Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. LIFE Trial Members, Investigators, and Committees

In addition to the Writing Committee, the following individuals participated in the LIFE study:

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eTable 1. Detailed Inclusion and Exclusion Criteria

Inclusion Criteria

1. Advanced HFrEF defined as including ALL
    a. LVEF ≤35% documented during the preceding 12 months
    b. NYHA class IV symptomatology, defined as chronic dyspnea or fatigue at rest or on minimal exertion in the previous 3 months, or patients who require chronic inotropic therapy
    c. Minimum of 3 months GDMT for HF and/or intolerant to therapy
2. Systolic blood pressure ≥90 mm Hg
3. Serum NT-proBNP ≥800 pg/mL OR BNP ≥250 pg/mL (most recent—less than 3 months old)
4. Any one or more of the following objective findings of advanced HF including:
    a. Current inotropic therapy or use of inotropes in the past 6 months
    b. ≥1 hospitalization for heart failure in the past 6 months (not including the index hospitalization for inpatient participants)
    c. LVEF ≤25% (within the past 12 months)
    d. Peak VO_2 <55% predicted or peak VO_2 ≤16 mL/kg/min for men or ≤14 mL/kg/min for women (Respiratory Exchange Ratio [RER] ≥1.05) (within the past 12 months)
    e. 6 min walk test distance <300 m (within the past 3 months)
5. Age ≥18 years and ≤85 years
6. Signed Informed Consent form

Exclusion Criteria

1. Currently taking sacubitril/valsartan
2. History of hypersensitivity or intolerance (unmodifiable) to Entresto, an ACEI or ARB as well as known or suspected contraindications (including hereditary angioedema) to the study drugs
3. Estimated glomerular filtration rate (eGFR) <20 mL/min/1.73m^2 at baseline
4. Co-morbid conditions that may interfere with completing the study protocol (e.g., recent history of drug or alcohol abuse) or cause death within 1 year
5. Symptomatic hypotension at randomization or systolic blood pressure <90 mm Hg
6. Serum potassium >5.5 mmol/L
7. Severe liver dysfunction (Childs-Pugh Class C)
8. Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) changes and biomarkers of myocardial necrosis (e.g., troponin) in an appropriate clinical setting (chest discomfort or anginal equivalent)
9. Planned or recent (≤4 weeks) PCI, coronary artery bypass grafting, or biventricular pacing
10. Currently hospitalized and listed status 1A, 1B or 1-4 for heart transplant
11. Current or scheduled for LVAD implantation within 30 days of study enrollment
12. Active infection (current use of oral or IV antimicrobial agents)
13. Primary hypertrophic or infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade
14. Complex congenital heart disease
15. Concomitant use of aliskiren in patients with diabetes or renal impairment (eGFR <60 mL/min/1.73m²)
16. Known pregnancy or anticipated pregnancy within the next 6 months or breastfeeding mothers
17. Enrollment in any other investigational clinical trial within 30 days prior to screening
18. Inability to comply with study procedures

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with a reduced ejection fraction; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RER, respiratory exchange ratio; VO_2, oxygen consumption.

Table from Mann DL et al. Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial. JACC Heart Fail 2020;8:790-9.

eTable 2. Characteristics of Patients Who Did Not Tolerate Sacubitril/Valsartan During Run-In As Compared with Patients Who Completed Run-in*

	Discontinued Study Drug During Run-In (N=73)	Patients Who Passed Run-In (N=372)
Clinical Characteristics*		
Systolic blood pressure, mm Hg	109.0 ± 14.4	113.4 ± 15.2
Serum creatinine, mg/dL	1.55 ± 0.40	1.36 ± 0.46
Estimated GFR, mL/min/1.73m^2	54.3 ± 20.5	64.5 ± 24.6
Treatment at screening, no. (%)		
Furosemide equivalent diuretic dose, mg†	156.8 ± 124.0	123.5 ± 119.4
ACE inhibitor with 7 days of run-in	20 (27%)	151 (41%)
ARB with 7 days of run-in	16 (22%)	136 (37%)
Beta-blocker	46 (64%)	300 (81%)
ICD or CRT-D	60 (83%)	238 (64%)

*Plus–minus values are means ±SD.

