SUPPLEMENTARY APPENDIX

Efficacy of intravenous ferric carboxymaltose in patients with iron deficiency after acute heart failure in AFFIRM-AHF: impact of ischaemic vs non-ischaemic heart failure aetiology on outcomes

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on behalf of the AFFIRM-AHF investigators

Contents

Supplementary Table 1: Baseline demographics and clinical characteristics in the FCM and placebo groups by HF aetiology (mITT population)

Baseline characteristics	Ischaemic HF (N=590)			Non ischaemic HF (N=492)		
	FCM (n=300)	Placebo (n=290)	p-value	FCM (n=248)	Placebo (n=244)	p-value
Age, years	71.9 (9.1)	71.3 (9.9)	0.45	70.4 (12.6)	70.4 (12.3)	0.97
Male, n (%)	201 (67.0)	190 (65.5)	0.70	106 (42.7)	103 (42.2)	0.90
Race, n (%)						
White	279 (93.0)	270 (93.1)	0.79	239 (96.4)	238 (97.5)	0.73
Asian	20 (6.7)	18 (6.2)		6 (2.4)	4 (1.6)	
Other	1 (0.3)	2 (0.7)		3 (1.2)	2 (0.8)	
BMI, kg/m^2	27.53 (4.924)	27.75 (5.205)	0.60	28.94 (6.362)	28.36 (6.148)	0.31
Comorbidities, n (%)						
Smoking	33 (11.0)	27 (9.3)	0.96	23 (9.3)	19 (7.8)	0.28
Hypertension	259 (86.3)	250 (86.2)	0.96	203 (81.9)	206 (84.4)	0.45
Dyslipidaemia	198 (66.0)	194 (66.9)	0.82	98 (39.5)	93 (38.1)	0.75
Diabetes	147 (49.0)	163 (56.2)	0.0797	77 (31.0)	72 (29.5)	0.71
Atrial fibrillation	162 (54.0)	148 (51.0)	0.47	147 (59.3)	149 (61.1)	0.68
Myocardial infarction	229 (76.3)	213 (73.4)	0.42	0	0	NA
Angina pectoris	74 (24.7)	69 (23.8)	0.80	17 (6.9)	8 (3.3)	0.07
Stroke	29 (9.7)	44 (15.2)	0.0423	24 (9.7)	21 (8.6)	0.68
Coronary revascularisation,	195 (65.0)	206 (71.0)	0.12	0	0	NA
Chronic kidney disease	143 (47.7)	143 (49.3)	0.69	76 (30.6)	78 (32.0)	0.75
Systolic blood pressure, mm Hg	119.4 (15.64)	118.4 (15.45)	0.44	120.2 (14.44)	121.0 (15.65)	0.51
Diastolic blood pressure, mm Hg	71.7 (10.10)	70.0 (9.77)	0.043	73.7 (10.54)	74.0 (9.68)	0.75
Heart rate, beats per minute	72.4 (12.37)	72.0 (11.59)	0.68	77.0 (13.76)	76.5 (13.63)	0.67

