Clinical data update and options for iron replacement

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Conflict of interest: Received honorarium from Novartis, Vifor, MSD, Servier, Medtronic, Astra Zeneca

Vifor Pharma UK have fully funded this meeting, including the honoraria for the chair and speakers and have contributed to the design of the agenda. The case studies, slides and clinical content are the speaker's own.

Job code: UK-NP-1800005 Date of Preparation: September 2018

Iron replacement therapy for heart failure

- New guidelines
- Existing trial data
- New and ongoing trials

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK),

ESC, European Society of Cardiology; HF, heart failure

Ponikowski P et al. Eur Heart J. 2016;37:2129−2200.

ESC GUIDELINES HF 2016 RECOMMEND SCREENING ALL PATIENTS WITH NEWLY DIAGNOSED HF FOR IRON DEFICIENCY

Guidelines recommend measurement of ferritin and TSAT for initial assessment of iron status (Class I, Level C evidence)[1]

Cut-off values for iron deficiency based on FAIR-HF[2] and CONFIRM-HF[3] studies:

- Serum **ferritin <100 µg/L**, or
- Serum **ferritin 100–299 µg/L**, when **TSAT <20%**

Recommendations	Class [a]	Level [b]
The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:		
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C
- natriuretic peptides	IIa	C

Ponikowski P et al. Eur Heart J. 2016;37:2129−2200.

ESC GUIDELINES ON HF 2016

Recommendations	Class [a]	Level [b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A

Recommendation based on:
FAIR-HF &
CONFIRM-HF

Ponikowski P et al. Eur Heart J. 2016;37:2129−2200.

TREATMENT OF ID IN CHF: SIGN AND ESC GUIDELINES

Scottish Intercollegiate Guidelines Network (SIGN) Management of chronic heart failure National clinical guidelines[2]	European Society of Cardiology (ESC) 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure[1]
Treatment[2]: Level of recommendation: Conditional / Based on Ferinject clinical data, Level of evidence: 1++ /1+	Treatment[1]: Level of recommendation Class IIa/Level of evidence A
Consider intravenous iron (ferric carboxymaltose) with standard pharmacotherapy and device therapy in patients with heart failure - reduced ejection fraction (HF-REF) , NYHA class II-IV who remain symptomatic and have a haemoglobin of 9.5-13.5 g/dL and iron deficiency (defined as ferritin <100µg/L or <300 µg/L if transferrin saturation (TSAT) <20%)	ESC 2016 Heart Failure Guidelines recommend that ferric carboxymaltose should be considered in symptomatic HF patients with reduced ejection fraction and ID (serum ferritin < 100 µg/L, or ferritin between 100-299 µg/L and TSAT of <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.

1. Ponikowski P et al. Eur Heart J. 2016;37:2129−2200
2. Scottish Intercollegiate Guidelines Network: SIGN 147: Management of chronic heart failure A national clinical guideline March 2016

National Institute for Health and Care Excellence

Final

Chronic heart failure in adults

Diagnosis and management

NG106

Full Guideline

September 2018

UK NICE guidelines published 12 Sept 2018

6.2.5.6 Recommendations and link to evidence

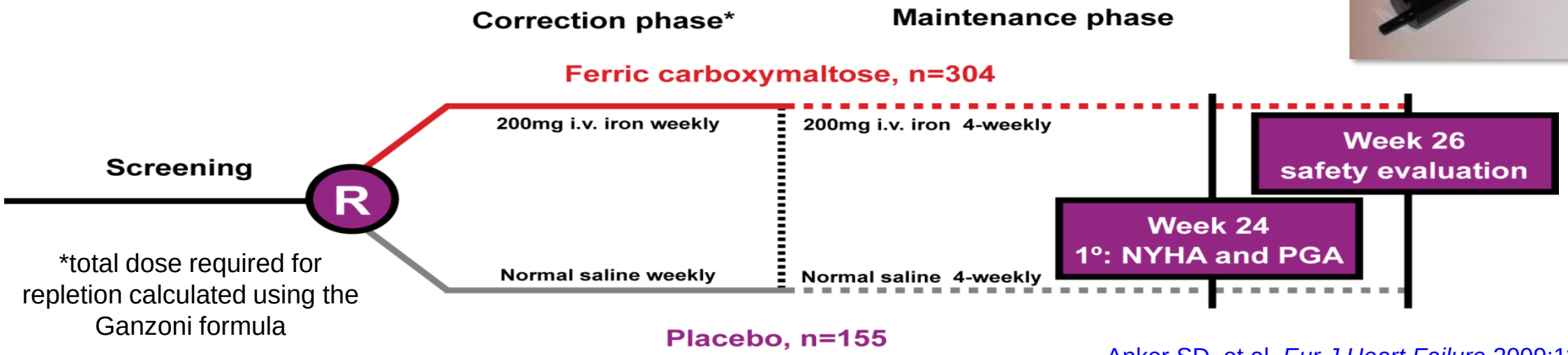
Recommendation	No recommendation
Relative values of different outcomes	The committee agreed that all-cause mortality, quality of life and unplanned hospitalisation were the most critical outcomes for decision making. The committee agreed that the impact of iron on improvement in exercise tolerance, change in haemoglobin in anaemic patients, withdrawal due to adverse events/tolerability and adverse events (including hypertension, anaphylaxis/hypersensitivity, stroke and gastrointestinal issues) were also important outcomes. The committee discussed the outcome change in haemoglobin and agreed that it was only relevant to capture this information in people who had low baseline haemoglobin levels (people with anaemia) as increasing haemoglobin levels in these people was likely to have a beneficial clinical effect. Conversely in people with normal haemoglobin levels, increasing this was less likely to have a clinical effect. The incidence of anaphylaxis/hypersensitivity was not reported in any of the included trials.

Trials

- FAIR-HF
- CONFIRM-HF
- EFFECT-HF
- IRONOUT
- Meta analysis

FAIR-HF Design

- **Main inclusion criteria:**
  - ✓ NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - ✓ Hb: 9.5–13.5g/dL
  - ✓ Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%
- **Treatment adjustment algorithm:**
  - ✓ Interruption: Hb>16.0g/dL or ferritin>800µg/L or ferritin>500µg/L, if TSAT>50%
  - ✓ Restart: Hb <16.0g/dL and serum ferritin <400µg/L and TSAT<45%

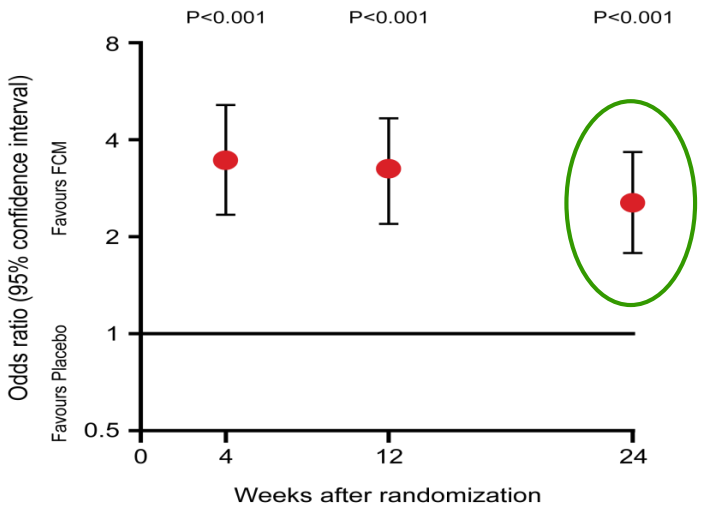


*total dose required for repletion calculated using the Ganzoni formula

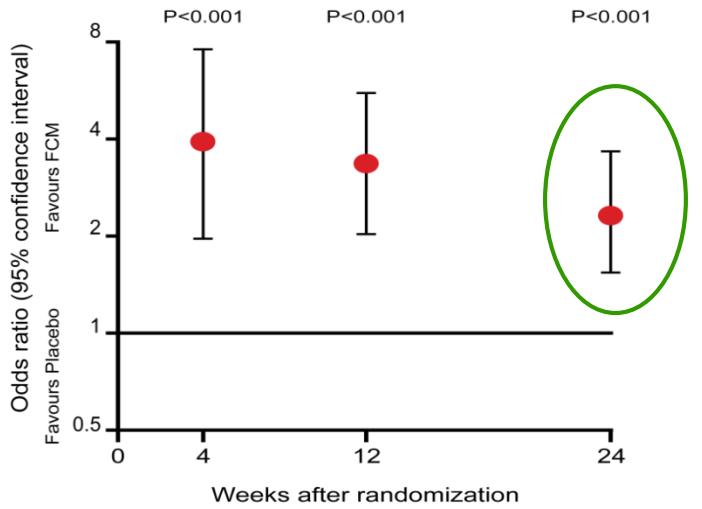
Anker SD, et al. *Eur J Heart Failure* 2009;11:1084-91.

