## **Supplementary Appendix**

# Health Status Improvement with Ferric Carboxymaltose in Heart Failure with Reduced Ejection Fraction and Iron Deficiency

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Supplementary Table 1: Key characteristics of the two randomised controlled trials (FAIR-HF and CONFIRM-HF) in patients with HFrEF and iron deficiency included in the analysis

	FAIR-HF <sup>1</sup>	CONFIRM-HF <sup>2</sup>	
Randomisation	2:1 (FCM:placebo)	1:1 (FCM:placebo)	
Number of patients (FCM/placebo)	304/155	150/151	
Centre	Multicentre	Multicentre	
Study duration	24 weeks	52 weeks	
Setting	Ambulatory	Ambulatory	
HF type and severity	Optimally treated, systolic CHF with ID, NYHA class II/III	Optimally treated, systolic CHF with ID, NYHA class II/III	
Haemoglobin	9.5–13.5 g/dL	<15 g/dL	
Primary endpoint	Change in PGA and NYHA class from baseline to week 24	Change in 6MWT from baseline to week 24	

**Legend:** 6MWT, six-minute walk test; CHF, chronic heart failure; CONFIRM-HF, Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure; FAIR-HF, Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure; FCM, ferric carboxymaltose; HF, heart failure; ID, iron deficiency; NYHA, New York Heart Association; PGA, patient global assessment.

Supplementary Table 2: Number needed to treat with ferric carboxymaltose to achieve defined change vs baseline in KCCQ OSS, CSS, or TSS at weeks 12 and 24 (random-effects model)

	Week 12	Week 24
KCCQ OSS		
Improvement		
≥4.3 points	7	9
≥8.6 points	8	13
≥5 points	7	10
≥10 points	10	14
≥15 points	18	19
Deterioration		
≥ 5 points	22	19
KCCQ CSS		
Improvement		
≥4.5 points	11	10
≥9 points	12	15
≥5 points	12	10
≥10 points	11	17
≥15 points	14	16
Deterioration		
≥ 5 points	177	28
KCCQ TSS		
Improvement		
≥4.9 points	10	13
≥9.8 points	8	15
≥5 points	10	13
≥10 points	8	15
≥15 points	11	9
Deterioration		
≥ 5 points	22	20

**Legend**: ORs from the random-effects responder analysis were converted into NNT using the formula described in Hutton et al<sup>3</sup> and the placebo control response/deterioration proportion. CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; NNT, number needed to treat; OSS, overall summary score; TSS, total symptom score.

Supplementary Figure 1: Mean change from baseline in KCCQ OSS, CSS, and TSS with FCM vs placebo at weeks 12 and 24 (random effects model)

	LS mean (SD) change vs baseline		Random-effects model				
	FCM pool	Placebo pool		LS mean difference [95% CI]	p-value		
OSS							
Week 12	10.6 (17.7)	4.8 (13.9)	<b>⊢</b>	4.33 [1.81; 6.84]	0.0008		
Week 24	11.4 (18.7)	5.7 (15.0)		4.42 [1.86; 6.97]	0.0007		
CSS							
Week 12	9.7 (17.5)	4.8 (13.6)	⊨ <b></b>	3.80 [-0.46; 8.07]	0.0805		
Week 24	10.0 (18.5)	4.9 (14.9)	₽;	4.08 [-0.21; 8.37]	0.0621		
TSS							
Week 12	10.9 (18.5)	5.3 (15.7)	₽	4.58 [0.25; 8.91]	0.0384		
Week 24	10.9 (19.4)	4.8 (16.7)	 ∕	5.02 [0.68; 9.36]	0.0233		
	-10.0 -7.5 -5.0 -2.5 0.0 2.5 5.0 7.5 10.0 LS mean difference (95% CI)						
			Favours placebo ← → Favours FCM				

**Legend:** Random-effects MMRM analysis adjusted for study, baseline KCCQ score, age, eGFR, diabetes status, sex and left ventricular ejection fraction. This model is an expanded version of the fixed-effects model that included random treatment-by-study interactions. CI, confidence interval; CSS, clinical summary score; FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire; MMRM, mixed-model for repeated measures; OSS, overall summary score; SD, standard deviation; TSS, total symptom score.