New York Heart Association Classification, n (%)						
Class I	9 (3.0)	6 (2.1)	0.08	4 (1.6)	2 (0.8)	0.63
Class II	145 (48.3)	117 (40.3)		105 (42.3)	115 (47.1)	
Class III	139 (46.3)	151 (52.1)		131 (52.8)	119 (48.8)	
Class IV	7 (2.3)	15 (5.2)		7 (2.8)	6 (2.5)	
Left ventricular ejection fraction, %*	31.9 (9.4)	31.7 (9.9)	0.74	33.5 (9.8)	34.0 (9.7)	0.60
Left ventricular ejection fraction, n (%)						
<25%	59 (19.7)	70 (24.1)	0.0347	44 (17.7)	48 (19.7)	0.85
25% to <40%	167 (55.7)	130 (44.8)		114 (46.0)	108 (44.3)	
40% to <50%	74 (24.7)	89 (30.7)		90 (36.3)	88 (36.1)	
HF history, n (%)						
de novo at index hospitalisation	57 (19.0)	43 (14.8)	0.18	91 (36.7)	113 (46.3)	0.0304
Documented HF prior to index hospitalisation	243 (81.0)	247 (85.2)		157 (63.3)	131 (53.7)	
Non-ischaemic HF details, n (%)						
Hypertensive	NA	NA	NA	95 (38.3)	107 (43.9)	0.32
Valvular	NA	NA		42 (16.9)	46 (18.9)	
Idiopathic	NA	NA		74 (29.8)	55 (22.5)	
Congenital	NA	NA		3 (1.2)	1 (0.4)	
Other	NA	NA		34 (13.7)	35 (14.3)	
Pharmacotherapy, n (%)†						
ACEi	149 (49.7)	148 (51.0)	0.7397	137 (55.2)	124 (50.8)	0.3258
ARB	54 (18.0)	38 (13.1)	0.1012	42 (16.9)	57 (23.4)	0.0755
ARNI	22 (7.3)	24 (8.3)	0.6695	13 (5.2)	11 (4.5)	0.7056
Aldosterone antagonist	204 (68.0)	178 (61.4)	0.0924	166 (66.9)	167 (68.4)	0.7208
Beta blocker	244 (81.3)	242 (83.4)	0.5003	199 (80.2)	205 (84.0)	0.2747
Digitalis glycoside	43 (14.3)	49 (16.9)	0.3909	39 (15.7)	50 (20.5)	0.1697

Loop diuretic	265 (88.3)	250 (86.2)	0.4382	209 (84.3)	200 (82.0)	0.4945
Laboratory test results						
NT-pro-BNP, pg/mL, median (IQR)	5022 (2830; 8620)	4767 (2792; 9000)	0.89	4555 (2701; 7427)	4600 (2719; 7230)	0.52
Brain natriuretic peptide (pg/mL), median (IQR)	1197 (885; 1760)	1170 (807; 1701)	0.87	970 (628; 1386)	1217 (785; 2001)	0.13
Hb, g/dL	12.0 (1.6)	12.1 (1.56)	0.81	12.5 (1.5)	12.2 (1.7)	0.0488
Hb category, n (%)						
<10 g/dL	36 (12.0)	33 (11.4)	0.97	16 (6.5)	26 (10.7)	0.11
≥10 to ≤14 g/dL	228 (76.0)	222 (76.6)		183 (73.8)	183 (75.0)	
>14 g/dL	36 (12.0)	35 (12.1)		48 (19.4)	35 (14.3)	
Anaemia, n (%)	186 (62.0)	181 (62.4)	0.92	102 (41.3)	124 (50.8)	0.0343
Serum ferritin, ng/mL	86.7 (64.4)	89.7 (69.7)	0.58	79.4 (57.9)	86.7 (66.8)	0.20
Serum ferritin <100 ng/mL, n (%)	209 (69.7)	196 (67.6)	0.59	193 (77.8)	173 (70.9)	0.13
TSAT, %	14.8 (7.6)	13.6 (6.1)	0.0298	15.6 (9.1)	15.2 (8.8)	0.62
TSAT <20%, n (%)	249 (83.0)	258 (89.0)	0.0327	199 (80.2)	195 (79.9)	0.86
eGFR, <60 mL/min per 1.73m^2, n (%)	52.2 (20.2)	52.4 (21.6)	0.92	58.6 (21.8)	59.2 (24.0)	0.79
Phosphorus, mg/dL	3.7 (0.7)	3.7 (0.8)	0.32	3.7 (0.8)	4.0 (1.1)	0.0009