IMPROVEMENT IN PRIMARY AND ALL SECONDARY ENDPOINTS WITH IV FERRIC CARBOXYMALTOSE

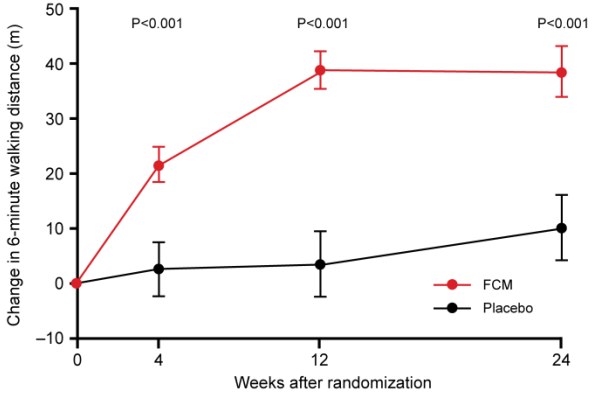
Patient Global Assessment



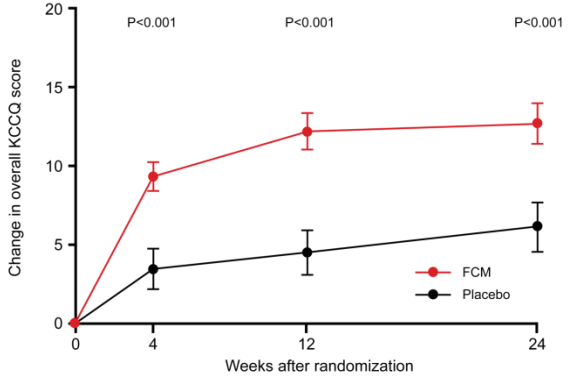
NYHA functional class



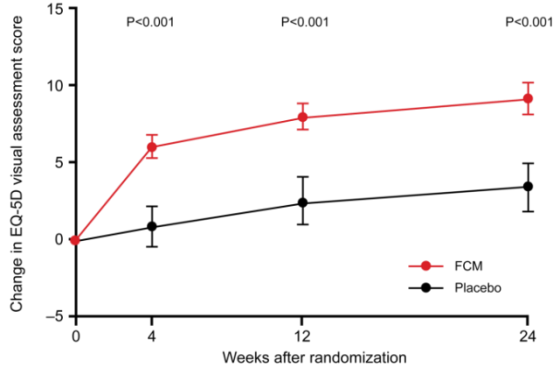
6-minute walk test



KCCQ overall score

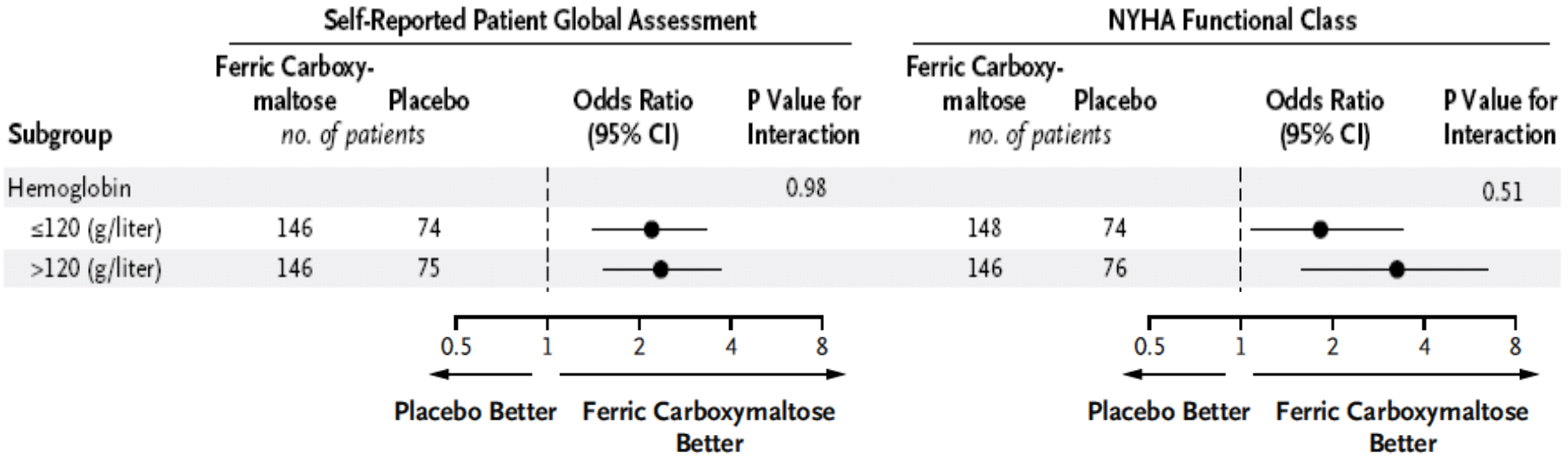


EQ-5D VAS score



Anker SD et al. N Eng J Med 2009;361:2436-48

IMPROVEMENT OF PGA & NYHA CLASS IN CHF PATIENTS WITH AND WITHOUT ANAEMIA



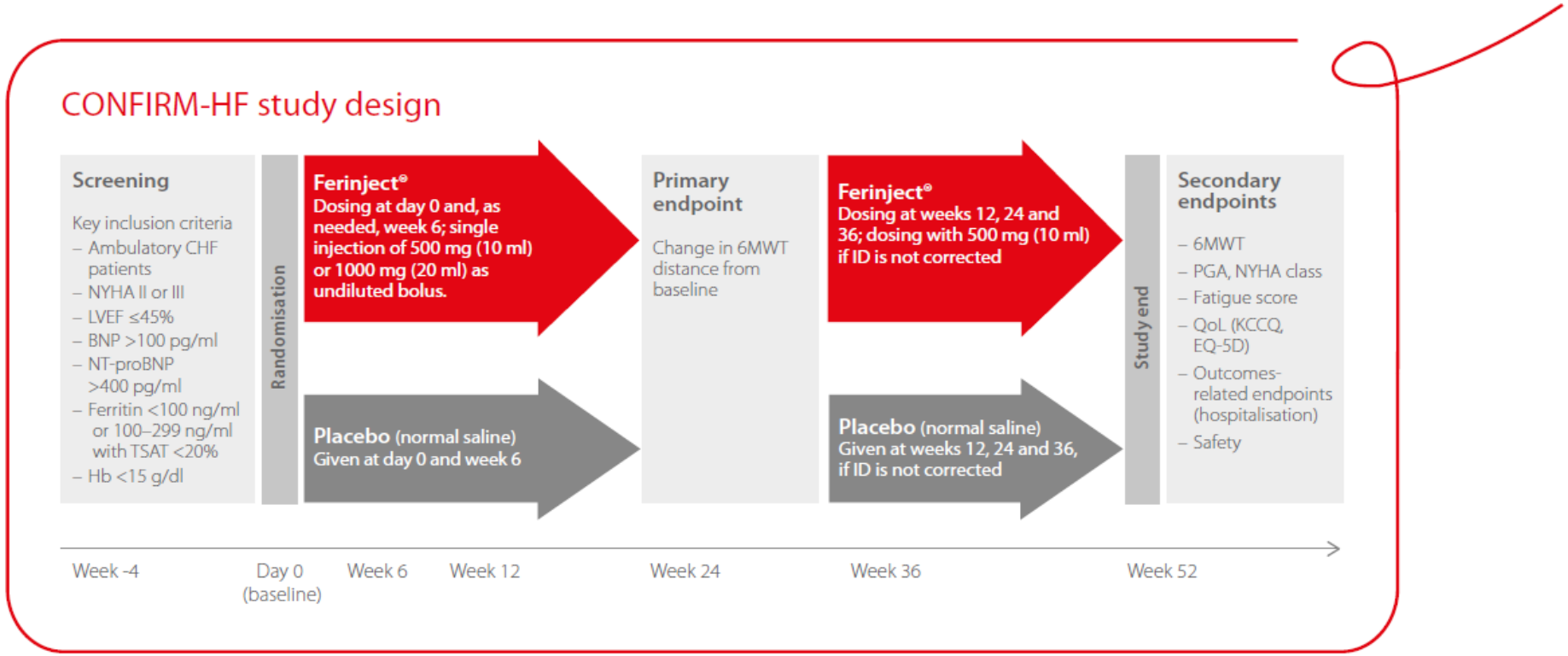
Results at week 24	FCM	Placebo	p value*
Patients with anaemia			
Serum ferritin (µg/L)	275±18	68±11	<0.001
TSAT (%)	29±1	17±1	<0.001
Haemoglobin (g/L)	127±1	118±2	<0.001
Patients without anaemia			
Serum ferritin (µg/L)	349±19	80±11	<0.001
TSAT (%)	30±1	22±1	<0.001
Haemoglobin (g/L)	133±1	132±1	0.21

*Mean treatment effect, adjusted for the baseline value

Anker SD et al. N Eng J Med 2009;361:2436-48

CONFIRM-HF: TRIAL DESIGN

A randomized, placebo-controlled trial to investigate the longer-term sustainability of beneficial effects, safety and potential impact on outcomes from the use of IV iron in patients with heart failure.



