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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Inspra® / Eplerenone

PROTOCOL NO.: A6141114

PROTOCOL TITLE:

The Effect of Eplerenone Versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Japanese Subjects With Chronic Heart Failure

Study Centers:

A total of 52 centers in Japan took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates:

30 July 2010 to 07 September 2015

Phase of Development:

Phase 3

Study Objectives:

Primary Objective:

- To evaluate whether eplerenone shows efficacy (based on the primary and secondary endpoints) in chronic heart failure (CHF) subjects with New York Heart Association (NYHA) classification ≥Class II regardless of the severity of heart failure (HF).

Secondary Objectives:

- To compare the efficacy and safety of eplerenone in NYHA Class II CHF subjects with placebo;
- To compare the safety of eplerenone in NYHA Class III/IV CHF subjects with placebo;
- To evaluate the pharmacokinetics (PK) of eplerenone at steady state in Japanese CHF subjects.

METHODS

Study Design:

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in Japanese CHF subjects. Subjects were assigned to receive eplerenone 25 mg or matching

placebo in a 1:1 ratio by centralized randomization with a stratification factor of NYHA (Class II, III/IV) at Randomization and estimated glomerular filtration rate (eGFR) (30 to <50 mL/min/1.73 m^2, ≥50 mL/min/1.73 m^2) at Screening. At Week 1 following randomization and at each visit after Week 4 (except for Months 2, 3, 4), the dose of study drug was adjusted according to serum potassium level.

Frequency of dose (once daily [OD] or once every other day [EOD]) for the first 4 weeks of treatment was determined according to eGFR. After Week 4, the dose was not to exceed 50 mg OD in subjects with eGFR ≥50 mL/min/1.73 m^2 and 25 mg OD in subjects with eGFR 30-<50 mL/min/1.73 m^2. This study was completed when the last subject was followed up for 1 year. Subjects were to be treated for a maximum of 48 months and clinical events were to be captured until study completion. The schedule of activities is summarized in Table 1. The "incidence of cardiovascular (CV) mortality or HF hospitalization" as the primary endpoint was decided to define comparison with placebo as the primary objective and to confirm that the results are consistent with the results of NCT00232180 (The Effect of Eplerenone Versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects With NYHA Class II Chronic Systolic Heart Failure - EMPHASIS-HF Study), in which a hazard ratio of <1 was defined for the primary endpoint.

Table 1. Schedule of Activities

Study Activity	Screening	Treatment Period[a]					End of Study/Early Termination
	V 1	V 2	V 3	V 4	V 5-7	V 8-17	V 18
		Week 0	Week 1	Week 4	Months 2, 3, 4	Months 5-37 (Every 4 Months), and Month 42	Month 48[b]
Visit Window			±2 Days	±4 Days	±4 Days	±2 Weeks	±2 Weeks
Informed consent	X						
Subject background	X						
Vital signs	X	X	X	X	X	X	X
Height	X						
Weight	X	X	X	X	X	X	X
Physical examination including waist circumference	X	X[c]	X	X	X	X	X
Serum potassium	X[d]		X	X		X	X
Laboratory test	X			X		X	X
Estimated glomerular filtration rate	X[d]					X	X
BNP/NT-proBNP	X					X	X
UACR[e]	X					X	X
Pregnancy test	X[f] (Serum or urine)					X[g] (Urine)	X (Urine)
12-Lead electrocardiogram	X						X
Concomitant medications	X	X	X	X	X	X	X
Recording of doses of selected CHF medications	X	X	X	X	X	X	X
NYHA class	X	X	X	X	X	X	X
LVEF (echocardiogram)	X					X	X
Specific activity scale	X			X		X	X
Study endpoints assessment			X	X	X	X	X[h]
Adverse events		X	X	X	X	X	X
Serious adverse event	X	X	X	X	X	X	X
New onset atrial fibrillation/flutter and diabetes			X	X	X	X	X
Randomization		X					
Dispensing of study drug		X		X	X	X[b]	
Initiation of study drug		X					
Study drug compliance check			X	X	X	X	X
PK blood sampling			X	X	X[i]	X[i]	
Sample banking for exploratory study (sample collection)[j]	X						

Table 1. Schedule of Activities

BNP = Brain natriuretic peptide; CHF = chronic heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; UACR = urinary albumin-to-creatinine ratio; V = visit.

a. One (1) month was considered as a 30-day period.
b. The subjects were treated with the study drug for a maximum of 48 months. Some subjects had not reached Month 48.
c. If randomization occurred >30 days after Screening.
d. Within 24 hours prior to randomization.
e. Spot urinary albumin-to-creatinine ratio.
f. Within 72 hours of randomization in women of childbearing potential.
g. Every 8 months in women of childbearing potential (Months 5, 13, 21, 29, 37).
h. Clinical events were captured until study completion (equally applied for those subjects who completed the 48-month follow-up period and those who discontinued). For those subjects who completed the 48-month follow-up period, confirmation of whether events occurred or not was performed every 6 months until the end of the study.
i. Blood sampling for PK evaluation was performed at 2 visits from Month 2 to Month 9.
j. Optional; subjects without consent to this sample collection were allowed to participate in this study.

Number of Subjects (Planned and Analyzed):

A total of 220 subjects were planned to be enrolled in the study (180 with NYHA Class II HF and 40 with NYHA Class III/IV HF); 221 subjects were enrolled, 111 subjects were randomized to the eplerenone group and 110 subjects were randomized to the placebo group.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male or female Japanese CHF subjects of either ischemic or non-ischemic etiology with ≥55 years and NYHA Class ≥II, whose disease duration was at least 4 weeks, with left ventricular ejection fraction (LVEF) ≤30% by echocardiography, or LVEF ≤35% in addition to QRS duration >130 msec; subjects were to be receiving standard therapy (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers or diuretics); serum potassium level ≤5.0 mmol/L within 24 hours prior to randomization; eGFR ≥30 mL/min/1.73 m^2 within 24 hours prior to randomization were included in the study. Randomization had to occur no later than 6 months from the date of admission to hospital for a CV reason; in the absence of a recent admission to hospital for a CV reason, documentation of a plasma concentration of brain natriuretic peptide (BNP) of at least 250 pg/mL or N-terminal proBNP (NT-proBNP) of at least 500 pg/mL for males and 750 pg/mL for females, within 15 days of randomization, was required.

Main Exclusion Criteria: Subjects with a myocardial infarction, stroke, cardiac surgery or percutaneous coronary intervention within 30 days prior to randomization; subjects with serum potassium >5.0 mmol/L or eGFR <30 mL/min/1.73 m^2 were excluded from the study.

Study Treatment:

Subjects received eplerenone 25 mg or matching placebo (1 tablet) OD for the first 4 weeks of treatment. For subjects with an eGFR between 30 to <50 mL/min/1.73 m^2, the initial dose of eplerenone was 25 mg or matching placebo (1 tablet) EOD for the first 4 weeks of treatment. At Week 1 following randomization and at each visit after Week 4 (except for Months 2, 3, 4), the dose of study drug was adjusted according to serum potassium level. After Week 4, the dose was not exceeded 25 mg OD in subjects with eGFR between 30 to <50 mL/min/1.73 m^2 and 50 mg OD in subjects with eGFR ≥50 mL/min/1.73 m^2. The Sponsor provided eplerenone 25 mg tablets and matching placebo tablets.

Efficacy Endpoints:

Primary Endpoints: The primary efficacy endpoint was the first occurrence of CV mortality or HF hospitalization.

Secondary Endpoints: Secondary endpoints, which were measured as time to event, included:

- First occurrence of CV mortality, HF hospitalization or addition/increase of HF medication due to HF worsening;
- All-cause mortality;
- CV mortality;

- All-cause hospitalization;
- HF hospitalization;
- All-cause mortality or all-cause hospitalization;
- HF mortality or HF hospitalization;
- CV hospitalization;
- Addition/increase of HF medication due to HF worsening;
- Fatal/non-fatal myocardial infarction;
- Fatal/non-fatal stroke;
- New onset atrial fibrillation/flutter;
- New onset diabetes mellitus;
- Worsening renal function (if it results in hospitalization);
- Hospitalization for hyperkalemia.

