Supplementary Online Content

Margulies KB, Hernandez AF, Redfield MM, et al; for the NHLBI Heart Failure Clinical Research Network. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure With Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA*. doi:10.1001/jama.2016.10260

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

HFN Member Clinical Centers: Boston VA Healthcare System: N. Lakdawala, S. Ly, J-M. Do; Brigham and Women's Hospital: M. Givertz, S. Anello, K. Brooks; Christiana Care Health Services: M. Saltzberg, J. Willis, A. Herman; Cleveland Clinic Foundation: W. Tang, R. Starling, T. Fonk, C. Geither; Duke University Medical Center: M. Felker, P. Adams, A. Mbugua, T. Wall; Emory University Hospital: A. Smith, G. Snell, T. Dickson, T. Burns, C. Bosier; George E. Wahlen VA Medical Center: J. Stehlik, J. Gibbs, J. Kirk; Johns Hopkins Hospital: S. Russell, A. Bacher; Lancaster General Hospital: T. Nossuli, S. Pointer, H. Testa; Massachusetts General Hospital: M. Semigran, D. Cocca-Spofford, K. Verkouw; Mayo Clinic: M. Redfield, J. Gatzke, S-Y. Cho; MetroHealth System: M. Dunlap, J. Nichols, P. Leo; Michael E. DeBakey VA Medical Center: A. Deswal, A. Chee, F. Kamil, K. Zihlman; Northwestern Memorial Hospital: S. Shah, J. Corona-Cox, H. Mkrdichian; Saint Louis University Hospital: P. Hauptman, M. Lesko, E. Weber; Southeastern Regional Medical Center: M. Echols, L. Phillips, N. McNeill; Temple University Hospital: R. Alvarez, F. McGonagle; Thomas Jefferson University Hospital: P. Mather, D. Whellan, M. Fox, B. Gallagher, S. Heckard; Tufts Medical Center: M. Kiernan, M. Konstam, A. Cronkright, G. Jamieson, R. O'Kelly; University Hospitals Case Medical Center: G. Oliveira, M. Scheutzow, T. Semenec; University of Pennsylvania Health System: K. Margulies, T. Cappola, C. Damon, C. Olt. F. Pickering; University of Utah Hospitals and Clinics: J. Stehlik, J. Gibbs, M. Johnson; University of Vermont Medical Center: M. LeWinter, M. Rowen, M. Roth; Washington University School of Medicine: G. Ewald, D. Mann, D. Whitehead, J. Flanagan, K. Bult, P. Grow.

FIGHT Data and Safety Monitoring Board: D. Vaughan (Chair), E. Rose, J. Berg, B. Greenberg, J. Johnson, K. Davis Kennedy, J. Parrillo, M. Penn, M. Johnson, R. Agarwal, J. Ambrose, M. Powers

FIGHT Protocol Review Committee: W. Abraham (Chair), J. Berg, J. Cai, D. McNamara, D. Vaughan, R. Virmani, J. Parrillo, E. Rose, R. Agarwal, M. Powers