Ponikowski P et al. Eur Heart J 2015;36:657-68

PRIMARY & KEY SECONDARY ENDPOINTS

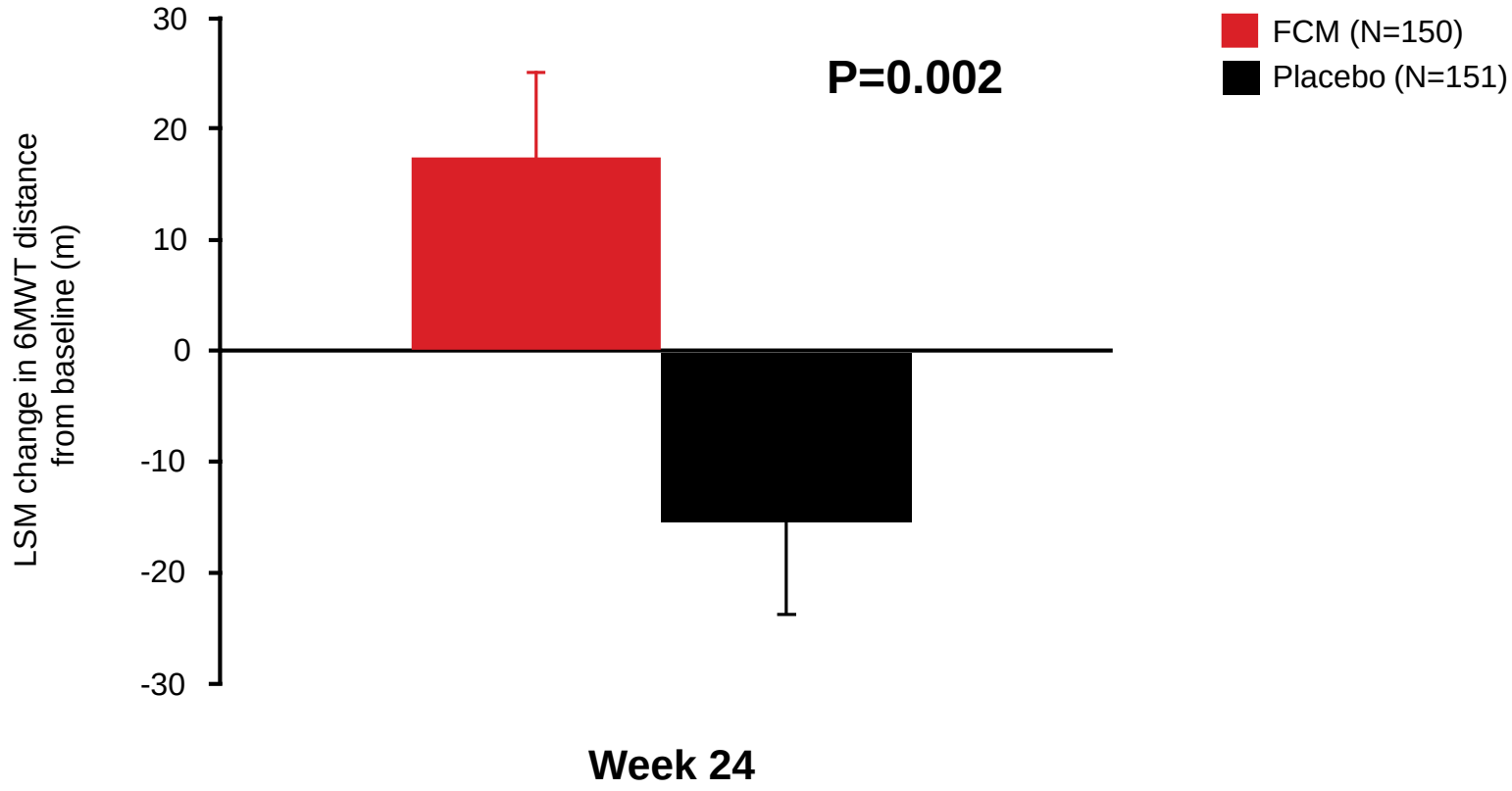
- Primary:
  - Change in 6-minute walking test (6MWT) distance from baseline to Week 24
- Key secondary:
  - 6MWT distance at Week 6, 12, 36 and 52
  - PGA score and NYHA class at Week 6, 12, 24, 36 and 52
  - KCCQ, EQ-5D and Fatigue scores at Week 6, 12, 24, 36 and 52
  - Outcome-related secondary endpoints:
    - hospitalisation rate (all hospitalisation, for any CV reason, due to worsening HF)
    - time to first hospitalisation (all hospitalisation, for any CV reason, due to worsening HF)
    - time to death (any death, death for any CV reason, due to worsening HF)

Ponikowski P et al. Eur Heart J 2015;36:657-68

PRIMARY ENDPOINT: CHANGE IN 6MWT AT WEEK 24

FCM improved 6MWT at week 24

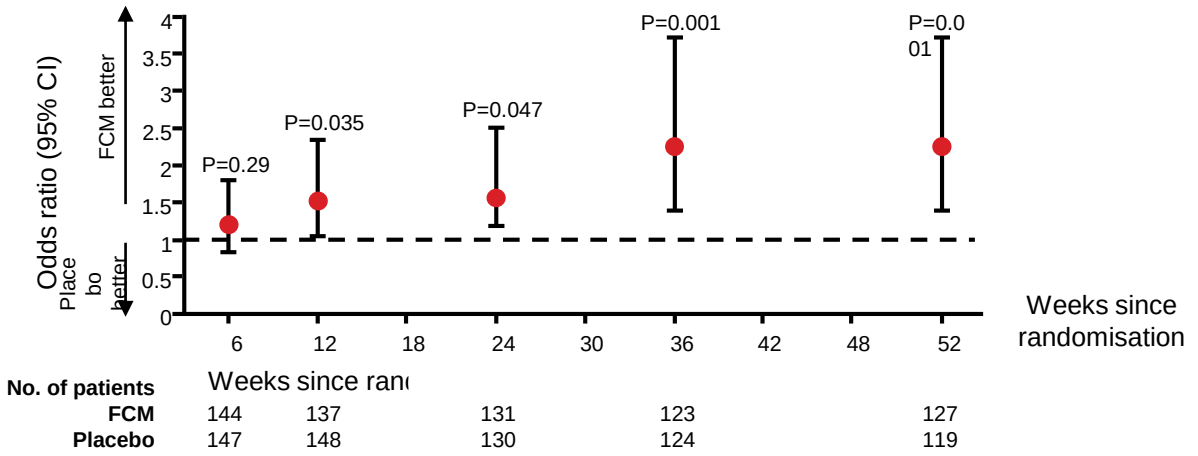
FCM vs placebo: 33 ± 11 m *(least squares mean ± SE)*



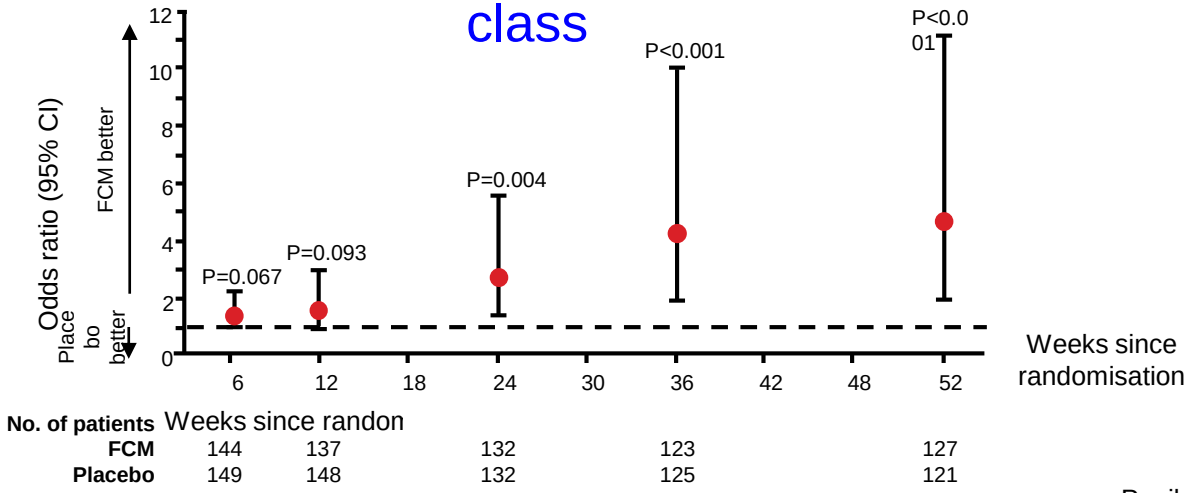
Ponikowski P et al. Eur Heart J 2015;36:657-68

SECONDARY ENDPOINTS: CHANGES IN PGA & NYHA CLASS OVER TIME

Self-reported Patient Global Assessment (PGA) score



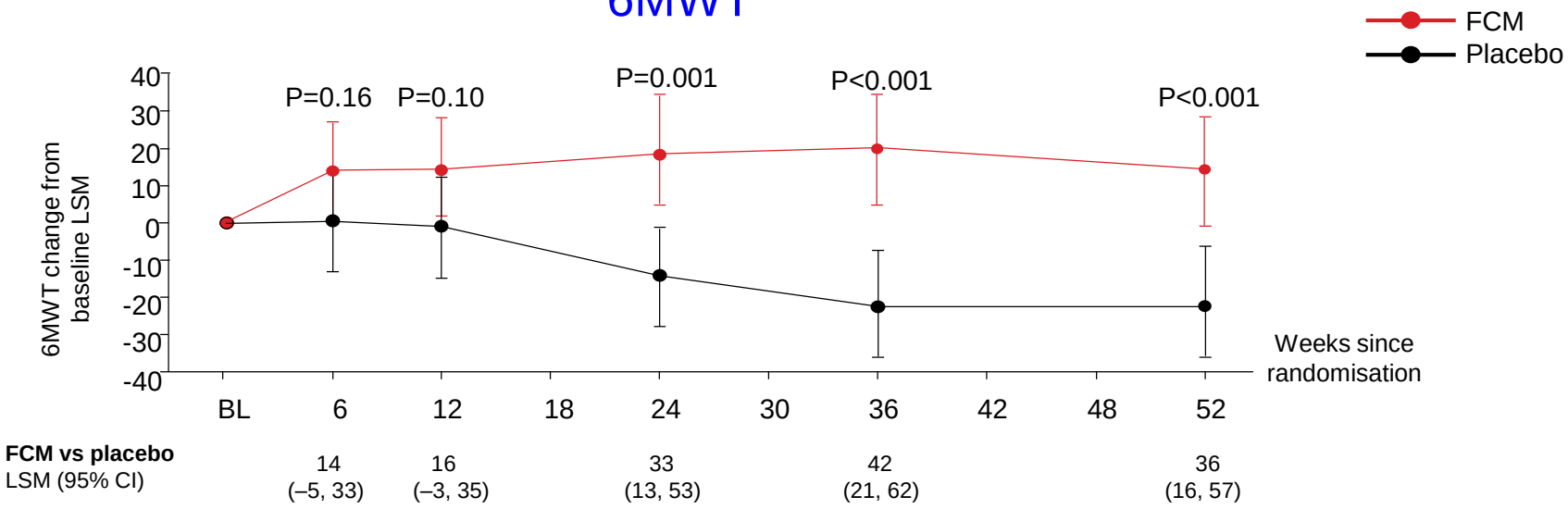
New York Heart Association (NYHA) Functional class