Supplementary Figure 2: Responder analyses for ferric carboxymaltose vs. placebo across conventional and MCID thresholds for (A) OSS, (B) CSS and (C) TSS KCCQ domains (random effects model)

### (A) KCCQ OSS

	Random-effects model				
	FCM pool n (%)	Placebo pool n (%)		OR [95% CI]	p-value
Week 12					
Ν	415	283			
Improvement					
≥4.3 points	251 (60.5)	132 (46.6)	¦ ⊢∎(	1.821 [1.177; 2.817]	0.0071
≥8.6 points	193 (46.5)	89 (31.5)	¦ ⊢∎i	1.914 [1.222; 2.997]	0.0046
≥5 points	242 (58.3)	123 (43.5)	¦ ⊢_∎(	1.910 [1.367; 2.669]	0.0001
≥10 points	176 (42.4)	83 (29.3)	₽	1.758 [1.048; 2.948]	0.0326
≥15 points	133 (32.1)	64 (22.6)	⊢───┤	1.413 [0.495; 4.032]	0.5180
			Favours PBO - Favours FCM		
Deterioration					
≥5 points	62 (14.9)	53 (18.7)		0.761 [0.490; 1.184]	0.2261
			Favours FCM - Favours PBO		
Week 24					
Ν	420	284			
Improvement					
≥4.3 points	249 (59.3)	137 (48.2)	⊢ <b>∔</b> i	1.566 [0.922; 2.662]	0.0973
≥8.6 points	197 (46.9)	105 (37.0)	⊢ <b>⊢</b>	1.412 [0.789; 2.529]	0.2452
≥5 points	240 (57.1)	133 (46.8)	⊢ <u>∔</u>	1.500 [0.919; 2.449]	0.1047
≥10 points	185 (44.1)	96 (33.8)		1.400 [0.751; 2.607]	0.2895
≥15 points	154 (36.7)	80 (28.2)	⊢₋₊	1.311 [0.789; 2.177]	0.2961
			Favours PBO ← → Favours FCM		
Deterioration					
≥5 points	76 (18.1)	64 (22.5)		0.759 [0.504; 1.144]	0.1879
			Favours FCM - Favours PBO		
		_	i i		
			3 10 20		
		0.3			
			OR [95% CI]		

## (B) KCCQ CSS

			Random-ef	fects model	
	FCM pool n (%)	Placebo pool n (%)		OR [95% CI]	p-value
Week 12					
N	415	283			
Improvement					
≥4.5 points	235 (56.6)	135 (47.7)	<u>}</u>	1.472 [1.006; 2.153]	0.0462
≥9.0 points	188 (45.3)	98 (34.6)	⊢ <mark>∤</mark> i	1.470 [0.943; 2.291]	0.0890
≥5 points	229 (55.2)	133 (47.0)	┝──■──┤	1.420 [1.018; 1.982]	0.0388
≥10 points	180 (43.4)	90 (31.8)	┟───■───┤	1.557 [1.016; 2.386]	0.0419
≥15 points	146 (35.2)	67 (23.7)		1.591 [0.801; 3.161]	0.1851
Deterioration			Favours PBO - Favours FCM		
	75 /10 1)	E4 (10 1)		0.002 [0.022, 1.409]	0.9615
25 points	75 (18.1)	54 (19.1)		0.963 [0.632; 1.468]	0.8615
			Favours FCM - Favours PBO		
Week 24					
N	420	284			
Improvement					
≥4.5 points	237 (56.4)	134 (47.2)	<b>⊢</b> ∎	1.514 [0.874; 2.622]	0.1390
≥9.0 points	186 (44.3)	104 (36.6)	H <b></b> H	1.343 [0.954; 1.890]	0.0911
≥5 points	236 (56.2)	132 (46.5)	<b>⊢</b> ∎−−−−−1	1.537 [0.915; 2.582]	0.1043
≥10 points	177 (42.1)	98 (34.5)	<b>⊢⊢</b> ∎−−−−−1	1.311 [0.834; 2.060]	0.2412
≥15 points	158 (36.7)	81 (28.5)	₽	1.390 [0.966; 2.000]	0.0759
			Favours PBO - Favours FCM		
Deterioration					
≥5 points	88 (21.0)	69 (24.3)	⊢ <b></b>	0.833 [0.559; 1.241]	0.3696
			Favours FCM ← → Favours PBO		
		0.1	3 10 3.0	)	
			OR [95% CI]		
		0.	Favours FCM ← Favours PBO 3 1.0 3.0 OR [95% CI]	)	

