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

PROTOCOL NO.: A6141079

PROTOCOL TITLE: 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 Centers: Double-Blind (DB) Phase: Two hundred eighty-six (286) centers took part in the study and randomized subjects: 3 each in Argentina, Australia, Ireland, Republic of Korea, and Venezuela; 10 each in Belgium, Greece, and Poland; 9 each in Canada, India, Russian Federation, and Slovakia; 12 each in Czech Republic, Portugal, and the Netherlands; 15 each in France, Italy, and Sweden; 19 in Germany; 2 each in Hong Kong, Singapore, and United Arab Emirates; 7 each in Hungary and Mexico; 5 in South Africa; 6 in Spain; 18 in Ukraine; 13 in the United Kingdom; and 43 in the United States.

Open-Label Extension (OLE) Phase: Two hundred eighteen (218) centers in total took part in the study and enrolled subjects: 3 each in Argentina, Australia, Ireland, and Venezuela; 7 each in Belgium and Hungary; 8 each in Canada and Greece; 12 each in Czech Republic, France, and Portugal; 14 in Germany; 2 each in Hong Kong, Republic of Korea, and South Africa; 9 each in India, the Netherlands, Poland, and Slovakia; 1 in Singapore; 4 in Spain; 13 in Sweden; 17 in Ukraine; 10 in the United Kingdom; and 39 in the United States.

Study Initiation Date and Final Completion Date: 30 March 2006 to 24 January 2012

Study Initiation, Primary Completion and Completion Dates of DB Phase: 30 March 2006, 25 May 2010 and 18 March 2011;

Study Initiation and Completion Dates of OLE Phase: 29 July 2010 to 24 January 2012

Phase of Development: Phase 3

Study Objectives: DB Phase: The primary objective of this trial was to evaluate the efficacy and safety of eplerenone plus standard heart failure (HF) therapy versus placebo plus standard HF therapy on the cumulative incidence of cardiovascular (CV) mortality or HF hospitalization (a composite primary endpoint).

Standard HF therapy included angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) and β-blockers at the optimal target or maximally tolerated doses (unless contraindicated), and diuretics, if clinically indicated to minimize fluid retention.

A separate objective of this study was to collect data to further investigate the incidence of stroke in very elderly subjects (>75 years, inclusive) with chronic systolic HF with mild symptoms. This was part of a post-approval commitment agreed to by the sponsor as part of the approval of Inspra in Europe in 2004.

OLE Phase: The objective of the open-label phase was to ensure that all subjects could be offered treatment with eplerenone.

METHODS

Study Design: This was a multinational (29 countries), randomized, DB, placebo-controlled, parallel group study. Subjects ≥55 years of age with chronic systolic HF of either ischemic or non-ischemic etiology were included in this study. The study was planned to continue until 813 primary endpoints had occurred. At the protocol specified second interim analyses by the Data Safety Monitoring Committee (DSMC), a total of 501 adjudicated primary endpoint events were reviewed and analyzed. These analyses showed benefit in the eplerenone treated group compared to the placebo arm, according to the pre-specified stopping rules. As the pre-specified stopping rules for efficacy had been met, the DSMC advised the Executive Steering Committee to recommend terminating the study for efficacy. Consequently, the Executive Steering Committee subsequently recommended that further recruitment of subjects in the DB phase of the study be stopped. Hence, the study design was amended to incorporate a 12-month OLE, eplerenone-only phase to permit the continued administration of eplerenone to these subjects once appropriate regulatory and ethics committee approvals were obtained. Recruitment was stopped on 26 May 2010, by the recommendation of the DSMC and Executive Steering Committee, and a 12-month OLE phase was added.

The purpose of the OLE phase was to ensure that all active subjects who previously participated in the DB phase of this study were offered treatment with eplerenone.

The schedule of study activities for the DB phase is provided in Table 1. The schedule of study activities for the OLE phase is provided in Table 2

Table 1. Schedule of Activities for the DB Phase

Protocol Activity	Screen	Rand Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 etc	Final Visit
			W1	W4	M5	M9	M13	M17	M21	M25	M29	M33	M37	M42	M48	Every 6 Months Until Open Label Phase	Double-Blind End of Study/Early Term Visit
Informed consent	X																
Medical history	X																
Significant medical conditions	X																
Physical examination including waist circumference	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (HR and BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum potassium[b,c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine[b]	X				X		X		X		X		X	X	X	X	X
Serum albumin[b]	X				X		X		X		X		X	X	X	X	X
Blood urea nitrogen[b]	X				X		X		X		X		X	X	X	X	X
Serum pregnancy test[d]	X																
Estimated GFR (MDRD-6)[b]	X				X		X		X		X		X	X	X	X	X
Serum sodium	X																
ALT/AST	X																
Bilirubin, total	X																
Hemoglobin	X																
12-Lead ECG	X																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of doses of selected CHF medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study endpoints assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs assessment		X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
New-onset AF/flutter and DM assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities for the DB Phase

Protocol Activity	Screen	Rand Visit														
			V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 etc	Final Visit
			W1	W4	M5	M9	M13	M17	M21	M25	M29	M33	M37	M42	M48	Every 6 Months Until Open Label Phase	Double-Blind End of Study/Early Term Visit
Dispensing of study drug		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Initiation of study drug		X															
Study drug compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

One month should be considered as a 30-day period.
At the end of study drug treatment/DB phase, all subjects were required to complete the DB early termination visit, regardless of their continued participation in the open-label phase.
AE = adverse event; AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CHF = congestive heart failure; DB = double-blind; DM = diabetes mellitus; ECG = electrocardiogram; GFR = glomerular filtration rate; HR = heart rate; M = month; MDRD-6 = Modification of Diet in Renal Disease – 6; NYHA = New York Heart Association; Rand = randomization; SAE = serious adverse event; Screen = screening; Term = termination; V = visit; W = week.

a. If randomization occurred more than 30 days after screening.
b. Within 24 hours prior to randomization.
c. Serum potassium levels were checked 1 week after any dose adjustment.
d. Within 72 hours of randomization in women of childbearing potential.
e. SAE reporting began at the time of informed consent, while AE reporting began at randomization.

Table 2. Schedule of Activities for the Open-Label Phase

Protocol Activity						
		V1	V2	V3	V4	Final Visit
	Initiation of Open Label	W1	W2	M4	M8	M12: End of Study / Early Termination
Informed consent	X	X				
Vital signs (HR and BP)	X[a]	X	X	X	X	X
Serum potassium[b]		X	X	X	X	X
Concomitant medications		X	X	X	X	X
Adverse events assessment		X	X	X	X	X
Dispensing of eplerenone	X	X	X	X	X	X
Study drug compliance check			X	X	X	X

BP = blood pressure; HR = heart rate; M = month; V = visit; W = week.

a. If the termination visit phase of the double-blind phase and the initiation visit of the open-label phase were not the same, the vital signs had to be redone.

b. Serum potassium levels were to be checked 1 week after any dose adjustments.

Number of Subjects (Planned and Analyzed): DB Phase: To reach the 813 primary endpoints required for DB phase completion, approximately 3100 subjects (1550 per treatment arm) were planned in this study. A total of 3033 subjects were screened for participation in the DB phase of the study, and 1367 subjects were assigned to the eplerenone group and 1376 subjects were assigned to placebo group. A total of 1364 subjects and 1372 subjects in the eplerenone and placebo groups, respectively, were treated. All subjects who were assigned to study treatment were included in the full analysis set (FAS) and were analyzed for efficacy. All subjects who were randomized and received at least 1 dose of study treatment were analyzed for safety.

OLE Phase: Of the total 1597 subjects who completed the DB phase of the study, 1246 subjects entered the OLE phase and were assigned to open-label eplerenone treatment. A total of 1245 subjects were treated and analyzed for safety.

Diagnosis and Main Criteria for Inclusion: DB Phase: The DB phase of the study included subjects with history of chronic systolic HF of ischemic or non-ischemic etiology of at least 4 weeks duration; left ventricular ejection fraction (LVEF) ≤30% or LVEF ≤35% in addition to QRS duration ≥130 msec; current functional capacity categorized as New York Heart Association (NYHA) II; treated with ACE inhibitors and/or ARBs, beta blockers, diuretics; serum potassium level ≤5.0 mmol/L within 24 hours before randomization; estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 within 24 hours before randomization.

OLE Phase: All subjects who had been randomized into the DB phase of the study and had not withdrawn consent were eligible to participate in the OLE phase if their eGFR was ≥30 mL/min/1.73 m^2 at the DB closeout visit. Subjects with an eGFR of <30 mL/min/1.73 m^2 at the DB closeout visit and who were confirmed to be on placebo were ineligible to participate in the OLE phase.

Study Treatment: DB Phase: Subjects received eplerenone 25 mg or matching placebo (1 tablet) once daily (once every other day for subjects with an eGFR between 30 and 49 mL/min/1.73 m^2) for the first 4 weeks of treatment. The first dose of study drug was to be taken at randomization. All subsequent doses of study drug were to be taken orally each morning with water (with or without food). At Week 1 following randomization, the dose of study drug could be adjusted (according to serum potassium level).

OLE Phase: Upon entry into the OLE phase, subjects received 25 mg eplerenone (1 tablet) once daily. At 4 weeks, the dose of eplerenone could be increased to 50 mg once daily (two 25 mg tablets of eplerenone tablets once daily). For subjects with an eGFR between 30 and 49 mL/min/1.73 m^2 at the DB screening visit, the initial dose of eplerenone was to be 25 mg once every other day. At 4 weeks, the dose of eplerenone could be increased to 25 mg once daily based on the serum potassium level. The first dose of eplerenone was to be taken upon entry into the OLE phase.

Efficacy Endpoints: DB Phase: For the DB phase, at each study visit / follow-up contact, subjects were questioned specifically (by using targeted prompts) regarding clinical endpoints. The primary efficacy endpoint was the first occurrence of CV mortality or HF hospitalization. The secondary efficacy endpoint was the first occurrence of all-cause mortality or HF hospitalization.

Other secondary endpoints included first occurrence of: all-cause mortality; CV mortality; all-cause hospitalization; HF hospitalization; all-cause mortality or all-cause hospitalization; HF mortality or HF hospitalization; CV hospitalization; fatal/nonfatal myocardial infarction (MI); fatal/nonfatal stroke; implantation of cardiac defibrillator (ICD); implantation of resynchronization device (cardiac resynchronization therapy [CRT]); new-onset atrial fibrillation (AF)/flutter; new-onset diabetes mellitus (DM); worsening renal function (if it resulted in hospitalization); and hospitalization for hyperkalemia.

OLE Phase: No efficacy evaluations were conducted for the OLE phase.

Safety Evaluations: DB Phase: Safety was assessed by description of adverse events (AEs), clinical laboratory measurements, physical examinations, and vital signs.

OLE Phase: In the OLE phase, safety assessment was based on listing of AEs, clinical laboratory measurements (serum potassium), and vital signs.

Statistical Methods: DB Phase: All randomized subjects were included in the full analysis set (FAS). All efficacy analyses were performed on the FAS. Safety analysis set included all randomized subjects who received at least 1 dose of the randomized study drug during the DB phase.

For all efficacy analyses during the DB phase, available data from the FAS was analyzed according to the intention-to-treat (ITT) principle based on the subjects' randomized treatment assignment, and all subjects were followed for mortality and other major endpoints for the duration of the DB treatment period, regardless of compliance with the study drug and the protocol.

The primary statistical analysis model for the DB phase was determined as the Cox proportional hazards (PH) regression model adjusting for Baseline prognostic factors based on the FAS. All pre-specified primary and secondary efficacy endpoints for the DB phase listed were analyzed using this adjusted Cox PH model. All hypothesis tests for efficacy endpoints were 2-sided. Results were to be considered statistically significant if a p-value of <0.049 (adjusted for interim analyses) was obtained for the primary hypotheses and <0.01 for the secondary hypotheses. When statistically significant results were found when comparing composite endpoints, the results were to be broken down by each component of the composite endpoint in order to ascertain which component(s) were contributing to the statistical significance.

All safety analyses were conducted based on the safety analysis set. The safety data (AEs, serious AEs [SAEs], laboratory measurements, and vital signs) were analyzed for all treated subjects and by age subgroups.

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

Changes from Baseline to final follow-up assessment in vital signs and clinically relevant laboratory values such as serum creatinine were assessed by analysis of covariance, with the Baseline value as a covariate. Additionally, the incidence rates of AEs of special interest, such as hyperkalemia and hypokalemia, were analyzed by Fisher's exact test. Other laboratory data were summarized.

The vital sign characteristics (eg, blood pressure, heart rate) at Baseline and change from Baseline to final follow-up assessment visit and the time course of these changes were summarized by treatment groups.

An independent DSMC, not otherwise involved in the conduct of the study, reviewed unblinded data and provided recommendations to the Executive Steering Committee on early termination and conduct of the study. Interim analyses examining the primary efficacy endpoint were performed after a total of approximately 271 and 542 primary endpoint events had occurred.

OLE Phase: Safety analysis set for the open-label phase included all enrolled subjects who received at least 1 dose of open-label eplerenone.

The standard safety tables (including demographics and Baseline characteristics, AEs, serum potassium levels and abnormalities, vital signs, prior and concomitant medications, and extent of exposure to study treatment) were generated based on data standards of the sponsor. Additionally, for vital signs data, the descriptive summary statistics on the change from Baseline were presented, where the Baseline value was defined as the observed value measured at the beginning of the first visit of the OLE phase.

RESULTS

Subject Disposition and Demography: Subject disposition for the complete DB phase is summarized in Table 3. Subject disposition for the OLE phase is summarized in Table 4.