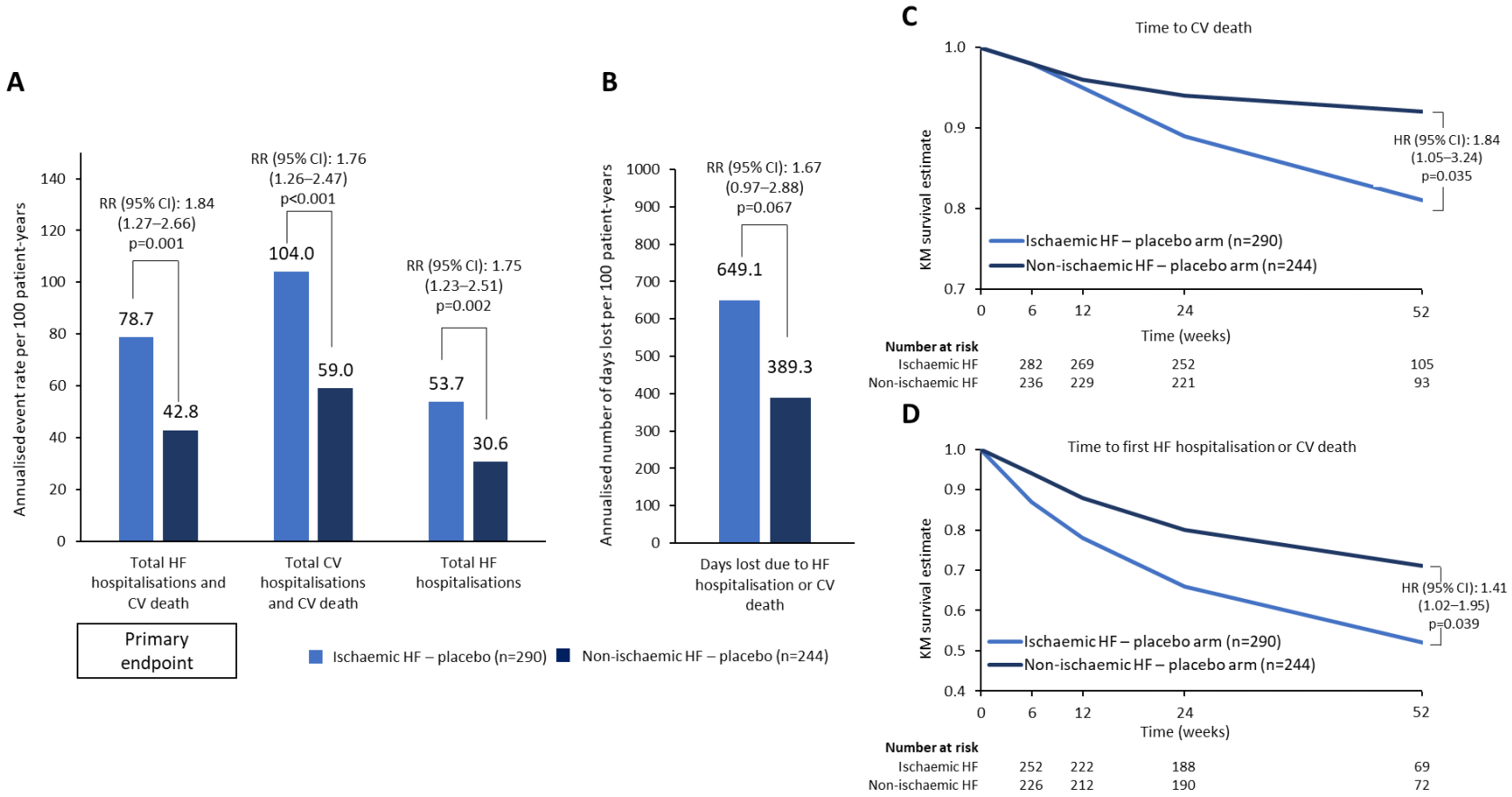
*Measured within 12 months prior screening. †Any medication that is current on the first day of study drug administration. Data are mean (standard deviation) unless otherwise specified. Percentages might not add to 100% due to rounding and are based on the number of subjects in mITT population with available data per treatment group. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; IQR, interquartile range; mITT, modified intention-to-treat; NA, not applicable; NT-pro-BNP, N-terminal-pro brain natriuretic peptide; TSAT, transferrin saturation.