Safety Evaluations:

Safety evaluations included adverse events (AEs), laboratory tests, vital signs, waist circumference, and 12-lead electrocardiogram. AEs that occurred between the first dose of study drug and the last visit were recorded. Serious adverse events (SAEs) were to be reported from the time that the subject provided informed consent through 28 calendar days after the last dose of study drug or study-specified last visit for an individual subject (whichever was later).

Statistical Methods:

The following population datasets were analyzed:

Full Analysis Set (FAS): It was defined as all randomized subjects. All efficacy analyses were performed on the FAS based on the subjects' randomization treatment assignment.

Safety Analysis Set: It was defined as all subjects who received at least 1 dose of study drug. They were analyzed based on their actual treatment received.

Primary Analysis: The hazard ratio of the eplerenone group to the placebo group and the 95% confidence interval (CI) in time to event of the primary endpoint from randomization were estimated in the entire study population (ie, combining both NYHA II and III/IV cohorts), using a Cox proportional hazard model with the NYHA cohort (II, III/IV) and the baseline eGFR (30-<50 ml/min/1.73 m^2, ≥50 ml/min/1.73 m^2) as covariates.

Secondary Analyses of the Primary Endpoint: Firstly, a similar analysis to the primary analysis was performed, using a Cox proportional hazard model without any covariates.

Secondly, similar analyses to the primary endpoint were performed, with the HR estimate using Cox proportional hazard models with the covariates of 1) the NYHA cohort and the underlying heart disease (ischemic/non-ischemic) and 2) the NYHA cohort and the baseline BNP level (< median, ≥ median).

Thirdly, on the NYHA cohort (II and III/IV), similar analyses to the primary analysis were performed with only 1 covariate of the baseline, eGFR classification (30-<50 ml/min/1.73 m^2, ≥50 ml/min/1.73 m^2 or 30-<60 ml/min/1.73 m^2, ≥60 ml/min/1.73 m^2).

Fourthly, similar analysis to the primary analysis were performed, using a Cox proportional hazard model with the NYHA cohort (II, III/IV) and the baseline eGFR classification (30-<60 ml/min/1.73 m^2, ≥60 ml/min/1.73 m^2) as covariates.

Analyses of the Secondary Endpoints: While time-to-event analyses were carried out for the secondary endpoints in the same manner of the analysis for the primary endpoint, a simple summary of the number of events as well as the proportion for those secondary endpoints were to be generated in case of too few events.

Standard safety analyses were conducted based on algorithms or Statistical Analysis Software (SAS®) programs according to the Sponsor data standards. Standard tabulations were produced by treatment group.

For the evaluation of drug safety including AEs and marked clinical laboratory abnormalities, the incidence of treatment-emergent AEs were summarized by the treatment group, system organ class and preferred term. The severity and relationship to study drug of AEs were summarized by the treatment group and system organ class and preferred term. In addition, the incidence of AEs causing discontinuation of study drug and SAEs were summarized by treatment groups.

PK analysis set was defined and consisted of the safety population subjects who had PK data recorded.

RESULTS

Subject Disposition and Demography:

A total of 111 and 110 subjects were randomized to the eplerenone and placebo groups, respectively and all subjects were treated with study drug. Seventy-five (75) (67.6%) subjects in the eplerenone group and 74 (67.3%) subjects in the placebo group completed the treatment.

Thirty-six (36) (32.4%) subjects in the eplerenone group and 36 (32.7%) subjects in the placebo group discontinued the treatment. The most common reasons for treatment discontinuation were AE (16 [14.4%] subjects in the eplerenone group, 18 [16.4%] subjects in the placebo group) and subject died (6 [5.4%] subjects in the eplerenone group, 5 [4.5%] subjects in the placebo group).

The FAS included 111 subjects in the eplerenone group and 110 subjects in the placebo group. The safety analysis set included 111 subjects in the eplerenone group and 110 subjects in the placebo group. The PK analysis set included 111 subjects in the eplerenone group. Subject disposition and data sets analyzed are summarized in Table 2.

Table 2. Disposition of Subjects: FAS

Number of Subjects (%)	Eplerenone N=111	Placebo N=110
Subject randomized:		
Treated	111 (100.0)	110 (100.0)
Completed	75 (67.6)	74 (67.3)
Discontinued from treatment	36 (32.4)	36 (32.7)
Reasons for discontinuation during treatment period:		
Adverse event	16 (14.4)	18 (16.4)
Lab abnormality	1 (0.9)	1 (0.9)
Subject died	6 (5.4)	5 (4.5)
Protocol violation	0	1 (0.9)
No longer willing to participate in study	5 (4.5)	5 (4.5)
Other	8 (7.2)[a]	6 (5.5)[b]
Analyzed for efficacy		
Full analysis set	111 (100.0)	110 (100.0)
Analyzed for safety		
Safety population	111 (100.0)	110 (100.0)
Laboratory data	111 (100.0)	110 (100.0)
Analyzed for pharmacokinetics		
Concentration analysis set	111 (100.0)	0

FAS = full analysis set; N = number of subjects.

a. Poor compliance (2 subjects), subject wanted to receive care from another hospital (1 subject), due to a change of address (1 subject), moved in to a nursing home (1 subject), subject's request to be withdrawn from the study so that they could apply for welfare (2 subjects), moved into care by adult guardianship system (1 subject).

b. Subject wanted to receive care from another hospital (2 subjects), poor compliance (1 subject), subject became unable to comply with the clinical study visit schedule (1 subject), transferred to another hospital (1 subject), worsening of heart failure (1 subject).

The majority of subjects were male (76.6% in the eplerenone group, 82.7% in the placebo group) and the mean age was 69.0 years in the eplerenone group and 68.4 years in the placebo group. The demographic characteristics are summarized in Table 3. The demographic and baseline disease characteristics were generally similar between the treatment groups. The majority of subjects had non-ischemic HF (72.1% in the eplerenone group, 60.9% in the placebo group). The principal cause of HF at Baseline was idiopathic dilated cardiomyopathy (46.8% in the eplerenone group, 43.6% in the placebo group). The principal causes of HF reported more frequently in the eplerenone group compared with the placebo group were hypertension (9 [8.1%] subjects in the eplerenone group, 6 [5.5%] subjects in the placebo group) and atrial fibrillation/flutter (4 [3.6%] subjects in the eplerenone group, 2 [1.8%] subjects in the placebo group). The number of subjects with CV hospitalization within 6 months before randomization was higher in the eplerenone group (69 [62.2%] subjects) than in the placebo group (57 [51.8%] subjects).

Deaths were reported in 17 subjects in the eplerenone group and 10 subjects in the placebo group. More death cases in the eplerenone group had LVEF >15%, ≥75 years, smoker, duration of HF ≥10 years and SAS <4 at Baseline compared with the placebo group.

Table 3. Demographic Characteristics - Randomized Subjects

Number of Subject (%)	Eplerenone N=111	Placebo N=110	Total N=221
Age (years):			
<65	41 (36.9)	36 (32.7)	77 (34.8)
65-<75	38 (34.2)	47 (42.7)	85 (38.5)
->75	32 (28.8)	27 (24.5)	59 (26.7)
Mean	69.0	68.4	68.7
SD	8.7	7.7	8.2
Range (min-max)	55-89	55-89	55-89
Gender:			
Male	85 (76.6)	91 (82.7)	176 (79.6)
Female	26 (23.4)	19 (17.3)	45 (20.4)
Race:			
Asian	111 (100.0)	110 (100.0)	221 (100.0)
NYHA Class:			
NYHA II	91 (82.0)	92 (83.6)	183 (82.8)
NYHA III or IV	20 (18.0)	18 (16.4)	38 (17.2)
eGFR (mL/minute/1.73 m^2) at Baseline:			
30 - <50	37 (33.3)	39 (35.5)	76 (34.4)
≥50	74 (66.7)	71 (64.5)	145 (65.6)
30 - <60	67 (60.4)	66 (60.0)	133 (60.2)
≥60	44 (39.6)	44 (40.0)	88 (39.8)
Mean	57.13	56.05	56.60
SD	15.82	14.60	15.20
Range(min-max)	31.9-129.1	30.2-105.8	30.2-129.1

eGFR = estimated glomerular filtration rate; max = maximum; min = minimum; NYHA = New York Heart Association; N = number of subjects; SD = standard deviation.