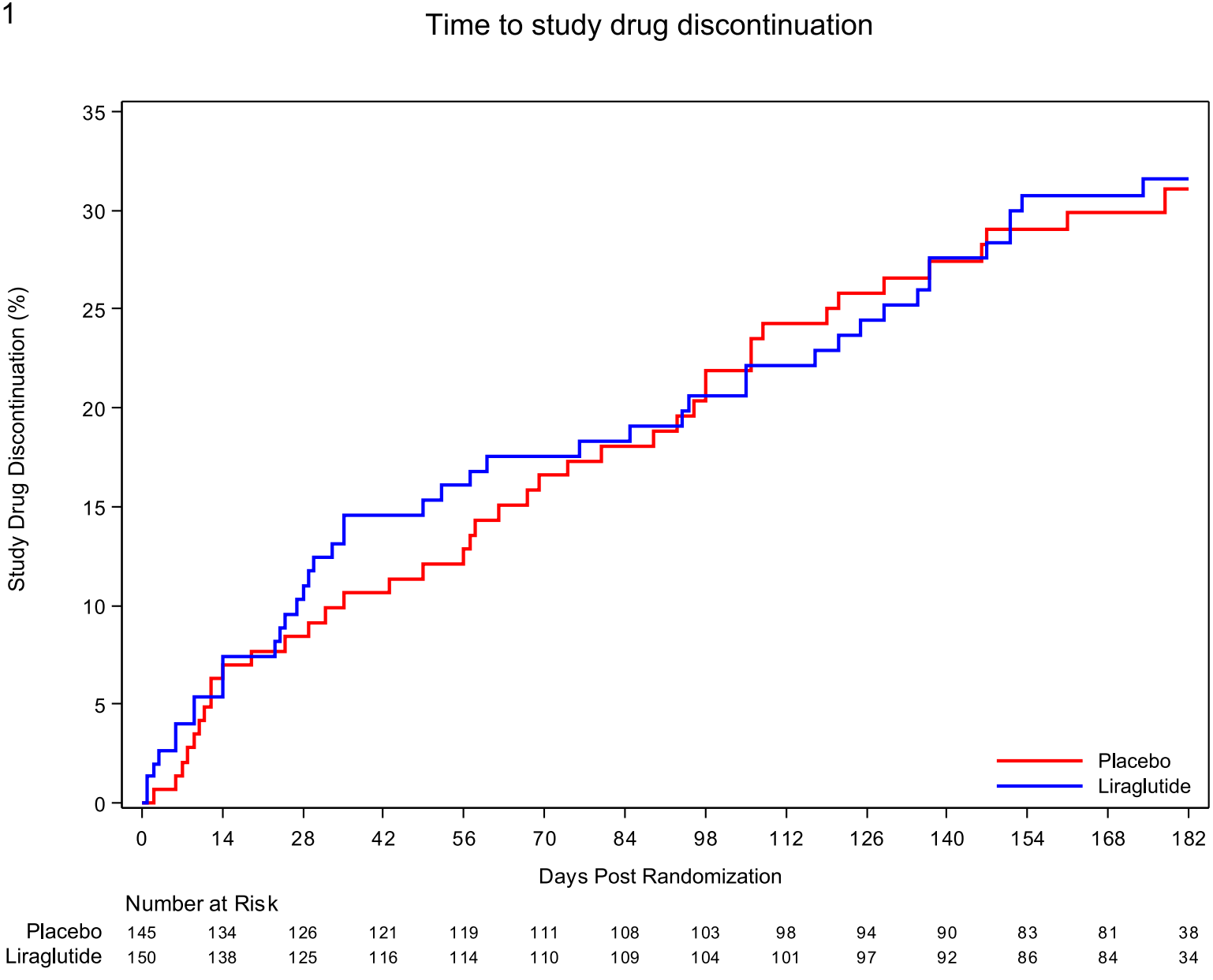
Biomarker Core Lab: University of Vermont: R. Tracy

Echo Core Lab: Duke University Medical Center: F. Alenezi, A. DeVore, H-K. Kim

Coordinating Center: Duke Clinical Research Institute: A. Hernandez, E. Velazquez, M.A. Sellers, P. Monds, T. Atwood, K. Hwang, T. Haddock