Table 3. Subject Disposition and Subjects Analyzed (Double-Blind Phase)

Number (%) of Subjects	Eplerenone n (%)	Placebo n (%)
Screened (N=3033)		
Assigned to study treatment	1367	1376
Treated	1364	1372
Completed	826 (60.4)	771 (56.0)
Discontinued	352 (25.7)	379 (27.5)
Withdrawn during active/double-blind treatment period	352 (25.7)	379 (27.5)
Analyzed for efficacy		
Full analysis set (FAS)	1367 (100.0)	1376 (100.0)
Analyzed for safety		
Adverse events	1364 (99.8)	1372 (99.7)
Laboratory data	1344 (98.3)	1349 (98.0)

Additionally, 186 subjects in the eplerenone group and 222 subjects in the placebo group died.
N = total number of subjects; n = number of subjects in a given treatment group.

Table 4. Subject Disposition and Subjects Analyzed (Open-Label Phase)

Number (%) of Subjects	Eplerenone n (%)
Screened	1246
Assigned to study treatment	1246
Treated	1245
Completed	1098 (88.2)
Discontinued	147 (11.8)
Due to death	48 (3.9)[a]
Relation to study drug not defined	64 (5.1)
Lost to follow-up	5 (0.4)
Protocol violation	3 (0.2)
Study terminated by sponsor[b]	3 (0.2)
Subject no longer willing to participate	37 (3.0)
Other	16 (1.3)
Related to study drug	23 (1.8)
Adverse event	16 (1.3)
Laboratory abnormality	7 (0.6)
Not related to study drug	12 (1.0)
Adverse event	9 (0.7)
Laboratory abnormality	3 (0.2)
Analyzed for safety	
Adverse events	1245 (100.0)
Laboratory data	1240 (99.6)

CRF = case report form; n = number of subjects in a given treatment group.
a. These deaths were recorded on the CRFs and included in the project database.
b. The study sites were terminated by the sponsor.

Demographic characteristics of subjects in the DB phase are summarized in Table 5.
Demographic characteristics of subjects in the OLE phase are summarized in Table 6.

Table 5. Demographic Characteristics (Double-Blind Phase)

	Eplerenone			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of subjects	1058	309	1367	1074	302	1376
Age (years)						
<65	349 (33.0)	94 (30.4)	443 (32.4)	356 (33.1)	85 (28.1)	441 (32.0)
65-74	457 (43.2)	137 (44.3)	594 (43.5)	471 (43.9)	136 (45.0)	607 (44.1)
75-84	234 (22.1)	68 (22.0)	302 (22.1)	231 (21.5)	68 (22.5)	299 (21.7)
≥85	18 (1.7)	10 (3.2)	28 (2.0)	16 (1.5)	13 (4.3)	29 (2.1)
Mean	68.6	69.0	68.7	68.4	69.6	68.6
SD	7.6	7.8	7.7	7.6	7.8	7.6
Range	52-95	50-94	50-95	43-91	54-90	43-91
Race						
White	890 (84.1)	239 (77.3)	1129 (82.6)	913 (85.0)	230 (76.2)	1143 (83.1)
Black	24 (2.3)	14 (4.5)	38 (2.8)	15 (1.4)	15 (5.0)	30 (2.2)
Asian	118 (11.2)	40 (12.9)	158 (11.6)	113 (10.5)	46 (15.2)	159 (11.6)
Other	26 (2.5)	16 (5.2)	42 (3.1)	33 (3.1)	11 (3.6)	44 (3.2)
Weight (kg)						
Mean	81.7	70.6	79.2	82.0	69.9	79.4
SD	16.0	17.1	16.9	16.1	16.0	16.9
Range	43.0-137.7	31.0-130.0	31.0-137.7	40.0-149.9	34.0-130.0	34.0-149.9
N	1056 (99.8)	309 (100.0)	1365 (99.9)	1073 (99.9)	301 (99.7)	1374 (99.9)
Body mass index (kg/m^2)						
Mean	27.4	27.8	27.5	27.5	27.7	27.5
SD	4.5	6.0	4.9	4.6	5.8	4.8
Range	15.7-46.2	15.0-50.8	15.0-50.8	13.2-50.1	13.8-57.8	13.2-57.8
N	1053 (99.5)	308 (99.7)	1361 (99.6)	1069 (99.5)	298 (98.7)	1367 (99.3)
Height (cm)						
Mean	172.2	158.9	169.2	172.5	158.7	169.5
SD	7.4	7.9	9.3	7.9	7.0	9.6
Range	137.0-197.0	120.0-177.8	120.0-197.0	133.0-198.0	138.0-180.0	133.0-198.0
N	1055 (99.7)	308 (99.7)	1363 (99.7)	1070 (99.6)	299 (99.0)	1369 (99.5)

Body mass index was calculated as weight / (height × 0.01)^2.
N = Number of subjects; SD = standard deviation.

Table 6. Demographic Characteristics (Open-Label Phase)

	Eplerenone		
	Male	**Female**	**Total**
Number of subjects	960	285	1245
Age (years)			
<65	337 (35.1)	87 (30.5)	424 (34.1)
65-74	406 (42.3)	134 (47.0)	540 (43.4)
75-84	208 (21.7)	55 (19.3)	263 (21.1)
≥85	9 (0.9)	9 (3.2)	18 (1.4)
Mean (SD)	68.0 (7.5)	68.6 (7.6)	68.1 (7.5)
Range	47–91	50–90	47–91
Race			
White	867 (90.3)	241 (84.6)	1108 (89.0)
Black	10 (1.0)	11 (3.9)	21 (1.7)
Asian	78 (8.1)	27 (9.5)	105 (8.4)
Other	5 (0.5)	6 (2.1)	11 (0.9)
Body mass index (kg/m^2)			
n (%)	956 (99.6)	284 (99.6)	1240 (99.6)
Mean (SD)	27.9 (4.5)	28.1 (5.9)	27.9 (4.8)
Range	16.1–49.8	13.8–57.8	13.8–57.8
Weight (kg)			
n (%)	959 (99.9)	285 (100)	1244 (99.9)
Mean (SD)	84.0 (15.7)	71.8 (16.0)	81.2 (16.6)
Range	43.0–142.0	35.0–130.0	35.0–142.0
Height (cm)			
n (%)	957 (99.7)	284 (99.6)	1241 (99.7)
Mean (SD)	173.2 (7.5)	159.9 (7.2)	170.2 (9.3)
Range	133.0–197.0	137.0–177.8	133.0–197.0

Age, height, and weight as presented at the time when the subject was randomized for the start of the double-blind phase of the study.
Body mass index was calculated as weight / (height × 0.01)^2.
SD = standard deviation.

Efficacy Results: DB Phase: The primary endpoint was time to the first occurrence of either CV death or hospitalization for HF. The survival analysis of the primary and secondary endpoints is summarized in Table 7.

Table 8 summarizes subjects with at least 1 primary adjudicated endpoint for the complete DB phase. A total of 288 subjects (21.1%) in the eplerenone group and 392 subjects (28.5%) in the placebo group met the primary endpoint. CV mortality occurred in 178 subjects (13.0%) in the eplerenone group and 215 subjects (15.6%) in the placebo group. The most common causes of CV mortality were sudden cardiac death (eplerenone, 5.0%; placebo, 6.0%) and worsening of HF (eplerenone, 4.1%; placebo, 5.4%). HF hospitalization occurred in 186 subjects (13.6%) in the eplerenone group and 277 subjects (20.1%) in the placebo group.

Table 7. Survival Analysis of the Primary and Secondary Endpoints (Full Analysis Set)

	Number (%) of Subjects		Hazard Ratio	P-value	95% CI for Hazard Ratio
	Eplerenone (N=1364)	Placebo (N=1373)			
Primary endpoints					
HF hospitalization/CV death	249 (18.3)	356 (25.9)	0.630	<0.0001	0.535, 0.741
HF hospitalization	164 (12.0)	253 (18.4)	0.576	<0.0001	0.473, 0.702
CV death	147 (10.8)	185 (13.5)	0.757	0.0120	0.609, 0.941
Secondary endpoints					
All-cause mortality or HF hospitalization	270 (19.8)	376 (27.4)	0.647	<0.0001	0.552, 0.757
All-cause mortality	171 (12.5)	213 (15.5)	0.761	0.0081	0.622, 0.932
CV mortality	147 (10.8)	185 (13.5)	0.757	0.0120	0.609, 0.941
All-cause hospitalization	408 (29.9)	491 (35.8)	0.768	<0.0001	0.673, 0.876
HF hospitalization	164 (12.0)	253 (18.4)	0.576	<0.0001	0.473, 0.702
All-cause death or all-cause hospitalization	462 (33.9)	569 (41.4)	0.751	<0.0001	0.664, 0.849
HF death or HF hospitalization	170 (12.5)	262 (19.1)	0.577	<0.0001	0.475, 0.701
CV hospitalization	304 (22.3)	399 (29.1)	0.694	<0.0001	0.598, 0.806
Fatal/nonfatal MI	45 (3.3)	33 (2.4)	1.316	0.2321	0.839, 2.064
Fatal/nonfatal stroke	21 (1.5)	26 (1.9)	0.789	0.4213	0.443, 1.406
ICD	61 (4.5)	59 (4.3)	0.994	0.9754	0.694, 1.424
Implantation of resynchronization device (CRT)	33 (2.4)	41 (3.0)	0.770	0.2652	0.485, 1.220
Hospitalization for worsening renal function	9 (0.7)	8 (0.6)	0.971	0.9537	0.366, 2.578
Hospitalization for hyperkalemia	4 (0.3)	3 (0.2)	1.154	0.8539	0.251, 5.312

Hazard ratio, 95% CI of hazard ratio, and p-value were based on a Cox proportional hazard model including treatment as the major factor, adjusting for age, eGFR, LVEF, BMI, hemoglobin, heart rate, SBP, diabetes, history of hypertension, prior MI, baseline LBBB and QRS, and atrial fibrillation as covariates.
AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; CRT = cardiac resynchronization therapy; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantation of cardiac defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; QRS = time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; SBP = systolic blood pressure.

Table 8. Summary of Subjects With at Least 1 Adjudicated Primary Endpoint (Full Analysis Sets)

	No. of Subjects (%)	
	Complete DB Phase	
	Eplerenone	Placebo
Total number of subjects	1367	1376
Subjects with HF hospitalization or CV death	288 (21.1)	392 (28.5)
Subjects with HF hospitalization	186 (13.6)	277 (20.1)
Subjects with CV death	178 (13.0)	215 (15.6)
Sudden cardiac death	69 (5.0)	83 (6.0)
Worsening HF	56 (4.1)	74 (5.4)
Myocardial infarction	13 (1.0)	10 (0.7)
Arrhythmia	7 (0.5)	8 (0.6)
Stroke	7 (0.5)	7 (0.5)
Emergency CV procedure/operation	0	1 (0.1)
Other CV event	3 (0.2)	2 (0.1)
Unknown[a]	23 (1.7)	30 (2.2)
Subjects with CV hospitalization	346 (25.3)	439 (31.9)
HF	186 (13.6)	277 (20.1)
Arrhythmia	57 (4.2)	82 (6.0)
Myocardial infarction, unstable angina, other chest pain	74 (5.4)	73 (5.3)
Stroke, TIA	28 (2.0)	38 (2.8)
Syncope/near syncope, hypotension	22 (1.6)	23 (1.7)
Cardiac tamponade, endocarditis, hypertension, valvular heart disease, other CV event, other	29 (2.1)	49 (3.6)
Pulmonary embolism	2 (0.1)	3 (0.2)
Other peripheral arterial problem	15 (1.1)	11 (0.8)
Ruptured aneurysm	1 (0.1)	0

CV = cardiovascular; DB = double-blind; HF = heart failure; TIA = transient ischemic attack.
a. Exact cause of death could not be determined by the endpoint adjudication committee; these deaths defaulted to CV death in the analyses.

The incidence of all adjudicated clinical endpoints for the complete DB phase is summarized in Table 9. The incidence of all secondary endpoints was lower in the eplerenone group than in the placebo group, except for fatal/nonfatal MI (eplerenone, 3.6%; placebo, 2.9%), hospitalization for worsening renal function (0.7% in both eplerenone and placebo groups), and hospitalization for hyperkalemia (eplerenone, 0.3%; placebo, 0.2%).

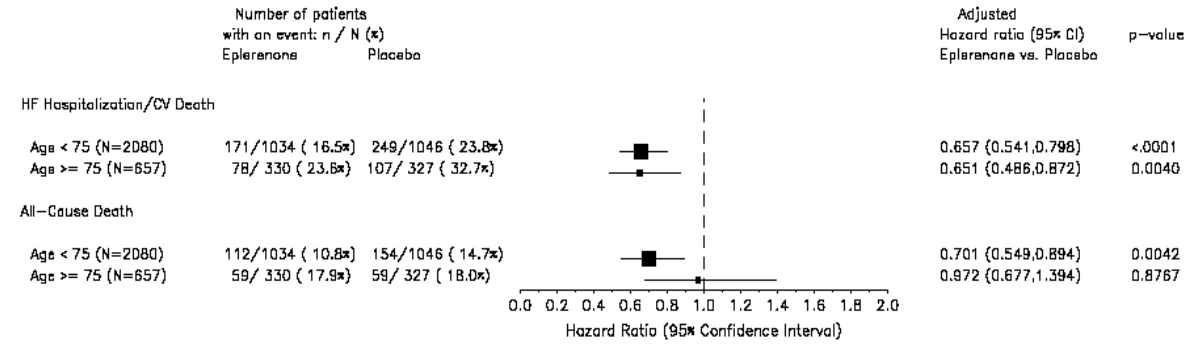
Table 9. Summary of Adjudicated Secondary Endpoints (Full Analysis Sets)

	No. of Subjects (%)	
	Complete DB Phase	
	Eplerenone	Placebo
Total no. of subjects	1367	1376
Total no. of adjudicated cases	1425	1752
Total no. of adjudicated endpoints	1068	1377
Total no. of subjects with at least 1 endpoint	599 (43.8)	708 (51.5)
Total no. of subjects with at least 1 event:		
All-cause mortality or HF hospitalization	311 (22.8)	418 (30.4)
All-cause mortality	205 (15.0)	253 (18.4)
All-cause hospitalization	463 (33.9)	552 (40.1)
All-cause death or all-cause hospitalization	530 (38.8)	636 (46.2)
HF death or HF hospitalization	194 (14.2)	287 (20.9)
Fatal / nonfatal MI	49 (3.6)	40 (2.9)
Fatal / nonfatal stroke	24 (1.8)	31 (2.3)
Implantation of cardiac defibrillator	76 (5.6)	78 (5.7)
Implantation of CRT	45 (3.3)	53 (3.9)
New-onset atrial fibrillation / flutter	57 (4.2)	87 (6.3)
New-onset diabetes mellitus	44 (3.2)	49 (3.6)
Hospitalization for worsening renal function	10 (0.7)	10 (0.7)
Hospitalization for hyperkalemia	4 (0.3)	3 (0.2)

CRT = cardiac resynchronization therapy; DB = double-blind; HF = heart failure; MI = myocardial infarction.