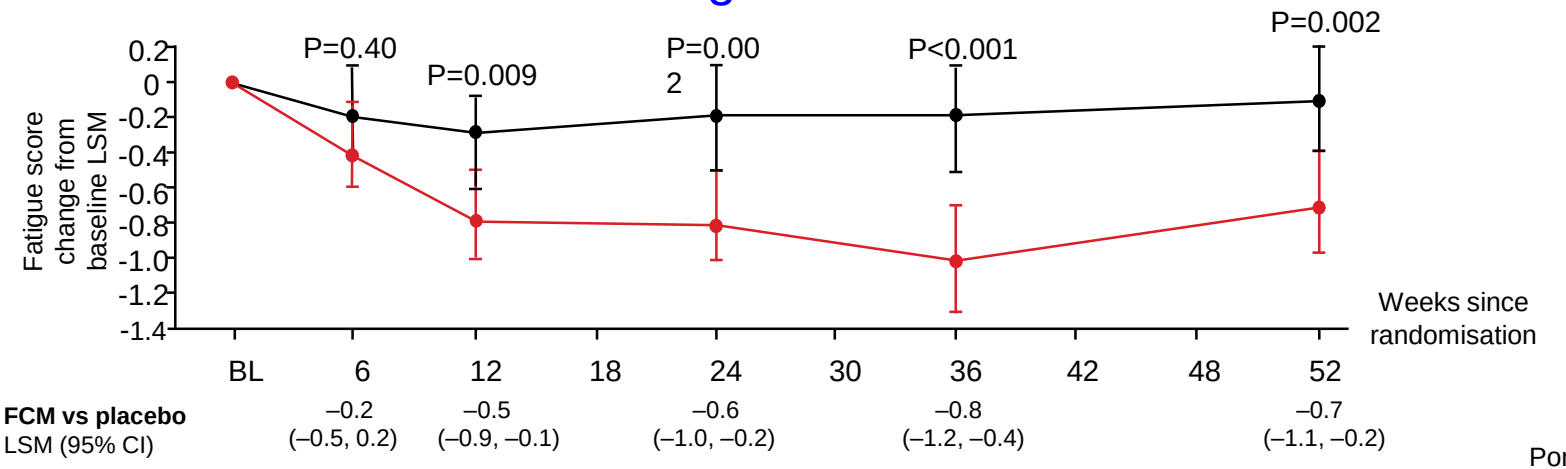
Ponikowski P et al. Eur Heart J 2015;36:657-68

SECONDARY ENDPOINTS: CHANGES IN 6MWT AND FATIGUE SCORE OVER TIME

6MWT



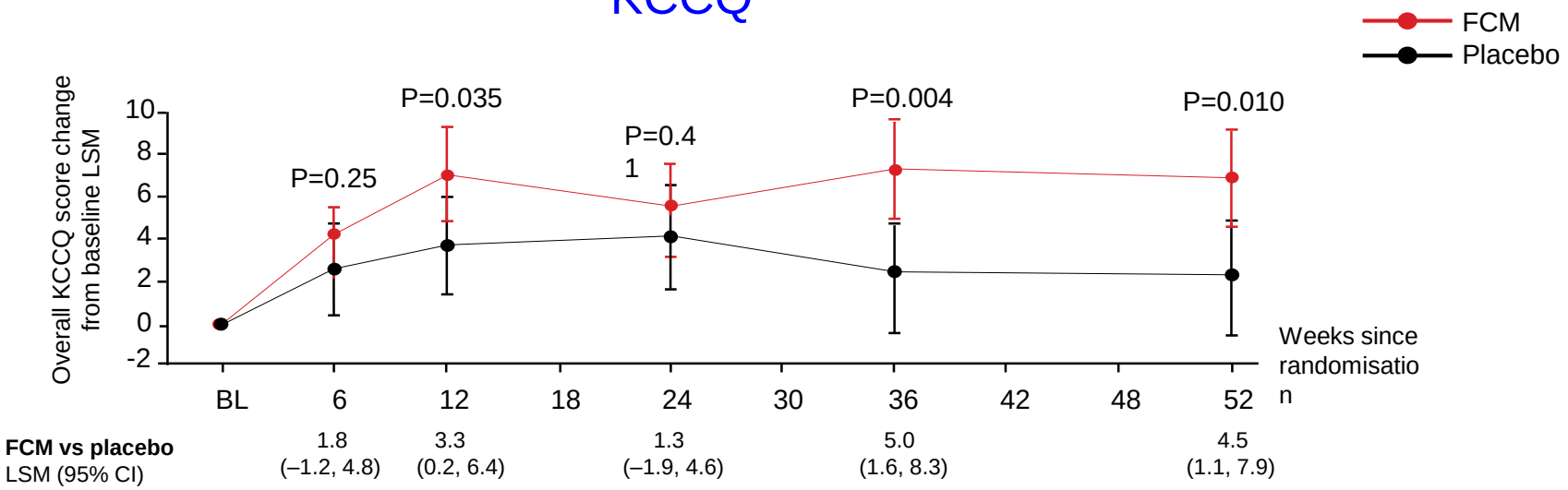
Fatigue score



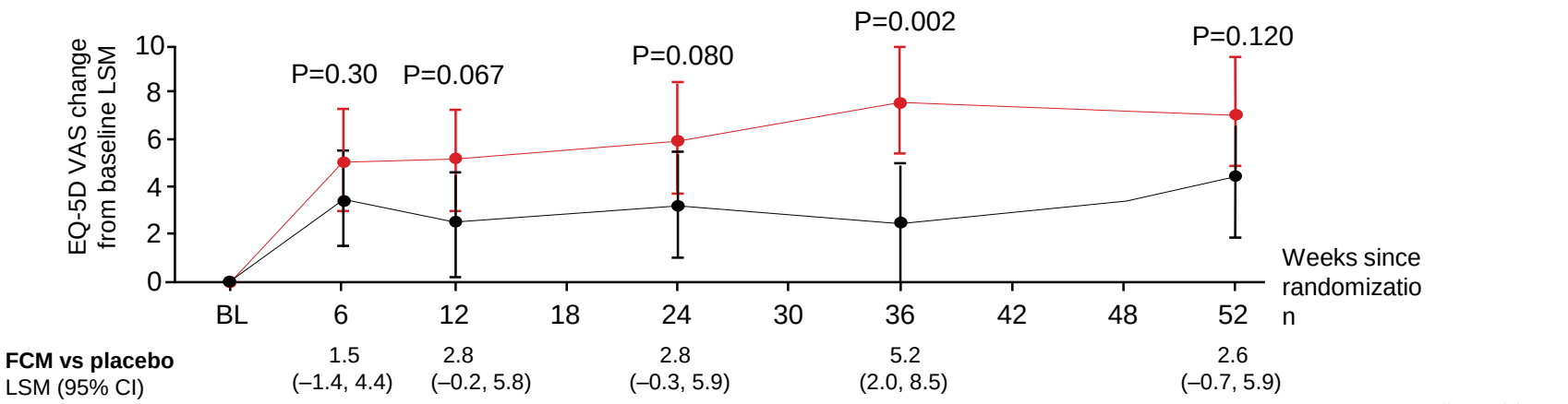
Ponikowski P et al. Eur Heart J 2015;36:657-68

SECONDARY ENDPOINTS: CHANGES IN QUALITY OF LIFE OVER TIME

KCCQ



EQ-5D VAS score



Ponikowski P et al. Eur Heart J 2015;36:657-68

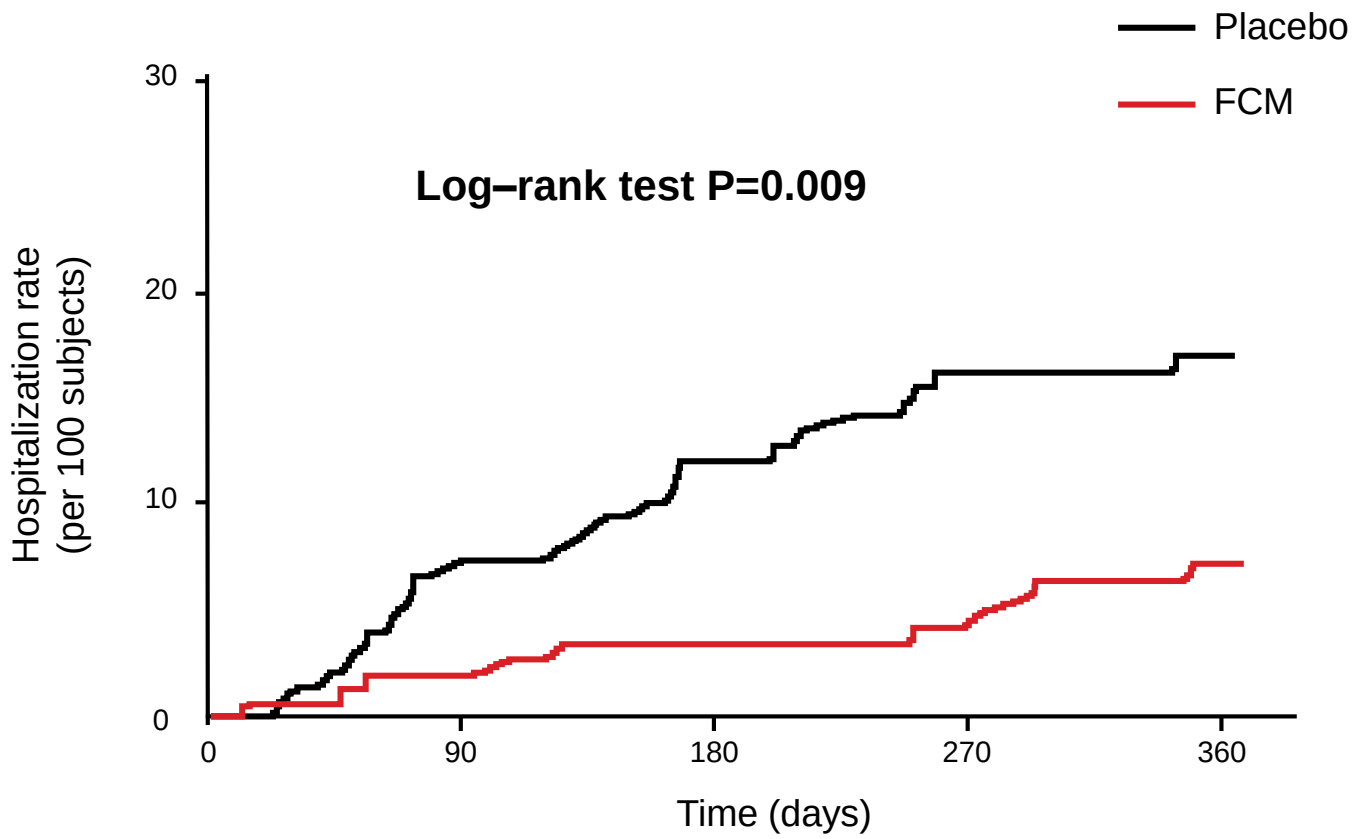
SECONDARY ENDPOINTS: OUTCOME EVENTS

	FCM (N=150)		Placebo (N=151)			
End-point or event	**Total events (n)**	**Incidence/ (100 patient risk-year)**	**Total events (n)**	**Incidence/ (100 patient risk-year**	**Time to first event Hazard ratio 95% CI**	**P-value**
Death	12	12 (8.9)	14	14 (9.9)	0.89 (0.41 – 1.93)	0.77
Death for any CV reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42 – 2.16)	0.91
Hospitalisation	46	32 (26.3)	69	44 (37.0)	0.71 (0.45 – 1.12)	0.14
Hospitalisation for any CV reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37 – 1.09)	0.097
Hospitalisation due to worsening HF	**10**	**10 (7.6)**	**32**	**25 (19.4)**	**0.39 (0.19 – 0.82)**	**0.009**