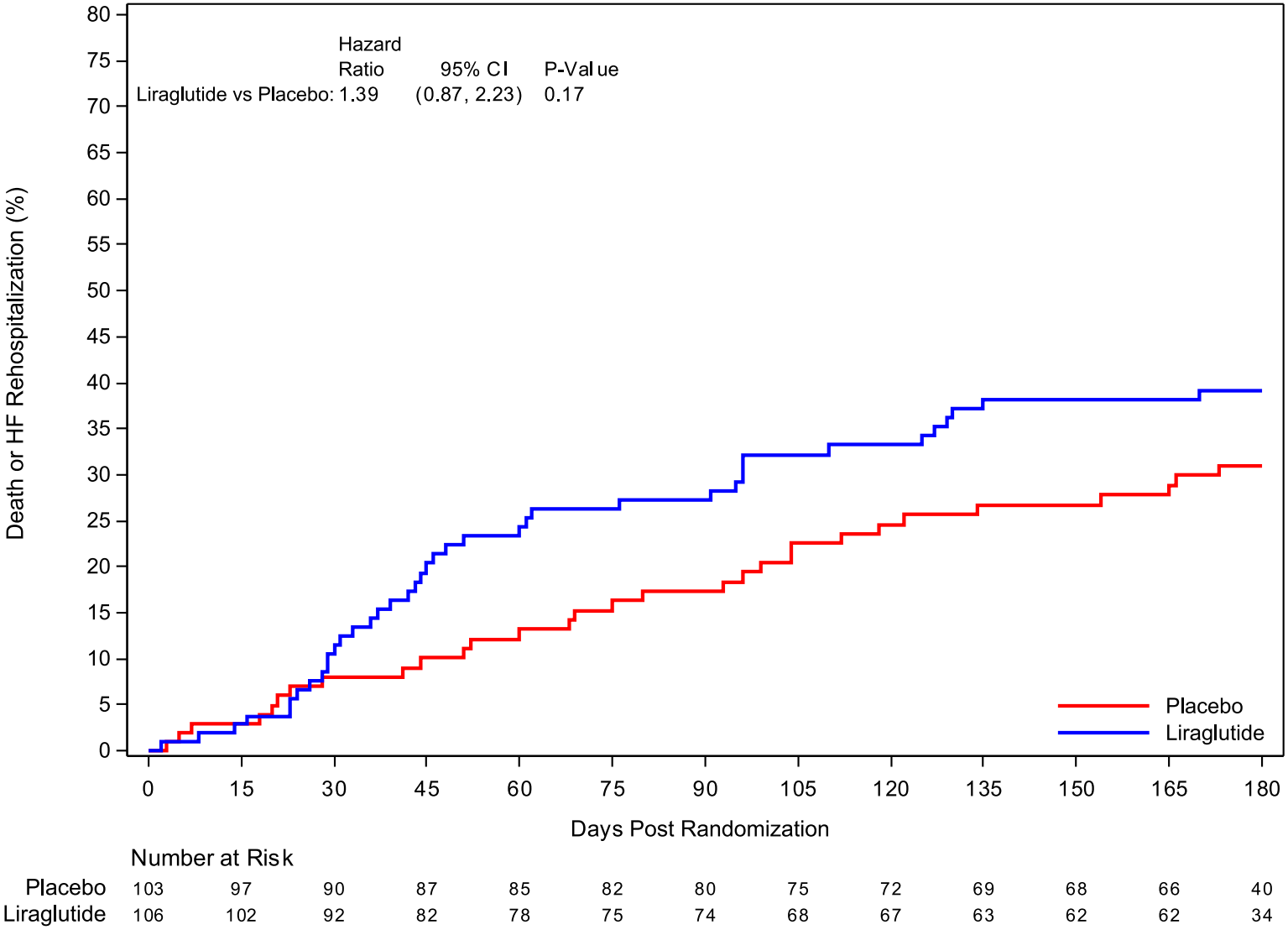
NHLBI Representatives: P. Desvigne-Nickens, K. Cooper- Arnold, M. Shah

eFigure 1


Time to study drug discontinuation
Study Drug Discontinuation (%)
35
30
25
20
15
10
5
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
Days Post Randomization
Placebo
Liraglutide
Number at Risk
Placebo 145 134 126 121 119 111 108 103 98 94 90 83 81 38
Liraglutide 150 138 125 116 114 110 109 104 101 97 92 86 84 34

