Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure (EFFECT-HF)

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for the EFFECT-HF Investigators.

Sponsor: Vifor Pharma Ltd.

Conflict of interests / disclosures

- Prof. van Veldhuisen has received Board Membership Fees and Travel Expenses from Vifor Pharma Ltd.

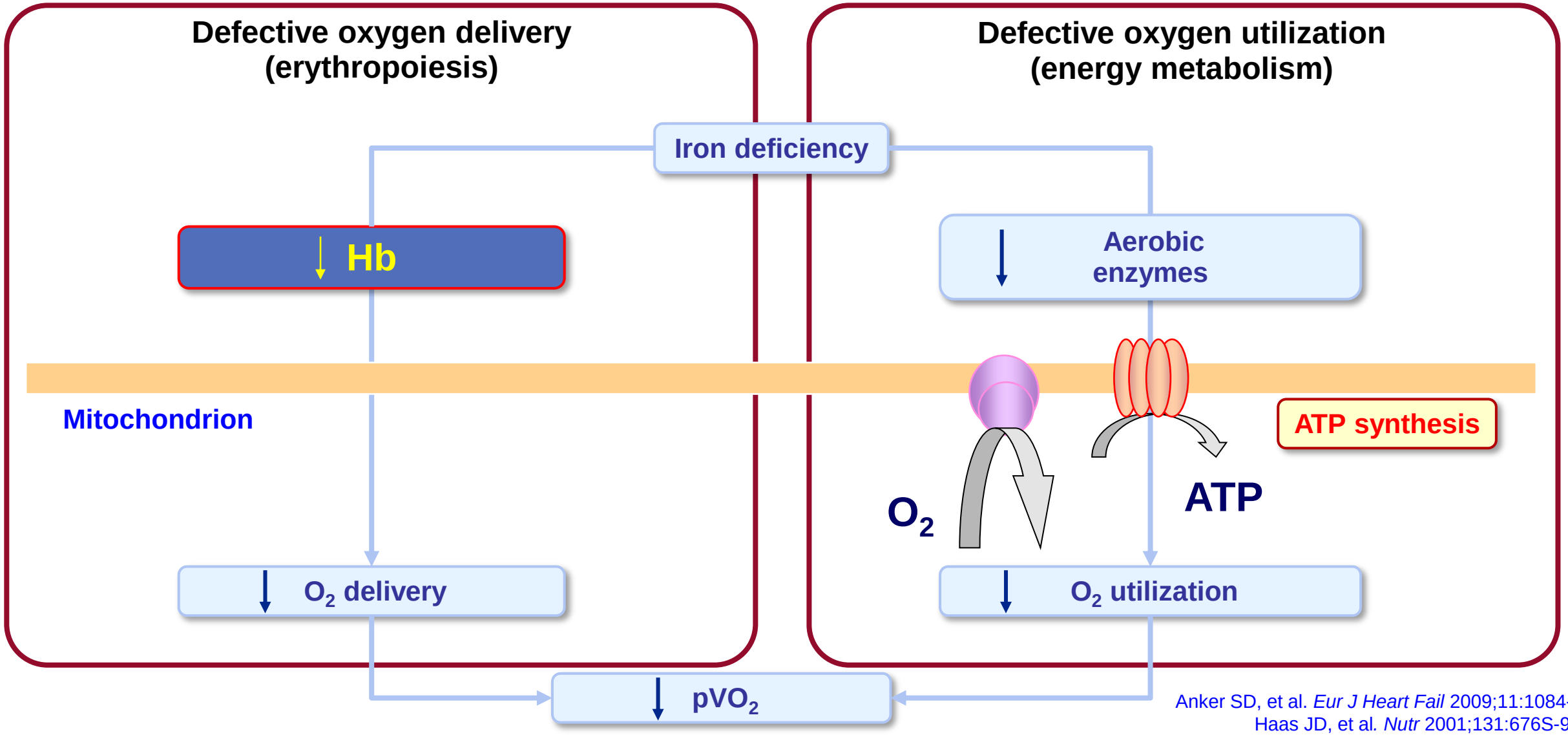
Iron deficiency:
A therapeutic target in heart failure?

- Iron deficiency – frequent co-morbidity in stable HF and in patients admitted to hospital due to HF worsening[1,2]
- HF complicated with iron deficiency – associated with impaired functional capacity, poor quality of life and increased mortality[1,3,4]
- Deleterious consequences of iron deficiency in HF irrespective of anaemia[1,3,4]
- **Iron deficiency: a therapeutic target in HF**[5,6]

HF, heart failure

1. Klip IT, et al. *Am Heart J* 2013;165:575-82.
2. Jankowska EA, et al. *Eur Heart J* 2014;35:2468-76.
3. Jankowska EA, et al. *J Cardiac Fail* 2011;17:899-906.
4. Enjuanes C, et al. *Int J Cardiol* 2014;174:268-75.
5. Anker SD, et al. *N Engl J Med* 2009;361:2436-48.
6. Ponikowski P, et al. *Eur Heart J* 2015;36:657-68.