To fulfill a European postapproval commitment issued at the time of approval on 10 March 2004, efficacy analyses were conducted for the "very elderly" (age ≥75 years) subjects in the FAS up to the 25 May 2010 data cutoff. The subgroup analysis by age group ≥75 years for the primary endpoint and all-cause mortality is summarized in Figure 1. The incidence rate of stroke was 2.7% (9/330) for eplerenone and 2.4% (8/327) for placebo in subjects ≥75 years of age.

Figure 1. Subgroup Analysis by Age Group (<75 Years and ≥75 years) for the Primary Endpoint and All-Cause Mortality (Full Analysis Set)



CI = confidence interval; CV = cardiovascular; HF = heart failure.

The frequency of strokes by age (<75 years and ≥75 years) is summarized in Table 10.

Table 10. Summary of Frequency of Strokes by Age (<75 years and ≥75 years) (Full Analysis Set)

Endpoint	Age Group	Eplerenone n/N (%) of subjects	Placebo n/N (%) of subjects
Fatal/nonfatal stroke	<75 years	12/1034 (1.2)	18/1046 (1.7)
	≥75 years	9/330 (2.7)	8/327 (2.4)

n = number of subjects who had a stroke; N = total number of subjects.

A summary of subjects ≥75 years and <75 years of age with at least 1 adjudicated primary endpoint in the post-cutoff data set is presented in Table 11.

Table 11. Summary of Subjects With at Least 1 Adjudicated Primary Endpoint and All-Cause Death, by Age, After the 25 May 2010 Data Cutoff (Full Analysis Set)

		n/N Subjects (%)	
Endpoint	Age Group	Eplerenone	Placebo
All-cause death	<75 years	29/813 (3.6)	26/777 (3.3)
	≥75 years	3/228 (1.3)	14/229 (6.1)
Primary endpoint	<75 years	33/813 (4.1)	28/777 (3.6)
	≥75 years	4/228 (1.8)	6/229 (2.6)

n = number of subjects with at least one adjudicated primary endpoint and all-cause death; N = total number of subjects.

The incidence of fatal or nonfatal stroke in these age groups after 25 May 2010 was 0 in subjects ≥75 years.

OLE Phase: No efficacy evaluations were conducted for the OLE phase.

Safety Results: DB Phase: An overview of treatment-emergent AEs is provided in Table 12.

Table 12. Overview of Treatment-Emergent Adverse Events (All Causalities and Treatment Related), Safety Populations (Double-Blind Phase)

	All Causalities		Treatment Related	
	Eplerenone	Placebo	Eplerenone	Placebo
Subjects evaluable for AEs	1364	1372	1364	1372
Number of AEs	3989	4126	457	348
Subjects with AEs (%)	1047 (76.8)	1072 (78.1)	290 (21.3)	235 (17.1)
Subjects with SAEs (%)	586 (43.0)	686 (50.0)	39 (2.9)	29 (2.1)
Subjects with severe AEs (%)	426 (31.2)	504 (36.7)	33 (2.4)	18 (1.3)
Subjects discontinued due to AEs (%)	215 (15.8)	257 (18.7)	52 (3.8)	48 (3.5)
Subjects with dose reduced or temporary discontinuation of study drug due to AEs (%)	242 (17.7)	207 (15.1)	123 (9.0)	72 (5.2)

Except for number of AEs, subjects are counted only once per treatment in each row.
AEs and SAEs are not separated out while reporting AEs.
DB = double–blind; AEs = adverse events; SAEs = serious adverse events.

The incidence of treatment-emergent non serious AEs occurring in ≥5% subjects in either group during the DB phase is summarized in Table 13. The highest number of subjects experienced treatment-related AEs in the metabolism and nutrition disorders system organ class. The only treatment-related AE that occurred in ≥2% of subjects in either treatment group during the DB phase was hyperkalemia. The majority of both all-causality and treatment-related AEs were mild or moderate in severity. Nine subjects in the eplerenone group and 4 subjects in the placebo group experienced severe hyperkalemia.

Table 13. Treatment-Emergent Non Serious Adverse Events (All Causalities) in ≥5% of Subjects in Either Treatment Group (Double-Blind Phase)

	Number of Subjects (%)	
	Complete DB Phase	
	Eplerenone	**Placebo**
Number (%) of subjects:		
Evaluable for adverse events	1364	1372
With adverse events	172 (12.6)	148 (10.8)
SOC/MedDRA preferred term		
Cardiac disorders	84 (6.2)	107 (7.8)
Cardiac failure	84 (6.2)	107 (7.8)
Metabolism and nutrition disorders	101 (7.4)	48 (3.5)
Hyperkalemia	101 (7.4)	48 (3.5)