Supplementary Table 2. Treatment-emergent adverse events by MedDRA system organ class (safety analysis set)

	Ischaemic HF (N=592)				Non-ischaemic HF (N=492)			
Treatment-emergent adverse event	**FCM (n=301)**		**Placebo (n=291)**		**FCM (n=248)**		**Placebo (n=244)**	
	Subjects n (%)	**Adjusted incidence rate**	**Subjects n (%)**	**Adjusted incidence rate**	**Subjects n (%)**	**Adjusted incidence rate**	**Subjects n (%)**	**Adjusted incidence rate**
Cardiac disorders	138 (45.8)	0.525	158 (54.3)	0.623	83 (33.5)	0.382	80 (32.8)	0.359
Infections and infestations	64 (21.3)	0.243	77 (26.5)	0.304	34 (13.7)	0.156	42 (17.2)	0.188
Gastrointestinal disorders	42 (14.0)	0.160	44 (15.1)	0.173	22 (8.9)	0.101	14 (5.7)	0.063
Diarrhoea	14 (4.7)	0.053	10 (3.4)	0.039	3 (1.2)	0.014	4 (1.6)	0.018
Constipation	4 (1.3)	0.015	9 (3.1)	0.035	6 (2.4)	0.028	1 (0.4)	0.004
Metabolism and nutrition disorders	30 (10.0)	0.114	32 (11.0)	0.126	14 (5.6)	0.064	23 (9.4)	0.103
Hypophosphataemia	1 (0.3)	0.004	1 (0.3)	0.004	0	0	0	0
Musculoskeletal and connective tissue disorders	16 (5.3)	0.061	17 (5.8)	0.067	7 (2.8)	0.032	11 (4.5)	0.049
Skin and subcutaneous tissue disorders	10 (3.3)	0.038	6 (2.1)	0.024	3 (1.2)	0.014	6 (2.5)	0.027
Pruritus	3 (1.0)	0.011	1 (0.3)	0.004	0	0	2 (0.8)	0.009
Rash	2 (0.7)	0.008	0	0	0	0	2 (0.8)	0.009
Urticaria	1 (0.3)	0.004	1 (0.3)	0.004	0	0	0	0
Immune system disorders	2 (0.7)	0.008	1 (0.3)	0.004	1 (0.4)	0.005	0	0
Drug hypersensitivity	2 (0.7)	0.008	0	0	0	0	0	0
Hypersensitivity	0	0	1 (0.3)	0.004	0	0	0	0

FCM, ferric carboxymaltose; MeDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

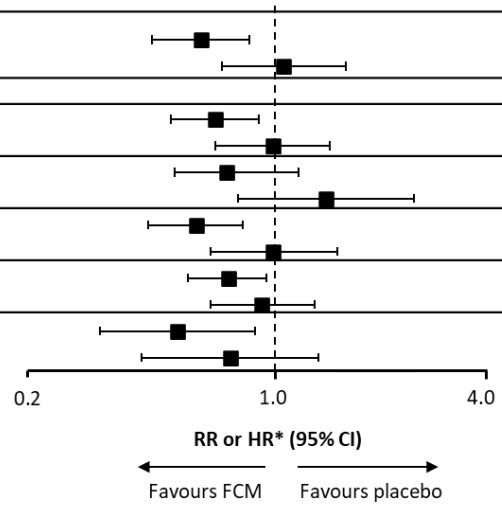
Supplementary Figure 1: (A) Annualised event rate per 100 patient-years for recurrent event-based primary and secondary outcomes; (B) annualised days lost per 100 patient-years; (C) Kaplan–Meier estimates for time to CV death; and (D) Kaplan–Meier estimates for time to first hospitalisation or death in the placebo arms of ischaemic vs non-ischaemic HF aetiology subgroups (mITT population)



Annualised event RR for ischaemic HF vs non-ischaemic HF subgroups analysed using a negative binomial model. HR for ischaemic vs non-ischaemic HF subgroups analysed using Cox regression model. Both models were adjusted for the following baseline covariates: sex, age, HF history, region and subgroup of ischaemic aetiology of HF. Respective n values for patients with ischaemic vs non-ischaemic HF at baseline assigned to the placebo arm were 290 and 244. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio; KM, Kaplan–Meier; mITT, modified intention-to-treat; RR, rate ratio.

