Supplemental Material for Ferric Carboxymaltose in Iron-Deficient Patients With Hospitalized Heart Failure and Reduced Kidney Function: A Post Hoc Analysis of AFFIRM-AHF

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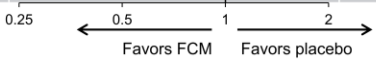
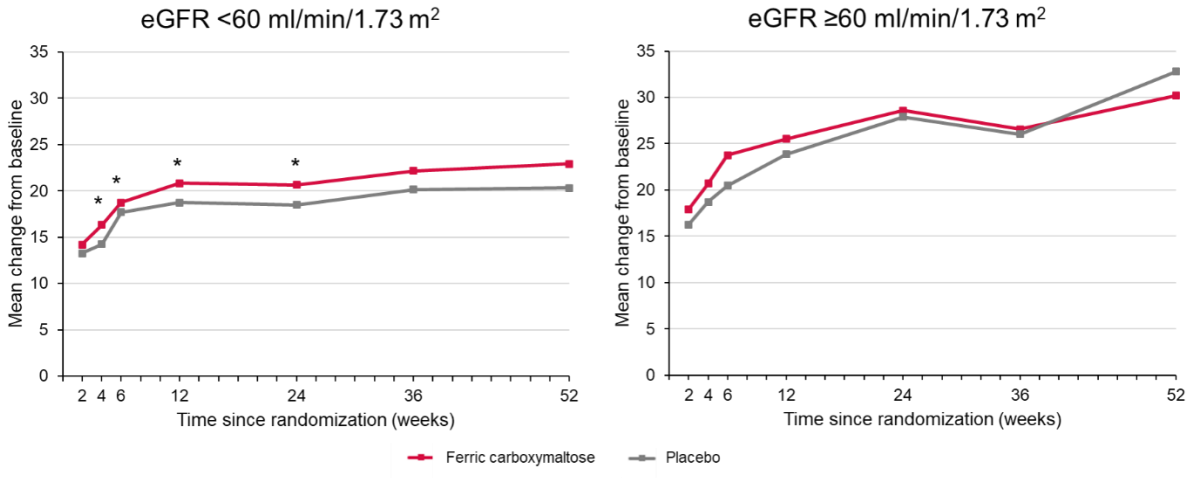
Supplemental Figure 1. Prespecified study endpoints by eGFR tertile. [a]Negative binomial model adjusted for baseline covariates: sex, age, heart failure etiology, heart failure duration, country, baseline eGFR dichotomized, and baseline eGFR dichotomized*treatment. [b]Rate ratio. [c]Hazard ratio. The number of days lost due to heart failure hospitalizations or cardiovascular death was calculated for each patient, summed for each treatment group, and divided by the total patient-years of follow-up in each treatment group multiplied by 100. A negative binomial model was fitted on the number of days lost due to heart failure hospitalizations or cardiovascular death with the log-transformed time on study of each participant in years as an offset. Unadjusted data included in Supplemental Table 4. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; HR, hazard ratio; RR, rate ratio.

Endpoint	eGFR Category (mL/min/1.73 m²)	Adjusted Annualized Event Rate per 100 Patient-Years[a]		Treatment Effect HR/RR (95% CI)	*P* Value	Interaction *P* Value[a]
		FCM	Placebo			
Total heart failure hospitalizations and CV death	<43.0	75.73	99.79	0.76 (0.50, 1.16)[b]	0.20	0.94
	43.0 to <64.3	42.07	55.25	0.76 (0.48, 1.22)[b]	0.26	
	≥64.3	40.75	59.45	0.69 (0.42, 1.12)[b]	0.13	
Total CV hospitalizations and CV death	<43.0	90.81	124.21	0.73 (0.50, 1.07)[b]	0.11	0.46
	43.0 to <64.3	59.35	67.33	0.88 (0.58, 1.33)[b]	0.55	
	≥64.3	50.84	84.15	0.60 (0.39, 0.93)[b]	0.02	
Time to CV death	<43.0	–	–	0.79 (0.49, 1.28)[c]	0.34	0.98
	43.0 to <64.3	–	–	0.82 (0.39, 1.70)[c]	0.59	
	≥64.3	–	–	0.87 (0.39, 1.91)[c]	0.72	
Total heart failure hospitalizations	<43.0	42.85	54.44	0.79 (0.52, 1.19)[b]	0.25	0.72
	43.0 to <64.3	27.98	35.58	0.79 (0.50, 1.24)[b]	0.30	
	≥64.3	24.30	39.07	0.62 (0.38, 1.01)[b]	0.06	
Time to first heart failure hospitalization or CV death	<43.0	–	–	0.74 (0.53, 1.02)[c]	0.07	0.51
	43.0 to <64.3	–	–	0.91 (0.60, 1.36)[c]	0.64	
	≥64.3	–	–	0.64 (0.42, 0.98)[c]	0.04	
Days lost due to heart failure hospitalizations or CV death	<43.0	503.2	793.6	0.63 (0.32, 1.25)[b]	0.19	0.98
	43.0 to <64.3	310.8	502.2	0.62 (0.31, 1.24)[b]	0.18	
	≥64.3	283.6	489.6	0.58 (0.29, 1.18)[b]	0.13	