Dual effects of iron deficiency in HF: Defective oxygen delivery and utilization



Anker SD, et al. *Eur J Heart Fail* 2009;11:1084-91.
Haas JD, et al. *Nutr* 2001;131:676S-90S.
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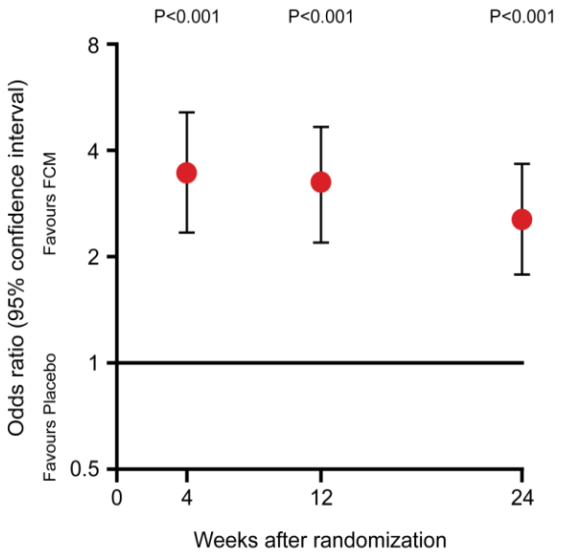
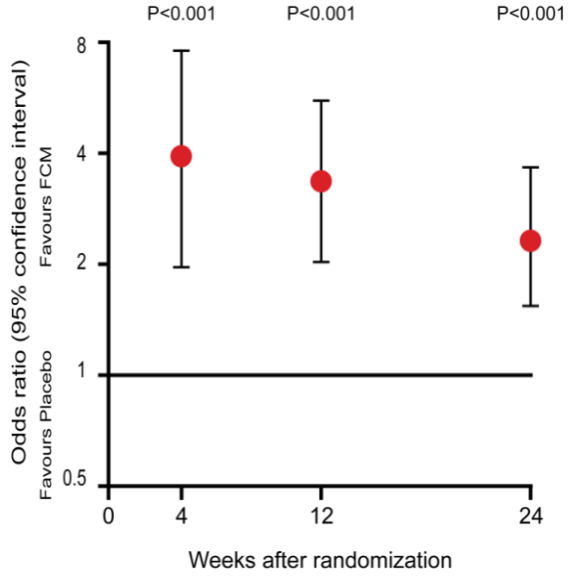
Benefits of ferric carboxymaltose in CHF: FAIR-HF and CONFIRM-HF studies

FAIR-HF[1]

Patient Global Assessment

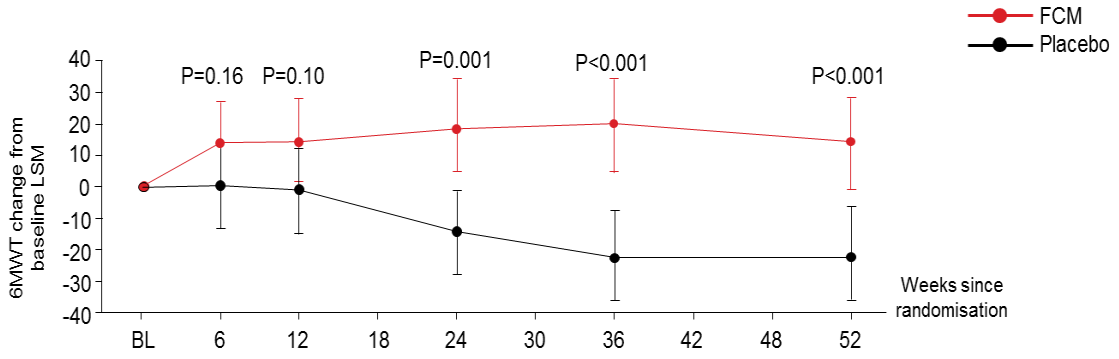


NYHA functional class



CONFIRM-HF[2]

6MWT



CHF, chronic heart failure; FCM, ferric carboxymaltose; NYHA, New York Heart Association; 6MWT, 6 minute walk test