Supplementary Figure 2. Primary and secondary outcomes at week 52 with FCM vs placebo by HF aetiology: COVID-19 sensitivity analysis

	Subgroup	Annualised event rate per 100 patient-years: FCM	Placebo	RR or HR* [95% CI]	p-value	$p_{interaction}$
Primary outcome						
Total HF hospitalisations and CV death	Ischaemic HF	63.1†	101.8†	0.62 (0.45–0.85)†	0.003	0.039
	Non-ischaemic HF	58.5†	55.1†	1.06 (0.71–1.59)†	0.77	
Secondary outcomes						
Total CV hospitalisations and CV death	Ischaemic HF	85.2†	126.0†	0.68 (0.51-0.90)†	0.008	0.12
	Non-ischaemic HF	71.7†	72.7†	0.99 (0.68–1.43)†	0.95	
Time to CV death	Ischaemic HF	14.3§	18.3§	0.78 (0.52–1.17)‡	0.23	0. 11
	Non-ischaemic HF	11.7§	8.2§	1.40 (0.79–2.48)‡	0.26	
Total HF hospitalisations	Ischaemic HF	40.4†	67.8†	0.60 (0.44–0.81)†	<0.001	0.05
	Non-ischaemic HF	34.9†	35.1†	0.99 (0.66–1.50)†	0.98	
Time to first HF hospitalisation or CV death	Ischaemic HF	35.7§	45.9§	0.74 (0.57–0.95)‡	0.02	0.31
	Non-ischaemic HF	26.6§	27.5§	0.92 (0.66–1.30)‡	0.65	
Days lost due to HF hospitalisation and CV death	Ischaemic HF	504.7†	950.2†	0.53 (0.32–0.88)†	0.014	0.38
	Non-ischaemic HF	387.9†	516.9†	0.75 (0.42–1.33)†	0.32	

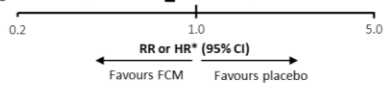


*RR or HR for FCM versus placebo in each subgroup. †Annualised event rate per 100 person-years and RR analysed using a negative binomial model. ‡HR for treatment difference analysed using Cox regression model. §Percentage of subjects with (at least one) event. Negative binomial model and Cox regression model were adjusted for baseline covariates: sex, age, HF aetiology, HF duration, country, and included interaction between treatment group and HF aetiology. Respective n values for patients with ischaemic and non-ischaemic HF at baseline were 300 and 248 for FCM and 290 and 244 for placebo. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio; mITT, modified intention-to-treat; RR, rate ratio.

Supplementary Figure 3: (A) Primary and secondary outcomes at week 52 and (B) QoL outcomes at week 24, according to HF aetiology and history of HF (mITT population)