FCM reduced the risk of recurrent hospitalisations due to worsening HF (post hoc analysis): **Hazard Ratio (95% CI) – 0.30 (0.14-0.64), p=0.0019**

Ponikowski P et al. Eur Heart J 2015;36:657-68

SECONDARY ENDPOINT: FIRST HOSPITALIZATION DUE TO WORSENING HEART FAILURE

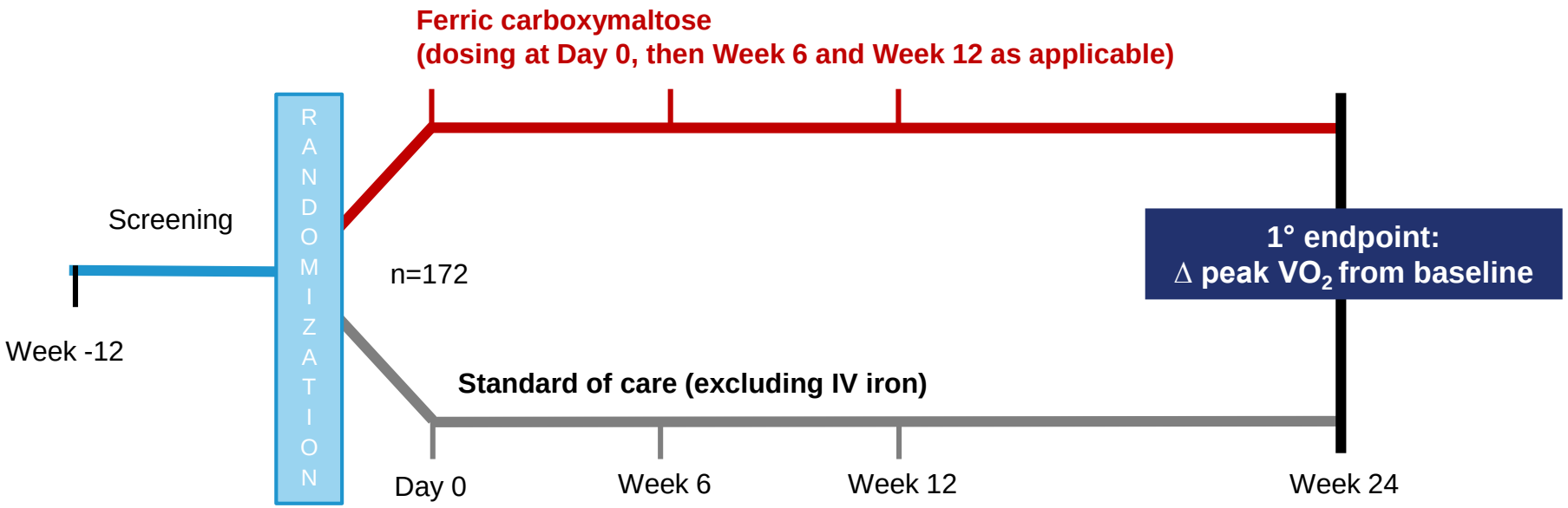


No. of subjects at risk					
Placebo	151	138	127	117	78
FCM	150	140	131	126	77

Ponikowski P et al. Eur Heart J 2015;36:657-68

EFFECT-HF: STUDY DESIGN

- **Design:** Multicenter, randomized (1:1), open label, assessor/endpoint-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



van Veldhuisen DJ et al. Circulation 2017; 136:1374-83

PRIMARY AND KEY SECONDARY ENDPOINTS

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

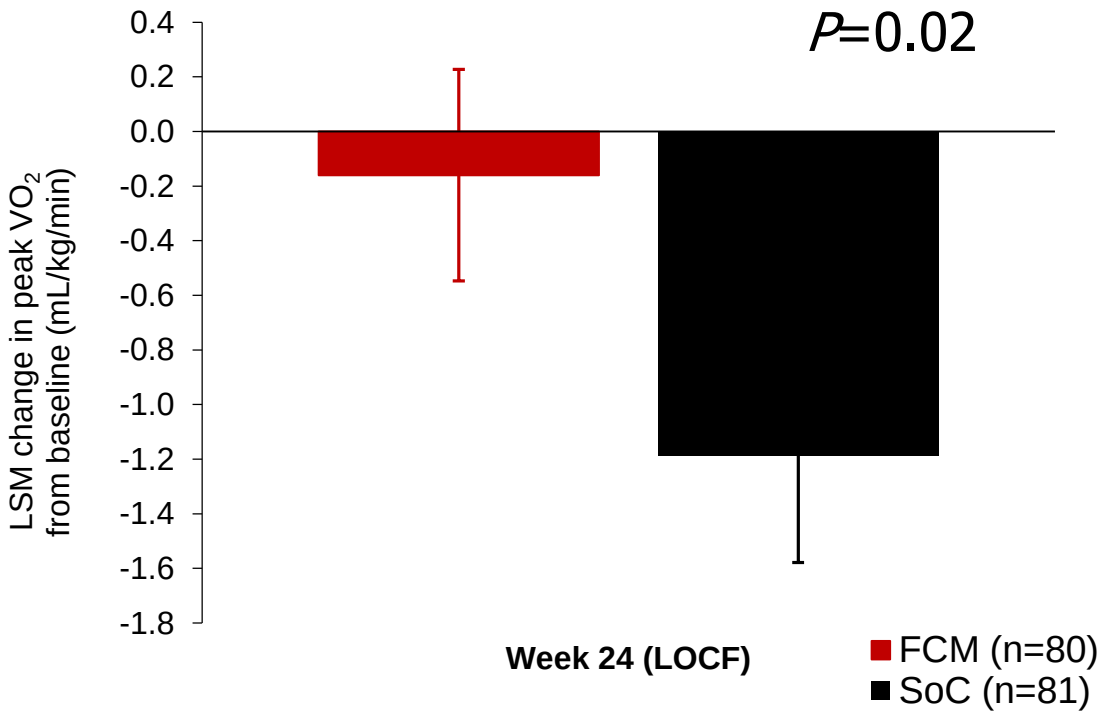
- Key secondary endpoints
  - Change in peak VO_2 (mL/kg/min) from baseline to Week 12
  - Change in other exercise parameters (VE-VCO_2 slope, work rate) at Weeks 12 and 24
  - Change in biomarkers for iron deficiency, renal function, cardiac function (including BNP and NT-proBNP), NYHA functional class,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

PRIMARY ENDPOINT ANALYSIS: CHANGE IN PEAK VO_2 FROM BASELINE TO WEEK 24

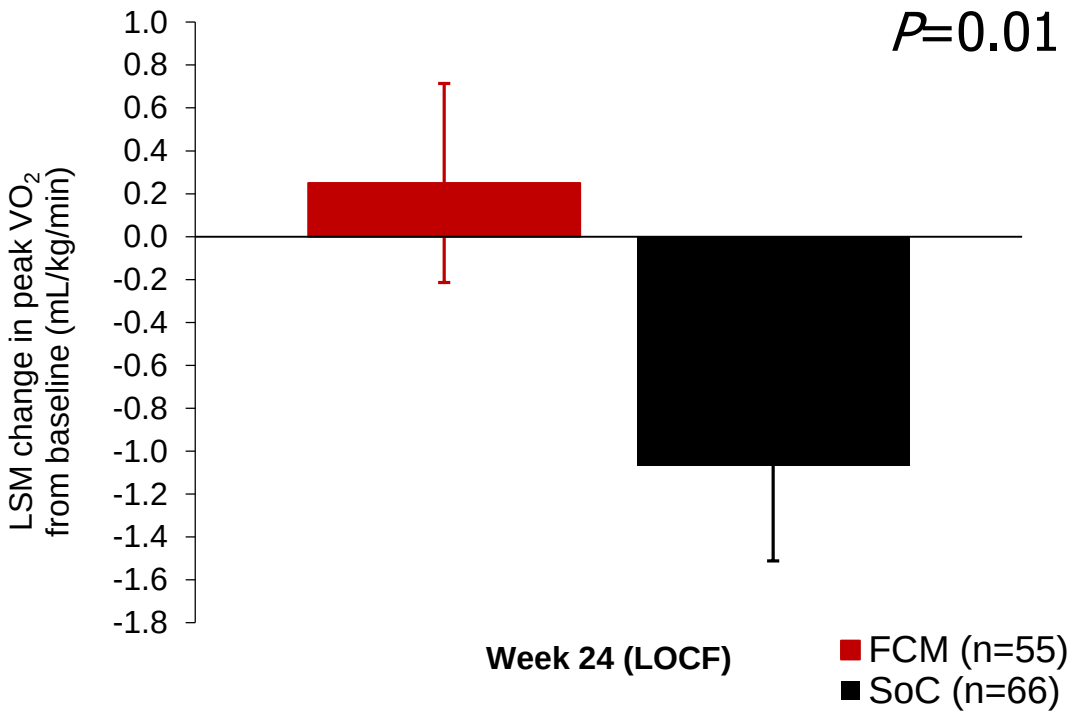
Full analysis set (N=172)