1. Anker SD, et al. *N Engl J Med* 2009;361:2436-48.
2. Ponikowski P, et al. *Eur Heart J* 2015;36:657-68.

Rationale for EFFECT-HF

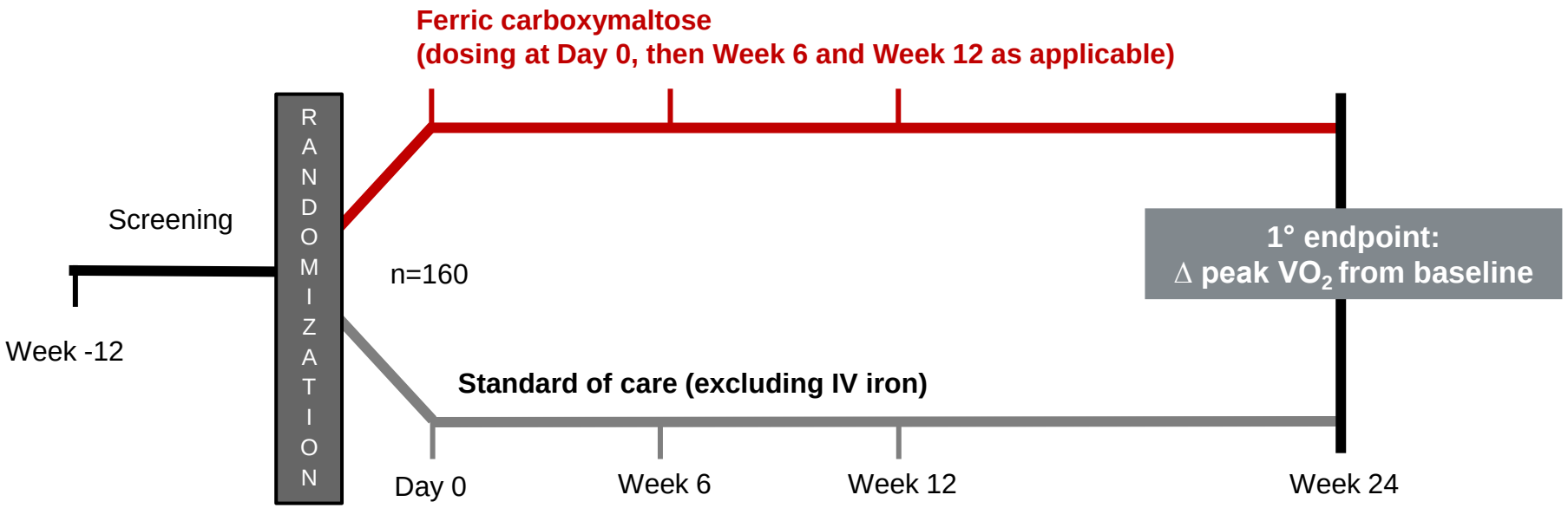
- Exercise intolerance (dyspnea and fatigue) is a key symptom of HF[1]
- Cardiopulmonary exercise testing defines maximum exercise capacity through peak oxygen uptake (peak VO_2)[1]
- Peak VO_2 is an important predictor of prognosis in HF, is objective, reproducible, and used to evaluate cardiac transplantation and LVAD[2]
- Even a modest increase in peak VO_2 has been associated with a more favorable outcome in HF patients[2]

HF, heart failure; LVAD, left ventricular assist device; NYHA, New York Heart Association

1. Malhotra R, et al. *JACC Heart Fail* 2016;4:607-16.
2. Swank AM, et al. *Circ Heart Fail* 2012;5:579-585.

EFFECT-HF: Study design

- **Design:** Multicenter, open label, randomized (1:1), assessor-blinded, standard of care-controlled
- **Main inclusion criteria**
  - ✓ NYHA class II/III
  - ✓ LVEF ≤45%
  - ✓ Peak VO_2 10-20 mL/kg/min (reproducible)
  - ✓ BNP >100 pg/mL and/or NT-proBNP >400 pg/mL
  - ✓ Iron deficiency: serum ferritin <100 µg/L OR 100–300 µg/L if TSAT <20%
  - ✓ Hb <15 g/dL



ClinicalTrials.gov identifier: NCT01394562

Primary and key secondary endpoints

- Primary endpoint
  - Change in weight-adjusted peak VO_2 from baseline to Week 24

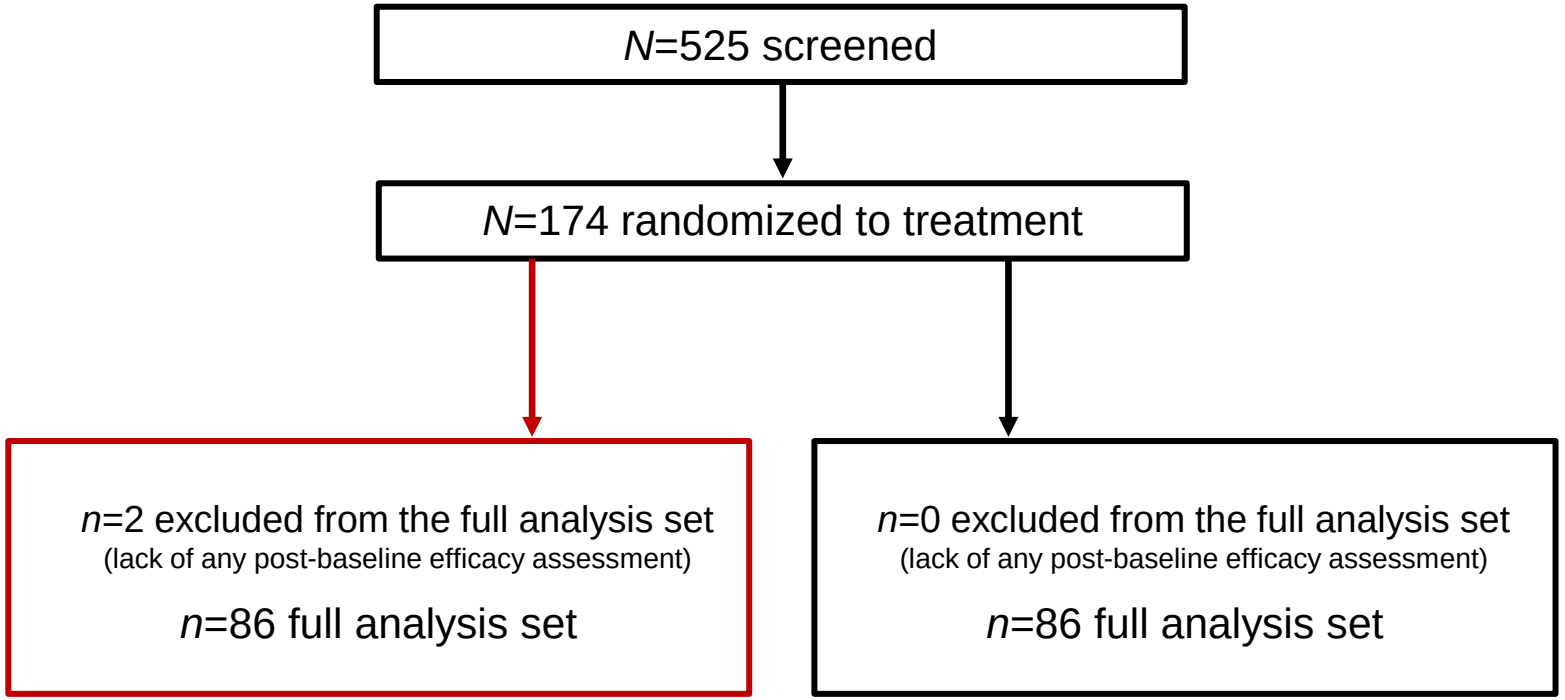
- Key secondary endpoints
  - Change in peak VO_2 (mL/kg/min) from baseline to Week 12
  - Change in VE-VCO_2 slope from baseline to Weeks 12 and 24
  - Change in work rate achieved at peak exercise from baseline to Weeks 12 and 24
  - Change in biomarkers for iron deficiency, renal function, cardiac function (including BNP and NT-proBNP), NYHA functional class, PGA and QoL
  - Safety over the treatment period