† Doses of pre-trial furosemide dose equivalents are provided in the Supplementary Appendix.

ACE indicates, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy with cardioverter defibrillator; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator

eTable 3. Additional Patient Characteristics

	Sacubitril/Valsartan (N=167)	Valsartan (N=168)	All Patients (N=335)
Time since initial diagnosis of HF, yrs			
Median (25th, 75th)	4.8 (1.3, 10.2)	3.9 (1.9, 9.8)	4.3 (1.6, 10.1)
Mean ± SD	6.6 ± 6.3	6.6 ± 6.7	6.6 ± 6.5
HF hospitalizations within past 6 months, no. (%)			
0	37 (22%)	40 (24%)	77 (23%)
1	65 (39%)	67 (40 %)	132 (39%)
2	39 (23%)	35 (21%)	74 (22%)
3	19 (11%)	17 (10%)	36 (11%)
4 or more	7 (4%)	9 (5%)	16 (5%)
LVEF, median (25th, 75th), %	20 (15, 25)	20 (15, 25)	20 (15, 25)
Pre-randomization medications, no. (%)			
ACE inhibitor	49 (29%)	55 (33%)	104 (31%)
ARB	56 (34%)	58 (35%)	114 (34%)
Furosemide	83 (50%)	88 (52%)	171 (51%)
Torsemide	48 (29%)	54 (32%)	102 (30%)
Bumetanide	27 (16%)	14 (8%)	41 (12%)
Furosemide equivalent diuretic dose, mg			
N	157 (94%)	155 (92%)	312 (93%)
Median (25th, 75th)	80 (40, 160)	80 (40, 160)	80 (40, 160)
Mean ± SD	127.5 ± 121.0	125.8 ± 122.8	126.6 ± 121.7
Randomization location, no. (%)			
Outpatient	144 (86%)	146 (87%)	290 (87%)
Inpatient	23 (14%)	22 (13%)	45 (13%)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; LVEF, left ventricular ejection fraction; SD, standard deviation.

eTable 4. Tertiary Clinical End points*

	Sacubitri/Valsartan (N=167)	Valsartan (N=168)	HR, Difference, or OR (95% CI)	P value
Key Clinical Endpoints, no. (%)**				
CV death or HF hospitalization	48 (29%)	37 (22%)	HR = 1.32 (0.86 to 2.03)	0.20
CV death	11 (7%)	7 (4%)	HR = 1.58 (0.61 to 4.07)	0.35
HF hospitalization	44 (26%)	36 (21%)	HR = 1.24 (0.80 to 1.93)	0.33
All-cause death	13 (8%)	8 (5%)	HR = 1.63 (0.68 to 3.94)	0.28
All-cause death or HF hospitalization	49 (29%)	38 (23%)	HR = 1.31 (0.86 - 2.00)	0.21
Outpatient visit requiring IV diuretic administration	10 (6%)	8 (5%)	HR = 1.27 (0.50 to 3.23)	0.61
Additional Clinical Endpoints				
Total number of HF hospitalizations††	61	50	RR =1.23 (0.85 – 1.79)	0.27
Listed, received cardiac transplantation or LVAD, no. (%)	15 (9%)	14 (8%)	OR = 1.10 (0.51 - 2.37)	0.81
Unanticipated use of IV diuretics, no. (%)‡‡	44 (26%)	40 (24%)	OR = 1.14 (0.69 to 1.87)	0.60
Patients on inotropic therapy ≥1 day(s), no. (%)§§	47 (28%)	40 (24%),	OR = 1.26 (0.77 - 2.06)	0.36
Patients on continuous inotropic therapy >7 days, no. (%)‖‖	43 (26%)	36 (21%)	OR = 1.28 (0.77 - 2.12)	0.34
Additional Tertiary Outcomes				
Change in AUC in KCCQ overall summary score¶¶	0.32 ± 0.49	0.27 ± 0.41	0.02 (-0.05 to 0.09)	0.61
Change in AUC in KCCQ clinical summary score¶¶	0.27 ± 0.54	0.23 ± 0.42	0.02 (-0.05 to 0.09)	0.56