The mean duration of study treatment was 786.8 days in the eplerenone group and 774.9 days in the placebo group, and no notable differences in demographics were observed between the treatment groups.

Efficacy Results:

Primary Endpoint: Results of the primary and secondary analyses of the primary efficacy endpoint, CV mortality or HF hospitalization, are summarized in Table 4 and Table 5, respectively. Kaplan-Meier plots of CV mortality or HF hospitalization are presented in Figure 1. CV mortality or HF hospitalization was reported in 33/111 (29.7%) subjects in the eplerenone group and 36/110 (32.7%) subjects in the placebo group and this represents a hazard ratio of 0.85 with a 95% CI of 0.53-1.36 in the primary analysis.

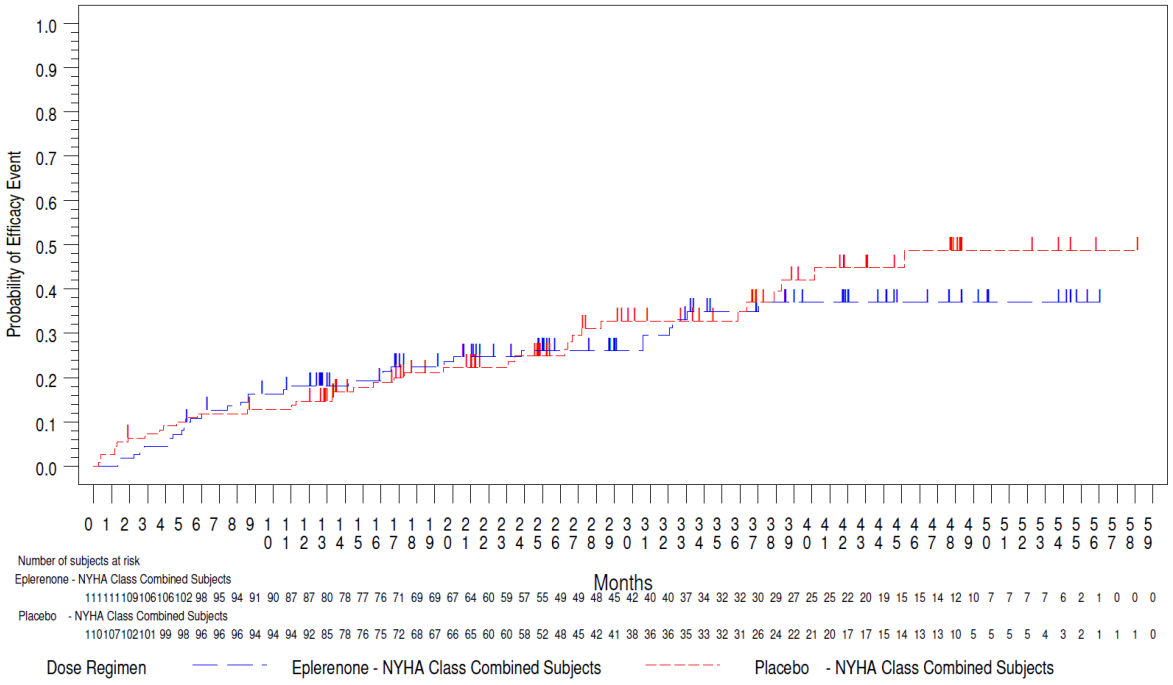
Table 4. Analysis of CV Mortality or HF Hospitalization (Primary Analysis): FAS

	Eplerenone N=111	Placebo N=110	Hazard Ratio[a]	95% CI[a]
CV mortality/HF hospitalization	33 (29.7)	36 (32.7)	0.85	(0.53, 1.36)

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HF = heart failure; NYHA = New York Heart Association.

a. Cox proportional hazard model with covariates of NYHA cohort (II, III/IV) and baseline eGFR (30-<50 mL/min/1.73 m^2, ≥50 mL/min/1.73 m^2).

Figure 1: Kaplan-Meier Plot of Time to CV Mortality or HF Hospitalization: FAS



CV = cardiovascular; FAS = full analysis set; HF = heart failure; NYHA = New York Heart Association.

In the secondary analysis for the subpopulation by NYHA cohort (II, III/IV), CV mortality or HF hospitalization was reported in 21/91 (23.1%) subjects in the eplerenone group and 25/92 (27.2%) subjects in the placebo group in the subjects with NYHA Class II HF (hazard ratio: 0.81, 95% CI: 0.45-1.45) and reported in 12 (60.0%) subjects in the eplerenone group and 11 (61.1%) subjects in the placebo group in the subjects with NYHA Class III/IV HF (hazard ratio: 0.95, 95% CI: 0.41-2.16) (Table 5). The results of secondary analysis using a Cox proportional hazard model without any covariate for total subjects were similar to the results of primary analysis (hazard ratio: 0.89, 95% CI: 0.55-1.42), and other results of secondary analysis using a Cox proportional hazard model with any covariate for total subjects were consistent with the results of primary analysis (hazard ratio: 0.91 [0.57-1.47], 0.87 [0.54-1.39], 0.84 [0.52-1.35]).

Table 5. Analysis of CV Mortality or HF Hospitalization (Secondary Analysis): FAS

	Eplerenone	Placebo	Hazard Ratio	95% CI
NYHA Class II-IV HF (total population)	N=111	N=110		
CV mortality/HF hospitalization	33 (29.7)	36 (32.7)	0.89[a]	(0.55, 1.42)[a]
			0.91[b]	(0.57, 1.47)[b]
			0.87[c]	(0.54, 1.39)[c]
			0.84[d]	(0.52, 1.35)[d]
NYHA Class II HF	N=91	N=92		
CV mortality/HF hospitalization	21 (23.1)	25 (27.2)	0.81[e]	(0.45, 1.45)[e]
			0.75[f]	(0.42, 1.35)[f]
NYHA Class III/IV HF	N=20	N=18		
CV mortality/HF hospitalization	12 (60.0)	11 (61.1)	0.95[e]	(0.41, 2.16)[e]
			1.01[f]	(0.44, 2.30)[f]

BNP = brain natriuretic peptide; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HF = heart failure; NYHA = New York Heart Association.

a. Cox proportional hazard model without covariates.
b. Cox proportional hazard model with covariates of NYHA class and underlying heart disease (ischemic/ non-ischemic).
c. Cox proportional hazard model with covariates of NYHA class and baseline BNP (< median and ≥ median).
d. Cox proportional hazard model with covariates of NYHA class and baseline eGFR (30-<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2).
e. Cox proportional hazard model with covariate of baseline eGFR (30-<50 mL/min/1.73 m^2, ≥50 mL/min/1.73 m^2) by NYHA class.
f. Cox proportional hazard model with covariate of baseline eGFR (30-<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2) by NYHA class.

There was no subpopulation that showed obviously different trend from the total subject group. The results in some subpopulations were difficult to interpret due to the limited number of sample size.

Secondary Endpoints: Results of analysis of secondary endpoints are summarized in Table 6. The results of secondary endpoints were generally consistent with the results of primary endpoint. The number of events in some endpoints was limited.