BNP, brain natriuretic peptide; NYHA, New York Heart Association; PGA, patient global asessment; QoL, quality of life

Statistical methods

- The primary efficacy analysis was an intention-to-treat analysis which modeled the effect of treatment using an analysis of covariance (ANCOVA) adjusted for baseline peak VO_2, hemoglobin level at screening (<12 g/dL or ≥12g/dL) and country
  - This analysis was performed on data for the full analysis set (FAS), which consisted of all randomized patients who received ≥1 dose of study treatment and for whom ≥1 post-baseline assessment was available
  - Missing peak VO_2 values were imputed using last observation carried forward (LOCF) for subjects who were known to be alive at the time of assessment
- The safety analysis was performed on the safety population, which consisted of all randomized subjects who received ≥1 dose of study medication
- In addition, a per-protocol analysis was also performed. The per-protocol set (PPS) was defined as all subjects in the FAS who had no major protocol deviations

Patient disposition



Country (*N*=9)	No. of study sites (*N*=41)	Patients randomized (*N*=174)
Australia	3 sites	*n*=4
Belgium	1 site	*n*=8
France	2 sites	*n*=10
Germany	3 sites	*n*=24
Italy	4 sites	*n*=18
Netherlands	2 sites	*n*=22
Poland	1 site	*n*=36
Russia	10 sites	*n*=42
Spain	2 sites	*n*=10

Baseline characteristics – (1/2)

	FCM (N=86)	SoC (N=86)
Age *years**	62.7 (11.56)	64.4 (11.42)
Female *n (%)*	26 (30.2)	17 (19.8)
NYHA class		
II *n (%)*	61 (70.9)	54 (62.8)
III *n (%)*	25 (29.1)	32 (37.2)
LVEF *%**	32.5 (8.7)	31.0 (7.5)
Ischemic etiology *n (%)*	60 (69.8)	64 (74.4)
Peak VO_2 *ml/min/kg**	13.55 (2.28)	13.36 (2.42)
Medical history		
Hypertension *n (%)*	62 (72.1)	56 (65.1)
Atrial fibrillation *n (%)*	35 (40.7)	41 (47.7)
Diabetes mellitus *n (%)*	26 (30.2)	32 (37.2)
Myocardial infarction *n (%)*	58 (67.4)	55 (64.0)

*mean (standard deviation)

FCM, ferric carboxymaltose; SoC, standard of care

Baseline characteristics – (2/2)

	FCM (N=86)	SoC (N=86)
Concomitant medications		
Diuretics *n (%)*	80 (93.0)	82 (95.3)
ACEi/ARB *n (%)*	81 (94.2)	77 (89.5)
Beta-blocker *n (%)*	84 (97.7)	84 (97.7)
Aldosterone antagonists (MRA) *n (%)*	58 (67.4)	62 (72.1)
Laboratory parameters		
BNP *pg/mL**	838 (762)	796 (819)
NT-proBNP *pg/mL**	2631 (3141)	2415 (2592)
Estimated GFR *mL/min/1.73m^2**	51.5 (13.3)	50.8 (12.3)
Hb *g/dL* *	12.93 (1.30)	12.99 (1.46)
Ferritin *ng/mL**	62.06 (60.64)	64.72 (51.44)
<100 ng/mL n (%)	74 (86.0)	71 (82.6)
TSAT *%* *	19.65 (13.71)	20.07 (9.63)
<20% n (%)	53 (61.6)	46 (53.5)
sTfR *mg/L**	4.77 (2.44)	4.52 (2.35)
hsCRP *mg/L*°*	5.67 (12.20)	3.17 (5.44)