Subjects were only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

The incidence of treatment-emergent serious AEs occurring in the DB phase is summarized in Table 14.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Number (%) of subjects:		
Evaluable for adverse events	1364	1372
With adverse events	586 (43.0)	686 (50.0)
SOC/MedDRA Preferred Term		
Blood and lymphatic system disorders	19 (1.4)	17 (1.2)
Anaemia	12 (0.9)	9 (0.7)
Coagulopathy	1 (0.1)	3 (0.2)
Disseminated intravascular coagulation	0	1 (0.1)
Heparin-induced thrombocytopenia	0	1 (0.1)
Hilar lymphadenopathy	1 (0.1)	0
Iron deficiency anaemia	1 (0.1)	1 (0.1)
Lymphadenopathy	0	1 (0.1)
Lymphadenopathy mediastinal	1 (0.1)	0
Microcytic anaemia	1 (0.1)	0
Neutropenia	1 (0.1)	0
Polycythaemia	0	1 (0.1)
Thrombocytopenia	2 (0.1)	0
Cardiac disorders	355 (26.0)	442 (32.2)
Acute coronary syndrome	2 (0.1)	5 (0.4)
Acute left ventricular failure	0	3 (0.2)
Acute myocardial infarction	11 (0.8)	10 (0.7)
Angina pectoris	11 (0.8)	18 (1.3)
Angina unstable	27 (2.0)	30 (2.2)
Aortic valve disease	0	1 (0.1)
Arrhythmia	10 (0.7)	20 (1.5)
Arrhythmia supraventricular	2 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	1 (0.1)
Atrial fibrillation	28 (2.1)	33 (2.4)
Atrial flutter	5 (0.4)	7 (0.5)
Atrial tachycardia	0	3 (0.2)
Atrial thrombosis	0	1 (0.1)
Atrioventricular block	1 (0.1)	0
Atrioventricular block complete	3 (0.2)	6 (0.4)
Atrioventricular block second degree	0	2 (0.1)
Bradyarrhythmia	3 (0.2)	3 (0.2)
Bradycardia	5 (0.4)	4 (0.3)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Bundle branch block left	2 (0.1)	1 (0.1)
Cardiac aneurysm	0	1 (0.1)
Cardiac arrest	15 (1.1)	17 (1.2)
Cardiac asthma	3 (0.2)	2 (0.1)
Cardiac failure	218 (16.0)	270 (19.7)
Cardiac failure acute	1 (0.1)	5 (0.4)
Cardiac failure chronic	2 (0.1)	4 (0.3)
Cardiac failure congestive	14 (1.0)	18 (1.3)
Cardiac perforation	1 (0.1)	0
Cardiac tamponade	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	0	4 (0.3)
Cardiogenic shock	5 (0.4)	6 (0.4)
Cardiomyopathy	0	2 (0.1)
Cardiopulmonary failure	3 (0.2)	3 (0.2)
Cardiovascular disorder	3 (0.2)	1 (0.1)
Conduction disorder	3 (0.2)	3 (0.2)
Congestive cardiomyopathy	3 (0.2)	1 (0.1)
Coronary artery disease	7 (0.5)	5 (0.4)
Coronary artery occlusion	1 (0.1)	0
Coronary artery stenosis	6 (0.4)	4 (0.3)
Coronary artery thrombosis	0	1 (0.1)
Intracardiac thrombus	0	1 (0.1)
Ischaemic cardiomyopathy	2 (0.1)	2 (0.1)
Left ventricular dysfunction	0	1 (0.1)
Left ventricular failure	5 (0.4)	10 (0.7)
Low cardiac output syndrome	1 (0.1)	1 (0.1)
Mitral valve disease	0	1 (0.1)
Mitral valve incompetence	1 (0.1)	0
Myocardial infarction	36 (2.6)	34 (2.5)
Myocardial ischaemia	5 (0.4)	3 (0.2)
Palpitations	1 (0.1)	3 (0.2)
Pericardial effusion	1 (0.1)	1 (0.1)
Pericardial haemorrhage	0	1 (0.1)
Sick sinus syndrome	1 (0.1)	3 (0.2)
Sinus arrest	0	1 (0.1)
Sinus tachycardia	1 (0.1)	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Supraventricular tachyarrhythmia	0	1 (0.1)
Supraventricular tachycardia	3 (0.2)	1 (0.1)
Tachycardia	5 (0.4)	4 (0.3)
Tachycardia paroxysmal	0	1 (0.1)
Ventricular arrhythmia	4 (0.3)	3 (0.2)
Ventricular dysfunction	0	1 (0.1)
Ventricular extrasystoles	0	1 (0.1)
Ventricular fibrillation	11 (0.8)	10 (0.7)
Ventricular tachyarrhythmia	0	1 (0.1)
Ventricular tachycardia	19 (1.4)	33 (2.4)
Ear and labyrinth disorders	2 (0.1)	2 (0.1)
Hypoacusis	0	1 (0.1)
Tympanic membrane perforation	1 (0.1)	0
Vertigo	1 (0.1)	1 (0.1)
Endocrine disorders	3 (0.2)	3 (0.2)
Goitre	0	1 (0.1)
Hyperthyroidism	2 (0.1)	2 (0.1)
Hypothyroidism	1 (0.1)	0
Eye disorders	4 (0.3)	3 (0.2)
Amaurosis fugax	1 (0.1)	0
Cataract	1 (0.1)	3 (0.2)
Diplopia	1 (0.1)	0
Phacolytic glaucoma	0	1 (0.1)
Retinal detachment	1 (0.1)	0
Gastrointestinal disorders	35 (2.6)	46 (3.4)
Abdominal discomfort	1 (0.1)	0
Abdominal hernia obstructive	0	1 (0.1)
Abdominal pain	2 (0.1)	6 (0.4)
Abdominal pain lower	0	1 (0.1)
Abdominal pain upper	1 (0.1)	2 (0.1)
Anal fissure	1 (0.1)	0
Anal haemorrhage	0	1 (0.1)
Ascites	1 (0.1)	2 (0.1)
Colitis	0	1 (0.1)
Colitis ischaemic	0	1 (0.1)
Colonic polyp	2 (0.1)	3 (0.2)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Constipation	2 (0.1)	0
Crohn's disease	1 (0.1)	0
Diarrhoea	4 (0.3)	2 (0.1)
Diverticulum intestinal	1 (0.1)	0
Duodenal ulcer haemorrhage	0	1 (0.1)
Duodenitis	1 (0.1)	0
Dyspepsia	1 (0.1)	1 (0.1)
Gastric ulcer	1 (0.1)	1 (0.1)
Gastric ulcer perforation	0	1 (0.1)
Gastritis	2 (0.1)	2 (0.1)
Gastritis erosive	0	1 (0.1)
Gastrointestinal angiodysplasia	0	1 (0.1)
Gastrointestinal haemorrhage	4 (0.3)	4 (0.3)
Gastrooesophageal reflux disease	0	1 (0.1)
Haemorrhoids	1 (0.1)	0
Ileus	0	2 (0.1)
Ileus paralytic	0	1 (0.1)
Inguinal hernia	4 (0.3)	3 (0.2)
Inguinal hernia, obstructive	0	2 (0.1)
Intestinal ischaemia	0	2 (0.1)
Intestinal obstruction	0	2 (0.1)
Melaena	1 (0.1)	0
Nausea	1 (0.1)	1 (0.1)
Oesophagiti	1 (0.1)	1 (0.1)
Pancreatitis	1 (0.1)	1 (0.1)
Pancreatitis acute	1 (0.1)	2 (0.1)
Pancreatitis chronic	1 (0.1)	0
Pancreatitis necrotising	1 (0.1)	0
Pancreatolithiasis	0	1 (0.1)
Proctitis	1 (0.1)	0
Proctitis haemorrhagic	0	1 (0.1)
Small intestinal obstruction	0	1 (0.1)
Swollen tongue	0	1 (0.1)
Umbilical hernia	1 (0.1)	0
Vomiting	2 (0.1)	4 (0.3)
General disorders and administration site conditions	107 (7.8)	144 (10.5)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Asthenia	2 (0.1)	6 (0.4)
Cardiac death	0	2 (0.1)
Chest pain	22 (1.6)	31 (2.3)
Condition aggravated	0	2 (0.1)
Crepitations	0	1 (0.1)
Death	39 (2.9)	50 (3.6)
Device breakage	1 (0.1)	0
Device dislocation	0	1 (0.1)
Device lead damage	1 (0.1)	0
Device malfunction	2 (0.1)	1 (0.1)
Device occlusion	1 (0.1)	1 (0.1)
Device pacing issue	0	1 (0.1)
Device stimulation issue	1 (0.1)	0
Face oedema	0	1 (0.1)
Fatigue	1 (0.1)	0
General physical health deterioration	5 (0.4)	3 (0.2)
Hyperplasia	0	1 (0.1)
Impaired healing	1 (0.1)	0
Implant site discharge	0	1 (0.1)
Lipogranuloma	1 (0.1)	0
Malaise	2 (0.1)	1 (0.1)
Mass	0	1 (0.1)
Medical device complication	0	1 (0.1)
Multi-organ failure	1 (0.1)	3 (0.2)
Necrosis	1 (0.1)	0
Oedema	1 (0.1)	0
Oedema peripheral	1 (0.1)	3 (0.2)
Pain	2 (0.1)	0
Pyrexia	1 (0.1)	4 (0.3)
Spinal pain	0	1 (0.1)
Sudden cardiac death	8 (0.6)	12 (0.9)
Sudden death	15 (1.1)	24 (1.7)
Hepatobiliary disorders	15 (1.1)	19 (1.4)
Bile duct obstruction	1 (0.1)	0
Bile duct stone	0	1 (0.1)
Cholangitis	0	2 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Cholangitis acute	0	2 (0.1)
Cholecystitis	4 (0.3)	3 (0.2)
Cholecystitis acute	2 (0.1)	3 (0.2)
Cholecystitis chronic	1 (0.1)	0
Cholelithiasis	2 (0.1)	5 (0.4)
Hepatic failure	1 (0.1)	0
Hepatic function abnormal	1 (0.1)	1 (0.1)
Hepatitis	0	1 (0.1)
Hepatitis alcoholic	1 (0.1)	0
Hepatitis toxic	0	1 (0.1)
Hepatomegaly	0	1 (0.1)
Hepatorenal failure	2 (0.1)	0
Jaundice	0	3 (0.2)
Jaundice cholestatic	0	1 (0.1)
Immune system disorders	0	1 (0.1)
Drug hypersensitivity	0	1 (0.1)
Infections and infestations	95 (7.0)	127 (9.3)
Abscess limb	1 (0.1)	1 (0.1)
Abscess neck	0	1 (0.1)
Acute sinusitis	0	1 (0.1)
Anal abscess	0	1 (0.1)
Appendicitis	0	1 (0.1)
Bacteraemia	1 (0.1)	0
Breast abscess	1 (0.1)	0
Bronchitis	6 (0.4)	13 (0.9)
Bronchopneumonia	6 (0.4)	5 (0.4)
Cellulitis	4 (0.3)	2 (0.1)
Cholecystitis infective	1 (0.1)	0
Chronic sinusitis	1 (0.1)	0
Cystitis	1 (0.1)	2 (0.1)
Dengue fever	1 (0.1)	0
Dermo-hypodermitis	0	1 (0.1)
Device related infection	1 (0.1)	2 (0.1)
Diabetic gangrene	0	1 (0.1)
Diverticulitis	1 (0.1)	1 (0.1)
Endocarditis	0	2 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Erysipelas	0	7 (0.5)
Gangrene	4 (0.3)	0
Gastroenteritis	6 (0.4)	3 (0.2)
Haematoma infection	1 (0.1)	0
Hepatobiliary infection	0	1 (0.1)
Implant site infection	2 (0.1)	1 (0.1)
Infected dermal cyst	0	1 (0.1)
Infected skin ulcer	1 (0.1)	0
Infection	1 (0.1)	4 (0.3)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.1)
Influenza	0	1 (0.1)
Intervertebral discitis	1 (0.1)	1 (0.1)
Joint tuberculosis	0	1 (0.1)
Kidney infection	1 (0.1)	0
Laryngitis	0	1 (0.1)
Localised infection	1 (0.1)	1 (0.1)
Lower respiratory tract infection	4 (0.3)	5 (0.4)
Lung infection	2 (0.1)	2 (0.1)
Meningitis	0	1 (0.1)
Orchitis	1 (0.1)	1 (0.1)
Osteomyelitis	0	1 (0.1)
Phlebitis infective	0	1 (0.1)
Pneumonia	29 (2.1)	32 (2.3)
Pneumonia staphylococcal	1 (0.1)	0
Postoperative wound infection	1 (0.1)	1 (0.1)
Pseudomembranous colitis	0	1 (0.1)
Pyelonephritis	2 (0.1)	1 (0.1)
Respiratory tract infection	3 (0.2)	12 (0.9)
Sepsis	3 (0.2)	4 (0.3)
Septic shock	7 (0.5)	7 (0.5)
Skin infection	0	1 (0.1)
Staphylococcal bacteraemia	2 (0.1)	0
Staphylococcal infection	1 (0.1)	2 (0.1)
Systemic candida	0	1 (0.1)
Tracheobronchitis	0	1 (0.1)
Upper respiratory tract infection	1 (0.1)	1 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Urinary tract infection	8 (0.6)	10 (0.7)
Urosepsis	3 (0.2)	4 (0.3)
Viral infection	2 (0.1)	0
Wound infection	0	2 (0.1)
Injury, poisoning and procedural complications	26 (1.9)	43 (3.1)
Ankle fracture	0	1 (0.1)
Back injury	0	1 (0.1)
Bone fissure	0	1 (0.1)
Cervical vertebral fracture	1 (0.1)	0
Concussion	2 (0.1)	0
Contusion	0	1 (0.1)
Excoriation	0	1 (0.1)
Face injury	0	1 (0.1)
Facial bones fracture	0	1 (0.1)
Fall	9 (0.7)	12 (0.9)
Femoral neck fracture	2 (0.1)	0
Femur fracture	3 (0.2)	4 (0.3)
Foot fracture	1 (0.1)	2 (0.1)
Haematuria traumatic	0	1 (0.1)
Head injury	2 (0.1)	2 (0.1)
Hip fracture	0	2 (0.1)
Humerus fracture	0	2 (0.1)
Joint dislocation	1 (0.1)	1 (0.1)
Joint injury	0	1 (0.1)
Laceration	0	1 (0.1)
Ligament sprain	0	1 (0.1)
Lip injury	0	1 (0.1)
Lower limb fracture	1 (0.1)	0
Lumbar vertebral fracture	0	1 (0.1)
Multiple fractures	1 (0.1)	0
Muscle injury	0	1 (0.1)
Overdose	2 (0.1)	1 (0.1)
Pelvic fracture	0	1 (0.1)
Poisoning	0	1 (0.1)
Post procedural haematoma	1 (0.1)	1 (0.1)
Post procedural haemorrhage	0	1 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Postoperative hernia	0	1 (0.1)
Pubis fracture	0	1 (0.1)
Rib fracture	0	1 (0.1)
Road traffic accident	2 (0.1)	1 (0.1)
Spinal compression fracture	0	1 (0.1)
Spinal fracture	2 (0.1)	0
Sternal fracture	0	1 (0.1)
Subdural haematoma	2 (0.1)	2 (0.1)
Subdural haemorrhage	0	1 (0.1)
Tendon rupture	1 (0.1)	0
Toxicity to various agents	0	3 (0.2)
Traumatic haematoma	1 (0.1)	0
Upper limb fracture	2 (0.1)	0
Vascular graft occlusion	1 (0.1)	0
Investigations	16 (1.2)	13 (0.9)
Arteriogram	1 (0.1)	0
Arteriogram coronary	1 (0.1)	3 (0.2)
Arthroscopy	1 (0.1)	0
Blood creatine phosphokinase increased	0	1 (0.1)
Blood creatinine increased	1 (0.1)	2 (0.1)
Blood glucose abnormal	1 (0.1)	0
Blood glucose increased	1 (0.1)	0
Blood potassium increased	0	1 (0.1)
Blood pressure increased	0	1 (0.1)
Blood urea increased	1 (0.1)	1 (0.1)
Carotid bruit	1 (0.1)	0
Ejection fraction decreased	0	1 (0.1)
Electrocardiogram QT prolonged	1 (0.1)	0
Glycosylated haemoglobin increased	1 (0.1)	0
Hepatic enzyme increased	1 (0.1)	0
International normalised ratio decreased	0	1 (0.1)
International normalised ratio increased	3 (0.2)	1 (0.1)
Liver function test abnormal	1 (0.1)	1 (0.1)
Oxygen saturation decreased	0	1 (0.1)
Platelet count decreased	1 (0.1)	0
Urine output decreased	1 (0.1)	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Weight decreased	0	1 (0.1)
Metabolism and nutrition disorders	52 (3.8)	31 (2.3)
Cachexia	1 (0.1)	0
Decreased appetite	2 (0.1)	1 (0.1)
Dehydration	8 (0.6)	3 (0.2)
Diabetes mellitus	6 (0.4)	2 (0.1)
Diabetes mellitus inadequate control	1 (0.1)	2 (0.1)
Gout	6 (0.4)	2 (0.1)
Hypercholesterolaemia	0	1 (0.1)
Hyperglycaemia	2 (0.1)	3 (0.2)
Hyperkalaemia	19 (1.4)	7 (0.5)
Hypoglycaemia	3 (0.2)	4 (0.3)
Hypokalaemia	4 (0.3)	6 (0.4)
Hyponatraemia	3 (0.2)	2 (0.1)
Hypovolaemia	1 (0.1)	0
Metabolic acidosis	1 (0.1)	1 (0.1)
Obesity	1 (0.1)	0
Type 2 diabetes mellitus	4 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	23 (1.7)	21 (1.5)
Arthritis	2 (0.1)	1 (0.1)
Back pain	1 (0.1)	3 (0.2)
Bursitis	0	2 (0.1)
Dupuytren’s contracture	1 (0.1)	0
Fistula	1 (0.1)	0
Gouty arthritis	1 (0.1)	2 (0.1)
Groin pain	1 (0.1)	1 (0.1)
Intervertebral disc protrusion	0	1 (0.1)
Muscle haemorrhage	0	1 (0.1)
Muscle spasms	1 (0.1)	0
Muscular weakness	1 (0.1)	2 (0.1)
Musculoskeletal chest pain	2 (0.1)	0
Neck pain	1 (0.1)	0
Osteitis	1 (0.1)	0
Osteoarthritis	7 (0.5)	3 (0.2)
Pain in extremity	1 (0.1)	2 (0.1)
Polymyalgia rheumatica	1 (0.1)	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Rheumatic disorder	1 (0.1)	0
Rheumatoid arthritis	1 (0.1)	0
Spinal column stenosis	1 (0.1)	2 (0.1)
Spinal osteoarthritis	0	1 (0.1)
Spondyloarthropathy	0	1 (0.1)
Spondylolisthesis	1 (0.1)	0
Sympathetic posterior cervical syndrome	0	1 (0.1)
Synovial cyst	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	36 (2.6)	49 (3.6)
Acute myeloid leukaemia	0	1 (0.1)
Adenocarcinoma	0	1 (0.1)
Adenoma benign	0	1 (0.1)
Adrenal neoplasm	1 (0.1)	0
Basal cell carcinoma	1 (0.1)	2 (0.1)
Benign laryngeal neoplasm	1 (0.1)	0
Biliary neoplasm	0	2 (0.1)
Bladder neoplasm	2 (0.1)	2 (0.1)
Brain neoplasm	1 (0.1)	0
Breast cancer	0	1 (0.1)
Breast neoplasm	2 (0.1)	0
Bronchial carcinoma	3 (0.2)	0
Bronchial neoplasm benign	1 (0.1)	0
Chronic myeloid leukaemia	0	1 (0.1)
Colon cancer	2 (0.1)	4 (0.3)
Colon neoplasm	4 (0.3)	1 (0.1)
Colorectal cancer	1 (0.1)	0
Gastric cancer	1 (0.1)	0
Hepatic neoplasm malignant	0	1 (0.1)
Lung adenocarcinoma	1 (0.1)	0
Lung cancer metastatic	0	1 (0.1)
Lung neoplasm	4 (0.3)	2 (0.1)
Lung neoplasm malignant	4 (0.3)	4 (0.3)
Lung squamous cell carcinoma stage unspecified	0	1 (0.1)
Malignant melanoma	0	2 (0.1)
Malignant neoplasm of ampulla of Vater	1 (0.1)	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Malignant neoplasm of pleura	0	1 (0.1)
Metastases to bone	0	1 (0.1)
Metastases to liver	1 (0.1)	1 (0.1)
Multiple myeloma	1 (0.1)	1 (0.1)
Myelofibrosis	1 (0.1)	0
Neoplasm malignant	0	1 (0.1)
Neoplasm prostate	1 (0.1)	1 (0.1)
Oesophageal carcinoma	0	1 (0.1)
Ovarian cancer	0	1 (0.1)
Ovarian neoplasm	0	1 (0.1)
Pancreatic carcinoma	0	1 (0.1)
Pituitary tumour	0	1 (0.1)
Prostate cancer	4 (0.3)	4 (0.3)
Prostatic adenoma	0	1 (0.1)
Rectal cancer	0	1 (0.1)
Rectal cancer metastatic	0	1 (0.1)
Renal cancer	0	1 (0.1)
Renal cell carcinoma	0	1 (0.1)
Renal neoplasm	0	1 (0.1)
Uterine leiomyoma	0	1 (0.1)
Vulval cancer	0	1 (0.1)
Nervous system disorders	79 (5.8)	87 (6.3)
Ataxia	1 (0.1)	0
Balance disorder	1 (0.1)	0
Brain injury	1 (0.1)	0
Carotid artery aneurysm	1 (0.1)	0
Carotid artery disease	0	1 (0.1)
Carotid artery stenosis	3 (0.2)	1 (0.1)
Cerebral atrophy	1 (0.1)	0
Cerebral haematoma	1 (0.1)	0
Cerebral haemorrhage	1 (0.1)	2 (0.1)
Cerebral infarction	2 (0.1)	2 (0.1)
Cerebral ischaemia	1 (0.1)	2 (0.1)
Cerebrovascular accident	20 (1.5)	22 (1.6)
Coma	1 (0.1)	0
Convulsion	1 (0.1)	2 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Dementia	1 (0.1)	1 (0.1)
Diabetic neuropathy	1 (0.1)	0
Dizziness	3 (0.2)	5 (0.4)
Dysarthria	2 (0.1)	0
Encephalopathy	1 (0.1)	1 (0.1)
Epilepsy	2 (0.1)	0
Haemorrhagic cerebral infarction	0	1 (0.1)
Headache	1 (0.1)	0
Hemianopia	0	1 (0.1)
Hypoxic-ischaemic encephalopathy	0	2 (0.1)
Ischaemic stroke	3 (0.2)	7 (0.5)
Loss of consciousness	3 (0.2)	3 (0.2)
Lumbar radiculopathy	1 (0.1)	0
Monoparesis	0	1 (0.1)
Nervous system disorder	0	1 (0.1)
Neuralgia	0	1 (0.1)
Parkinsonism	0	1 (0.1)
Polyneuropathy	1 (0.1)	0
Presyncope	0	4 (0.3)
Psychomotor hyperactivity	1 (0.1)	0
Sciatica	0	1 (0.1)
Somnolence	0	1 (0.1)
Spinal cord disorder	0	1 (0.1)
Spinal cord ischaemia	0	1 (0.1)
Syncope	26 (1.9)	22 (1.6)
Transient ischaemic attack	7 (0.5)	9 (0.7)
Tremor	1 (0.1)	0
Psychiatric disorders	10 (0.7)	13 (0.9)
Abnormal behaviour	0	1 (0.1)
Anxiety	2 (0.1)	1 (0.1)
Confusional state	3 (0.2)	3 (0.2)
Delirium	0	2 (0.1)
Depression	2 (0.1)	2 (0.1)
Drug dependence	0	1 (0.1)
Hallucination	1 (0.1)	0
Mental disorder	0	1 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Mental status changes	0	1 (0.1)
Pseudodementia	0	1 (0.1)
Restlessness	1 (0.1)	0
Schizophrenia, paranoid type	1 (0.1)	0
Somatoform disorder cardiovascular	0	1 (0.1)
Suicide attempt	1 (0.1)	1 (0.1)
Renal and urinary disorders	51 (3.7)	50 (3.6)
Bladder mass	0	1 (0.1)
Diabetic nephropathy	1 (0.1)	0
Dysuria	0	1 (0.1)
Haematuria	2 (0.1)	2 (0.1)
Haemorrhage urinary tract	1 (0.1)	0
Hydronephrosis	0	1 (0.1)
Nephrolithiasis	0	1 (0.1)
Nephropathy	0	1 (0.1)
Obstructive uropathy	0	1 (0.1)
Pyuria	1 (0.1)	0
Renal failure	10 (0.7)	17 (1.2)
Renal failure acute	9 (0.7)	10 (0.7)
Renal failure chronic	2 (0.1)	1 (0.1)
Renal impairment	27 (2.0)	21 (1.5)
Urinary retention	1 (0.1)	0
Reproductive system and breast disorders	7 (0.5)	3 (0.2)
Benign prostatic hyperplasia	4 (0.3)	1 (0.1)
Cervical dysplasia	1 (0.1)	0
Endometrial hyperplasia	0	1 (0.1)
Epididymitis	1 (0.1)	0
Ovarian cyst	0	1 (0.1)
Postmenopausal haemorrhage	1 (0.1)	0
Uterine polyp	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	69 (5.1)	88 (6.4)
Acute pulmonary oedema	8 (0.6)	8 (0.6)
Acute respiratory distress syndrome	0	1 (0.1)
Acute respiratory failure	1 (0.1)	1 (0.1)
Asthma	0	1 (0.1)
Brain hypoxia	1 (0.1)	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Bronchial disorder	1 (0.1)	0
Bronchiectasis	1 (0.1)	0
Bronchitis chronic	0	1 (0.1)
Bronchospasm	1 (0.1)	0
Cheyne-Stokes respiration	0	1 (0.1)
Chronic obstructive pulmonary disease	7 (0.5)	8 (0.6)
Cough	1 (0.1)	1 (0.1)
Diaphragmatic disorder	1 (0.1)	0
Dyspnoea	16 (1.2)	29 (2.1)
Dyspnoea at rest	1 (0.1)	0
Dyspnoea exertional	1 (0.1)	1 (0.1)
Emphysema	0	1 (0.1)
Epistaxis	2 (0.1)	4 (0.3)
Haemoptysis	2 (0.1)	2 (0.1)
Haemothorax	1 (0.1)	0
Hydrothorax	1 (0.1)	1 (0.1)
Hypoxia	1 (0.1)	0
Interstitial lung disease	0	1 (0.1)
Lung disorder	2 (0.1)	2 (0.1)
Mediastinal haemorrhage	0	1 (0.1)
Orthopnoea	1 (0.1)	1 (0.1)
Pleural disorder	1 (0.1)	0
Pleural effusion	5 (0.4)	7 (0.5)
Pleural haemorrhage	0	1 (0.1)
Pneumonia aspiration	0	1 (0.1)
Pneumothorax	3 (0.2)	0
Productive cough	2 (0.1)	0
Pulmonary embolism	5 (0.4)	6 (0.4)
Pulmonary hypertension	0	1 (0.1)
Pulmonary mass	0	1 (0.1)
Pulmonary oedema	7 (0.5)	12 (0.9)
Respiratory disorder	1 (0.1)	0
Respiratory failure	3 (0.2)	2 (0.1)
Sleep apnoea syndrome	1 (0.1)	2 (0.1)
Vocal cord disorder	1 (0.1)	0
Skin and subcutaneous tissue disorders	6 (0.4)	3 (0.2)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Dermatitis allergic	1 (0.1)	0
Diabetic foot	1 (0.1)	1 (0.1)
Prurigo	1 (0.1)	0
Psoriasis	1 (0.1)	0
Purpura	1 (0.1)	0
Skin disorder	0	1 (0.1)
Skin ulcer	1 (0.1)	1 (0.1)
Surgical and medical procedures	25 (1.8)	43 (3.1)
Aortic aneurysm repair	0	1 (0.1)
Bladder operation	0	1 (0.1)
Cardiac ablation	1 (0.1)	0
Cardiac pacemaker insertion	1 (0.1)	5 (0.4)
Cardiac pacemaker replacement	1 (0.1)	0
Cardiac pacemaker revision	0	1 (0.1)
Cardiac resynchronisation therapy	1 (0.1)	6 (0.4)
Cardiovascular event prophylaxis	0	1 (0.1)
Cardioversion	2 (0.1)	1 (0.1)
Cataract operation	1 (0.1)	1 (0.1)
Cervical conisation	1 (0.1)	0
Colectomy	1 (0.1)	0
Coronary angioplasty	0	1 (0.1)
Coronary arterial stent insertion	0	1 (0.1)
Coronary artery bypass	0	3 (0.2)
Foot amputation	0	1 (0.1)
Gallbladder operation	0	1 (0.1)
Heart transplant	1 (0.1)	0
Hip arthroplasty	0	2 (0.1)
Implantable defibrillator insertion	10 (0.7)	13 (0.9)
Inguinal hernia repair	0	1 (0.1)
Lipoma excision	0	1 (0.1)
Lung lobectomy	1 (0.1)	0
Lung neoplasm surgery	0	1 (0.1)
Medical device implantation	1 (0.1)	0
Mitral valve repair	0	1 (0.1)
Mitral valve replacement	0	1 (0.1)
Prophylaxis	3 (0.2)	1 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Renal transplant	1 (0.1)	0
Therapeutic procedure	1 (0.1)	0
Thrombolysis	0	1 (0.1)
Vascular operation	0	1 (0.1)
Vascular disorders	42 (3.1)	60 (4.4)
Aortic aneurysm	4 (0.3)	2 (0.1)
Aortic aneurysm rupture	1 (0.1)	1 (0.1)
Aortic dissection	0	1 (0.1)
Aortic stenosis	0	2 (0.1)
Arterial disorder	0	1 (0.1)
Arterial insufficiency	1 (0.1)	0
Arteriosclerosis	1 (0.1)	0
Arteritis	0	1 (0.1)
Circulatory collapse	4 (0.3)	4 (0.3)
Deep vein thrombosis	0	1 (0.1)
Embolism	1 (0.1)	0
Extremity necrosis	3 (0.2)	0
Femoral artery occlusion	1 (0.1)	1 (0.1)
Haematoma	3 (0.2)	3 (0.2)
Hypertension	5 (0.4)	6 (0.4)
Hypertensive crisis	1 (0.1)	5 (0.4)
Hypertensive emergency	1 (0.1)	0
Hypotension	2 (0.1)	10 (0.7)
Iliac artery occlusion	2 (0.1)	1 (0.1)
Intermittent claudication	1 (0.1)	0
Ischaemia	0	1 (0.1)
Lymphoedema	0	1 (0.1)
Microangiopathy	1 (0.1)	0
Orthostatic hypotension	0	3 (0.2)
Peripheral arterial occlusive disease	6 (0.4)	7 (0.5)
Peripheral artery aneurysm	0	1 (0.1)
Peripheral artery thrombosis	0	1 (0.1)
Peripheral ischaemia	3 (0.2)	3 (0.2)
Peripheral vascular disorder	1 (0.1)	0
Thrombophlebitis	1 (0.1)	0
Thrombophlebitis superficial	0	2 (0.1)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Thrombosis	0	2 (0.1)
Varicose vein	0	1 (0.1)
Vasculitis	1 (0.1)	0
Venous insufficiency	0	1 (0.1)
Venous thrombosis	1 (0.1)	0