Supplemental Figure 2. Mean change in KCCQ-12: (A) overall summary scores, and (B) clinical summary scores by baseline eGFR category (dichotomized). **P*<0.05 for ferric carboxymaltose vs. placebo. eGFR, estimated glomerular filtration rate; KCCQ-12, Kansas City Cardiomyopathy Questionnaire–12.

A



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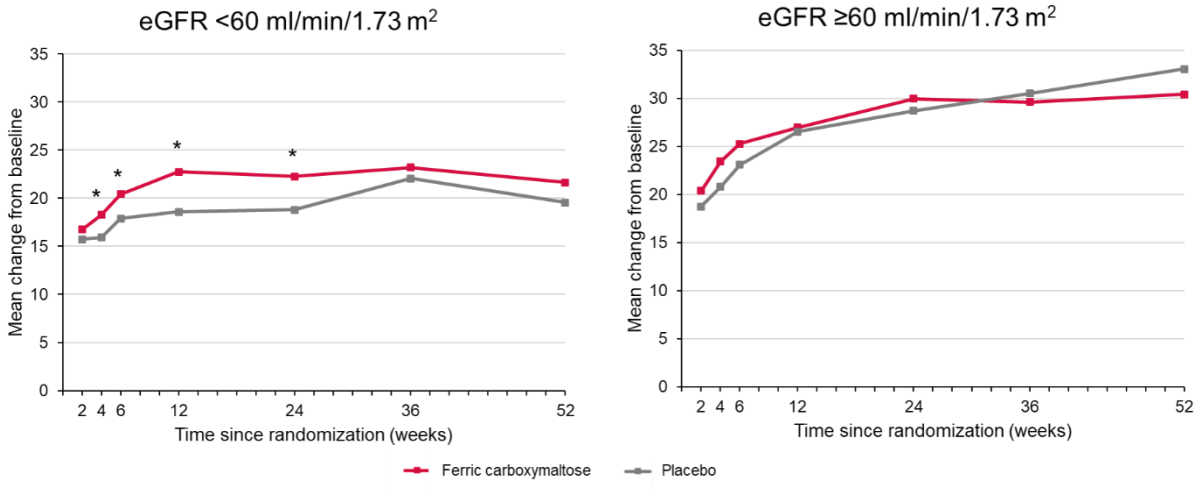