*mean (standard deviation); ° p-value=0.03

FCM, ferric carboxymaltose; SoC, standard of care

Results: Iron-related parameters: Change from baseline to Week 24

	FCM (N=86)		SoC (N=86)		Contrast: FCM – SoC**	
Parameter	Baseline	Week 24	Baseline	Week 24	Change from baseline	*P*-value
Ferritin *ng/mL**	62.06 (60.64)	283.17 (150.28)	64.72 (51.44)	92.31 (65.43)	188.7 (17.27)	0.0001
TSAT *%**	19.65 (13.71)	26.54 (8.25)	20.07 (9.63)	21.90 (10.17)	4.7 (1.35)	0.0007
Hb *g/dL**	12.93 (1.30)	13.90 (1.30)	12.99 (1.46)	13.19 (1.47)	0.74 (0.17)	<0.0001
sTfR *mg/L**	4.77 (2.44)	3.56 (1.45)	4.52 (2.35)	4.45 (2.49)	-1.01 (0.26)	0.0002

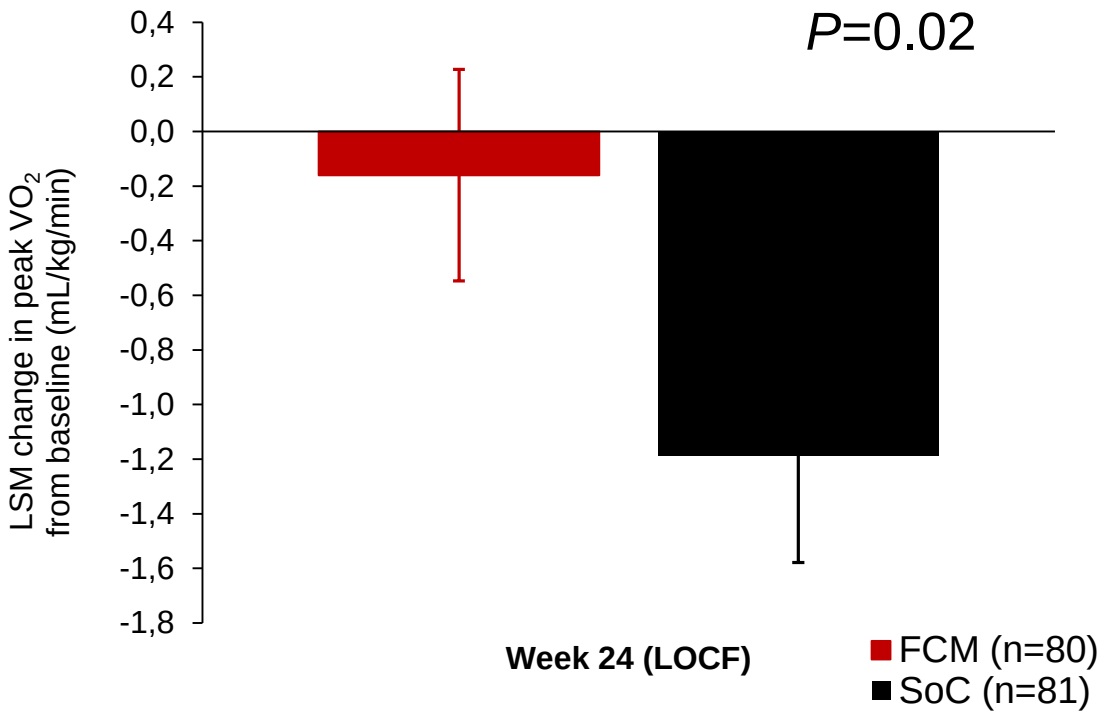
*mean (standard deviation); **least squares means (standard error)

FCM, ferric carboxymaltose; SoC, standard of care

Primary endpoint analysis: Change in peak VO_2 from baseline to Week 24

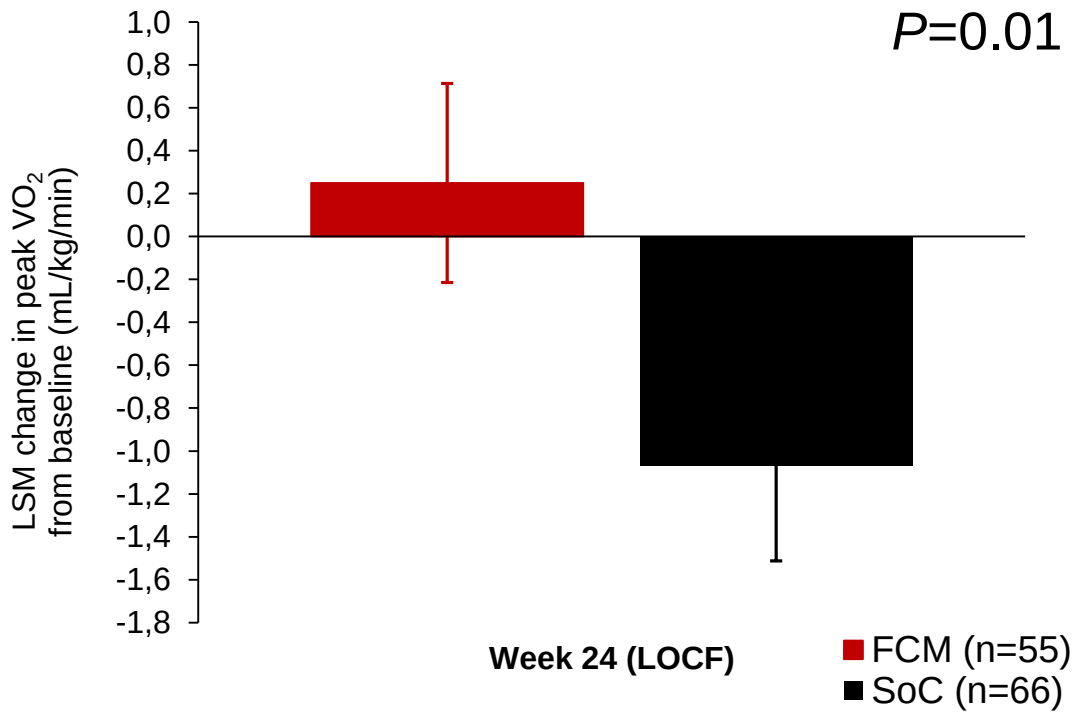
Full analysis set (N=172)