Except for number of AEs, subjects are counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
MedDRA (v15.0) coding dictionary applied.
DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

Cardiac failure was the most common SAE in both treatment groups (occurring in 16.0% of subjects in the eplerenone group and 19.7% of subjects in the placebo group). Cardiac failure was considered treatment related in 4 subjects in the eplerenone group and in 3 subjects in the placebo group.

The incidence of treatment-emergent treatment related AEs occurring in the DB phase is summarized in Table 15.

Table 15. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	Placebo
Number (%) of subjects: Evaluable for adverse events	1364	1372
SOC/MedDRA Preferred Term		
Blood and lymphatic system disorders	2 (0.1)	1 (0.1)
Anaemia	1 (0.1)	1 (0.1)
Anaemia vitamin B12 deficiency	1 (0.1)	0
Cardiac disorders	22 (1.6)	7 (0.5)
Acute myocardial infarction	1 (0.1)	0
Atrial fibrillation	1 (0.1)	2 (0.1)
Bradycardia	2 (0.1)	0
Cardiac arrest	1 (0.1)	0
Cardiac failure	8 (0.6)	3 (0.2)
Cardiac failure acute	1 (0.1)	0
Cardiac failure congestive	1 (0.1)	0
Cardiogenic shock	0	1 (0.1)
Conduction disorder	1 (0.1)	1 (0.1)
Palpitations	3 (0.2)	0
Sinus tachycardia	1 (0.1)	0
Tachycardia	1 (0.1)	0
Ventricular fibrillation	2 (0.1)	0
Ventricular tachycardia	1 (0.1)	1 (0.1)
Ear and labyrinth disorders	3 (0.2)	2 (0.1)
Tinnitus	2 (0.1)	0
Vertigo	1 (0.1)	2 (0.1)
Eye disorders	3 (0.2)	4 (0.3)
Age-related macular degeneration	0	1 (0.1)
Cataract	1 (0.1)	0
Diabetic retinopathy	1 (0.1)	0
Dry eye	0	1 (0.1)
Eye pain	0	2 (0.1)
Vision blurred	0	1 (0.1)
Visual impairment	1 (0.1)	1 (0.1)
Gastrointestinal disorders	38 (2.8)	40 (2.9)
Abdominal discomfort	3 (0.2)	1 (0.1)
Abdominal distension	1 (0.1)	1 (0.1)
Abdominal pain	3 (0.2)	2 (0.1)
Abdominal pain upper	7 (0.5)	1 (0.1)
Abdominal tenderness	0	1 (0.1)
Constipation	2 (0.1)	2 (0.1)
Diarrhoea	5 (0.4)	11 (0.8)
Diverticulum intestinal	1 (0.1)	0
Dry mouth	2 (0.1)	0
Dyspepsia	1 (0.1)	3 (0.2)
Epigastric discomfort	1 (0.1)	0
Flatulence	1 (0.1)	2 (0.1)
Frequent bowel movements	1 (0.1)	0
Gastric disorder	1 (0.1)	2 (0.1)
Gastritis	3 (0.2)	1 (0.1)
Gastritis erosive	0	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)	2 (0.1)