Table 6. Analysis of Secondary Endpoints: FAS Subjects

	Eplerenone	Placebo	Hazard Ratio	95% CI
NYHA Total	**N=111**	**N=110**		
Class II	**N=91**	**N=92**		
Class III/IV	**N=20**	**N=18**		
CV mortality/HF hospitalization/addition/increase of HF medication due to HF worsening				
NYHA total	42 (37.8)	45 (40.9)	0.86[a]	(0.56, 1.31)[a]
			0.86[b]	(0.56, 1.31)[b]
NYHA Class II	29 (31.9)	33 (35.9)	0.86[c]	(0.52, 1.41)[c]
			0.82[d]	(0.49, 1.35)[d]
NYHA Class III/IV	13 (65.0)	12 (66.7)	0.88[c]	(0.39, 1.94)[c]
			0.94[d]	(0.43, 2.07)[d]
All-cause death				
NYHA total	17 (15.3)	10 (9.1)	1.77[a]	(0.81, 3.87)[a]
			1.73[b]	(0.79, 3.78)[b]
NYHA Class II	10 (11.0)	6 (6.5)	1.74[c]	(0.63, 4.80)[c]
			1.64[d]	(0.59, 4.53)[d]
NYHA Class III/IV	7 (35.0)	4 (22.2)	1.89[c]	(0.55, 6.52)[c]
			1.86[d]	(0.54, 6.38)[d]
CV mortality				
NYHA total	14 (12.6)	6 (5.5)	2.40[a]	(0.92, 6.24)[a]
			2.39[b]	(0.92, 6.23)[b]
NYHA Class II	9 (9.9)	4 (4.3)	2.33[c]	(0.72, 7.58)[c]
			2.27[d]	(0.70, 7.41)[d]
NYHA Class III/IV	5 (25.0)	2 (11.1)	2.66[c]	(0.51, 13.83)[c]
			2.60[d]	(0.50, 13.49)[d]
All-cause hospitalization				
NYHA total	45 (40.5)	58 (52.7)	0.65[a]	(0.44, 0.97)[a]
			0.65[b]	(0.44, 0.96)[b]
NYHA Class II	29 (31.9)	44 (47.8)	0.57[c]	(0.35, 0.91)[c]
			0.54[d]	(0.34, 0.87)[d]
NYHA Class III/IV	16 (80.0)	14 (77.8)	0.91[c]	(0.44, 1.89)[c]
			0.98[d]	(0.48, 2.03)[d]
HF hospitalization				
NYHA total	27 (24.3)	33 (30.0)	0.75[a]	(0.45, 1.25)[a]
			0.75[b]	(0.45, 1.25)[b]
NYHA Class II	17 (18.7)	22 (23.9)	0.73[c]	(0.39, 1.38)[c]
			0.68[d]	(0.36, 1.29)[d]
NYHA Class III/IV	10 (50.0)	11 (61.1)	0.81[c]	(0.34, 1.92)[c]
			0.85[d]	(0.36, 2.01)[d]
All-cause death/all-cause hospitalization				
NYHA total	48 (43.2)	61 (55.5)	0.66[a]	(0.45, 0.97)[a]
			0.66[b]	(0.45, 0.96)[b]
NYHA Class II	32 (35.2)	47 (51.1)	0.59[c]	(0.37, 0.92)[c]
			0.56[d]	(0.36, 0.88)[d]
NYHA Class III/IV	16 (80.0)	14 (77.8)	0.91[c]	(0.44, 1.89)[c]
			0.98[d]	(0.48, 2.03)[d]
HF mortality/HF hospitalization				
NYHA total	29 (26.1)	33 (30.0)	0.81[a]	(0.49, 1.33)[a]
			0.80[b]	(0.49, 1.33)[b]
NYHA Class II	18 (19.8)	22 (23.9)	0.78[c]	(0.42, 1.45)[c]

Table 6. Analysis of Secondary Endpoints: FAS Subjects

	Eplerenone	Placebo	Hazard Ratio	95% CI
NYHA Total	**N=111**	**N=110**		
Class II	**N=91**	**N=92**		
Class III/IV	**N=20**	**N=18**		
			0.72[d]	(0.39, 1.35)[d]
NYHA Class III/IV	11 (55.0)	11 (61.1)	0.88[c]	(0.38, 2.04)[c]
			0.93[d]	(0.40, 2.17)[d]
CV hospitalization				
NYHA total	35 (31.5)	44 (40.0)	0.70[a]	(0.45, 1.10)[a]
			0.70[b]	(0.45, 1.10)[b]
NYHA Class II	23 (25.3)	32 (34.8)	0.66[c]	(0.39, 1.13)[c]
			0.63[d]	(0.37, 1.08)[d]
NYHA Class III/IV	12 (60.0)	12 (66.7)	0.85[c]	(0.38, 1.90)[c]
			0.89[d]	(0.40, 2.00)[d]
Addition/increase of HF medication due to HF worsening				
NYHA total	38 (34.2)	43 (39.1)	0.83[a]	(0.53, 1.28)[a]
			0.83[b]	(0.54, 1.29)[b]
NYHA Class II	26 (28.6)	31 (33.7)	0.84[c]	(0.50, 1.42)[c]
			0.80[d]	(0.48, 1.36)[d]
NYHA Class III/IV	12 (60.0)	12 (66.7)	0.82[c]	(0.37, 1.86)[c]
			0.90[d]	(0.40, 2.01)[d]
Fatal/non-fatal stroke				
NYHA total	3 (2.7)	4 (3.6)	0.79[a]	(0.18, 3.53)[a]
			0.76[b]	(0.17, 3.39)[b]
NYHA Class II	1 (1.1)	4 (4.3)	0.26[c]	(0.03, 2.32)[c]
			0.25[d]	(0.03, 2.29)[d]
NYHA Class III/IV	2 (10.0)	0		
Fatal/non-fatal myocardial infarction				
NYHA total	1 (0.9)	1 (0.9)	1.11[a]	(0.07, 17.85)[a]
			0.95[b]	(0.06, 15.12)[b]
NYHA Class II	1 (1.1)	1 (1.1)	1.11[c]	(0.07, 17.85)[c]
			0.95[d]	(0.06, 15.12)[d]
NYHA Class III/IV	0	0		
New onset atrial fibrillation/flutter				
NYHA total	4 (3.6)	2 (1.8)	2.11[a]	(0.39, 11.56)[a]
			2.26[b]	(0.41, 12.47)[b]
NYHA Class II	1 (1.1)	2 (2.2)	0.51[c]	(0.05, 5.58)[c]
			0.54[d]	(0.05, 5.99)[d]
NYHA Class III/IV	3 (15.0)	0		
New onset diabetes mellitus				
NYHA total	1 (0.9)	2 (1.8)	0.51[a]	(0.05, 5.66)[a]
			0.55[b]	(0.05, 6.09)[b]
NYHA Class II	1 (1.1)	1 (1.1)	1.10[c]	(0.07, 17.66)[c]
			1.08[d]	(0.07, 17.25)[d]
NYHA Class III/IV	0	1 (5.6)		
Worsening renal function (if it results in hospitalization)				
NYHA total	2 (1.8)	2 (1.8)	1.13[a]	(0.16, 8.04)[a]
			0.92[b]	(0.13, 6.53)[b]
NYHA Class II	1 (1.1)	2 (2.2)	0.57[c]	(0.05, 6.28)[c]

Table 6. Analysis of Secondary Endpoints: FAS Subjects

	Eplerenone	Placebo	Hazard Ratio	95% CI
NYHA Total	**N=111**	**N=110**		
Class II	**N=91**	**N=92**		
Class III/IV	**N=20**	**N=18**		
			0.43[d]	(0.04, 4.77)[d]
NYHA Class III/IV	1 (5.0)	0		
Hospitalization for hyperkalemia				
NYHA total	0	0		

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FAS = full analysis set; NYHA = New York Heart Association.

a. Cox proportional hazard model with covariates of NYHA class and baseline eGFR (30-<50 mL/min/1.73 m^2, ≥50 mL/min/1.73 m^2).

b. Cox proportional hazard model with covariates of NYHA class and baseline eGFR (30-<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2).

c. Cox proportional hazard model with baseline eGFR (30-<50 mL/min/1.73 m^2, ≥50 mL/min/1.73 m^2) covariates.

d. Cox proportional hazard model with baseline eGFR(30-<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2) covariates.

