 (1.1) | 336 | 9 (2.7) |
| | >1.2 x ULN | 351 | 1 (0.3) | 336 | 0 (0.0) |
| Renal function | | | | | |
| Blood urea nitrogen | >1.3 x ULN | 441 | 49 (11.1) | 426 | 42 (9.9) |
| Creatinine | >1.3 x ULN | 498 | 20 (4.0) | 495 | 21 (4.2) |
| Electrolytes | | | | | |
| Sodium | <0.95 x LLN | 54 | 0 (0.0) | 51 | 0 (0.0) |
| | >1.05 x ULN | 54 | 0 (0.0) | 51 | 0 (0.0) |
| Potassium | <0.9 x LLN | 498 | 1 (0.2) | 496 | 8 (1.6) |
| | >1.1 x ULN | 498 | 24 (4.8) | 496 | 17 (3.4) |
| Miscellaneous | | | | | |
| Glomerular filtration rate | <60 mL/min/1.73 $m^2$ | 457 | 104 (22.8) | 441 | 97 (22.0) |
| Brain natriuretic peptide | >200 pg/mL | 200 | 36 (18.0) | 200 | 51 (25.5) |
| Pro-brain natriuretic peptide | >900 pg/mL | 287 | 60 (20.9) | 287 | 86 (30.0) |

LLN=lower limit of normal; N=for each laboratory test, the number of subjects with a baseline observation and at least one post-baseline observation; n=for each laboratory test, the number of subjects with a baseline observation and at least one abnormal post-baseline observation; ULN=upper limit of normal.

A summary of the incidence of hyperkalemia and hypokalemia in the laboratory tests is provided in Table 25. There was a higher incidence of hyperkalemia for subjects in the eplerenone group compared with subjects in the placebo group. A total of 28 (5.6%) subjects

and 16 (3.2%) subjects in the eplerenone and placebo groups, respectively, reported potassium levels of >5.5 mEq/L and a total of 8 (1.6%) subjects and 2 (0.4%) subjects in the eplerenone and placebo groups, respectively, reported potassium levels of >6 mEq/L; between-group differences were not statistically significant for either category. Subjects in the eplerenone group reported a statistically significant lower incidence for potassium levels <4 mEq/L and <3.5 mEq/L (p=0.0002 for both categories).

**Table 25. Incidence of Hyperkalemia and Hypokalemia – Safety Population**

| Parameter | Criteria | Eplerenone | | Placebo | | Fisher's Exact Test (P-value) |
|---|---|---|---|---|---|---|
| | | N | n (%) | N | n (%) | |
| Potassium | >6 mEq/L | 498 | 8 (1.6) | 496 | 2 (0.4) | 0.1076 |
| | >5.5 mEq/L | 498 | 28 (5.6) | 496 | 16 (3.2) | 0.0888 |
| | <4 mEq/L | 498 | 177 (35.5) | 496 | 234 (47.2) | 0.0002 |
| | <3.5 mEq/L | 498 | 7 (1.4) | 496 | 28 (5.6) | 0.0002 |

N=number of subjects with a baseline observation for potassium and at least 1 post-baseline observation; n=for each criterion, the number of subjects with a baseline observation for potassium and at least 1 post-baseline observation that satisfies the criterion.

The median changes from baseline to last observation in vital signs were minimal and not clinically significant. The highest median change from baseline was in the pulse rate in the placebo group (-8.00 beats per minute). There were no statistically significant differences between treatment groups in the mean change from baseline to the final follow-up assessment for pulse rate. The observed mean SBP and diastolic blood pressure (DBP) at Week 1 and changes from baseline were comparable between treatment groups. There were statistically significant differences between treatment groups in mean (-0.1 mmHg in the eplerenone group and +2.4 mmHg in the placebo group [p=0.0009] for SBP; -0.3 mmHg in the eplerenone group and +0.8 mmHg in the placebo group [p=0.0049] for DBP).

Findings for physical examinations and ECG were similar between treatment groups at both baseline and the final follow-up assessment, with no clinically significant changes from baseline.

**Conclusions:**

- The results of this study demonstrated that compared with placebo, the addition of eplerenone to standard therapy within 24 hours of symptom onset met the composite primary endpoint of clinical events and established prognostic markers for subjects presenting with acute STEMI without previously known heart failure or LVEF <40%. The observed risk reduction was largely driven by a significant reduction of the BNP and NT-proBNP endpoint at 1-month post-randomization.

- Eplerenone significantly lowered BNP/NT-proBNP levels at 1-month post randomization compared with placebo in this study population.

- Given the small number of adjudicated clinical events as observed in this study, conclusions could not be made as to the benefit of eplerenone treatment compared with placebo on the frequency of clinical events.

- There were no conclusive results from the biomarker analysis in this study population.

- Treatment with eplerenone resulted in a significantly lower frequency of hypokalemia and a higher frequency of hyperkalemia that was not statistically significant compared with placebo. No deaths or discontinuations were reported due to hypokalemia or hyperkalemia. Treatment with eplerenone did not lower systolic BP at 1 week after MI, thus supporting the safety profile of eplerenone.

- The addition of eplerenone to standard medical therapy in this study population was generally well-tolerated, with an overall AE profile consistent with labeling.