Contrast FCM vs placebo for Δ pVO_2:
LS means ± SE difference of 1.04 ± 0.44 mL/kg/min
(95% CI: 0.164, 1.909)



Per-protocol set (N=146)*

Contrast FCM vs placebo for Δ pVO_2:
LS means ± SE difference of 1.32 ± 0.51 mL/kg/min
(95% CI: 0.306, 2.330)



No significant interaction when adjusted to baseline Hb <12 g/dL or > 12 g/dL

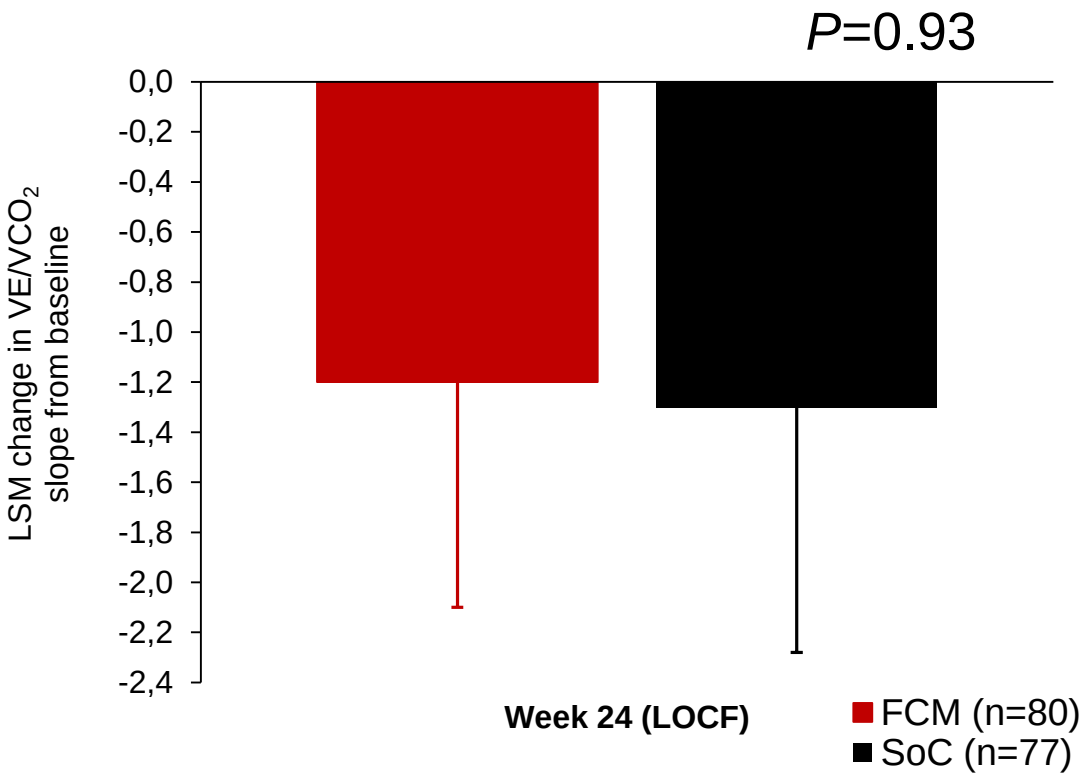
*population consisted of all subjects who, in addition to the full analysis set criteria, had no major protocol violations.

FCM, ferric carboxymaltose; LOCF, last observation carried forward; LSM, least-square means