eFigure 2A

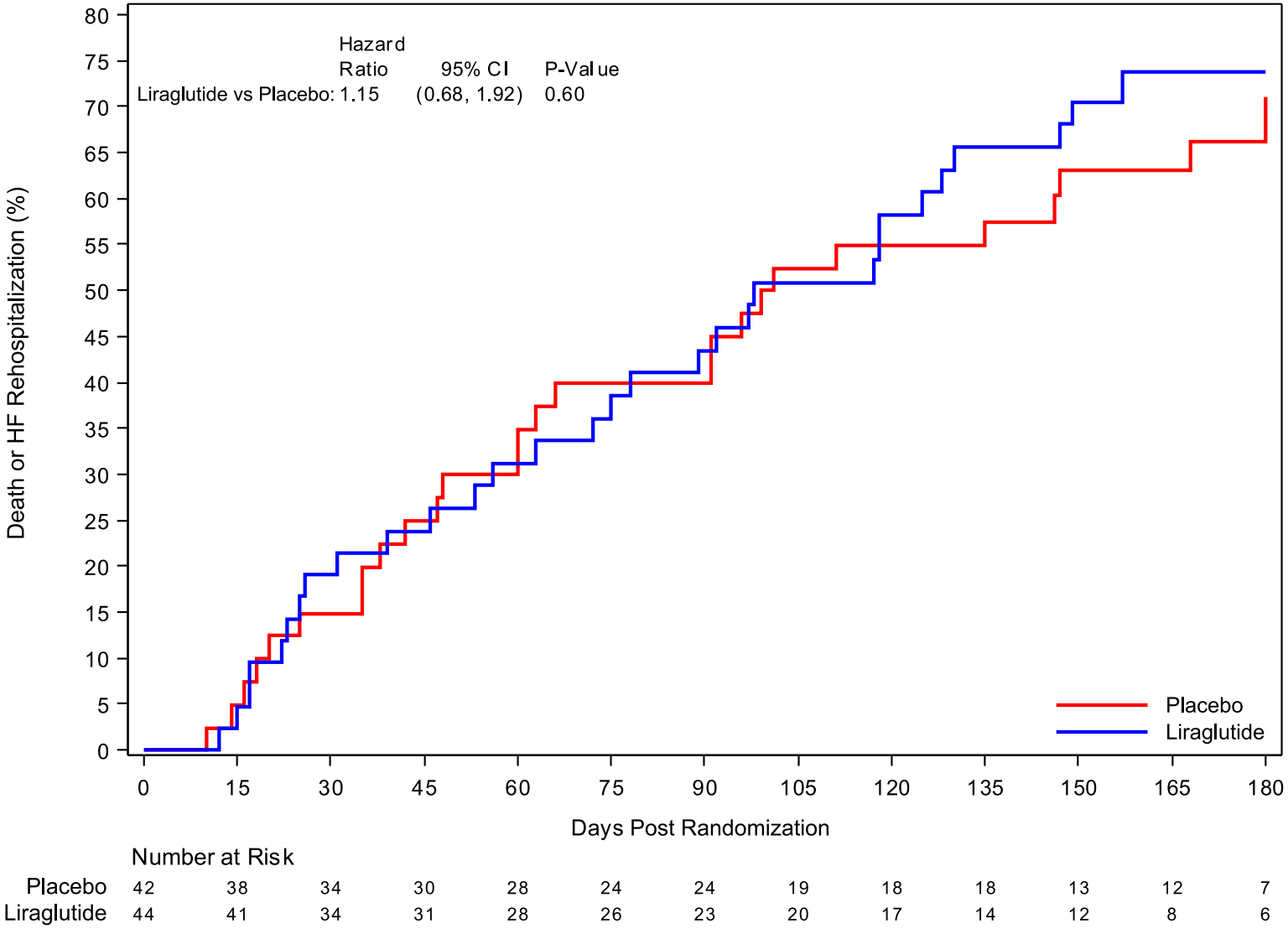
Time to Death or HF Re-Hospitalization Through Day 180 Assessment: Study Drug Not Discontinued Subgroup



Exploratory subgroup analysis in patients who remained on study drug showing a comparison of time death or hospitalization for heart failure according to treatment with liraglutide vs. placebo. For subjects who did not discontinue study drug, the median duration of treatment was 180 days (IQR 175-183 days) in the placebo group and 179 days (IQR 172-182 days) in the liraglutide group. The p-values were generated based on a log-rank statistic from the test of equality over strata using PROC LIFETEST in SAS, stratifying on treatment assignment.