Adjudicated all-cause death events by the independent Endpoint Adjudication Committee in blinded fashion are shown in Table 7. The most frequent cause of death was worsening HF (7 subjects in the eplerenone Group, 3 subjects in the placebo group). All of the 3 HF deaths in the placebo group were simply due to worsening of HF, while 4 of the 7 HF deaths in the eplerenone group were complicated simultaneously by other fatal events (rhabdomyolysis, multi-organ failure, disseminated intravascular coagulation, emphysema, sepsis, cardiac sarcoidosis, etc.). All of these events were considered not related to treatment, except rhabdomyolysis. Investigator reported event terms for adjudicated death due to worsening HF is presented in Table 8. CV risk factors among death cases are summarized in Table 9.

Table 7. Adjudicated Death Events: FAS

Adjudicated event name	Eplerenone N=111 (%)		Placebo N=110 (%)	
All-cause mortality	17		10	
Worsening heart failure	7	(41.2)	3	(30.0)
Sudden cardiac death	4	(23.5)	2	(20.0)
Stroke-haemorrhagic	1	(5.9)	1	(10.0)
Myocardial infarction	1	(5.9)	0	
Arrhythmia - ventricular fibrillation	1	(5.9)	0	
Cancer	2	(11.8)	2	(20.0)
Infection	1	(5.9)	1	(10.0)
Trauma	0		1	(10.0)

Additional analysis after unblinding.
FAS = full analysis set.

Table 8. Adjudicated Death due to Worsening Heart Failure: FAS

Serial Number	Adjudicated	Reported by Investigators as	Cause of Death in Safety Database (From SAE Reports) Preferred Term (MedDRA v18.0)
Eplerenone			
1	Worsening HF	Worsening HF	Cardiac failure
2	Worsening HF	Other CV event	Multiorgan failure Disseminated intravascular coagulation rhabdomyolysis Gastroenteritis
3	Worsening HF	Emphysema	Cardiac failure Emphysema
4	Worsening HF	Worsening HF	Cardiac failure
5	Worsening HF	Worsening HF	Cardiac failure Disseminated intravascular coagulation sepsis
6	Worsening HF	Worsening HF	Cardiac sarcoidosis
7	Worsening HF	Worsening HF	Cardiac failure Condition aggravated
Placebo			
8	Worsening HF	Worsening HF	Cardiac failure Condition aggravated
9	Worsening HF	Worsening HF	Cardiac failure Disease progression Cardiac hypertrophy
10	Worsening HF	Worsening HF	Cardiac failure Cardiac failure congestive Cardiac arrest Respiratory arrest

Additional analysis after unblinding.
CV = cardiovascular; FAS = full analysis set; HF = heart failure; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; v = version.

Table 9. Main CV Risk Factors per All-Cause Death Events: FAS

Adjudicated Event Name	Eplerenone					Placebo				
	Total	History of Myocardial Infarction	History of Stroke	History of Myocardial Infarction and Stroke	Coexisting of Atrial Fibrillation/ Flutter	Total	History of Myocardial Infarction	History of Stroke	History of Myocardial Infarction and Stroke	Coexisting of Atrial Fibrillation/ Flutter
All cause death	17	8	5	3	7	10	5	2	1	5
Worsening heart failure	7	1	3	1	4	3	1	0	0	2
Sudden cardiac death	4	3	1	1	2	2	1	0	0	0
Stroke – haemorrhagic	1	1	1	1	0	1	0	1	0	1
Myocardial infarction	1	1	0	0	0	0	0	0	0	0
Arrhythmia – ventricular fibrillation	1	1	0	0	1	0	0	0	0	0
Cancer	2	1	0	0	0	2	1	0	0	1
Infection	1	0	0	0	0	1	1	0	0	0
Trauma	0	0	0	0	0	1	1	1	1	1

Additional analysis after unblinding.
CV = cardiovascular; FAS = full analysis set.

All-cause mortality was reported in 17 (15.3%) subjects in the eplerenone group and 10 (9.1%) subjects in the placebo group and this represents a hazard ratio of 1.77 with a 95% CI of 0.81-3.87. CV mortality was reported in 14 (12.6%) subjects in the eplerenone group and 6 (5.5%) subjects in the placebo group and this represents a hazard ratio of 2.40 with a 95% CI of 0.92-6.24.

All-cause hospitalization was reported in 45 (40.5%) subjects in the eplerenone group and 58 (52.7%) subjects in the placebo group and this represents a hazard ratio of 0.65 with a 95% CI of 0.44-0.97. HF hospitalization was reported in 27 (24.3%) subjects in the eplerenone group and 33 (30.0%) subjects in the placebo group and this represents a hazard ratio of 0.75 with a 95% CI of 0.45-1.25.

CV hospitalization was reported in 35 (31.5%) subjects in the eplerenone group and 44 (40.0%) subjects in the placebo group and this represents a hazard ratio of 0.70 with a 95% CI of 0.45- 1.10.

Safety Results:

Serious Adverse Events: SAEs are presented in Table 10. SAEs were reported in 52 (46.8%) subjects in the eplerenone group and 65 (59.1%) subjects in the placebo group, respectively. Treatment-related SAEs were reported in 4 (3.6%) subjects in the eplerenone group and 8 (7.3%) subjects in the placebo group. All causality SAEs that occurred in 4 or more subjects in the eplerenone group were HF (27 subjects in the eplerenone group and 31 subjects in the placebo group), ventricular tachycardia (5 subjects in the eplerenone, 3 subjects in the placebo group), and pneumonia (4 subjects in the eplerenone group and 5 subjects in the placebo group). Treatment-related SAEs were cerebral infarction (2 subjects), pneumothorax, pneumonia and rhabdomyolysis (1 subject each) in the eplerenone group and sudden cardiac death (2 subjects), angina pectoris, acute renal failure, syncope, renal impairment, loss of consciousness, and diabetes mellitus (1 subject each) in the placebo group.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Evaluable for adverse events	111			110		
With adverse events	52 (46.8)			65 (59.1)		
Blood and lymphatic system disorders	4 (3.6)	5	0	0	0	0
Anaemia	1 (0.9)	1	0	0	0	0
Bone marrow failure	1 (0.9)	1	0	0	0	0
Disseminated intravascular coagulation	2 (1.8)	2	0	0	0	0
Haemorrhagic diathesis	1 (0.9)	1	0	0	0	0
Cardiac disorders	35 (31.5)	61	0	43 (39.1)	79	1
Angina pectoris	2 (1.8)	2	0	4 (3.6)	4	1
Angina unstable	0	0	0	1 (0.9)	1	0
Arrhythmia	0	0	0	1 (0.9)	1	0
Atrial fibrillation	1 (0.9)	1	0	2 (1.8)	2	0
Atrial flutter	0	0	0	1 (0.9)	1	0
Bradycardia	0	0	0	1 (0.9)	1	0
Cardiac failure	27 (24.3)	40	0	31 (28.2)	57	0
Cardiac failure acute	1 (0.9)	1	0	0	0	0
Cardiac failure chronic	2 (1.8)	3	0	1 (0.9)	1	0
Cardiac failure congestive	2 (1.8)	2	0	2 (1.8)	2	0
Cardiac sarcoidosis	1 (0.9)	1	0	0	0	0
Cardio-respiratory arrest	1 (0.9)	1	0	0	0	0
Congestive cardiomyopathy	1 (0.9)	1	0	0	0	0
Coronary artery stenosis	2 (1.8)	2	0	2 (1.8)	2	0
Intracardiac thrombus	0	0	0	1 (0.9)	1	0
Mitral valve incompetence	0	0	0	1 (0.9)	1	0
Myocardial infarction	1 (0.9)	1	0	0	0	0
Ventricular fibrillation	1 (0.9)	1	0	1 (0.9)	1	0
Ventricular tachycardia	5 (4.5)	5	0	3 (2.7)	4	0
Eye disorders	3 (2.7)	4	0	3 (2.7)	4	0
Cataract	2 (1.8)	3	0	3 (2.7)	4	0
Retinal detachment	1 (0.9)	1	0	0	0	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Gastrointestinal disorders	6 (5.4)	6	0	3 (2.7)	4	0
Abdominal pain upper	1 (0.9)	1	0	0	0	0
Gastric ulcer	1 (0.9)	1	0	0	0	0
Gastric ulcer haemorrhage	0	0	0	1 (0.9)	1	0
Gastrointestinal haemorrhage	1 (0.9)	1	0	2 (1.8)	2	0
Inguinal hernia	0	0	0	1 (0.9)	1	0
Large intestine polyp	1 (0.9)	1	0	0	0	0
Pancreatitis acute	1 (0.9)	1	0	0	0	0
Protein-losing gastroenteropathy	1 (0.9)	1	0	0	0	0
General disorders and administration site conditions	4 (3.6)	4	0	5 (4.5)	5	2
Chest discomfort	1 (0.9)	1	0	1 (0.9)	1	0
Chest pain	0	0	0	1 (0.9)	1	0
Malaise	0	0	0	1 (0.9)	1	0
Multi-organ failure	1 (0.9)	1	0	0	0	0
Sudden cardiac death	1 (0.9)	1	0	2 (1.8)	2	2
Sudden death	1 (0.9)	1	0	0	0	0
Hepatobiliary disorders	0	0	0	3 (2.7)	3	0
Cholecystitis	0	0	0	3 (2.7)	3	0
Infections and infestations	13 (11.7)	23	1	14 (12.7)	15	0
Appendicitis	0	0	0	1 (0.9)	1	0
Bronchitis	1 (0.9)	1	0	0	0	0
Bronchopneumonia	1 (0.9)	1	0	0	0	0
Cellulitis	0	0	0	1 (0.9)	1	0
Device related infection	0	0	0	2 (1.8)	2	0
Disseminated tuberculosis	0	0	0	1 (0.9)	1	0
Endocarditis bacterial	0	0	0	1 (0.9)	1	0
Gastroenteritis	2 (1.8)	2	0	1 (0.9)	1	0
Influenza	1 (0.9)	1	0	0	0	0
Peritonitis	1 (0.9)	1	0	0	0	0
Pneumonia	4 (3.6)	4	1	5 (4.5)	5	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Pneumonia bacterial	0	0	0	2 (1.8)	2	0
Pneumonia staphylococcal	1 (0.9)	8	0	0	0	0
Pyelonephritis	0	0	0	1 (0.9)	1	0
Sepsis	3 (2.7)	5	0	0	0	0
Injury, poisoning and procedural complications	4 (3.6)	4	0	4 (3.6)	4	0
Brain contusion	0	0	0	1 (0.9)	1	0
Femur fracture	0	0	0	1 (0.9)	1	0
Muscle injury	1 (0.9)	1	0	0	0	0
Postoperative ileus	1 (0.9)	1	0	0	0	0
Road traffic accident	0	0	0	1 (0.9)	1	0
Spinal compression fracture	2 (1.8)	2	0	0	0	0
Spinal cord injury cervical	0	0	0	1 (0.9)	1	0
Investigations	0	0	0	1 (0.9)	1	0
Blood pressure decreased	0	0	0	1 (0.9)	1	0
Metabolism and nutrition disorders	3 (2.7)	3	0	3 (2.7)	3	1
Dehydration	1 (0.9)	1	0	0	0	0
Diabetes mellitus	1 (0.9)	1	0	2 (1.8)	2	1
Fluid retention	1 (0.9)	1	0	0	0	0
Metabolic acidosis	0	0	0	1 (0.9)	1	0
Musculoskeletal and connective tissue disorders	4 (3.6)	4	1	1 (0.9)	1	0
Arthritis reactive	1 (0.9)	1	0	0	0	0
Lumbar spinal stenosis	1 (0.9)	1	0	0	0	0
Muscle haemorrhage	0	0	0	1 (0.9)	1	0
Rhabdomyolysis	1 (0.9)	1	1	0	0	0
Spinal column stenosis	1 (0.9)	1	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (5.4)	6	0	6 (5.5)	8	0
Bladder cancer	1 (0.9)	1	0	0	0	0
Colon adenoma	0	0	0	1 (0.9)	1	0
Colon cancer	1 (0.9)	1	0	0	0	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Gastric cancer	1 (0.9)	1	0	0	0	0
Lung neoplasm malignant	2 (1.8)	2	0	2 (1.8)	2	0
Metastases to bone	0	0	0	1 (0.9)	1	0
Oesophageal carcinoma recurrent	0	0	0	1 (0.9)	1	0
Prostate cancer	0	0	0	1 (1.1)	1	0
Prostate cancer metastatic	0	0	0	1 (1.1)	1	0
Rectal cancer	0	0	0	1 (0.9)	1	0
Thyroid cancer metastatic	1 (0.9)	1	0	0	0	0
Nervous system disorders	5 (4.5)	6	2	6 (5.5)	8	2
Cerebellar infarction	0	0	0	1 (0.9)	1	0
Cerebral haemorrhage	0	0	0	1 (0.9)	1	0
Cerebral infarction	3 (2.7)	3	1	2 (1.8)	2	0
Cerebrovascular accident	1 (0.9)	1	1	0	0	0
Cervical myelopathy	1 (0.9)	1	0	0	0	0
Loss of consciousness	0	0	0	1 (0.9)	1	1
Spondylitic myelopathy	0	0	0	1 (0.9)	1	0
Subarachnoid haemorrhage	1 (0.9)	1	0	0	0	0
Syncope	0	0	0	1 (0.9)	1	1
Transient ischaemic attack	0	0	0	1 (0.9)	1	0
Renal and urinary disorders	2 (1.8)	4	0	4 (3.6)	5	2
Acute kidney injury	0	0	0	1 (0.9)	1	1
Chronic kidney disease	1 (0.9)	1	0	0	0	0
Renal failure	2 (1.8)	3	0	1 (0.9)	1	0
Renal impairment	0	0	0	3 (2.7)	3	1
Respiratory, thoracic and mediastinal disorders	3 (2.7)	5	1	4 (3.6)	4	0
Chronic obstructive pulmonary disease	1 (0.9)	1	0	0	0	0
Organising pneumonia	0	0	0	1 (0.9)	1	0
Pleurisy	1 (0.9)	2	0	0	0	0
Pneumonia aspiration	0	0	0	1 (0.9)	1	0
Pneumothorax	1 (0.9)	2	1	0	0	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Sleep apnoea syndrome	0	0	0	1 (0.9)	1	0
Upper respiratory tract inflammation	0	0	0	1 (0.9)	1	0
Vascular disorders	3 (2.7)	3	0	3 (2.7)	3	0
Extremity necrosis	1 (0.9)	1	0	0	0	0
Haemorrhage	1 (0.9)	1	0	0	0	0
Hypotension	0	0	0	1 (0.9)	1	0
Peripheral arterial occlusive disease	0	0	0	2 (1.8)	2	0
Peripheral artery aneurysm	1 (0.9)	1	0	0	0	0

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1 = number of occurrences of treatment-emergent all causalities adverse events; n2 = number of occurrences of treatment-emergent causally related to treatment adverse events; v = version.

Incidence of Adverse Events: All-causality and treatment-related AEs that occurred in ≥5% of subjects in the eplerenone and placebo group are presented in Table 11. AEs were reported in 99 (89.2%) subjects in the eplerenone group and 100 (90.9%) subjects in the placebo group.