Secondary endpoints: VE/VCO_2 slope and peak work rate

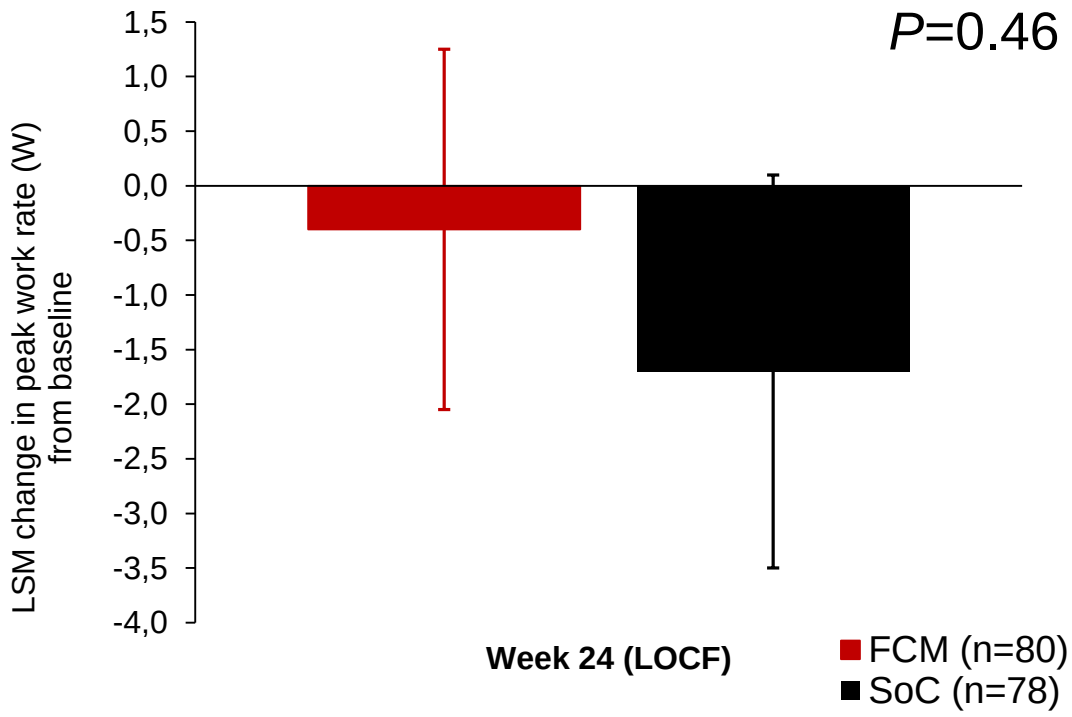
VE/VCO_2 slope

Contrast FCM vs placebo for VE/VCO_2 slope:
LS means ± SE difference of 0.1 ± 1.02
(95% CI: -1.93, 2.11)



Peak work rate (W)

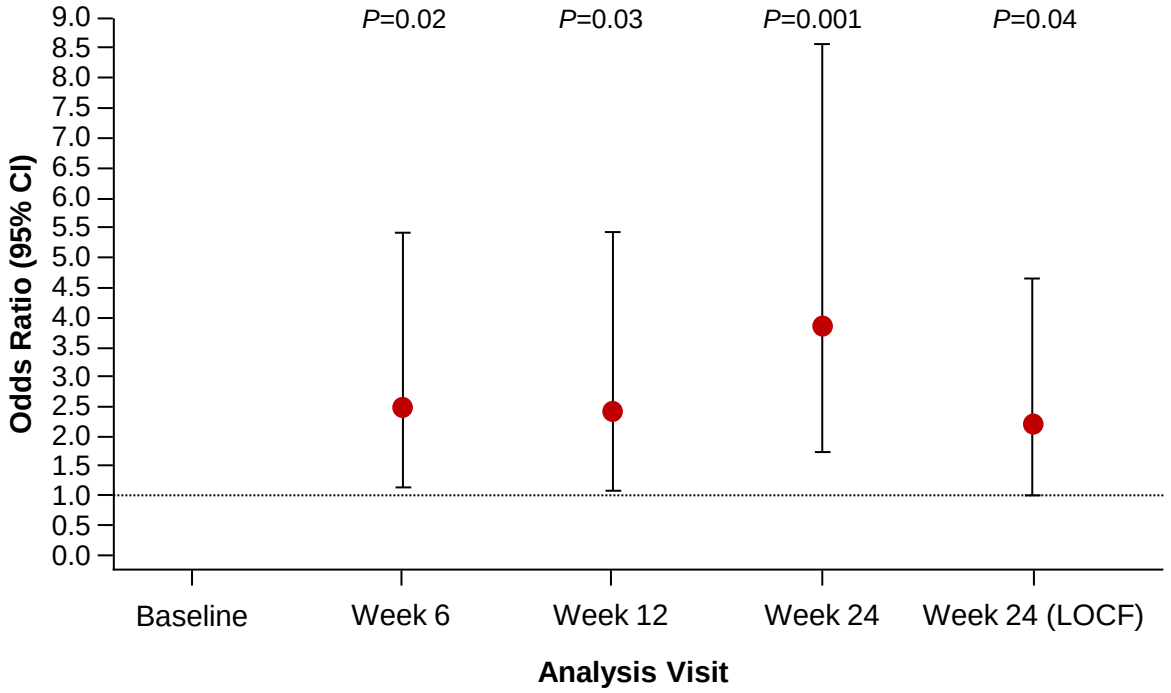
Contrast FCM vs placebo for Δ peak work rate:
LS means ± SE difference of 1.3 ± 1.80
(95% CI: -2.22, 4.88)