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)



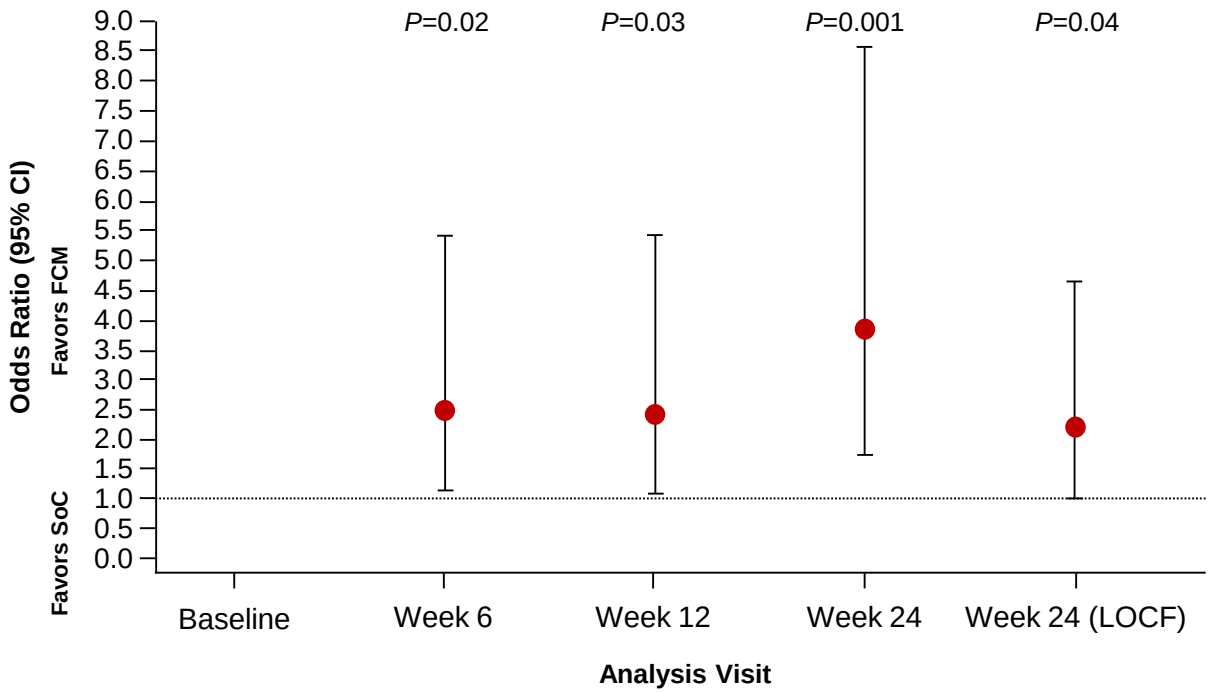
*population consisted of all subjects who, in addition to the full analysis set criteria, had no major protocol violations.

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

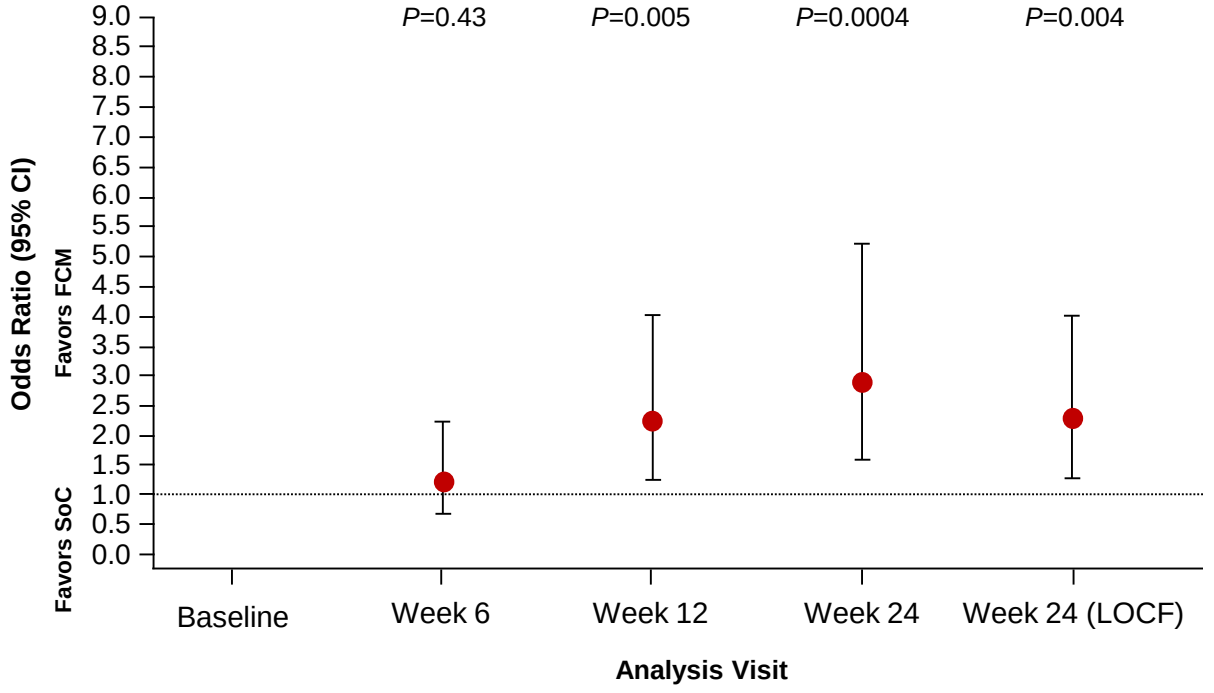
No significant interaction when adjusted to baseline Hb <12 g/dL or > 12 g/dL

SECONDARY ENDPOINTS: CHANGES IN PGA AND NYHA CLASS

New York Heart Association Functional (NYHA) class



Self-reported Patient Global Assessment (PGA) score



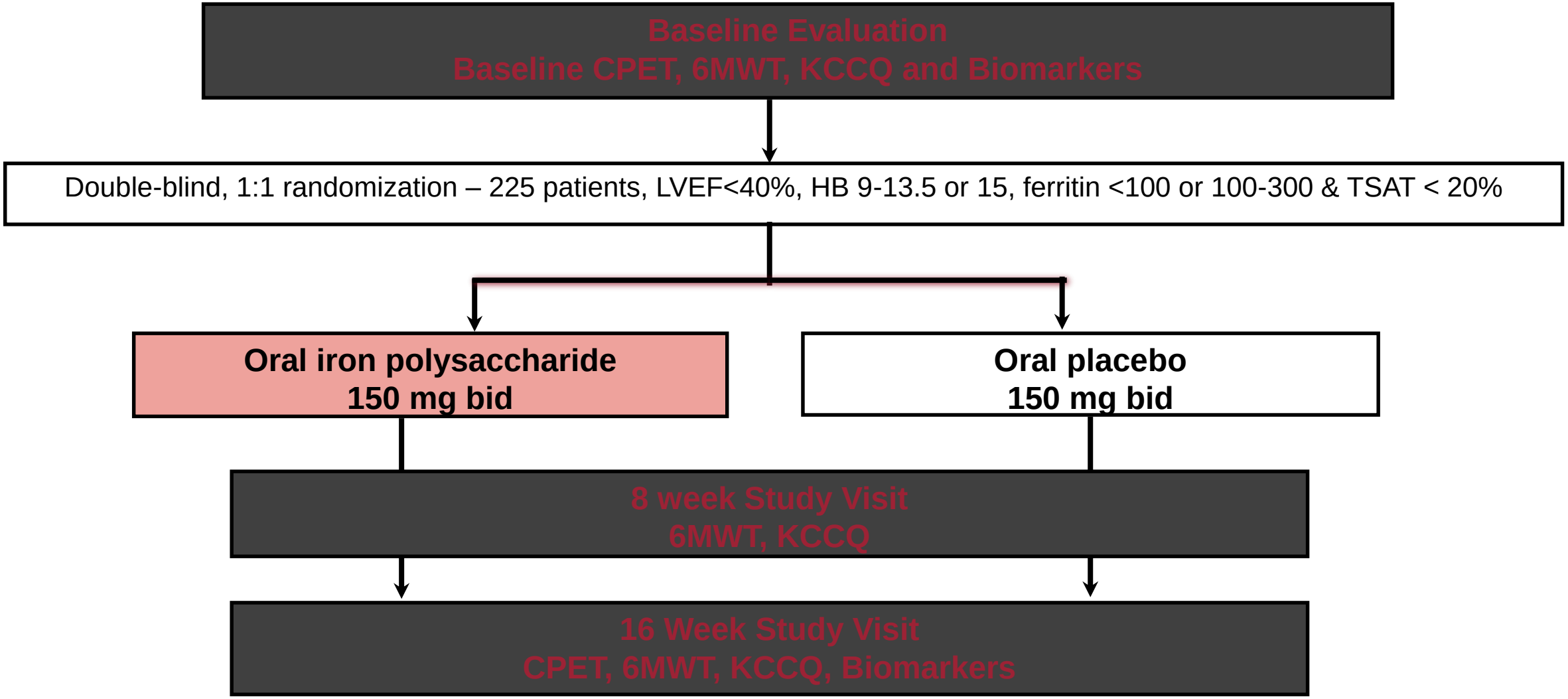
CI, confidence interval; FCM, ferric carboxymaltose; LOCF, last observation carried forward; SoC, standard of care

HOSPITALIZATIONS AND DEATHS (SAFETY POPULATION)