*All outcomes are assessed from baseline through 24 weeks. Plus–minus values are means ±SD.
‡Zero dose includes indicates that the patient stopped study drug early or was never started on study drug.
#Any anticipated disease-related event includes the following: Arrhythmia, Acute Coronary Syndrome, Unplanned Hospitalization, ER visit or Clinic visit for Worsening Heart Failure, Cerebrovascular Event, LVAD Implantation, Cardiac Transplantation, LVAD Implantation or Cardiac Transplantation, Hyperkalemia (≥ 5.5), Angioedema, Acute Renal Failure with Serum Creatinine > 2.5 mg/dL, Venous Thromboembolism, Symptomatic Hypotension, Worsening Renal Function, Sudden Cardiac Death, and Lightheadedness, Presyncope, or Syncope. See also Table S4.
**All time to events are shown in days.
††Total number of heart failure hospitalizations. Poisson regression was used to test whether there were differences between treatment groups for the number of heart failure admissions.
‡‡Unanticipated use of IV diuretics as an outpatient, ER, or as inpatient.
§§Number of patients on inotropic therapy ≥1 day(s) after discharge from the index hospitalization through 24 weeks.
‖‖Number of patients on continuous inotropic therapy after discharge from the index hospitalization through 24 weeks.
¶¶Change in AUC in the KCCQ Overall and Clinical Summary compared with baseline, 2, 4, 8, 12, and 24 weeks both for overall and clinical summary scores. A general linear model was used to test the significance of differences in the AUC for each KCCQ score between the two treatment arms.

AUC indicates area under the curve; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.
CI indicates confidence interval; OR, odds ratio.

eTable 5. Change from Baseline eGFR and Cystatin C Compared with Weeks 2, 4, 8, 12 and 24

	Sacubitril/ Valsartan (N=167)	Valsartan (N=168)	Difference (95% CI)	P value
Change in eGFR compared with baseline, Weeks 2-24				
Change in eGFR at 2 weeks, Difference (95% CI)*	-1.89 (-4.08 to 0.30)	-0.77 (-3.16 to 1.62)	-1.12 (-4.36 to 2.12)	0.497
Change in eGFR at 4 weeks, Difference (95% CI)*	-0.71 (-2.93 to 1.50)	-1.80 (-4.23 to 0.63)	1.09 (-2.19 to 4.37)	0.515
Change in eGFR at 8 weeks, Difference (95% CI)*	-2.55 (-4.80 to -0.31)	-1.90 (-4.36 to 0.56)	-0.66 (-3.98 to 2.67)	0.698
Change in eGFR at 12 weeks, Difference (95% CI)*	-5.99 (-8.27 to -3.71)	-3.17 (-5.64 to -0.71)	-2.81 (-6.17 to 0.54)	0.100
Change in eGFR at 24 weeks, Difference (95% CI)**	-3.96 (-6.35 to -1.58)	-4.48 (-7.06 to -1.89)	0.51 (-3.00 to 4.02)	0.775
Change in cystatin C compared with baseline, Weeks 2–24				
Change in cystatin C at 2 weeks, Difference (95% CI)*	-0.05 (-0.11 to 0.01)	0.02 (-0.03 to 0.08)	-0.07 (-0.15 to 0.01)	0.086
Change in cystatin C at 4 weeks, Difference (95% CI)*	0.01 (-0.05 to 0.07)	0.03 (-0.02 to 0.09)	-0.03 (-0.11 to 0.06)	0.554
Change in cystatin C at 8 weeks, Difference (95% CI)*	-0.02 (-0.08 to 0.05)	0.02 (-0.03 to 0.08)	-0.04 (-0.12 to 0.05)	0.369
Change in cystatin C at 12 weeks, Difference (95% CI)*	0.11 (0.05 to 0.17)	0.04 (-0.02 to 0.10)	0.07 (-0.02 to 0.15)	0.120
Change in cystatin C at 24 weeks, Difference (95% CI)**	0.01 (-0.06 to 0.07)	0.04 (-0.02 to 0.10)	-0.03 (-0.12 to 0.06)	0.485