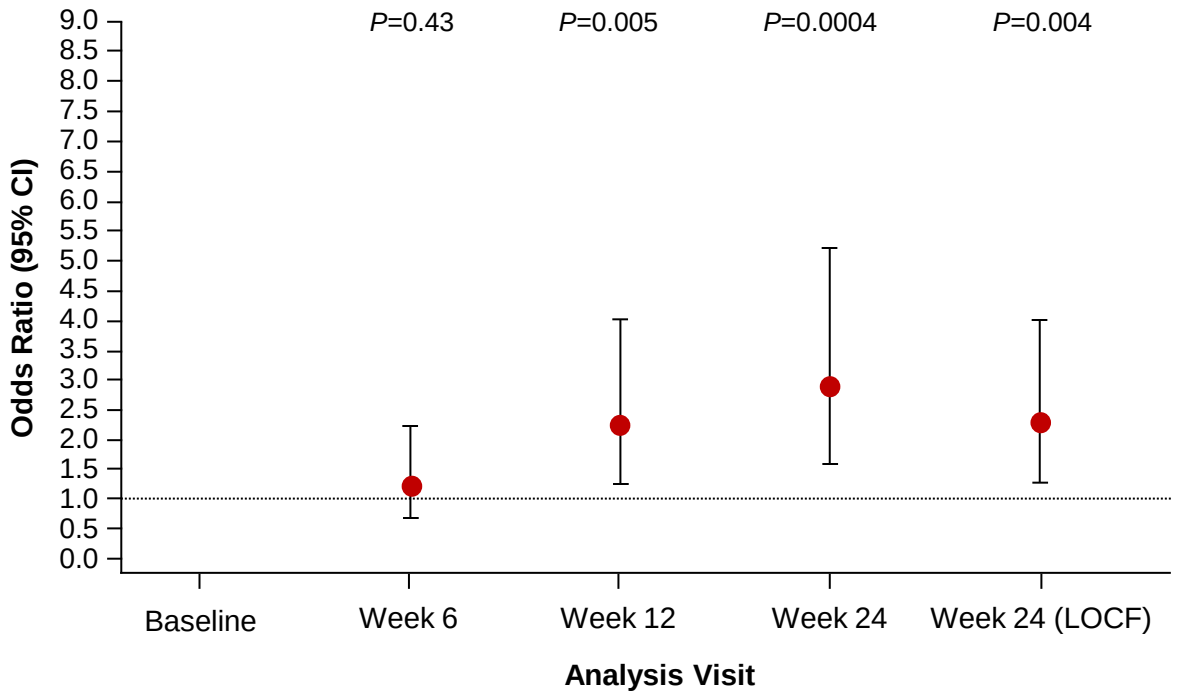
FCM, ferric carboxymaltose; LOCF, last observation carried forward; LSM, least-square means; VE/VCO_2, minute ventilation/carbon dioxide production

Secondary endpoints: Changes in PGA and NYHA class

New York Heart Association Functional (NYHA) class



Self-reported Patient Global Assessment (PGA) score



CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward

Hospitalizations and deaths (safety population)

Event description	FCM (N=88) n (%) E	SoC (N=85) n (%) E	Total (N=173) n (%) E
Any hospitalization	27 (30.7) 37	13 (15.3) 21	40 (23.1) 58
Death	0	4 (4.7) 4	4 (2.3) 4
Reason for hospitalization	27 (30.7) 37	13 (15.3) 21	40 (23.1) 58
Due to worsening of CHF	11 (12.5) 13	6 (7.1) 13	17 (9.8) 26
Due to other cardiovascular-related event	12 (13.6) 13	3 (3.5) 3	15 (8.7) 16
Due to a non-cardiovascular event	9 (10.2) 11	4 (4.7) 4	13 (7.5) 15
Due to a serious drug reaction	0	0	0
Unknown (insufficient data to adjudicate)	0	1 (1.2) 1	1 (0.6) 1

CHF, chronic heart failure; E, events; FCM, ferric carboxymaltose; SoC, standard of care; n, number of patients.
There was an additional death in the SoC arm; the subject died after completion of the study

Summary of treatment-emergent adverse events (safety population)

Parameter	FCM (N=88) n (%) E	SoC (N=85) n (%) E	Total (N=173) n (%) E
Any AE	53 (60.2) 158	41 (48.2) 117	94 (54.3) 275
Any severe AE	13 (14.8) 19	8 (9.4) 15	21 (12.1) 34
Any serious AE	28 (31.8) 45	16 (18.8) 28	44 (25.4) 73
Any AE leading to study drug withdrawal	2 (2.3) 2	5 (5.9) 5	7 (4.0) 7
Any AE with outcome of death	0 0	5 (5.9) 5	5 (2.9) 5
Any treatment-related AE	8 (9.1) 10	0 0	8 (4.6) 10
Any severe treatment-related AE	3 (3.4) 3	0 0	3 (1.7) 3
Any serious treatment-related AE	0 0	0 0	0 0
Any treatment-related AE leading to study drug withdrawal	0 0	0 0	0 0
Any treatment-related AE with outcome of death	0 0	0 0	0 0

Mean treatment dose of FCM=1204 mg (96% of the patients received a maximum of 2 injections). No serious hypersensitivity reactions and no hypophosphatemia were observed. Any treatment-related AEs are as expected for FCM. All severe treatment-related AEs were overdose without AEs reported

AE, adverse event; E, events; FCM, ferric carboxymaltose; SoC, standard of care

Conclusions

- In symptomatic patients with HF and iron deficiency, treatment with IV ferric carboxymaltose over a 6-month period resulted in:
  - A significant improvement in peak VO_2 compared with the SoC arm with or without anemia
- These findings confirm and extend the results of previous studies (FAIR-HF[1] and CONFIRM-HF[2]) that treatment with ferric carboxymaltose improves exercise capacity and symptoms
  - Ferric carboxymaltose was well tolerated in this patient population

SoC, standard of care

1. Anker SD, et al. *N Engl J Med* 2009;361:2436-48.
2. Ponikowski P, et al. *Eur Heart J* 2015;36:657-68.