eFigure 2B

Time to death or heart failure re-hospitalization among patients discontinuing study drug



Exploratory subgroup analysis in patients who discontinued study drug showing a comparison of time death or hospitalization for heart failure according to treatment with liraglutide vs. placebo. For subjects who discontinued study drug prior to 180 days, the median duration of treatment was 171 days (IQR 106-182 days) in the placebo group and 177 days (IQR 150-182 days) in the liraglutide group. The p-values were generated based on a log-rank statistic from the test of equality over strata using PROC LIFETEST in SAS, stratifying on treatment assignment.

eTable 1: Sensitivity Analysis to Account for Clustering of Responses by Site*

SAS Procedure	Comments	p-value for treatment
Proc NPAR1WAY with the Wilcoxon option	Standard Kruskal-Wallis / Mann-Whitney / Wilcoxon estimate	0.3087
Proc MIXED using the ranks as outcomes	Fixed effect term for treatment with no random effects	0.3092
Proc MIXED using the ranks as outcomes	Included random effects for the enrolling site	0.3083

*The primary analysis was based on a non-parametric statistic calculated using the NPAR1WAY procedure within SAS. This test can be approximated using PROC MIXED. A simple analysis using PROC MIXED with treatment as the only covariate yields a p-value of 0.3092. The difference between the two tests is very small and likely due to the inclusion of an intercept term in the mixed model specification. A second mixed model was computed with random effects for the 24 sites. The resulting p-value for the treatment effect was 0.3083, indicating no meaningful influence of clustering of treatment responses by site.

eTable 2. Diabetes Subgroup Analysis: Baseline Data

Characteristic	Placebo (N = 87)	Liraglutide (N = 91)
Age, median (IQR), years	62 (54-68)	63 (57-69)
Female sex, no. (%)	20 (23)	23 (25)
White Race, no. (%) †	53 (61)	49 (54)
Hispanic, no. (%) †	8 (9)	3 (3)
BMI, median (IQR), kg/m^2 ‡	34 (28-40)	32 (27-37)
Functional measures		
New York Heart Association Classification, no. (%)		
II	20 (24)	28 (31)
III	59 (71)	56 (63)
IV	3 (4)	5 (6)
Overall summary score on KCCQ §, median (IQR)	39 (28-58)	46 (29-63)
Clinical summary score on KCCQ §, median (IQR)	41 (28-63)	46 (33-67)
Six-minute walk distance, median (IQR), m	189 (130-280)	233 (146-310)
Physical examination		
Weight, median (IQR), lbs	225 (187-270)	208 (183-255)
Systolic blood pressure, median (IQR), mmHg	109 (99-125)	110 (99-120)
Heart rate, median (IQR), beats/min	75 (68-88)	75 (68-82)
Elevated jugular venous pressure, no. (%)	39 (46)	43 (50)
Edema, no. (%)	56 (65)	53 (59)
Duration since heart failure diagnosis, median (IQR), yr	7.2 (3.7-11.2)	8.0 (3.5-13.1)
Medical history, no. (%)		
Prior Hospitalization for heart failure in past year	77 (89)	84 (92)
Ischemic heart disease	73 (84)	83 (91)
Hypertension	74 (85)	73 (81)
Atrial Fibrillation	45 (52)	43 (49)
Type-2 diabetes mellitus	87 (100)	91 (100)
Chronic kidney disease, stage $\geq$ 3 #	34 (39)	35 (39)
Heart Failure Medications at enrollment, no. (%)		
Beta-blocker	82 (94)	86 (95)
ACE-inhibitor or ARB	61 (71)	70 (77)
Hydralazine	29 (33)	26 (29)
Long-acting nitrates	34 (40)	34 (37)

eTable 2. Diabetes Subgroup Analysis: Baseline Data (continued)