Supplemental Table 1. Baseline characteristics by eGFR tertile

	eGFR <43.0 ml/min/1.73 m^2 *N*=322		eGFR 43.0 to <64.3 ml/min/1.73 m^2 *N*=322		eGFR ≥64.3 ml/min/1.73 m^2 *N*=323	
	Ferric carboxymaltose *n*=157	Placebo *n*=165	Ferric carboxymaltose *n*=166	Placebo *n*=156	Ferric carboxymaltose *n*=164	Placebo *n*=159
Mean (SD) age, yr	77 (8)	75 (10)	71 (10)	72 (8)	67 (12)	66 (12)
Female, *n* (%)	72 (46)	80 (49)	75 (45)	72 (46)	65 (40)	64 (40)
Race, White, *n* (%)	150 (96)	158 (96)	155 (93)	149 (96)	158 (96)	149 (94)
Heart failure etiology, *n* (%)						
Ischemic	81 (52)	89 (54)	77 (46)	77 (49)	68 (42)	56 (35)
Nonischemic	72 (46)	72 (44)	88 (53)	73 (47)	91 (56)	98 (62)
Unknown	4 (3)	4 (2)	1 (0.6)	6 (4)	5 (3)	5 (3)
De novo heart failure (no previous diagnosis), *n* (%)	34 (22)	28 (17)	48 (29)	54 (35)	61 (37)	67 (42)
Heart failure hospitalization in prior 1 year, *n* (%)	53 (43)	52 (38)	36 (31)	44 (43)	37 (36)	34 (37)
Diabetes at baseline, n (%)	72 (46)	86 (52)	60 (36)	69 (44)	60 (37)	60 (38)
Baseline LVEF						
Mean (SD) LVEF, %	33 (10)	33 (9)	33 (9)	33 (10)	32 (10)	31 (10)
<40%, n (%)	105 (67)	105 (64)	117 (70)	104 (67)	117 (71)	112 (70)
≥40%, n (%)	52 (33)	60 (36)	49 (30)	52 (33)	47 (29)	46 (29)
NYHA functional class, *n* (%)						
I	4 (3)	2 (1)	2 (1)	1 (0.6)	6 (4)	3 (2)
II	70 (45)	65 (39)	76 (46)	61 (39)	77 (47)	78 (49)
III	79 (50)	93 (56)	84 (51)	87 (56)	77 (47)	74 (47)
IV	4 (3)	5 (3)	4 (2)	6 (4)	4 (2)	3 (2)
Hemoglobin category, *n* (%)						
	20 (13)	27 (16)	12 (7)	20 (13)	10 (6)	9 (6)

<10 g/dl	120 (76)	124 (75)	122 (74)	113 (72)	121 (74)	122 (77)
10–14 g/dl	16 (10)	14 (9)	32 (19)	23 (15)	33 (20)	28 (18)
>14 g/dl						
Anemic, *n* (%)[a]						
Male	61 (39)	64 (39)	46 (28)	49 (31)	46 (28)	44 (28)
Female	43 (27)	54 (33)	29 (18)	37 (24)	20 (12)	22 (14)
Ferritin category, *n* (%)						
<100 ng/ml	118 (75)	114 (69)	129 (78)	116 (74)	111 (68)	104 (65)
100–300 ng/ml	38 (24)	50 (30)	37 (22)	40 (26)	53 (32)	55 (35)
≥300 ng/ml	0	1 (0.6)	0	0	0	0
TSAT <20%, *n* (%)	126 (80)	143 (87)	130 (78)	126 (81)	142 (87)	135 (85)
Mean (SD) phosphate, mg/dl	3.7 (0.8)	3.9 (0.9)	3.6 (0.7)	3.8 (1.0)	3.7 (0.7)	3.7 (0.7)
Mean (SD) BNP, pg/ml	1392 (938)	1335 (936)	1330 (650)	1514 (930)	1182 (809)	1554 (924)
Mean (SD) NT-proBNP, pg/ml	7979 (7110)	7742 (6956)	6304 (6310)	6767 (6263)	5680 (4949)	5633 (4579)
Treatment at baseline, *n* (%)						
ACEi or ARB or ARNI	94 (60)	107 (65)	139 (84)	123 (79)	133 (81)	128 (81)
BB	125 (80)	133 (81)	143 (86)	132 (85)	127 (77)	138 (87)
MRA	76 (48)	78 (47)	125 (75)	105 (67)	124 (76)	126 (79)
Triple therapy (ACEi/ARB/ARNI+BB+MRA)	39 (25)	42 (26)	95 (57)	72 (46)	82 (50)	93 (59)
SGLT2i	2 (1)	2 (1)	3 (2)	2 (1)	0	2 (1)

Percentages may not total 100% as a result of rounding.

[a]Defined as hemoglobin <13 g/dl in males and <12 g/dl in females.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TSAT, transferrin saturation.