Table 11. Treatment-Emergent Non-Serious Adverse Events in ≥5% Subjects by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v 18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Evaluable for adverse events	111			110		
With adverse events	99 (89.2)			100 (90.9)		
Blood and lymphatic system disorders	11 (9.9)	12	0	14 (12.7)	17	0
Anaemia	7 (6.3)	7	0	6 (5.5)	6	0
Cardiac disorders	25 (22.5)	43	2	39 (35.5)	73	0
Cardiac failure	21 (18.9)	23	1	32 (29.1)	49	0
Gastrointestinal disorders	39 (35.1)	65	5	44 (40.0)	89	0
Chronic gastritis	6 (5.4)	6	0	3 (2.7)	3	0
Constipation	8 (7.2)	8	1	18 (16.4)	24	0
Diarrhoea	7 (6.3)	7	0	10 (9.1)	13	0
Haemorrhoids	2 (1.8)	2	0	6 (5.5)	6	0
Hepatobiliary disorders	5 (4.5)	6	0	10 (9.1)	10	0
Hepatic function abnormal	4 (3.6)	5	0	7 (6.4)	7	0
Infections and infestations	67 (60.4)	148	0	66 (60.0)	149	0
Bronchitis	6 (5.4)	10	0	8 (7.3)	9	0
Conjunctivitis	7 (6.3)	7	0	5 (4.5)	5	0
Nasopharyngitis	37 (33.3)	68	0	40 (36.4)	71	0
Upper respiratory tract infection	5 (4.5)	7	0	6 (5.5)	14	0
Injury, poisoning and procedural complications	28 (25.2)	70	0	32 (29.1)	60	1
Contusion	12 (10.8)	17	0	5 (4.5)	7	0
Fall	20 (18.0)	35	0	20 (18.2)	28	1
Investigations	26 (23.4)	37	10	19 (17.3)	33	4
Blood pressure decreased	6 (5.4)	7	5	4 (3.6)	5	2
Metabolism and nutrition disorders	37 (33.3)	53	14	40 (36.4)	105	8
Dehydration	10 (9.0)	12	5	5 (4.5)	5	0
Diabetes mellitus	7 (6.3)	7	0	7 (6.4)	8	1
Hyperkalaemia	8 (7.2)	10	6	6 (5.5)	9	6
Hyperuricaemia	11 (9.9)	11	2	14 (12.7)	15	1
Hypokalaemia	2 (1.8)	2	0	11 (10.0)	12	0
Musculoskeletal and connective tissue disorders	28 (25.2)	43	1	30 (27.3)	46	0

Table 11. Treatment-Emergent Non-Serious Adverse Events in ≥5% Subjects by System Organ Class and Preferred Term

Number (%) of Subjects with Adverse Events by:	Treatment					
System Organ Class and MedDRA (v 18.0)	Eplerenone			Placebo		
Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Back pain	11 (9.9)	13	0	9 (8.2)	9	0
Pain in extremity	6 (5.4)	6	0	3 (2.7)	4	0
Nervous system disorders	20 (18.0)	31	8	18 (16.4)	24	5
Dizziness	8 (7.2)	9	7	5 (4.5)	6	2
Renal and urinary disorders	13 (11.7)	14	2	18 (16.4)	25	4
Renal impairment	5 (4.5)	5	1	7 (6.4)	8	0
Respiratory, thoracic and mediastinal disorders	18 (16.2)	24	0	32 (29.1)	56	0
Cough	8 (7.2)	8	0	9 (8.2)	14	0
Sleep apnoea syndrome	0	0	0	6 (5.5)	6	0
Upper respiratory tract inflammation	1 (0.9)	1	0	8 (7.3)	17	0
Skin and subcutaneous tissue disorders	30 (27.0)	43	3	31 (28.2)	50	1
Eczema	4 (3.6)	4	0	6 (5.5)	7	0
Vascular disorders	23 (20.7)	23	4	15 (13.6)	18	6
Hypertension	9 (8.1)	9	0	3 (2.7)	4	0
Hypotension	4 (3.6)	4	4	6 (5.5)	6	4

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1 = number of occurrences of treatment-emergent all causalities adverse events; n2 = number of occurrences of treatment-emergent causally related to treatment adverse events; v = version.

Discontinuations due to Adverse Events: Permanent discontinuations due to AEs were reported in 19 (17.1%) subjects in the eplerenone group and 20 (18.2%) subjects in the placebo group. Permanent discontinuations due to treatment-related AEs were reported in 5 (4.5%) subjects in the eplerenone group and 2 (1.8%) subjects in the placebo group. Permanent discontinuations due to SAEs were reported in 12 subjects in the eplerenone group and 17 subjects in the placebo group. Of the treatment-related AEs resulting in permanent discontinuation, AEs that had not resolved were reported in 2 subjects in the placebo group.

Deaths: Deaths were reported in 17 subjects (NYHA Class II: 10 subjects, Class III/IV: 7 subjects) in the eplerenone group and 10 subjects (NYHA Class II: 6 subjects, Class III/IV: 4 subjects) in the placebo group (Table 12). Excluding treatment discontinuations due to death (6 deaths in the eplerenone group, 5 deaths in the placebo group), there was 1 death in the eplerenone group and 1 death in the placebo group within 30 days following treatment discontinuation. Similarly, there were 10 deaths in the eplerenone group and 4 deaths in the placebo group more than 30 days after treatment discontinuation. The majority of deaths in the eplerenone group occurred more than 30 days after treatment discontinuation. Considering the temporal relevance, treatment with eplerenone was not deemed as the direct cause of these deaths.

Table 12. Deaths

Treatment Group NYHA Class	Serial Number	Sex	Age[a] (Years)	Adverse Events[b] Preferred Term (MedDRA v18.0)	Day of Death	Causality	Severity
Eplerenone: NYHA Class II							
	1	Male	65	Lung neoplasm malignant	770	No	severe
	2	Male	76	Sudden cardiac death	591	No	severe
	3	Male	75	Gastroenteritis	88	No	severe
				Rhabdomyolysis		Yes	severe
				Multi-organ failure		No	severe
				Disseminated intravascular coagulation		No	severe
	4	Male	83	Cardiac failure	1019	No	moderate
	5	Male	68	Cardiac failure	264	No	severe
				Sepsis		No	severe
				Disseminated intravascular coagulation		No	severe
	6	Female	61	Cardiac sarcoidosis	1138	No	severe
	7	Male	77	Acute myocardial infarction*	497	No	severe
	8	Male	78	Sudden death	601	No	severe
	9	Male	67	Cardiac failure chronic**	317	No	severe
	10	Male	76	Cardiac failure	426	No	severe
Eplerenone: NYHA Class III/IV							
	11	Female	88	Colon cancer	574	No	severe
	12	Male	79	Cardiac failure	1481	No	severe
	13	Male	76	Cardio-respiratory arrest	1220	No	severe
	14	Female	68	Cardiac failure	226	No	severe
				Pneumonia		No	moderate
				Chronic obstructive pulmonary disease		No	severe
	15	Female	78	Pneumonia staphylococcal	697	No	severe
	16	Male	65	Cardiac failure	967	No	moderate
	17	Female	83	Subarachnoid haemorrhage	126	No	severe
Placebo: NYHA Class II							
	1	Male	79	Sudden cardiac death	692	Yes	severe
	2	Male	73	Oesophageal carcinoma recurrent	892	No	severe
				Metastases to bone		No	severe
	3	Male	66	Disseminated tuberculosis	1012	No	severe
	4	Male	70	Cardiac failure	1253	No	severe
	5	Male	67	Cerebral haemorrhage	792	No	severe
	6	Male	58	Sudden cardiac death	502	Yes	severe
Placebo: NYHA Class III/IV							
	7	Male	91	Lung neoplasm malignant	925	No	severe
	8	Male	81	Brain contusion	1225	No	severe

Table 12. Deaths

Treatment Group NYHA Class	Serial Number	Sex	Age[a] (Years)	Adverse Events[b] Preferred Term (MedDRA v18.0)	Day of Death	Causality	Severity
	9	Male	89	Cardiac failure	219	No	severe
	10	Male	70	Cardiac failure	726	No	moderate

∗ This event was entered into the database of this study as myocardial infarction (preferred term).