*****Renal function was assessed at baseline, weeks 2, 4, 8, 12, and 24. The eGFR (mL/min/1.73m^2) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Cystatin C levels were measured as ng/mL. A mixed model was used to estimate and statistically compare changes in GFR and cystatin C between baseline and weeks 2, 4, 8, 12, and 24 values (mean [IQR]). Changes from baseline to 24 weeks are shown in Table 3. Changes in from baseline to 2, 4, 8, and 12 weeks are shown in Table S4.

CI indicates confidence interval; eGFR, estimated glomerular filtration rate.

eTable 6. Sensitivity Analysis of Complete Cases, All Randomized Patients, Patients with Full Follow-up, and NHYA Class I Patients Excluded

Primary Efficacy Endpoint (Log NT-proBNP AUC, mean ± SD)	**Sacubitril/Valsartan**	**Valsartan**	**Treatment Difference (95% CI) or P-value**
Population			
Complete cases (n=232)*	(n=113) 0.07 ± 0.68	(n=119) 0.18 ± 0.47	-0.10 (-0.24 to 0.05)
All randomized (n=365)	(n=166) 0.14 ± 0.66	(n=172) 0.18 ± 0.51	-0.05 (-0.17 to 0.08)
Full follow-up (n=310)*	(n=142) 0.12 ± 0.66	(n=148) 0.19 ± 0.48	-0.08 (-0.21 to 0.06)
Worst Rank (n = 335)	160.34 ± 98.01 (n= 167)	156.66 ± 84.47 (n=168)	P = 0.72
NYHA class I patients excluded (n= 305)	0.12 ± 0.65 (n = 153)	0.20 ± 0.49 (n = 153)	-0.08 (-0.21 to 0.04)
Secondary Efficacy Endpoint Population (Days alive, out of hospital, or free from HF events, model mean (95% CI)†	**Sacubitril/Valsartan**	**Valsartan**	**Treatment Difference (95% CI)**
Population			
All randomized (n=365)	(n=179) 108.4 (95.6, 121.2)	(n=186) 119.8 (108.1, 131.5)	-11.4 (-25.8, 2.9)
Full follow-up (n=310)	(n=152) 108.2 (94.4, 121.9)	(n=158) 119.3 (106.8, 131.8)	-11.1 (-26.7 to 4.5)

*Patients with complete cases had NT-proBNP levels at baseline and at the week 24 visit. Patients with full-follow were randomized patients who completed their week 24 study visit prior to March 1, 2020.

† HF events defined as listing for cardiac transplantation (status 1 to 4), cardiac transplantation, LVAD implantation or placed on continuous inotropic therapy for ≥ 7 days, hospitalization for HF on ≥ 2 occasions (other than the index admission)