Supplemental Table 2. Study endpoints by dichotomized eGFR category (data supporting Figure 2)

Endpoint	eGFR Category	*n/N* (%)		Annualized Event Rate per 100 Patient-Years		Rate Difference per 100 Patient-Years	Unadjusted RR
		Ferric carboxymaltose	Placebo	Ferric carboxymaltose	Placebo		
Total heart failure hospitalizations and CV death	<60	104/292 (36)	119/288 (41)	68.96	86.30	17.34	0.80
	≥60	46/195 (24)	62/192 (32)	39.93	56.89	16.96	0.70
Total CV hospitalizations and CV death	<60	121/292 (41)	133/288 (46)	86.10	100.35	14.25	0.86
	≥60	55/195 (28)	78/192 (41)	47.91	75.28	27.37	0.64
Time to CV death	<60	40/292 (14)	47/288 (16)	–	–	–	N/A
	≥60	17/195 (9)	19/192 (10)	–	–	–	N/A
Total heart failure hospitalizations	<60	88/292 (30)	100/288 (35)	53.37	67.43	14.06	0.79
	≥60	35/195 (18)	54/192 (28)	30.23	45.97	15.74	0.66
Time to first heart failure hospitalization or CV death	<60	104/292 (36)	119/288 (41)	–	–	–	N/A
	≥60	46/195 (24)	62/192 (32)	–	–	–	N/A
Days lost due to heart failure hospitalizations or CV death	<60	5 (11)[a]	7 (16)[a]	546.20	854.55	308.35	0.64
	≥60	2 (7)[a]	4 (10)[a]	271.50	484.98	457.48	0.56

Event rates and RR not available for time-to-event analyses.

[a]Presented as mean (SD) days lost per participant. The number of days lost due to heart failure hospitalizations or cardiovascular death was calculated for each patient, summed for each treatment group, and divided by the total patient-years of follow-up in each treatment group multiplied by 100.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; RR, rate ratio.

Supplemental Table 3. Primary endpoints by dichotomized eGFR category and subgroups of interest (data supporting Figure 3)

Endpoint	eGFR Category	*n/N* (%)		Annualized Event Rate per 100 Patient-Years		Rate Difference per 100 Patient-Years	Unadjusted RR
		Ferric carboxymaltose	Placebo	Ferric carboxymaltose	Placebo		
Ischemic heart failure	<60	56/145 (39)	72/154 (47)	72.86	111.52	38.66	0.65
	≥60	21/81 (26)	30/68 (44)	44.58	93.15	48.57	0.48
Nonischemic heart failure	<60	47/142 (33)	44/127 (35)	65.88	56.74	−9.14	1.16
	≥60	23/109 (21)	30/116 (26)	35.84	38.80	2.96	0.92
Anemia	<60	62/169 (37)	80/181 (44)	77.54	86.84	9.30	0.89
	≥60	23/76 (30)	34/86 (40)	54.98	74.70	19.72	0.74
No anemia	<60	41/122 (34)	39/104 (38)	57.08	85.32	28.24	0.67
	≥60	23/119 (19)	28/106 (26)	30.13	42.98	12.85	0.70
De novo heart failure	<60	19/72 (26)	14/68 (21)	44.62	24.38	−20.24	1.83
	≥60	10/71 (14)	14/81 (17)	17.25	23.77	6.52	0.73
History of heart failure	<60	85/220 (39)	105/220 (48)	77.21	106.61	29.4	0.72
	≥60	36/124 (29)	48/111 (43)	52.89	82.40	29.51	0.64

eGFR, estimated glomerular filtration rate; RR, rate ratio; SD, standard deviation.

Supplemental Table 4. Study endpoints by eGFR tertiles (data supporting Supplemental Figure 1)