Table 15. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Mouth ulceration	1 (0.1)	0
Nausea	8 (0.6)	14 (1.0)
Stomatitis	1 (0.1)	0
Vomiting	3 (0.2)	3 (0.2)
General disorders and administration site conditions	20 (1.5)	20 (1.5)
Asthenia	0	1 (0.1)
Chest discomfort	1 (0.1)	0
Chest pain	1 (0.1)	1 (0.1)
Chills	0	1 (0.1)
Death	1 (0.1)	2 (0.1)
Fatigue	5 (0.4)	9 (0.7)
Influenza like illness	1 (0.1)	0
Malaise	3 (0.2)	4 (0.3)
Oedema	1 (0.1)	1 (0.1)
Oedema peripheral	0	1 (0.1)
Pain	4 (0.3)	1 (0.1)
Pyrexia	3 (0.2)	0
Temperature regulation disorder	0	1 (0.1)
Infections and infestations	3 (0.2)	4 (0.3)
Ear infection	1 (0.1)	0
Hepatobiliary infection	0	1 (0.1)
Localised infection	2 (0.1)	0
Oral candidiasis	0	1 (0.1)
Respiratory tract infection	0	1 (0.1)
Upper respiratory tract infection	1 (0.1)	0
Urosepsis	0	1 (0.1)
Viral infection	1 (0.1)	0
Injury, poisoning and procedural complications	3 (0.2)	5 (0.4)
Animal bite	1 (0.1)	0
Back injury	0	1 (0.1)
Drug exposure during pregnancy	1 (0.1)	0
Face injury	0	1 (0.1)
Fall	0	2 (0.1)
Head injury	0	1 (0.1)
Radius fracture	0	1 (0.1)
Scratch	1 (0.1)	0
Skeletal injury	0	1 (0.1)
Vascular pseudoaneurysm	0	1 (0.1)
Investigations	39 (2.9)	24 (1.7)
Alanine aminotransferase increased	2 (0.1)	0
Blood alkaline phosphatase increased	0	1 (0.1)
Blood bilirubin increased	0	1 (0.1)
Blood cholesterol increased	1 (0.1)	0
Blood creatine increased	1 (0.1)	0
Blood creatinine increased	11 (0.8)	10 (0.7)
Blood potassium increased	12 (0.9)	4 (0.3)
Blood pressure decreased	1 (0.1)	0
Blood triglycerides increased	1 (0.1)	0
Blood urea increased	9 (0.7)	5 (0.4)
Blood uric acid abnormal	0	1 (0.1)

Table 15. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Epidermal growth factor receptor decreased	5 (0.4)	2 (0.1)
Gamma-glutamyltransferase increased	0	1 (0.1)
Glomerular filtration rate decreased	3 (0.2)	3 (0.2)
International normalised ratio abnormal	0	1 (0.1)
Laboratory test abnormal	1 (0.1)	0
Prostatic specific antigen increased	1 (0.1)	0
Waist circumference increased	1 (0.1)	0
Weight decreased	1 (0.1)	1 (0.1)
Weight increased	1 (0.1)	0
Metabolism and nutrition disorders	111 (8.1)	62 (4.5)
Decreased appetite	3 (0.2)	4 (0.3)
Dehydration	1 (0.1)	1 (0.1)
Diabetes mellitus	2 (0.1)	3 (0.2)
Dyslipidaemia	0	1 (0.1)
Gout	4 (0.3)	7 (0.5)
Hypercalcaemia	2 (0.1)	0
Hypercholesterolaemia	0	1 (0.1)
Hyperglycaemia	1 (0.1)	0
Hyperkalaemia	95 (7.0)	40 (2.9)
Hyperuricaemia	2 (0.1)	2 (0.1)
Hypoglycaemia	0	1 (0.1)
Hypokalaemia	0	2 (0.1)
Hyponatraemia	1 (0.1)	0
Hypovolaemia	1 (0.1)	0
Type 2 diabetes mellitus	1 (0.1)	0
Musculoskeletal and connective tissue disorders	20 (1.5)	18 (1.3)
Arthralgia	2 (0.1)	3 (0.2)
Back pain	2 (0.1)	3 (0.2)
Muscle disorder	0	1 (0.1)
Muscle fatigue	0	1 (0.1)
Muscle spasms	7 (0.5)	4 (0.3)
Muscular weakness	1 (0.1)	1 (0.1)
Musculoskeletal chest pain	0	1 (0.1)
Musculoskeletal pain	2 (0.1)	1 (0.1)
Musculoskeletal stiffness	1 (0.1)	0
Myalgia	1 (0.1)	2 (0.1)
Neck pain	1 (0.1)	1 (0.1)
Osteoporosis	0	1 (0.1)
Pain in extremity	3 (0.2)	1 (0.1)
Periarthritis	1 (0.1)	0
Sensation of heaviness	1 (0.1)	0
Tendonitis	0	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.4)	0
Bladder neoplasm	1 (0.1)	0
Breast neoplasm	1 (0.1)	0
Colon neoplasm	1 (0.1)	0
Myelodysplastic syndrome	1 (0.1)	0
Prostate cancer	1 (0.1)	0
Nervous system disorders	35 (2.6)	37 (2.7)

Table 15. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Ageusia	0	1 (0.1)
Amnesia	1 (0.1)	0
Dizziness	14 (1.0)	23 (1.7)
Dizziness postural	1 (0.1)	0
Dysaesthesia	0	1 (0.1)
Dysarthria	1 (0.1)	0
Headache	10 (0.7)	6 (0.4)
Hypoaesthesia	3 (0.2)	1 (0.1)
Hypotonia	0	1 (0.1)
Lethargy	1 (0.1)	1 (0.1)
Memory impairment	1 (0.1)	0
Migraine	0	1 (0.1)
Neuropathy peripheral	1 (0.1)	0
Paraesthesia	1 (0.1)	0
Polyneuropathy	1 (0.1)	0
Presyncope	1 (0.1)	3 (0.2)
Somnolence	0	1 (0.1)
Spinal cord disorder	0	1 (0.1)
Spinal cord ischaemia	0	1 (0.1)
Syncope	4 (0.3)	3 (0.2)
Tremor	1 (0.1)	0
Psychiatric disorders	9 (0.7)	11 (0.8)
Anxiety	1 (0.1)	1 (0.1)
Depression	3 (0.2)	0
Hallucination, auditory	0	1 (0.1)
Hallucination, visual	0	1 (0.1)
Insomnia	5 (0.4)	8 (0.6)
Sleep talking	0	1 (0.1)
Renal and urinary disorders	37 (2.7)	32 (2.3)
Haematuria	0	1 (0.1)
Nocturia	2 (0.1)	0
Pollakiuria	3 (0.2)	2 (0.1)
Polyuria	1 (0.1)	2 (0.1)
Renal failure	9 (0.7)	12 (0.9)
Renal failure acute	1 (0.1)	0
Renal failure chronic	1 (0.1)	0
Renal impairment	21 (1.5)	15 (1.1)
Reproductive system and breast disorders	10 (0.7)	12 (0.9)
Benign prostatic hyperplasia	1 (0.1)	0
Breast swelling	1 (0.1)	3 (0.2)
Breast tenderness	0	2 (0.1)
Erectile dysfunction	1 (0.1)	2 (0.1)
Gynaecomastia	6 (0.4)	7 (0.5)
Nipple pain	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	13 (1.0)	4 (0.3)
Acute pulmonary oedema	1 (0.1)	0
Bronchial disorder	1 (0.1)	0
Cough	3 (0.2)	2 (0.1)
Dry throat	1 (0.1)	0
Dyspnoea	4 (0.3)	1 (0.1)

Table 15. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Epistaxis	1 (0.1)	1 (0.1)
Lung disorder	1 (0.1)	0
Orthopnoea	0	1 (0.1)
Pleural effusion	1 (0.1)	0
Vasomotor rhinitis	1 (0.1)	0
Skin and subcutaneous tissue disorders	21 (1.5)	17 (1.2)
Dermatitis	0	1 (0.1)
Dry skin	1 (0.1)	0
Eczema	1 (0.1)	2 (0.1)
Erythema	0	1 (0.1)
Hyperhidrosis	2 (0.1)	3 (0.2)
Nail disorder	0	1 (0.1)
Onychoclasis	1 (0.1)	0
Pruritus	13 (1.0)	7 (0.5)
Psoriasis	0	1 (0.1)
Rash	1 (0.1)	1 (0.1)
Seborrhoeic dermatitis	1 (0.1)	0
Urticaria	1 (0.1)	0
Vascular disorders	26 (1.9)	12 (0.9)
Capillary fragility	1 (0.1)	0
Flushing	1 (0.1)	0
Haematoma	1 (0.1)	0
Hypertension	1 (0.1)	3 (0.2)
Hypotension	17 (1.2)	4 (0.3)
Orthostatic hypotension	3 (0.2)	4 (0.3)
Peripheral coldness	0	1 (0.1)
Subclavian vein thrombosis	0	1 (0.1)
Varicose vein	2 (0.1)	0
Vein disorder	1 (0.1)	0
Total preferred term events	457	348

Adverse events and serious adverse events were not separated out
Being queried means that the terms are not in the MedDRA Coding Dictionary.
MedDRA (version 14.0) coding dictionary applied.
DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

The incidence of treatment-emergent treatment related serious AEs occurring in the DB phase is summarized in Table 16.

Table 16. Treatment-Emergent Treatment Related Serious Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Number (%) of subjects:		
Evaluable for adverse events	1364	1372
SOC/MedDRA Preferred Term		
Cardiac disorders	12 (0.9)	4 (0.3)
Acute myocardial infarction	1 (0.1)	0
Atrial fibrillation	1 (0.1)	0
Bradycardia	1 (0.1)	0
Cardiac arrest	1 (0.1)	0
Cardiac failure	4 (0.3)	3 (0.2)
Cardiac failure acute	1 (0.1)	0
Cardiac failure congestive	1 (0.1)	0
Cardiogenic shock	0	1 (0.1)
Conduction disorder	1 (0.1)	0
Ventricular fibrillation	2 (0.1)	0
Ventricular tachycardia	1 (0.1)	1 (0.1)
Gastrointestinal disorders	1 (0.1)	1 (0.1)
Abdominal discomfort	1 (0.1)	0
Gastritis erosive	0	1 (0.1)
Vomiting	1 (0.1)	0
General disorders and administration site conditions	2 (0.1)	2 (0.1)
Death	1 (0.1)	2 (0.1)
Malaise	1 (0.1)	0
Infections and infestations	0	2 (0.1)
Hepatobiliary infection	0	1 (0.1)
Urosepsis	0	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.1)
Back injury	0	1 (0.1)
Face injury	0	1 (0.1)
Fall	0	1 (0.1)
Investigations	1 (0.1)	1 (0.1)
Blood creatinine increased	1 (0.1)	1 (0.1)
Blood urea increased	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders	14 (1.0)	6 (0.4)
Gout	1 (0.1)	1 (0.1)
Hypercholesterolaemia	0	1 (0.1)
Hyperkalaemia	12 (0.9)	3 (0.2)
Hypoglycaemia	0	1 (0.1)
Type 2 diabetes mellitus	1 (0.1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.3)	0
Bladder neoplasm	1 (0.1)	0
Breast neoplasm	1 (0.1)	0
Colon neoplasm	1 (0.1)	0
Prostate cancer	1 (0.1)	0
Nervous system disorders	4 (0.3)	4 (0.3)
Dizziness	1 (0.1)	0
Dysarthria	1 (0.1)	0
Presyncope	0	1 (0.1)
Spinal cord disorder	0	1 (0.1)
Spinal cord ischaemia	0	1 (0.1)

Table 16. Treatment-Emergent Treatment Related Serious Adverse Events by System Organ Class and Preferred Term in DB Phase

	Number of Subjects (%)	
	Eplerenone	**Placebo**
Syncope	2 (0.1)	1 (0.1)
Renal and urinary disorders	8 (0.6)	11 (0.8)
Renal failure	2 (0.1)	6 (0.4)
Renal failure acute	1 (0.1)	0
Renal impairment	5 (0.4)	5 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	0
Bronchial disorder	1 (0.1)	0
Vascular disorders	1 (0.1)	0
Hypotension	1 (0.1)	0
Total preferred term events	52	36

Being queried means that the terms were not in the MedDRA Coding Dictionary.
MedDRA (version 14.0) coding dictionary applied.
DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class.

The all-causality AEs by age group are summarized in Table 17.

Table 17. All-Causality Adverse Events Occurring in ≥4% of Subjects in Any Treatment Group, by Age Subgroups (Safety Populations: Double-Blind Phase)

System Organ Class / Preferred Term [a]	No. of Subjects (%) Eplerenone	Placebo
Age <75 years		
Cardiac disorders		
Atrial fibrillation	42 (4.1)	55 (5.3)
Cardiac failure	190 (18.4)	221 (21.2)
General disorders and administration site conditions		
Chest pain	41 (4.0)	50 (4.8)
Edema peripheral	41 (4.0)	49 (4.7)
Metabolism and nutrition disorders		
Hyperkalaemia	84 (8.1)	41 (3.9)
Nervous system disorders		
Dizziness	48 (4.6)	41 (3.9)
Renal and urinary disorders		
Renal impairment	47 (4.5)	31 (3.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	42 (4.1)	40 (3.8)
Dyspnoea	55 (5.3)	54 (5.2)
Age ≥75 years		
Cardiac disorders		
Atrial fibrillation	20 (6.1)	17 (5.2)
Cardiac failure	89 (27.0)	106 (32.3)
Myocardial infarction	13 (3.9)	15 (4.6)
Ventricular tachycardia	6 (1.8)	14 (4.3)
Gastrointestinal disorders		
Diarrhea	12 (3.6)	13 (4.0)
General disorders and administration site conditions		
Chest pain	12 (3.6)	13 (4.0)
Fatigue	9 (2.7)	17 (5.2)
Edema peripheral	12 (3.6)	20 (6.1)
Infections and infestations		
Bronchitis	20 (6.1)	22 (6.7)
Nasopharyngitis	10 (3.0)	13 (4.0)
Pneumonia	12 (3.6)	16 (4.9)
Urinary tract infection	9 (2.7)	14 (4.3)
Metabolism and nutrition disorders		
Hyperkalaemia	34 (10.3)	14 (4.3)
Musculoskeletal and connective tissue disorders		
Back pain	16 (4.8)	9 (2.7)
Nervous system disorders		
Dizziness	18 (5.5)	24 (7.3)
Syncope	6 (1.8)	13 (4.0)
Renal and urinary disorders		
Renal failure	12 (3.6)	13 (4.0)
Renal impairment	21 (6.4)	13 (4.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	15 (4.5)	8 (2.4)
Dyspnea	13 (3.9)	21 (6.4)
Vascular disorders		
Hypotension	20 (6.1)	13 (4.0)

Adverse events and serious adverse events were not separated out.

a. Medical dictionary for regulatory activities (version 14.0) coding applied.