eTable 7. Comparison of Baseline Demographics in LIFE and PARADIGM-HF

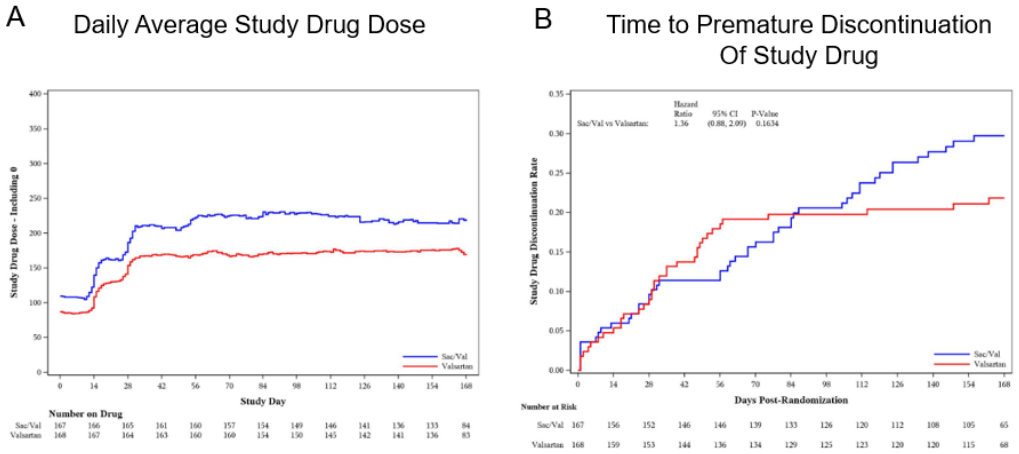
	LIFE	PARADIGM-HF*
Study population	Advanced HF	NYHA II–III
Age	59.3	63.8
Black	38%	5%
SBP, mm Hg	113	122
Heart rate, bpm	81	72
Ischemic etiology	78%	60%
Atrial fibrillation	46%	38%
Diabetes	47%	35%
Mean LVEF, %	20%	29%
Median NT-proBNP	1853	≈1620
Serum creatinine, mg/dL	1.36	1.13
ACE/ARB†	65%	100%
Beta-blocker	78%	93%
Inotrope use	20%	0%
Loop diuretics†	93%	80%
Mean furosemide equivalent dose	126 mg	47 mg

*Data from McMurray JJV, et al. N Engl J Med 2014;317:993-1004.(Key:

†Data from Screening Visit

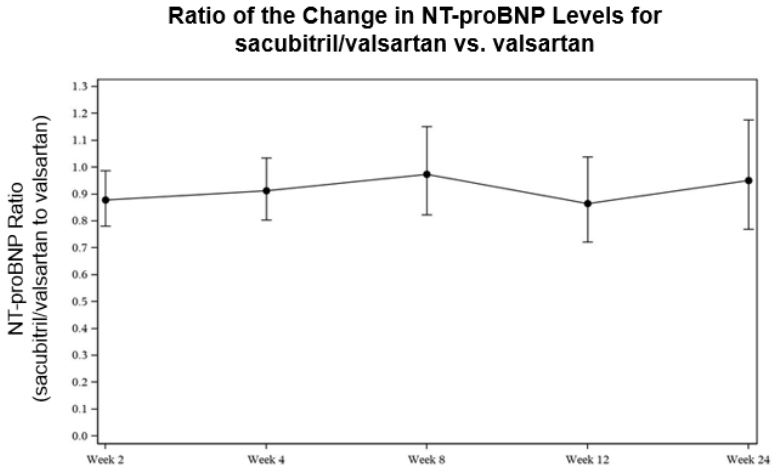
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bpm, beats per minute; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure)

eFigure 1. Average Study Drug Dose and Time to Premature Discontinuation of Study Drug



The daily average study drug dose was calculated as the average of the dose of study drug received across all available drug dose days for each patient, including days when not taking study drug for whatever reason. If a patient was not taking study drug a dose of 0 was assigned. The days included randomization through the earliest of last date of follow-up or day 168. For any patients still being followed after February 29, 2020, their date of last follow-up was set to February 29, 2020. (Panel A) Curve for time to discontinuation of study drug in each treatment group. The Hazard Ratio favored greater discontinuation in the sacubitril/valsartan arm as compared with the valsartan treatment arm (HR 1.36, 95% CI 0.88-2.09; p=0.36) (Panel B).

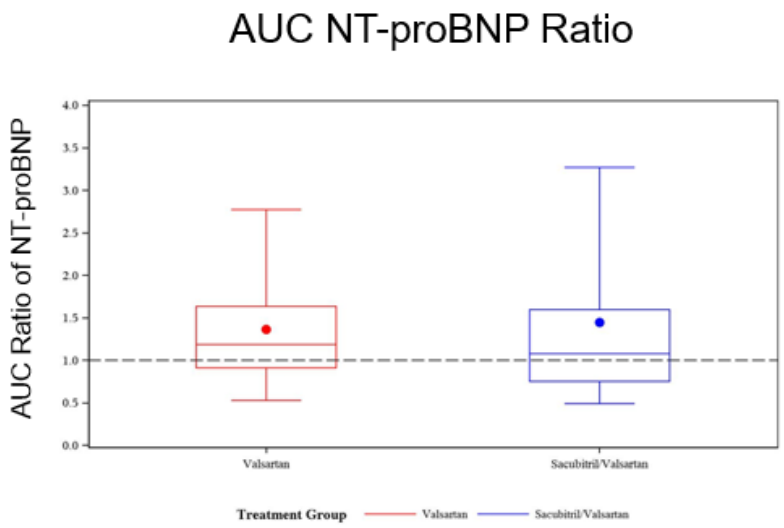
eFigure 2. Ratio of the Change in NT-proBNP levels for Sacubitril with Valsartan vs. Valsartan