Endpoint	eGFR Category	*n/N* (%)		Annualized Event Rate per 100 Patient-Years		Rate Difference per 100 Patient-Years	Unadjusted RR
		Ferric carboxymaltose	Placebo	Ferric carboxymaltose	Placebo		
Total heart failure hospitalizations and CV death	<43.0	64/157 (41)	85/165 (52)	88.16	112.17	24.01	0.79
	43.0 to <64.3	49/166 (30)	46/156 (30)	49.63	58.16	8.53	0.85
	≥64.3	37/164 (23)	50/159 (31)	37.73	54.50	16.77	0.69
Total CV hospitalizations and CV death	<43.0	70/157 (45)	94/165 (57)	101.19	132.81	31.62	0.76
	43.0 to <64.3	61/166 (37)	53/156 (34)	67.92	65.87	−2.05	1.03
	≥64.3	45/164 (27)	64/159 (40)	46.49	73.82	27.33	0.63
Time to CV death	<43.0	31/157 (20)	38/165 (23)	–	–	–	N/A
	43.0 to <64.3	14/166 (8)	15/156 (10)	–	–	–	N/A
	≥64.3	12/164 (7)	13/159 (8)	–	–	–	N/A
Total heart failure hospitalizations	<43.0	51/157 (33)	67/165 (41)	64.39	84.13	19.74	0.77
	43.0 to <64.3	43/166 (26)	43/156 (28)	40.49	47.65	7.16	0.85
	≥64.3	29/164 (18)	44/159 (28)	29.65	45.53	15.88	0.65
Time to first heart failure hospitalization or CV death	<43.0	64/157 (41)	85/165 (52)	–	–	–	N/A
	43.0 to <64.3	49/166 (30)	46/156 (30)	–	–	–	N/A
	≥64.3	37/164 (23)	50/159 (31)	–	–	–	N/A
Days lost due to heart failure hospitalizations or CV death	<43.0	6 (11)[a]	9 (17)[a]	690.68	1069.34	378.66	0.65
	43.0 to <64.3	4 (10)[a]	6 (16)[a]	391.82	623.63	231.81	0.63
	≥64.3	2 (7)[a]	4 (9)[a]	254.01	437.41	183.40	0.58

Event rates and RR not available for time-to-event analyses.

[a]Presented as mean (SD) days lost per participant. The number of days lost due to heart failure hospitalizations or cardiovascular death was calculated for each patient, summed for each treatment group, and divided by the total patient-years of follow-up in each treatment group multiplied by 100.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; RR, rate ratio; SD, standard deviation.

Supplemental Table 5. Adverse events by baseline eGFR tertile

	eGFR <43.0 ml/min/1.73 m²				eGFR 43.0–64.3 ml/min/1.73 m²				eGFR ≥64.3 ml/min/1.73 m²			
	Ferric carboxymaltose *N*=157		Placebo *N*=165		Ferric carboxymaltose *N*=166		Placebo *N*=156		Ferric carboxymaltose *N*=164		Placebo *N*=159	
	n (%)	Incidence rate per PY[a]	n (%)	Incidence rate per PY[a]	n (%)	Incidence rate per PY[a]	n (%)	Incidence rate per PY[a]	n (%)	Incidence rate per PY[a]	n (%)	Incidence rate per PY[a]
All AEs	118 (75)	0.894	131 (79)	0.958	107 (65)	0.692	98 (63)	0.682	101 (62)	0.676	98 (62)	0.668
TEAEs	115 (73)	0.871	127 (77)	0.929	105 (63)	0.679	93 (60)	0.647	89 (54)	0.596	95 (60)	0.648
Severe TEAEs	60 (38)	0.454	76 (46)	0.556	37 (22)	0.239	41 (26)	0.285	38 (23)	0.382	43 (27)	0.484
Serious TEAEs	84 (54)	0.636	110 (67)	0.804	71 (43)	0.459	66 (42)	0.459	57 (35)	0.382	71 (45)	0.484
Serious infection TEAEs	18 (11)	0.136	17 (10)	0.124	10 (6)	0.065	17 (11)	0.118	6 (4)	0.040	8 (5)	0.055
TEAEs leading to treatment discontinuation	23 (15)	0.174	38 (23)	0.278	11 (7)	0.071	29 (11)	0.118	10 (6)	0.067	16 (10)	0.109
TEAEs of clinical interest[b]	56 (36)	0.424	70 (42)	0.512	45 (27)	0.291	43 (28)	0.299	21	0.234	26	0.286
Fatal TEAEs	41 (26)	0.311	43 (26)	0.314	18 (11)	0.116	20 (13)	0.139	18 (11)	0.121	18 (11)	0.123
Related fatal TEAEs	0	0	0	0	0	0	0	0	0	0	0	0

[a]Incidence rate is computed as the number of all participants with an AE in the treatment group divided by the total participant-years of follow-up in the treatment group. % represents the proportion of patients in the treatment arm experiencing events.
[b]AEs of clinical interest include "CV death" and "HF hospitalization." AEs of special interest include "hypersensitivity reactions," "hypophosphatemia," "injection/infusion site reactions," and "hemosiderosis."
AE, adverse event; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; PY, patient-year; TEAE, treatment-emergent adverse event.