Event description	FCM (N=88) n (%) E	SoC (N=85) n (%) E	Total (N=173) n (%) E
Death	0	4 (4.7) 4	4 (2.3) 4
Any hospitalization	27 (30.7) 37	13 (15.3) 21	40 (23.1) 58
Reason for hospitalization			
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

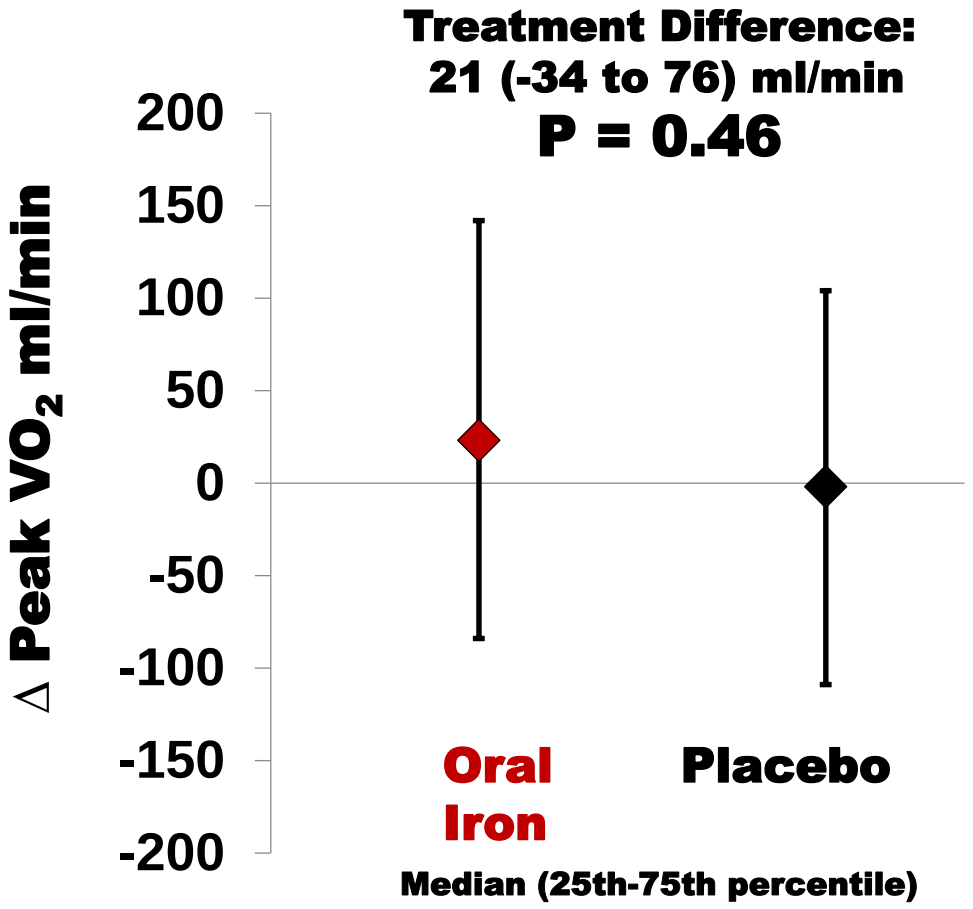
CHF, chronic heart failure; E, events; FCM, ferric carboxymaltose; SoC, standard of care; n, number of patients.
There was an additional death in the SoC arm; the subject died after completion of the study

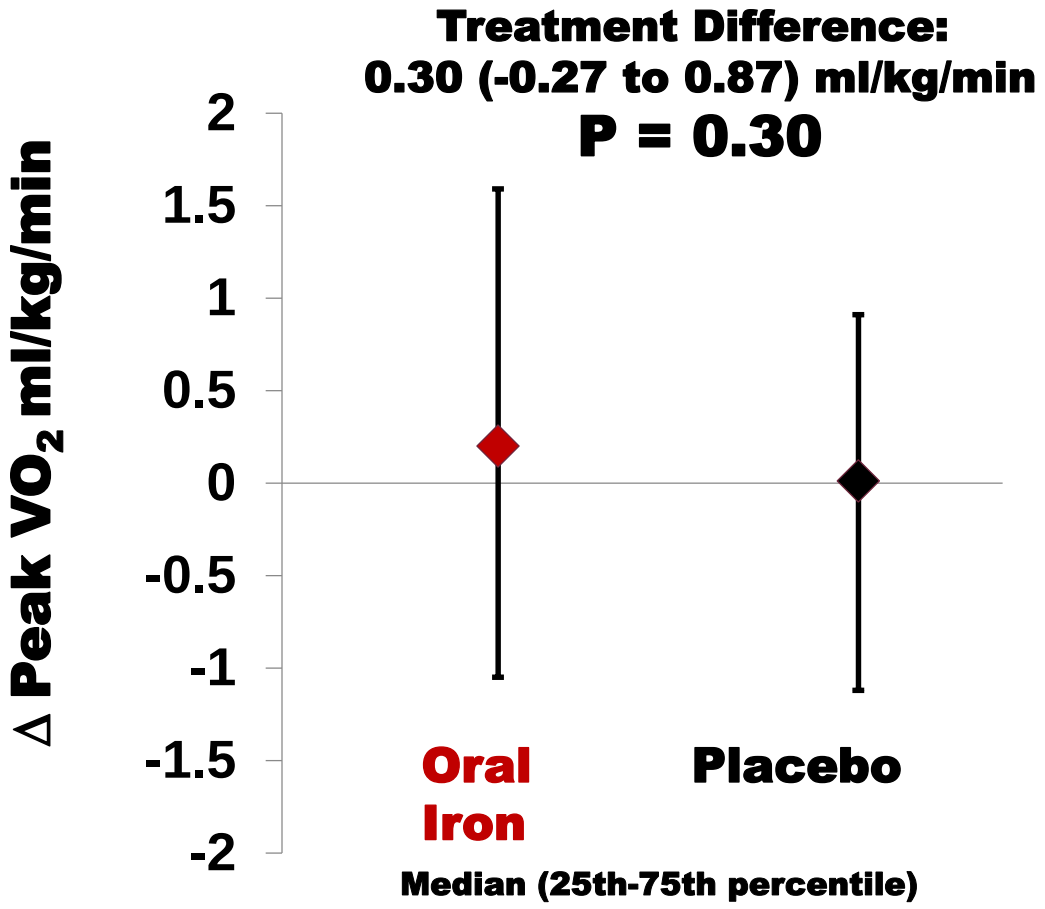
IRONOUT STUDY DESIGN



Lewis et al. JAMA 2017; 317:1958-66

IRONOUT RESULTS: PRIMARY ENDPOINT





IRONOUT SUMMARY AND CONCLUSIONS

High dose oral iron minimally repleted iron stores and did not improve peak VO_2 in iron deficient heart failure patients with reduced LVEF

These results do not support use of oral iron supplementation in patients with heart failure with reduced LVEF

CONGESTIVE HEART FAILURE META-ANALYSIS[1]

Data from several double-blind, randomized controlled trials with systolic heart failure and iron deficiency completed by Dec 2014 included.

Meta-analysis on individual patient data to explore the effect of IV ferric carboxymaltose vs placebo on hospitalisations and mortality.

4 RCTs included.

Composite primary outcome – cardiovascular hospitalisations and cardiovascular death.

1. Anker SD et al. Eur J Heart Fail. 2018;20:125-33

STUDY DESIGNS AND INCLUSION CRITERIA[1]

	FER-CARS-01	FAIR-HF	EFFICACY-HF*	CONFIRM-HF
Patient population	• Ambulatory • Optimally treated • Systolic CHF with ID • NYHA class II/III • Renal dysfunction (eGFR<60ml/min per 1.73m2)	• Ambulatory • Optimally treated • Systolic CHF with ID • NYHA class II/III	• Ambulatory • Optimally treated • Systolic CHF with ID • NYHA class II/III	• Ambulatory • Optimally treated • Systolic CHF with ID • NYHA class II/III
Randomisation	2 : 1 (FCM : Placebo)	2 : 1 (FCM : Placebo)	1 : 1 (FCM : Placebo)	1 : 1 (FCM : Placebo)
Number of patients (FAS) FCM / placebo	30 / 15	304 / 155	20 / 14*	150 / 151
Study duration	12 weeks	24 weeks	24 weeks	52 weeks
Calculation of iron repletion dose	Ganzoni Formula	Ganzoni Formula	Ganzoni Formula	Simplified dosing based on weight and Hb
Correction phase (i.e. until iron repletion)	Weekly IV injections (200mg/100mg) of FCM/placebo over 3 to 9 weeks	Weekly IV injections (200mg/100mg) of FCM/placebo for max 4 weeks	Weekly IV injections (200mg/100mg) of FCM/placebo over 3 to 9 weeks	2 IV injections (500mg/1000mg) of FCM/placebo for max 6 weeks
Maintenance phase	4-weekly 200mg iron IV injection (FCM/placebo) up to 24 weeks after randomisation	4-weekly 200mg iron IV injection (FCM/placebo) up to 12 weeks after randomisation	4-weekly 200mg iron IV injection (FCM/placebo) up to 24 weeks after randomisation	3-monthly 500mg iron IV injection (FCM/placebo) up to 36 weeks after randomisation, if ID present
Primary endpoint(s)	PGA at week 12 & NYHA class from baseline to Week 12	PGA at week 24 & NYHA class from baseline to Week 24	Change in 6MWT and NYHA class from baseline to Week 24	Change in 6MWT from baseline to Week 24

* EFFICACY-HF was discontinued due to recruitment issues.