The permanent discontinuations due to AEs in DB phase are summarized in Table 18.

Table 18. Summary of Permanent Discontinuations Due to Adverse Events (All Causality and Treatment Related) Occurring in ≥1% of Subjects in Either Treatment Group, Complete Double-Blind Phase (Safety Population)

	Number of Subjects (%)			
	Eplerenone (N=1364)		Placebo (N=1372)	
SOC/MedDRA Preferred Term	All Causality	TR	All Causality	TR
Cardiac disorders				
Cardiac failure	58 (4.3)	2 (0.1)	68 (5.0)	1 (0.1)
General disorders and administration site conditions				
Death	17 (1.2)	0	13 (0.9)	2 (0.1)
Metabolism and nutrition disorders				
Hyperkalemia	19 (1.4)	14 (1.0)	13 (0.9)	11 (0.8)
Renal and urinary disorders				
Renal impairment	16 (1.2)	6 (0.4)	8 (0.6)	6 (0.4)

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 14.0) coding applied.
MedDRA = medical dictionary for regulatory activities; N = total number of subjects; SOC = system organ class; TR = treatment related.

The temporary discontinuations due to AEs in DB phase are summarized in Table 19.

Table 19. Summary of Temporary Discontinuations or Dose Reductions Due to Adverse Events (All Causality and Treatment Related) Occurring in ≥1% of Subjects in Either Treatment Group, Complete Double-Blind Phase (Safety Population)

	Number of Subjects (%)			
	Eplerenone (N=1364)		Placebo (N=1372)	
SOC/MedDRA Preferred Term	All Causality	TR	All Causality	TR
Cardiac disorders				
Cardiac failure	25 (1.8)	0	26 (1.9)	2 (0.1)
Metabolism and nutrition disorders				
Hyperkalemia	83 (6.1)	73 (5.4)	33 (2.4)	28 (2.0)
Renal and urinary disorders				
Renal impairment	26 (1.9)	8 (0.6)	25 (1.8)	9 (0.7)

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 14.0) coding applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SOC = system organ class; TR = treatment related.

In the DB phase, 205 subjects (15.0%) in the eplerenone group and 253 subjects (18.4%) in the placebo group died.

For the DB phase, a total of 601 subjects (45%) in the eplerenone group and 523 subjects (39%) in the placebo group had laboratory abnormalities. The most common abnormalities were blood urea nitrogen (BUN) >1.3× upper limit of normal (ULN), creatinine >1.3× ULN, and potassium >1.1× ULN.

A summary of the incidence of laboratory abnormalities without regard to Baseline abnormality by age group is provided in Table 20.

Table 20. Incidence of Laboratory Test Abnormalities, Without Regard to Baseline Abnormality, Complete Double-Blind Phase (Safety Population)

Parameter	Criteria	Eplerenone		Placebo	
		N	n (%)a	N	n (%)a
Hematology					
Hemoglobin	<0.8x LLN	36	0	39	2
Liver function					
Total bilirubin	>1.5x ULN	37	5	34	3
AST	>3.0x ULN	35	0	30	0
ALT	>3.0x ULN	41	1	37	0
Albumin	<0.8x LLN	1218	18 (1.5)	1206	22 (1.8)
	>1.2x ULN	1218	2 (0.2)	1206	3 (0.2)
Renal function					
BUN	>1.3x ULN	1247	449 (36.0)	1235	377 (30.5)
Creatinine	>1.3x ULN	1257	285 (22.7)	1246	226 (18.1)
Electrolytes					
Sodium	<0.95x LLN	112	1 (0.9)	93	2 (2.2)
	>1.05x ULN	112	1 (0.9)	93	0
Potassium	<0.9x LLN	1344	49 (3.6)	1349	55 (4.1)
	>1.1x ULN	1344	131 (9.7)	1349	85 (6.3)
Miscellaneous					
Brain natriuretic peptide	<0.8x LLN	3	0	3	0
Pro-brain natriuretic peptide	<0.8x LLN	1	0		

Serum creatinine values higher than 10 mg/dL were considered erroneous and are excluded from the table.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LLN = lower limit of normal; N = total number of subjects with at least 1 post-treatment observation of the given laboratory test; n = number of subjects with at least 1 post-treatment laboratory abnormality meeting specified criteria; ULN = upper limit of normal.
a. Percentages are displayed for laboratory tests having a category with ≥50 evaluable subjects.

Vital Signs: The mean reduction from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were statistically significantly greater in the eplerenone group (SBP, -2.78 mm Hg; DBP, -2.06 mm Hg) than in the placebo group (SBP, –1.33 mm Hg; DBP, -1.09 mm Hg), with p=0.0263 and p=0.0039, respectively.

OLE Phase: An overview of the treatment-emergent AEs (all causality and treatment-related) reported during OLE phase is provided in Table 21.

Table 21. Treatment-Emergent Adverse Events (All Causalities and Treatment Related)

Number (%) of Subjects	All Causality	Treatment Related
Subjects evaluable for AEs	1245	1245
Number of AEs	2133	248
Subjects with AEs	767 (61.6)	166 (13.3)
Subjects with SAEs	251 (20.2)	12 (1.0)
Subjects with severe AEs	160 (12.9)	13 (1.0)
Subjects discontinued due to AEs	69 (5.5)	29 (2.3)
Subjects with dose reduced or temporary discontinuation due to AEs	99 (8.0)	40 (3.2)

Except for the number of AEs, subjects are counted only once per treatment in each row. Data in this table are derived from the AE data set.
AEs and SAEs are not separated out while reporting AEs
SAEs – according to the Investigator's assessment.
AE = adverse event; SAE = serious adverse event.

The treatment-emergent non serious AEs (reported in ≥3% subjects) by system organ class and preferred term in OLE phase are summarized in Table 22. The most common treatment-related AE was hyperkalemia; no other treatment-related TEAE occurred in >1.0% of subjects

Table 22. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term Occurring in ≥3% of Subjects (All Causalities) in OLE Phase

	No. of Subjects (%)
	Eplerenone
Number (%) of subjects:	
Evaluable for adverse events	1245
With adverse events	146 (11.7)
SOC/MedDRA preferred term	
Cardiac disorders	42 (3.4)
Atrial fibrillation	42 (3.4)
Metabolism and nutrition disorders	38 (3.1)
Hyperkalemia	38 (3.1)
Nervous system disorders	43 (3.5)
Dizziness	43 (3.5)
Respiratory, thoracic and mediastinal disorders	38 (3.1)
Dyspnoea	38 (3.1)

Subjects were only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; SOC = system organ class.

The treatment-emergent SAEs reported during the OLE phase are listed in Table 23. The majority of SAEs were considered unrelated to study treatment; only 12 of the 447 SAEs reported were considered to be treatment related.

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Number (%) of subjects:	
Evaluable for adverse events	1245
With adverse events	251 (20.2)
SOC/MedDRA Preferred Term	
Blood and lymphatic system disorders	7 (0.6)
Anaemia	6 (0.5)
Anaemia macrocytic	1 (0.1)
Cardiac disorders	108 (8.7)
Acute coronary syndrome	1 (0.1)
Acute myocardial infarction	11 (0.9)
Angina pectoris	5 (0.4)
Angina unstable	9 (0.7)
Arrhythmia	2 (0.2)
Arteriosclerosis coronary artery	1 (0.1)
Atrial fibrillation	7 (0.6)
Atrial flutter	5 (0.4)
Atrioventricular block complete	1 (0.1)
Bradycardia	3 (0.2)
Cardiac aneurysm	1 (0.1)
Cardiac arrest	2 (0.2)
Cardiac failure	44 (3.5)
Cardiac failure acute	3 (0.2)
Cardiac failure chronic	1 (0.1)
Cardiac failure congestive	6 (0.5)
Cardio-respiratory arrest	2 (0.2)
Cardiomyopathy	1 (0.1)
Coronary artery disease	1 (0.1)
Coronary artery occlusion	1 (0.1)
Coronary artery stenosis	1 (0.1)
Ischaemic cardiomyopathy	3 (0.2)
Left ventricular dysfunction	2 (0.2)
Left ventricular failure	1 (0.1)
Myocardial infarction	6 (0.5)
Myocardial ischaemia	1 (0.1)
Sinus tachycardia	1 (0.1)
Tachyarrhythmia	1 (0.1)
Ventricular arrhythmia	3 (0.2)
Ventricular fibrillation	4 (0.3)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Ventricular tachycardia	8 (0.6)
Ear and labyrinth disorders	1 (0.1)
Haematotympanum	1 (0.1)
Endocrine disorders	5 (0.4)
Goitre	1 (0.1)
Hyperthyroidism	2 (0.2)
Thyroid disorder	1 (0.1)
Thyroiditis	1 (0.1)
Eye disorders	1 (0.1)
Optic ischaemic neuropathy	1 (0.1)
Gastrointestinal disorders	25 (2.0)
Abdominal distension	1 (0.1)
Abdominal pain	1 (0.1)
Abdominal pain lower	1 (0.1)
Anal fissure	1 (0.1)
Anal fistula	1 (0.1)
Constipation	2 (0.2)
Crohn's disease	1 (0.1)
Diverticulum intestinal	1 (0.1)
Epigastric discomfort	1 (0.1)
Faeces discoloured	1 (0.1)
Gastric polyps	1 (0.1)
Gastritis	2 (0.2)
Gastrointestinal haemorrhage	3 (0.2)
Gastrointestinal obstruction	1 (0.1)
Ileus	1 (0.1)
Inguinal hernia	1 (0.1)
Intestinal obstruction	1 (0.1)
Lower gastrointestinal haemorrhage	1 (0.1)
Mesenteric occlusion	1 (0.1)
Pancreatic insufficiency	1 (0.1)
Umbilical hernia	1 (0.1)
Vomiting	1 (0.1)
General disorders and administration site conditions	36 (2.9)
Asthenia	1 (0.1)
Chest pain	7 (0.6)
Death	12 (1.0)
Device breakage	1 (0.1)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Device malfunction	2 (0.2)
Fatigue	1 (0.1)
Hyperplasia	1 (0.1)
Impaired healing	1 (0.1)
Oedema peripheral	1 (0.1)
Sudden cardiac death	4 (0.3)
Sudden death	7 (0.6)
Systemic inflammatory response syndrome	1 (0.1)
Hepatobiliary disorders	7 (0.6)
Cholecystitis	2 (0.2)
Cholecystitis acute	2 (0.2)
Cholelithiasis	1 (0.1)
Hepatic cyst	1 (0.1)
Hepatic function abnormal	1 (0.1)
Hepatomegaly	1 (0.1)
Infections and infestations	44 (3.5)
Abscess	1 (0.1)
Appendicitis perforated	1 (0.1)
Bronchitis	2 (0.2)
Bronchopneumonia	1 (0.1)
Device related infection	2 (0.2)
Diverticulitis	1 (0.1)
Empyema	1 (0.1)
Endocarditis	1 (0.1)
Gastroenteritis	4 (0.3)
Gastroenteritis viral	1 (0.1)
Herpes zoster	1 (0.1)
Herpes zoster ophthalmic	1 (0.1)
Joint abscess	1 (0.1)
Lower respiratory tract infection	2 (0.2)
Peritonitis	1 (0.1)
Pneumonia	17 (1.4)
Pyelonephritis acute	1 (0.1)
Respiratory tract infection	2 (0.2)
Sepsis	2 (0.2)
Tracheobronchitis	1 (0.1)
Tuberculous laryngitis	1 (0.1)
Upper respiratory tract infection	3 (0.2)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Urinary tract infection	3 (0.2)
Urosepsis	1 (0.1)
Injury, poisoning and procedural complications	20 (1.6)
Alcohol poisoning	1 (0.1)
Ankle fracture	1 (0.1)
Cervical vertebral fracture	2 (0.2)
Concussion	2 (0.2)
Limb injury	1 (0.1)
Open wound	1 (0.1)
Overdose	1 (0.1)
Pelvic fracture	1 (0.1)
Post procedural haematoma	1 (0.1)
Radiation skin injury	1 (0.1)
Radius fracture	1 (0.1)
Rib fracture	2 (0.2)
Road traffic accident	1 (0.1)
Skin injury	1 (0.1)
Skull fracture	1 (0.1)
Spinal compression fracture	1 (0.1)
Spinal fracture	2 (0.2)
Toxicity to various agents	1 (0.1)
Vascular graft occlusion	1 (0.1)
Investigations	2 (0.2)
Liver function test abnormal	1 (0.1)
Weight increased	1 (0.1)
Metabolism and nutrition disorders	15 (1.2)
Dehydration	2 (0.2)
Diabetes mellitus	3 (0.2)
Fluid overload	1 (0.1)
Gout	2 (0.2)
Hyperglycaemia	1 (0.1)
Hyperkalaemia	3 (0.2)
Hyponatraemia	2 (0.2)
Metabolic acidosis	1 (0.1)
Obesity	1 (0.1)
Musculoskeletal and connective tissue disorders	9 (0.7)
Axillary mass	1 (0.1)
Fistula	1 (0.1)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Intervertebral disc protrusion	1 (0.1)
Muscle spasms	1 (0.1)
Neck pain	1 (0.1)
Osteoarthritis	4 (0.3)
Spinal column stenosis	2 (0.2)
Neoplasms benign, malignant and unspecified (include cysts and polyps)	19 (1.5)
Adenocarcinoma pancreas	1 (0.1)
B-cell lymphoma	1 (0.1)
Bladder cancer	1 (0.1)
Bladder neoplasm	1 (0.1)
Chronic myelomonocytic leukaemia	1 (0.1)
Colon cancer	2 (0.2)
Colon neoplasm	1 (0.1)
Hepatic neoplasm malignant	3 (0.2)
Laryngeal cancer	1 (0.1)
Malignant neoplasm of ampulla of Vater	1 (0.1)
Metastases to central nervous system	1 (0.1)
Multiple myeloma	1 (0.1)
Neoplasm malignant	1 (0.1)
Prostate cancer	4 (0.3)
Nervous system disorders	23 (1.8)
Carotid artery stenosis	1 (0.1)
Cerebral ischaemia	1 (0.1)
Cerebrovascular accident	4 (0.3)
Dizziness	1 (0.1)
Haemorrhagic stroke	1 (0.1)
Ischaemic stroke	4 (0.3)
Loss of consciousness	1 (0.1)
Presyncope	1 (0.1)
Sciatica	1 (0.1)
Subarachnoid haemorrhage	1 (0.1)
Syncope	6 (0.5)
Transient ischaemic attack	1 (0.1)
Vocal cord paralysis	1 (0.1)
Psychiatric disorders	3 (0.2)
Depression	1 (0.1)
Mental status changes	1 (0.1)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Panic disorder	1 (0.1)
Renal and urinary disorders	14 (1.1)
Haematuria	1 (0.1)
Nephrolithiasis	1 (0.1)
Renal cyst	1 (0.1)
Renal failure	3 (0.2)
Renal failure acute	3 (0.2)
Renal impairment	2 (0.2)
Urethral stenosis	1 (0.1)
Urinary retention	2 (0.2)
Reproductive system and breast disorders	2 (0.2)
Benign prostatic hyperplasia	1 (0.1)
Cystocele	1 (0.1)
Respiratory, thoracic and mediastinal disorders	24 (1.9)
Acute pulmonary oedema	2 (0.2)
Acute respiratory failure	1 (0.1)
Asthma	1 (0.1)
Bronchitis chronic	1 (0.1)
Chronic obstructive pulmonary disease	4 (0.3)
Dyspnoea	3 (0.2)
Dyspnoea exertional	2 (0.2)
Epistaxis	2 (0.2)
Haemoptysis	1 (0.1)
Nasal turbinate hypertrophy	1 (0.1)
Pleural effusion	2 (0.2)
Pneumothorax	1 (0.1)
Pulmonary embolism	2 (0.2)
Pulmonary oedema	1 (0.1)
Respiratory failure	3 (0.2)
Sleep apnoea syndrome	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.2)
Skin ulcer	2 (0.2)
Surgical and medical procedures	5 (0.4)
Aortic valve replacement	1 (0.1)
Cardiac pacemaker insertion	1 (0.1)
Cardiac pacemaker replacement	1 (0.1)
Cholecystectomy	1 (0.1)
Coronary artery bypass	1 (0.1)