	Ratio of NT-proBNP (sacubitril/valsartan vs. valsartan)	(95% CI)
Week 2	0.88	(0.78 to 0.99)
Week 4	0.91	(0.80 to 1.03)
Week 8	0.97	(0.82 to 1.15)
Week 12	0.86	(0.72 to 1.04)
Week 24	0.95	(0.77 to 1.17)

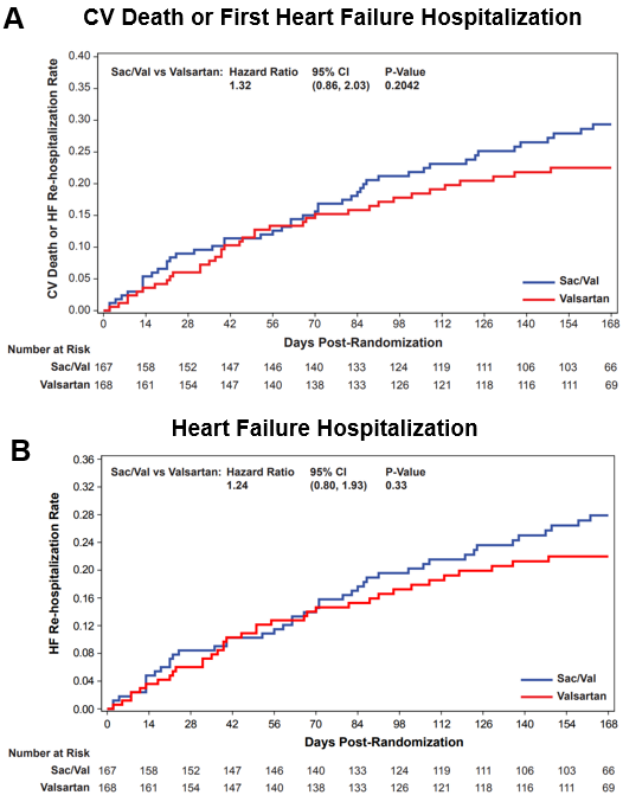
Shown are the point estimates of the ratios of the post-baseline visits to the baseline visit for NT-proBNP levels through 24 weeks of therapy. Values < 1 indicate a treatment effect in favor of sacubitril/valsartan. At 24 weeks, the ratio of change with sacubitril–valsartan vs. valsartan was 0.95 (95% CI, 0.77 to 1.17; P=0.64).

eFigure 3. Box and Whisker Plot of the Change in NT-proBNP AUC



AUC for the change in NT-proBNP ratio in the sacubitril/valsartan and valsartan treatment arms. The box plots for the AUC were formed by the 25th and 75th percentiles and the line within the box is the median; the error bars indicate the 95% confidence intervals and the data markers indicate the means. The dashed horizontal line reflects the value for no change in NT-proBNP from baseline. Values above the dashed line indicate an increase in the AUC from baseline, whereas values above the dashed line indicate an increase in the AUC from baseline. The log transformed AUC NT-proBNP change (primary end point) is shown in Figure 2B. (AUC, area under the curve)

eFigure 4. Cardiovascular Death or Heart Failure Hospitalization and Heart Failure Hospitalization



Kaplan–Meier Curves for the endpoint of cardiovascular death or heart failure hospitalization (Panel A) and heart failure hospitalization (Panel B) in each treatment group.