#### (C) KCCQ TSS

			Random-effects model		
	FCM pool n (%)	Placebo pool n (%)		OR [95% CI]	p-value
Week 12					
Ν	415	282			
Improvement					
≥4.9 points	243 (58.6)	137 (48.6)	¦ ⊢∎i	1.538 [1.096; 2.160]	0.0129
≥9.8 points	214 (51.6)	108 (38.3)	╏┝────╋────┤	1.736 [1.103; 2.732]	0.0172
≥5 points	243 (58.6)	137 (48.6)	¦ ⊢∎i	1.538 [1.096; 2.160]	0.0129
≥10 points	214 (51.6)	108 (38.3)	· <b>■</b> · · · · · · · · · · · · · · · · · · ·	1.736 [1.103; 2.732]	0.0172
≥15 points	178 (42.9)	88 (31.2)	↓■	1.607 [1.099; 2.348]	0.0143
Deterioration			Favours PBO - Favours FCM		
	75 /19 1)	61 (21 6)		0 776 [0 612.1 174]	0 2206
25 points	/5 (18.1)	01 (21.0)		0.776 [0.515, 1.174]	0.2296
			Favours FCWI + Favours PBO		
Week 24					
Ν	420	284			
Improvement					
≥4.9 points	233 (55.5)	135 (47.5)	₩	1.384 [0.985; 1.945]	0.0614
≥9.8 points	210 (50.0)	112 (39.4)	·∎	1.540 [1.107; 2.142]	0.0104
≥5 points	233 (55.5)	135 (47.5)	₽	1.384 [0.985; 1.945]	0.0614
≥10 points	210 (50.0)	112 (39.4)	·∎	1.540 [1.107; 2.142]	0.0104
≥15 points	188 (44.8)	87 (30.6)	·	1.777 [1.065; 2.964]	0.0276
			Favours PBO - Favours FCM		
Deterioration					
≥5 points	94 (22.4)	77 (27.1)	⊢ <b>_</b> ∎	0.790 [0.537; 1.163]	0.2320
			Favours FCM - Favours PBO		
		<b>r</b>			
		0.	5 1.0 5.0	,	
			OR [95% CI]		

**Legend:** ORs were obtained from logistic regression models including treatment group, study, and the following baseline factors: KCCQ score, age, eGFR, diabetes status, sex and left ventricular ejection fraction. The random-effects model included random treatment-by-study interactions. Covariate effects were allowed to vary across studies by introducing appropriate interactions. N = the number of patients with KCCQ data available at each time point, plus patients who died before assessment and were recorded as 'not improved' in the analysis of improvement and 'deteriorated' in the deterioration analysis. CI, confidence interval; CSS, clinical summary score; FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; OSS, overall summary score; PBO, placebo; TSS, total symptom score.

# Supplementary Figure 3: Response stability analysis – change in KCCQ CSS response between week 12 and week 24 with ferric carboxymaltose and placebo



**Legend:** N = the number of patients that had non-missing KCCQ data available at both week 12 and week 24. CSS, clinical summary score; FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire.

# Supplementary Figure 4: Response stability analysis – change in KCCQ TSS response between week 12 and week 24 with ferric carboxymaltose and placebo



**Legend:** N = the number of patients that had non-missing KCCQ data available at both week 12 and week 24. FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire; TSS, total symptom score.

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