Characteristic	Placebo (N = 87)	Liraglutide (N = 91)
Aldosterone Antagonist	54 (62)	49 (55)
Loop diuretic	87 (100)	89 (98)
Digoxin	30 (34)	24 (26)
Calcium-channel blocker	3 (3)	9 (10)
Lipid-lowering agent	76 (87)	77 (85)
Antiplatelet agent	66 (76)	75 (83)
Anticoagulant agent	54 (62)	43 (47)
Laboratory or echocardiographic measures, median (IQR)		
Creatinine, mg/dL	1.6 (1.2-1.9)	1.5 (1.1-1.8)
HbA1c, %	7.6 (6.8-8.5)	7.3 (6.6-8.5)
Total cholesterol, mg/dL	132 (110-159)	126 (98-160)
HDL cholesterol, mg/dL	35 (28-46)	35 (28-46)
LDL cholesterol, mg/dL	67 (58-92)	65 (51-90)
Triglycerides, mg/dL	100 (75-166)	101 (68-143)
Core laboratory NT-proBNP, pg/mL	1961 (1016-3302)	1913 (999-4227)
Core laboratory cystatin C, mg/L	1.6 (1.2-2.0)	1.4 (1.2-1.8)
LVEF, %	26 (19-33)	24 (19-33)
LVEDV index, mL/m^2	125 (108-153)	138 (111-173)
LVESV index, mL/m^2	92 (77-117)	102 (79-127)
Ratio of early mitral inflow velocity to early diastolic medial mitral annular velocity	23 (17-30)	23 (18-33)

† Race and ethnicity were self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ KCCQ denotes the Kansas City Cardiomyopathy Questionnaire; scores range from 1 to 100, with higher scores indicating better function. The clinical summary score is a composite of the functional status, quality of life and social limitation scores. The overall summary score is derived from the physical function, symptom (frequency and severity), social function and quality of life domains.

Chronic kidney disease of stage 3 or greater was determined by the enrolling site.

IQR denotes interquartile range; ACE denotes angiotensin-converting; ARB, angiotensin receptor blocker; BMI, body mass index; JVP, jugular venous pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide

eTable 3: Diabetes Subgroup Analysis: Responses to Treatment

End point	Placebo (N=87)	Liraglutide (N=91)	Treatment Effect (95% CI) ‡	p-value
Primary end point, mean global rank score *	94	85		0.27
Clinical outcomes, no. (%) †				
Death from baseline to 180 d, no. (%)	8 (9)	13 (14)	HR 1.57 (0.56, 3.80)	0.31
HF hospitalization from baseline to 180 d, no. (%)	28 (32)	36 (40)	HR 1.39 (0.85, 2.28)	0.19
CV hospitalization from baseline to 180 d, no. (%)	38 (44)	46 (51)	HR 1.28 (0.83, 1.96)	0.27
Death or HF hospitalization from baseline to 180 d, no (%)	30 (34)	43 (47)	HR 1.54 (0.97, 2.46)	0.07
ED visit through day 180, no. (%)	19 (22)	27 (30)	HR 1.50 (0.83, 2.70)	0.17
Death, CV hospitalization, or ED visit to 180 d, no. (%)	46 (53)	56 (62)	HR 1.35 (0.91, 1.99)	0.13
Death, HF hospitalization, or ED visit to 180 d, no. (%)	39 (45)	52 (57)	HR 1.51 (1.00, 2.29)	0.05
Metabolic end points, mean (95% CI)				
Change in HbA1c from baseline to 180 d, %	0.1 (-0.2, 0.5)	-0.3 (-0.6, 0.1)	-0.5 (-1.0, 0) ‡	0.06
Change in total cholesterol from baseline to 180 d, mg/dL	14 (3, 24)	10 (0, 20)	-5 (-18, 8) ‡	0.44
Change in HDL from baseline to 180 d, mg/dL	2 (-1, 5)	4.4 (1, 8)	3.1 (-1, 7) ‡	0.15
Change in LDL from baseline to 180 d, mg/dL	3 (-5, 12)	2 (-7, 9)	-3 (-14, 8) ‡	0.58
Change in triglycerides from baseline to 180 d, mg/dL	46 (21, 71)	21 (-3, 44)	-23 (-58, 11) ‡	0.18
Clinical measures, mean (95% CI)				
Change in heart rate from baseline to 180 d, beats/min	1.0 (-2.4, 4.3)	0.1 (-3.4, 3.6)	-2.0 (-6.1, 2.1) ‡	0.34
Change in weight from baseline to 180 d, lbs	-0.2 (-4.5, 4.2)	-5.5 (-9.8, -1.1)	-5.5 (-11.7, 0.6) ‡	0.08
Change in six-minute walk distance from baseline to 180 d, m	60 (27, 93)	43 (9, 76)	-4 (-48, 40) ‡	0.86
Change in NT-proBNP from baseline to 180 d, pg/mL	1592 (576, 2606)	1182 (134, 2230)	-272 (-1702, 1158) ‡	0.71
Time averaged proportional change in NT-proBNP, pg/mL	1.8 (1.3, 2.3)	2.0 (1.4, 2.6)	0.4 (-0.4, 1.1) ‡	0.38