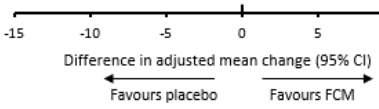
A

	Subgroup	Number of events: FCM	Number of events: Placebo	Annualised event rate per 100 patient-years: FCM	Annualised event rate per 100 patient-years: Placebo	RR or HR* [95% CI]	p-value	$p_{interaction}$
Primary outcome								
Total HF hospitalisations and CV death	Ischaemic HF + *de novo* HF	27	16	70.02†	55.88†	1.25 (0.52–3.03)†	0.62	0.10
	Ischaemic HF + history of HF	157	256	98.01†	165.76†	0.59 (0.42–0.83)†	0.002	
	Non-ischaemic HF + *de novo* HF	16	19	22.84†	24.10†	0.95 (0.43–2.08)†	0.89	
	Non-ischaemic HF + history of HF	91	74	105.62†	92.67†	1.14 (0.71–1.84)†	0. 59	
Total CV hospitalisations and CV death	Ischaemic HF + *de novo* HF	36	20	91.63†	70.85†	1.29 (0.58–2.90)†	0.53	0. 16
	Ischaemic HF + history of HF	204	304	121.42†	189.46†	0.64 (0.47–0.87)†	0.005	
	Non-ischaemic HF + *de novo* HF	23	28	32.58†	37.47†	0.87 (0.44–1.71)†	0.69	
	Non-ischaemic HF + history of HF	103	88	117.59†	108.28†	1.09 (0.70–1.69)†	0.72	
Time to CV death	Ischaemic HF + *de novo* HF	8	4	14.0§	9.3§	1.37 (0.41–4.60)‡	0.61	0. 39
	Ischaemic HF + history of HF	39	51	16.0§	20.6§	0.77 (0.51–1.17)‡	0.22	
	Non-ischaemic HF + *de novo* HF	4	4	4.4§	3.5§	1.08 (0.27–4.31)‡	0.92	
	Non-ischaemic HF + history of HF	25	16	15.9§	12.2§	1.44 (0.77–2.72)‡	0.26	
Total HF hospitalisations	Ischaemic HF + *de novo* HF	19	12	40.33†	33.48†	1.20 (0.49–2.95)†	0.68	0.10
	Ischaemic HF + history of HF	119	205	61.27†	107.92†	0.57 (0.41–0.78)†	<0.001	
	Non-ischaemic HF + *de novo* HF	12	15	15.43†	15.85†	0.97 (0.42–2.24)†	0.95	
	Non-ischaemic HF + history of HF	66	58	59.17†	56.49†	1.05 (0.66–1.67)†	0.85	
Time to first HF hospitalisation or CV death	Ischaemic HF + *de novo* HF	18	13	31.6§	30.2§	1.01 (0.49–2.08)‡	0.97	0.60
	Ischaemic HF + history of HF	92	123	37.9§	49.8§	0.71 (0.54–0.93)‡	0.013	
	Non-ischaemic HF + *de novo* HF	12	16	13.2§	14.2§	0.91 (0.43–1.93)‡	0.81	
	Non-ischaemic HF + history of HF	57	52	36.3§	39.7§	0.93 (0.64–1.36)‡	0.70	
Days lost due to HF hospitalisation and CV death	Ischaemic HF + *de novo* HF	3.6¶	2.7¶	535.5†	467.1†	1.15 (0.32–4.08)†	0.83	0.59
	Ischaemic HF + history of HF	5.1¶	10.1¶	886.8†	1800.7†	0.49 (0.28–0.86)†	0.012	
	Non-ischaemic HF + *de novo* HF	1.0¶	1.1¶	121.4†	165.1†	0. 74 (0.30–1.81)†	0.51	
	Non-ischaemic HF + history of HF	3.8¶	4.7¶	801.4†	1016.3†	0.79 (0.38–1.64)†	0.52	