1. Anker SD et al. Eur J Heart Fail. 2017 Apr 24. doi: 10.1002/ejhf.823.

META-ANALYSIS EFFICACY OUTCOMES[1]

Rate ratio analysis (recurrent event analyses)

Recurrent event outcomes	FCM* (N=504)	Placebo* (N=335)	Rate Ratio (95%CI)	p
CV hospitalization and CV death	69 (23.0)	92 (40.9)	0.59 (0.40-0.88)	0.009
HF hospitalization and CV death	39 (13.0)	60 (26.7)	0.53 (0.33-0.86)	0.011
CV hospitalization and all-cause death	71 (23.7)	94 (41.8)	0.60 (0.41-0.88)	0.009
HF hospitalization and all-cause death	41 (13.7)	62 (27.6)	0.54 (0.34-0.87)	0.011
All-cause hospitalization and all-cause death	108 (36.1)	118 (52.5)	0.73 (0.52-1.01)	0.060
HF hospitalization	22 (7.3)	43 (19.1)	0.41 (0.23-0.73)	0.003
CV hospitalization	52 (17.4)	75 (33.3)	0.54 (0.36-0.83)	0.004
All-cause hospitalization	89 (29.7)	99 (44.0)	0.71 (0.50-1.01)	0.056

* Total number of events (incidence per 100 patient years of follow-up)

1. Anker SD et al. Eur J Heart Fail. 2017 Apr 24. doi: 10.1002/ejhf.823.

META-ANALYSIS EFFICACY OUTCOMES[1]

Time to first event analysis

Recurrent event outcomes	FCM* (N=504)	Placebo* (N=335)	Rate Ratio (95%CI)	p
CV hospitalisation or CV death	55 (18.4)	59 (26.2)	0.70 (0.48-1.02)	0.062
HF hospitalisation or CV death	32 (10.7)	44 (19.6)	0.55 (0.35-0.88)	0.012
CV hospitalisation or all-cause death	57 (19.0)	61 (27.1)	0.70 (0.49-1.02)	0.060
HF hospitalisation or all-cause death	34 (11.4)	46 (20.4)	0.56 (0.36-0.88)	0.013
All-cause hospitalisation or all-cause death	81 (27.0)	75 (33.3)	0.81 (0.59-1.12)	0.199
HF hospitalisation	19 (6.3)	34 (15.1)	0.42 (0.24-0.74)	0.003
CV hospitalisation	43 (14.4)	52 (23.1)	0.61 (0.40-0.91)	0.017
All-cause hospitalisation	68 (22.7)	67 (29.8)	0.75 (0.53-1.06)	0.099
CV death	17 (5.7)	17 (7.6)	0.84 (0.43-1.66)	0.620
All-cause death	19 (6.3)	19 (8.4)	0.84 (0.44-1.61)	0.604

* Total number of events (incidence per 100 patient years of follow-up)

1. Anker SD et al. Eur J Heart Fail. 2017 Apr 24. doi: 10.1002/ejhf.823.

Future trials

- AFFIRM-AHF
- FAIR-HF2
- HEART FID
- IRONMAN

AFFIRM-AHF: FERRIC CARBOXYMALTOSE ACUTE HEART FAILURE STUDY

A Randomised, Double-Blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure

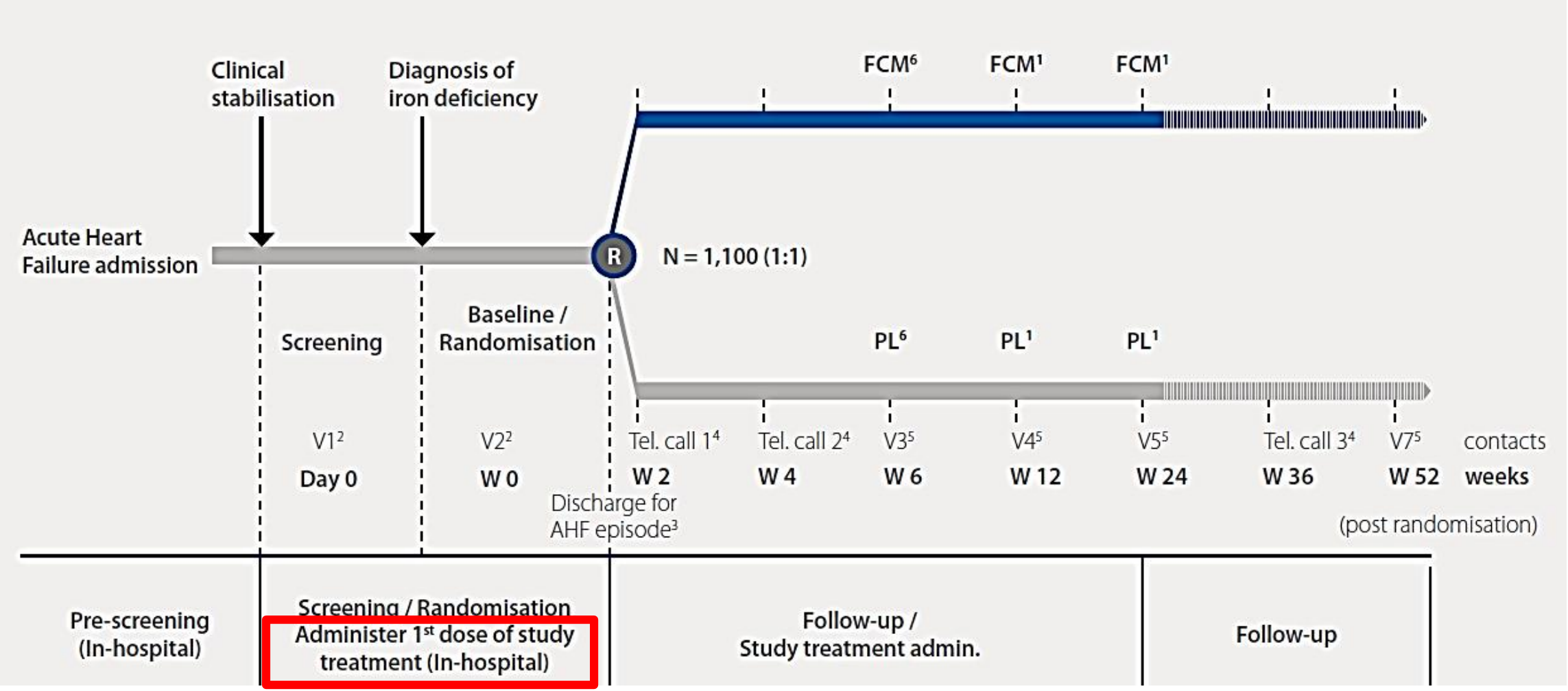
Study Code: FER-CARS-06
EudraCTNumber: 2016-001467-36
Principal Investigator: Prof. Piotr Ponikowski

Purpose:

•To evaluate the effect of i.v. FCM on the composite of recurrent HF hospitalisations for worsening HF and CV death up to 52 weeks after randomisation

https://clinicaltrials.gov/ct2/show/NCT02937454

AFFIRM-AHF: STUDY FLOW CHART



1. Study treatment to be administered only if iron deficiency persists; 2. Performed in hospital during the AHF admission (Index hospitalisation);
3. Discharge after administration of study treatment at the discretion of the investigator; 4. Telephone contact;
5. Outpatient clinic visit; 6. The repletion dose of study treatment will be administered based on iron need as assessed at the baseline visit

AHF, acute heart failure; FCM, ferric carboxymaltose; PL, placebo; V, visit; W, week

https://clinicaltrials.gov/ct2/show/NCT02937454

FAIR-HF2: INTRAVENOUS IRON IN PATIENTS WITH SYSTOLIC HEART FAILURE AND IRON DEFICIENCY TO IMPROVE MORBIDITY AND MORTALITY

Purpose:

- International, prospective, multi-centre, double-blind, parallel group, randomised, controlled, interventional trial

Primary outcome:

- Combined rate of recurrent hospitalisations for heart failure and of CV death (number of events) after at least 12 months of follow-up
- Combined rate of recurrent hospitalisations for heart failure and of CV death during follow-up

Secondary endpoints

- CV / HF hospitalisation, CV death (recurrent events, time-to-first event)
- Change in NYHA functional class, EQ-5D, and PGA

CV, cardiovascular; EQ-5D, EuroQol five dimensions questionnaire; HF, heart failure; NYHA, New York Heart Association; PGA, patient global assessment

https://clinicaltrials.gov/ct2/show/NCT03036462

HEART FID: RANDOMISED PLACEBO-CONTROLLED TRIAL OF FCM AS TREATMENT FOR HEART FAILURE WITH IRON DEFICIENCY

Purpose:

- The primary objective of this study is to determine the efficacy and safety of iron therapy using i.v. ferric carboxymaltose, relative to placebo, in the treatment of participants in heart failure with iron deficiency and with a reduced ejection fraction

Primary outcome:

Incidence of death (1 year)

Incidence of hospitalisation for heart failure (1 year)

Change in 6MWT distance (6 months)

FCM, ferric carboxymaltose; i.v., intravenous; 6MWT, six-minute walk test

https://clinicaltrials.gov/ct2/show/NCT03037931

IRONMAN, IRON (III) ISOMALTOSIDE: DETAILS

Principal Investigator: Paul Kalra, Portsmouth

ClinicalTrials.gov Identifier: NCT02642562

Estimated enrollment: N= 1300

Study Start Date: August 2016

Estimated Primary Completion Date: February 2021

IRON MAN: EFFECTIVENESS OF I.V. IRON (III) ISOMALTOSIDE TREATMENT VS STANDARD CARE IN PATIENTS WITH HF AND ID

Purpose:

- This study will address whether the additional use of i.v. iron on top of standard care will improve the outlook for patients with HF and ID. One group of participants will receive treatment with iron injections and the other group will not receive any iron injections.

Primary outcome:

CV mortality or hospitalisation for worsening HF (analysis will include first and recurrent hospitalisations) [Minimum 2.5 years follow up from last patient recruited]

HF, heart failure; ID, iron deficiency; i.v., intravenous

https://clinicaltrials.gov/ct2/show/NCT02642562

Summary

- Iron deficiency a problem in heart failure
- Often under-recognised
- Initial trial data shows symptomatic benefit and increased exercise capacity, possible reduction in hospitalisation
- Guidance (ESC/SIGN) positive
- No recommendation from NICE NG106
- Ongoing trials will address hard endpoints