Table 23. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in OLE Phase

	Number of Subjects (%)
	Eplerenone
Hip surgery	1 (0.1)
Implantable defibrillator replacement	1 (0.1)
Vascular disorders	16 (1.3)
Aortic aneurysm	2 (0.2)
Arterial thrombosis limb	1 (0.1)
Femoral artery embolism	1 (0.1)
Femoral artery occlusion	1 (0.1)
Haematoma	1 (0.1)
Hypertension	1 (0.1)
Hypertensive crisis	1 (0.1)
Hypotension	3 (0.2)
Iliac artery occlusion	1 (0.1)
Orthostatic hypotension	2 (0.2)
Peripheral ischaemia	1 (0.1)
Phlebitis	1 (0.1)
Shock	1 (0.1)
Venous insufficiency	1 (0.1)

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; SOC = system organ class.

The treatment-emergent treatment related AEs reported during the OLE phase are listed in Table 24.

Table 24. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in OLE Phase

	Number of Subjects (%)
	Eplerenone
Number (%) of subjects:	
Evaluable for adverse events	1245
SOC/MedDRA Preferred Term	
Cardiac disorders	6 (0.5)
Atrial fibrillation	1 (0.1)
Cardiac failure	3 (0.2)
Palpitations	2 (0.2)
Ear and labyrinth disorders	1 (0.1)
Tinnitus	1 (0.1)
Endocrine disorders	1 (0.1)
Goitre	1 (0.1)
Eye disorders	4 (0.3)
Dry eye	1 (0.1)
Eye pain	1 (0.1)
Eye pruritus	1 (0.1)
Lacrimation increased	1 (0.1)
Ocular hyperaemia	1 (0.1)
Visual impairment	1 (0.1)
Gastrointestinal disorders	15 (1.2)
Abdominal pain lower	1 (0.1)
Abdominal pain upper	1 (0.1)
Constipation	3 (0.2)
Diarrhoea	5 (0.4)
Diverticulum	1 (0.1)
Dry mouth	1 (0.1)
Dyspepsia	1 (0.1)
Flatulence	1 (0.1)
Gastritis	1 (0.1)
Gastrooesophageal reflux disease	1 (0.1)
Gingival bleeding	1 (0.1)
Hiatus hernia	1 (0.1)
Nausea	3 (0.2)
General disorders and administration site conditions	18 (1.4)
Asthenia	2 (0.2)
Chest discomfort	1 (0.1)
Chest pain	2 (0.2)
Death	2 (0.2)
Fatigue	7 (0.6)
Oedema peripheral	2 (0.2)
Pain	2 (0.2)
Sudden death	1 (0.1)
Infections and infestations	2 (0.2)
Diverticulitis	1 (0.1)
Pilonidal cyst	1 (0.1)
Injury, poisoning and procedural complications	1 (0.1)
Head injury	1 (0.1)
Investigations	25 (2.0)
Blood creatine increased	1 (0.1)
Blood creatinine increased	9 (0.7)
Blood insulin increased	1 (0.1)

Table 24. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in OLE Phase

	Number of Subjects (%)
	Eplerenone
Blood potassium increased	7 (0.6)
Blood triglycerides increased	1 (0.1)
Blood urea increased	2 (0.2)
Glomerular filtration rate decreased	2 (0.2)
Laboratory test abnormal	1 (0.1)
Prostatic specific antigen increased	1 (0.1)
Weight decreased	1 (0.1)
Weight increased	3 (0.2)
Metabolism and nutrition disorders	44 (3.5)
Decreased appetite	1 (0.1)
Diabetes mellitus	2 (0.2)
Gout	6 (0.5)
Hyperkalaemia	31 (2.5)
Hypernatraemia	1 (0.1)
Hyperuricaemia	1 (0.1)
Hypokalaemia	2 (0.2)
Hyponatraemia	1 (0.1)
Musculoskeletal and connective tissue disorders	14 (1.1)
Arthralgia	4 (0.3)
Back pain	1 (0.1)
Muscle spasms	4 (0.3)
Musculoskeletal chest pain	1 (0.1)
Musculoskeletal pain	1 (0.1)
Neck pain	1 (0.1)
Pain in extremity	4 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (0.5)
Malignant neoplasm of ampulla of Vater	1 (0.1)
Monoclonal gammopathy	1 (0.1)
Myelodysplastic syndrome	1 (0.1)
Prostate cancer	2 (0.2)
Renal neoplasm	1 (0.1)
Nervous system disorders	24 (1.9)
Dizziness	11 (0.9)
Dysaesthesia	1 (0.1)
Dysgeusia	1 (0.1)
Extrapyramidal disorder	1 (0.1)
Headache	4 (0.3)
Hypoaesthesia	1 (0.1)
Lethargy	1 (0.1)
Neuropathy peripheral	2 (0.2)
Presyncope	1 (0.1)
Somnolence	2 (0.2)
Psychiatric disorders	6 (0.5)
Anxiety	2 (0.2)
Depressed mood	1 (0.1)
Depression	2 (0.2)
Insomnia	1 (0.1)
Renal and urinary disorders	18 (1.4)
Haematuria	1 (0.1)
Nephrolithiasis	1 (0.1)

Table 24. Treatment-Emergent Treatment Related Adverse Events by System Organ Class and Preferred Term in OLE Phase

	Number of Subjects (%)
	Eplerenone
Polyuria	1 (0.1)
Renal failure	5 (0.4)
Renal failure acute	2 (0.2)
Renal impairment	8 (0.6)
Reproductive system and breast disorders	7 (0.6)
Breast swelling	2 (0.2)
Breast tenderness	2 (0.2)
Erectile dysfunction	2 (0.2)
Gynaecomastia	3 (0.2)
Respiratory, thoracic and mediastinal disorders	8 (0.6)
Cough	3 (0.2)
Dyspnoea	3 (0.2)
Emphysema	1 (0.1)
Epistaxis	1 (0.1)
Skin and subcutaneous tissue disorders	12 (1.0)
Erythema	1 (0.1)
Nail disorder	1 (0.1)
Onychoclasis	1 (0.1)
Pruritus	6 (0.5)
Rash	2 (0.2)
Seborrhoeic dermatitis	1 (0.1)
Skin ulcer	1 (0.1)
Vascular disorders	16 (1.3)
Flushing	1 (0.1)
Hypertension	2 (0.2)
Hypotension	11 (0.9)
Orthostatic hypotension	1 (0.1)
Varicose vein	1 (0.1)
Total preferred term events	248

Adverse events and serious adverse events were not separated out
Subjects were counted only once per treatment in each row.
Included all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; SOC = System Organ Class.

The treatment-emergent treatment related SAEs reported during the OLE phase are listed in Table 25.

Table 25. Treatment-Emergent Treatment Related Serious Adverse Events by System Organ Class and Preferred Term in OLE Phase

	Number of Subjects (%) Eplerenone
Number (%) of subjects:	
Evaluable for adverse events	1245
SOC/MedDRA Preferred Term	
Cardiac disorders	2 (0.2)
Cardiac failure	2 (0.2)
General disorders and administration site conditions	3 (0.2)
Death	2 (0.2)
Sudden death	1 (0.1)
Metabolism and nutrition disorders	2 (0.2)
Hyperkalaemia	1 (0.1)
Hyponatraemia	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.2)
Malignant neoplasm of ampulla of Vater	1 (0.1)
Prostate cancer	2 (0.2)
Renal and urinary disorders	2 (0.2)
Renal failure acute	2 (0.2)
Total preferred term events	12

Subjects were counted only once per treatment in each row.
Included all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension; SOC = System Organ Class.

A total of 147 subjects (11.8%) discontinued, including 48 subjects who discontinued due to death during the OLE phase.

A total of 56 subjects (4.5%) died during the OLE phase. The summary of deaths are presented in Table 26.

Table 26. Summary of Deaths During the Open-Label Extension Phase

System Organ Class/ MedDRA Preferred Term	Eplerenone (N=1245) Number of Subjects (%)
Blood and lymphatic system disorders	
Anaemia	1 (0.1)
Cardiac disorders	
Acute coronary syndrome	1 (0.1)
Acute myocardial infarction	2 (0.2)
Cardiac arrest	2 (0.2)
Cardiac failure	9 (0.7)
Cardiac failure acute	1 (0.1)
Cardiac failure congestive	2 (0.2)
Cardio-respiratory arrest	2 (0.2)
Cardiovascular disorder	1 (0.1)
Coronary artery insufficiency	1 (0.1)
Ischaemic cardiomyopathy	1 (0.1)
Left ventricular dysfunction	1 (0.1)
Myocardial infarction	5 (0.4)
Ventricular fibrillation	1 (0.1)
Gastrointestinal disorders	
Gastrointestinal haemorrhage	1 (0.1)
Ileus	1 (0.1)
General disorders and administration site conditions	
Condition aggravated	9 (0.7)
Death	5 (0.4)
Device breakage	1 (0.1)
Sudden cardiac death	5 (0.4)
Sudden death	5 (0.4)
Systemic inflammatory response syndrome	1 (0.1)
Infections and infestations	
Bronchopneumonia	1 (0.1)
Empyema	1 (0.1)
Pneumonia	5 (0.4)
Urinary tract infection	1 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	
Adenocarcinoma pancreas	1 (0.1)
Hepatic neoplasm	1 (0.1)
Recurrent cancer	1 (0.1)
Nervous system disorders	
Cerebrovascular accident	2 (0.2)
Haemorrhagic stroke	1 (0.1)
Subarachnoid hemorrhage	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	
Acute respiratory failure	1 (0.1)
Asthma	1 (0.1)
Pulmonary oedema	1 (0.1)
Respiratory failure	3(0.2)
Vascular disorders	
Femoral artery embolism	1 (0.1)
Shock	1 (0.1)
Total preferred-term events	81
Total number of subjects who died	56

Table 26. Summary of Deaths During the Open-Label Extension Phase

System Organ Class/ MedDRA Preferred Term	Eplerenone (N=1245) Number of Subjects (%)

A case was a single event or series of related events not separated in time occurring in a single subject. Serious adverse events were counted only once per subject. Medical Dictionary for Regulatory Activities (version 15.0) coding applied.
MedDRA = Medical Dictionary for Regulatory Activities.

Vital Signs Results: The mean changes from Baseline to last observation in vital signs were minimal.

CONCLUSIONS: The findings in the DB phase confirm that:

- Addition of eplerenone to standard HF therapy reduces CV mortality and HF hospitalization in subjects in NYHA functional class-II with chronic HF and mild symptoms.
- The results remain consistent across the majority of subgroups analyzed.
- The addition of eplerenone to standard HF therapy was well tolerated, with an overall profile of AEs consistent with the known profile of eplerenone.

The OLE phase concluded the following:

- The addition of eplerenone to standard medical therapy in subjects with NYHA class-II and left ventricular systolic dysfunction was generally well tolerated, with an overall profile of AEs consistent with labeling.
- There were no new AEs or other safety findings during the course of the OLE eplerenone-only phase of this study.