eTable 3: Diabetes Subgroup Analysis: Responses to Treatment (Continued)

End point	Placebo (N=87)	Liraglutide (N=91)	Treatment Effect (95% CI)	p-value
Quality of life endpoints, 95% CI				
Change in KCCQ clinical summary score from baseline to 180 d §	13 (7, 18)	14 (8, 19)	3.1 (-3.8, 10.1) ‡	0.38
Change in KCCQ overall summary score from baseline to 180 d §	11 (6, 16)	12 (7, 17)	2.4 (-4.4, 9.1) ‡	0.49
Renal function end points, 95% CI				
Change in cystatin C level from baseline to 180 d, mg/L	-0.08 (-0.20, 0.04)	0.10 (-0.02, 0.22)	0.15 (-0.01, 0.31) ‡	0.07

* The primary end point was a global rank score in which all participants, regardless of treatment assignment, were ranked across three hierarchical tiers: 1) time to death, 2) time to heart failure hospitalization, and 3) time-averaged proportional change in N-terminal pro-B type natriuretic peptide (NT-proBNP) from baseline to 180 days. All enrolled patients were ranked from the worst outcome (rank=1, an early death) to the best outcome (rank=300, a patient who survived free from hospitalization and had an improvement in NT-proBNP). The p-value is determined using a Wilcoxon-test statistic. This nonparametric analysis does not provide an informative estimate of variability.

‡ Treatment effect defined as difference between Liraglutide change from baseline and Placebo change from baseline, adjusting for baseline value, or as HR

†Data collected post-LVAD or heart transplantation was removed from the calculation.

§ KCCQ denotes the Kansas City Cardiomyopathy Questionnaire; scores range from 1 to 100, with higher scores indicating better function. The clinical summary score is a composite of the functional status, quality of life and social limitation scores. The overall summary score is derived from the physical function, symptom (frequency and severity), social function and quality of life domains.

CI indicates confidence interval; CV, cardiovascular; ED, emergency department; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

eTable 4: Investigator-reported safety events

Adverse Event, no. (%)	Placebo (N=146)	Liraglutide (N=154)
Severe hypoglycemic event*	9 (6)	12 (8)
Any hyperglycemic event†	27 (18)	16 (10)
Arrhythmia	16 (11)	26 (17)
Sudden cardiac death	1 (1)	1 (1)
Acute coronary syndrome	1 (1)	2 (1)
Cerebrovascular event	5 (3)	4 (3)
Venous thromboembolism	4 (3)	1 (1)
Lightheadedness, presyncope, or syncope	20 (14)	25 (16)
Worsened renal function§	15 (10)	27 (18)

N's represent the number of events or the number of individuals with that event.

*Severe hypoglycemic events were defined as events that required assistance of another individual.

†Events were based on site reports.

§Worsened renal function was defined at the discretion of site investigators