∗∗ This event was entered into the database of this study as heart failure (preferred term).

MedDRA = Medical Dictionary for Regulatory Activities; NYHA = New York Heart Association; v = version.

a. Age at the time of death.

b. Adverse event entered in the safety database.

Laboratory Evaluations: Hyperkalemia was reported in 8 (7.2%) subjects in the eplerenone group and 6 (5.5%) subjects in the placebo group. AEs related to reproductive hormone were reported in 2 (1.8%) subjects in the eplerenone group and 3 (2.7%) subjects in the placebo group. The incidences of hyperkalemia or reproductive hormone related AEs were similar between treatment groups.

The incidences of hypokalemia and AEs related to renal function were lower in the eplerenone group compared with the placebo group; 2 (1.8%) and 14 (12.6%) subjects in the eplerenone group and 11 (10.0%) and 22 (20.0%) subjects in the placebo group, respectively.

Changes in laboratory values (hematology, biochemistry, urine) from Baseline to the final visit were small and not clinically significant. No notable differences in mean changes from Baseline for derived eGFR, serum creatinine, and serum potassium were observed between treatment groups.

Number (%) of subjects with high or low potassium value is summarized in Table 13. The proportion of subjects with potassium values <3.5 mmol/L or <4 mmol/L were lower in the eplerenone group (11 [9.9%] subjects and 55 [49.5%] subjects, respectively) compared with the placebo group (22 [20.0%] subjects and 71 [64.5%] subjects, respectively). The incidences of high potassium (>5.5 mmol/L or >6 mmol/L) were similar in the eplerenone group (3 [2.7%] subjects) compared with the placebo group (1 [0.9%] subject).

Table 13. Number (%) of Subjects With High or Low Potassium Value: Safety Analysis Set

Number of Subjects (%)	Eplerenone N=111	Placebo N=110
<3.5 mmol/L	11 (9.9)	22 (20.0)
<4 mmol/L	55 (49.5)	71 (64.5)
>5.5 mmol/L	3 (2.7)	3 (2.7)
>6 mmol/L	1 (0.9)	1 (0.9)

N = number of subjects.

There were no clinically significant differences during the course of the study in blood pressure (systolic/diastolic), heart rate, body weight, and waist circumference between the treatment groups.

Changes to clinically significant 12-lead electrocardiogram abnormality from Screening to final visit were reported in 4 subjects in the eplerenone group and 2 subjects in the placebo group and no notable changes were reported in the other subjects.

CONCLUSIONS:

Consistency between the results of NCT00232180 and current study is discussed.

In order to conduct a study to verify superiority to placebo using the prognosis in subjects with CHF as the primary endpoint as was the case with international studies such as the NCT00232180 study, a placebo-controlled study with several thousand subjects would have been necessary. Hence, it was considered extremely difficult to conduct clinical studies of

such size in Japan. As in NCT00232180 study, we established the "CV mortality or HF hospitalization" as the primary endpoint and decided to define comparison with placebo as the primary purpose and confirm that the results are consistent with the results of NCT00232180 Study, instead of demonstrating superiority. Consistency was defined as a HR of the primary endpoint of <1 in favor of eplerenone over placebo.

In the current Japanese study, the point estimate of the HR of the primary endpoint in the primary analyses for the combined NYHA population was <1 which was a pre-determined threshold value [HR (95% CI): 0.85 (0.53 to 1.36)], therefore, the result was considered consistent with that of the NCT00232180 [HR (95% CI): 0.630 (0.535 to 0.741)]. The secondary analysis for which the baseline eGFR (30 to <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2) as covariate in the model as same as NCT00232180 study also showed same results as NCT00232180 [HR (95% CI): 0.84 (0.52 to 1.35)]. In addition, in the analysis for the NYHA Class II population, the point estimate of HR of the primary endpoint was <1 and therefore showed consistency with the NCT00232180.

Safety results were generally consistent with NCT00232180 study. In the current Japanese study, the incidence of hyperkalemia and AEs regarding reproductive hormone was almost the same between the eplerenone group and the placebo group. The incidence of hypokalemia and AEs regarding renal function was lower in the eplerenone group than in the placebo group. Hospitalization for hyperkalemia which was the efficacy endpoint did not occur in either group and hospitalization for worsening renal function occurred in 2 subjects each in both groups.

The following conclusions were drawn from this study after a maximum of 48 months of treatment (mean 780.9 days) with eplerenone or placebo (25 mg EOD, 25 mg OD, or 50 mg OD) and a maximum of 58 months (mean 922.6 days) of follow-up in a total of 221 Japanese subjects with NYHA ≥ Class II CHF.

- CV mortality or HF hospitalization, the primary efficacy endpoint, was reported in 33 (29.7%) subjects in the eplerenone group and 36 (32.7%) subjects in the placebo group and this represented a hazard ratio of 0.85 with a 95% CI of 0.53-1.36 for the primary analysis. There was no subpopulation that showed an obviously different trend from the total subject group.

- Except for all-cause mortality and CV mortality, the secondary efficacy endpoint results were generally consistent with the results of the primary endpoint.

- Least squares mean for decreases in plasma BNP from Baseline to Month 13 were greater in the eplerenone group compared with the placebo group. Least squares mean for decreases in serum NT-proBNP were also greater in the eplerenone group compared with the placebo group, however the variability was large. Least squares mean for changes from Baseline to Month 13 were greater with respect to LVEF in the eplerenone group. Least squares mean for changes from baseline to Month 13 for urine albumin creatinine ratioR was similar between treatment groups. Changes from Baseline to Month 13 or each evaluation time point for SAS and NYHA classification did not show any major difference between the 2 treatment groups.

- No notable differences of efficacy results were observed by NYHA classification (Class II, Class III/IV) and NYHA total.

- Incidences of AEs were generally similar between the eplerenone and the placebo groups.

- Deaths were reported in 17 subjects in the eplerenone group and 10 subjects in the placebo group. The number of discontinuations from treatment due to death was similar between the treatment groups. Excluding treatment discontinuations due to death, the majority of deaths in the eplerenone group occurred more than 30 days after treatment discontinuation. The most frequently reported death event was due to worsening HF. The number of subjects who subjects who had other complications other fatal event at the subject's death was higher in the eplerenone group than the placebo group. Death cases in the eplerenone group had the risk factors (e.g. elderly and medical history of myocardial infarction or stroke), and there were some subjects who did not receive standard drug for the treatment of HF. From these reported death cases, no new safety concern was observed.

- The incidences of serious or severe AEs were lower in the eplerenone group compared with the placebo group. The incidences of AEs resulting in treatment discontinuation were similar between the eplerenone and the placebo groups. The incidences of SAEs resulting in treatment discontinuation in the eplerenone group were lower than the placebo group.

- The incidences of hyperkalemia, and AEs related to reproductive hormones in the eplerenone group were similar with the placebo group. The incidence of hypokalemia and AEs related to renal function were lower in the eplerenone group compared with the placebo group. The incidence of hypokalemia based on laboratory test results was lower in the eplerenone group compared with the placebo group. The incidences of hyperkalemia based on laboratory test results were similar between the treatment groups.

- In both treatment groups, safety profiles for the subjects with NYHA Class II were generally similar to the total subjects. In subjects with NYHA Class III/IV, incidences of SAEs, severe AEs, and AEs resulting in permanent treatment discontinuation were higher in the eplerenone group compared with the placebo group, although the number of evaluable subjects were limited (approximately 20 subjects in both treatment groups).

- Blood samples for PK assessment were collected and reported separately.

Overall, the efficacy and safety of eplerenone at a maximum of 48 months of treatment (25 mg EOD, 25 mg OD, or 50 mg OD) were demonstrated in Japanese CHF subjects with NYHA ≥ Class II.