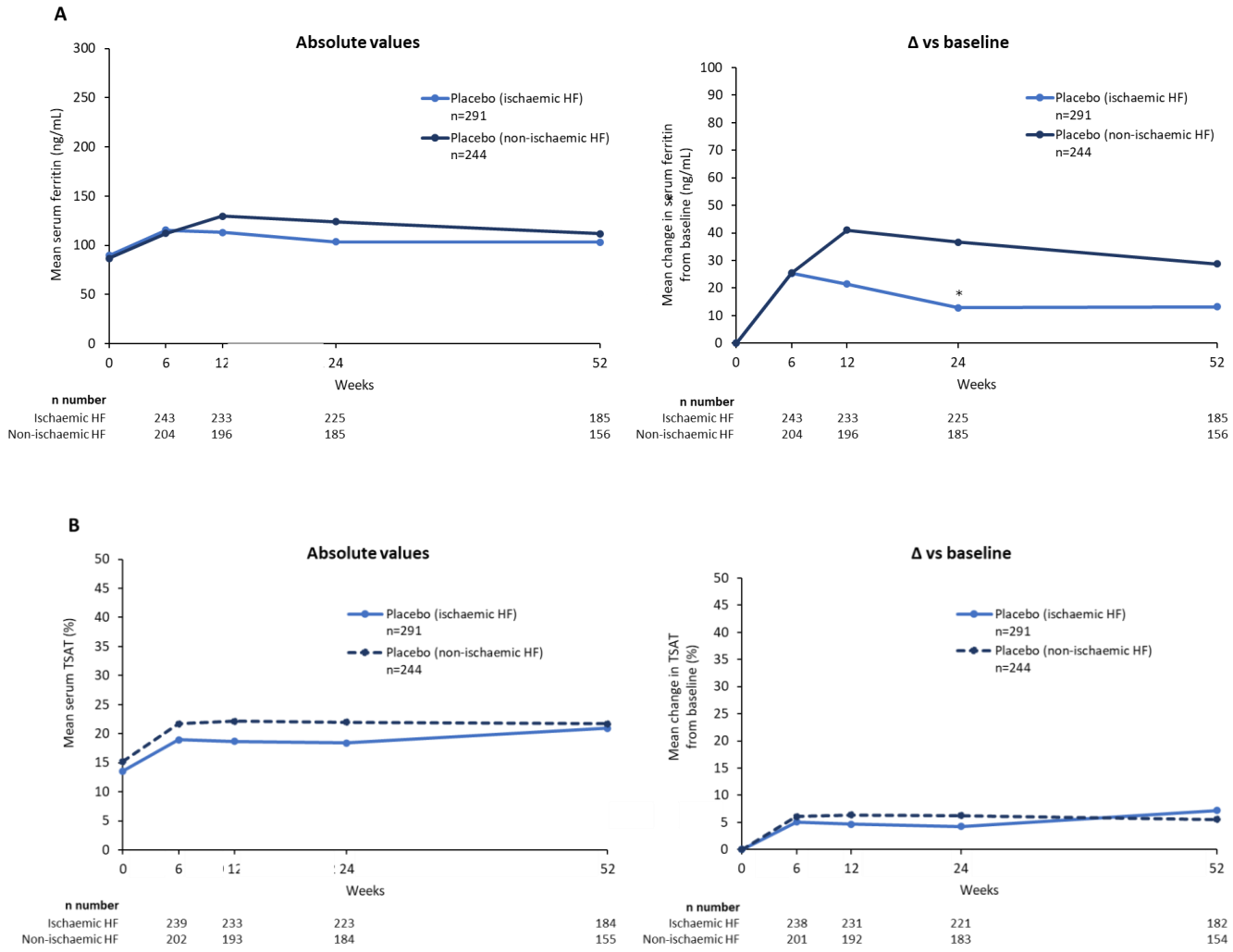
B

	Subgroup	FCM (n/N)	Placebo (n/N)	Difference in adjusted mean change (95% CI)	p-value	$p_{interaction}$
KCCQ-12 OSS	Ischaemic HF + *de novo* HF	44/57	31/43	-5.11 (-14.10; 3.87)	0.264	0.09
	Ischaemic HF + history of HF	189/243	190/247	5.28 (1.34; 9.22)	0.009	
	Non-ischaemic HF + *de novo* HF	68/91	87/113	0.16 (-6.01; 6.32)	0.960	
	Non-ischaemic HF + history of HF	114/157	97/131	5.06 (-0.21; 10.34)	0.060	
KCCQ-12 CSS	Ischaemic HF + *de novo* HF	44/57	31/43	-5.45 (-14.52; 3.62)	0.239	0.20
	Ischaemic HF + history of HF	188/243	190/247	5.04 (1.06; 9.03)	0.013	
	Non-ischaemic HF + *de novo* HF	68/91	87/113	2.02 (-4.20; 8.24)	0.525	
	Non-ischaemic HF + history of HF	114/157	97/131	3.84 (-1.48; 9.16)	0.157	



*RR or HR for FCM versus placebo in each subgroup. †Annualised event rate per 100 person-years and RR analysed using a negative binomial model. ‡HR for treatment difference analysed using Cox regression model. §Percentage of subjects with (at least one) event. ¶Data point is mean number of days lost per subject. Negative binomial model was adjusted for baseline covariates: sex, age, country, subgroup of HF aetiology and HF history at baseline and subgroup of HF aetiology and HF history at baseline x treatment. Cox regression model was adjusted for baseline covariates: sex, age, country, subgroup of HF aetiology and HF history at baseline and interaction between treatment group and subgroup of HF aetiology and HF history at baseline. Respective n values for the FCM and placebo arms within the different subgroups were as follows: 57 and 43 in ischaemic HF + *de novo* HF patients; 243 and 247 in ischaemic HF + documented history of HF patients; 91 and 113 in non-ischaemic HF + *de novo* HF patients; 157 and 131 in non-ischaemic HF + documented history of HF patients. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio; mITT, modified intention-to-treat; RR, rate ratio.

Supplementary Figure 4: Absolute values and mean change from baseline to week 52 in (A) serum ferritin and (B) transferrin saturation in the placebo arm of ischaemic and non-ischaemic HF subgroups



*p<0.05 for ischaemic vs non-ischaemic subgroups at timepoint indicated. FCM, ferric carboxymaltose; HF, heart failure; TSAT, transferrin saturation.