AFFIRM-AHF Trial:

Background, study design & results

Date of preparation: 15 December 2020

HQ-FCM-2000149

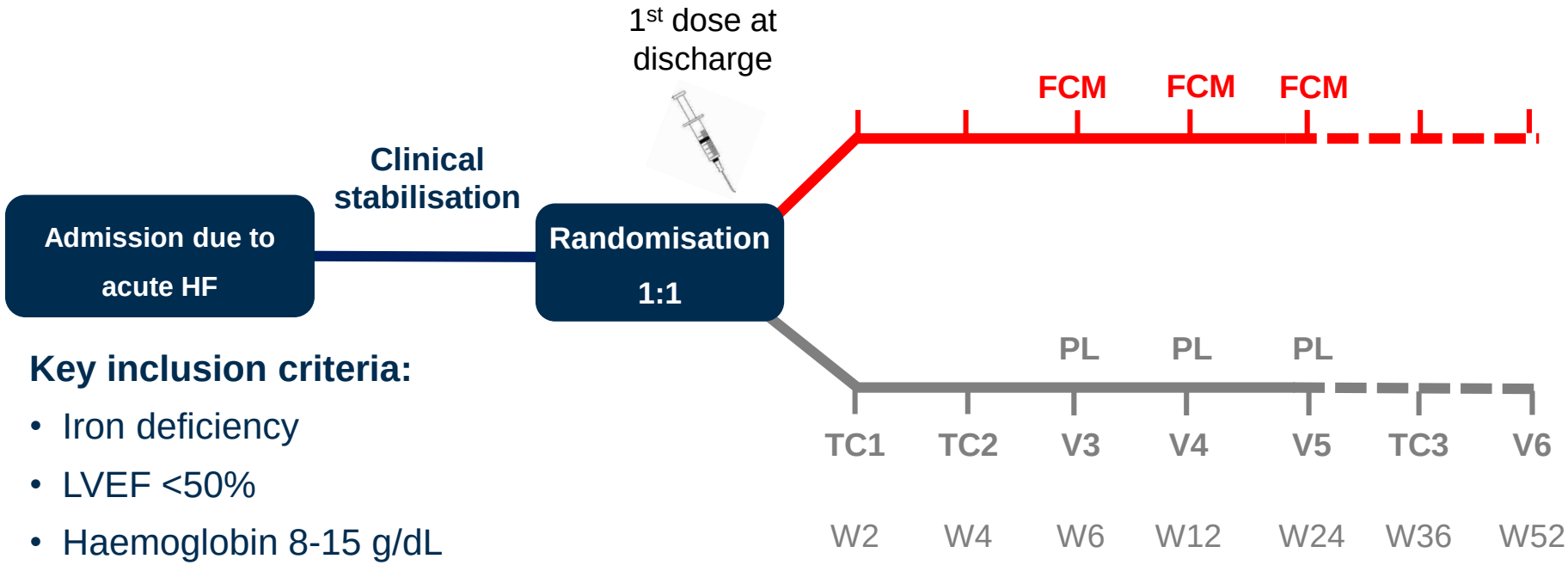
BACKGROUND AND RATIONALE

- Iron deficiency is common in heart failure (HF) and associated with reduced exercise capacity, poor quality of life, increased risk for hospitalisation, and mortality[1-3]
- In acute HF, iron deficiency is present in up to 80% of patients and is a predictor of poor outcome, independent from previous history of HF, natriuretic peptide levels, and ejection fraction[4,5]
- In stable HFrEF patients treatment of ID with ferric carboxymaltose (FCM) improves symptoms, exercise capacity and quality of life [6,7]
- The effects of FCM administered at hospital discharge in stabilised patients with acute HF and concomitant iron deficiency on the outcomes are unknown
- AFFIRM-AHF was designed to evaluate the effect of intravenous FCM or placebo initiated shortly before hospital discharge in patients with acute HF and iron deficiency on recurrent heart failure hospitalisations and cardiovascular death up to 52 weeks after randomisation[8]

HFrEF, Heart Failure with reduced Ejection Fraction

1.Klip IT, et al. Am Heart J 2013;165:575-582, 2.Cohen-Solal A, et al. Eur J Heart Fail 2014;16;984-991, 3.Marchi G, et al. Intern Emerg Med 2020;doi:10.1007/s11739-020-02434-9, 4.Jankowska EA et al. Eur Heart J 2014;35:2468–76;5.Núñez J et al. Eur J Heart Fail 2016;18:798–802;6. Anker SD, et al. N Engl J Med 2009;361:2436-48; 7.Ponikowski P, et al. Eur Heart J 2015;36:657-68; 8.Ponikowski P, et al. Eur J Heart Fail. 2019;21(12):1651-1658.

AFFIRM-AHF STUDY DESIGN



Key inclusion criteria:

- Iron deficiency
- LVEF <50%
- Haemoglobin 8-15 g/dL

Pre-screening (in-hospital)	Screening / Randomisation	Follow-up / Study treatment administration	Follow-up

PRIMARY OUTCOME:

Composite of total HF hospitalisations and CV death up to 52 weeks

SECONDARY OUTCOMES:

- Total HF hospitalisations
- CV death
- Time to first HF hospitalisation or CV death
- Total CV hospitalisations and CV death
- Days lost due to HF hospitalisations or CV death

CV, cardiovascular; PL, placebo; LVEF, left ventricular ejection fraction; TC, telephone contact; V, visit; W, week.

Ponikowski P, et al. *Eur J Heart Fail*. 2019;21(12):1651-1658.

BASELINE CHARACTERISTICS

Characteristic	FCM (N=558)	Placebo (N=550)
Age, year	71.2 ± 10.8	70.9 ± 11.1
Female, %	44	45
Systolic BP, mm Hg	120 ± 15	120 ± 16
NYHA Class III-IV, %	52	54
LVEF, %	32.6 ± 9.6	32.7 ± 10.0
Ischaemic aetiology of HF, %	47	47
Newly diagnosed HF at index hospitalisation, %	27	30
Comorbidities, %		
Atrial fibrillation and/or flutter	56	55
Diabetes mellitus	41	44
Chronic kidney disease	40	41

Results presented as mean ± SD unless otherwise noted.
mITT population.
BP, blood pressure; NYHA, New York Heart Association.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

BASELINE PHARMACOTHERAPY

Pharmacotherapy, %	FCM (N=558)	Placebo (N=550)
Angiotensin converting enzyme inhibitor	53	51
Angiotensin receptor blocker	17	18
Angiotensin receptor neprilysin inhibitor	6	7
Mineralocorticoid receptor antagonist	67	64
Beta-blocker	81	84
Loop diuretic	87	85

mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

BASELINE LABORATORY DATA

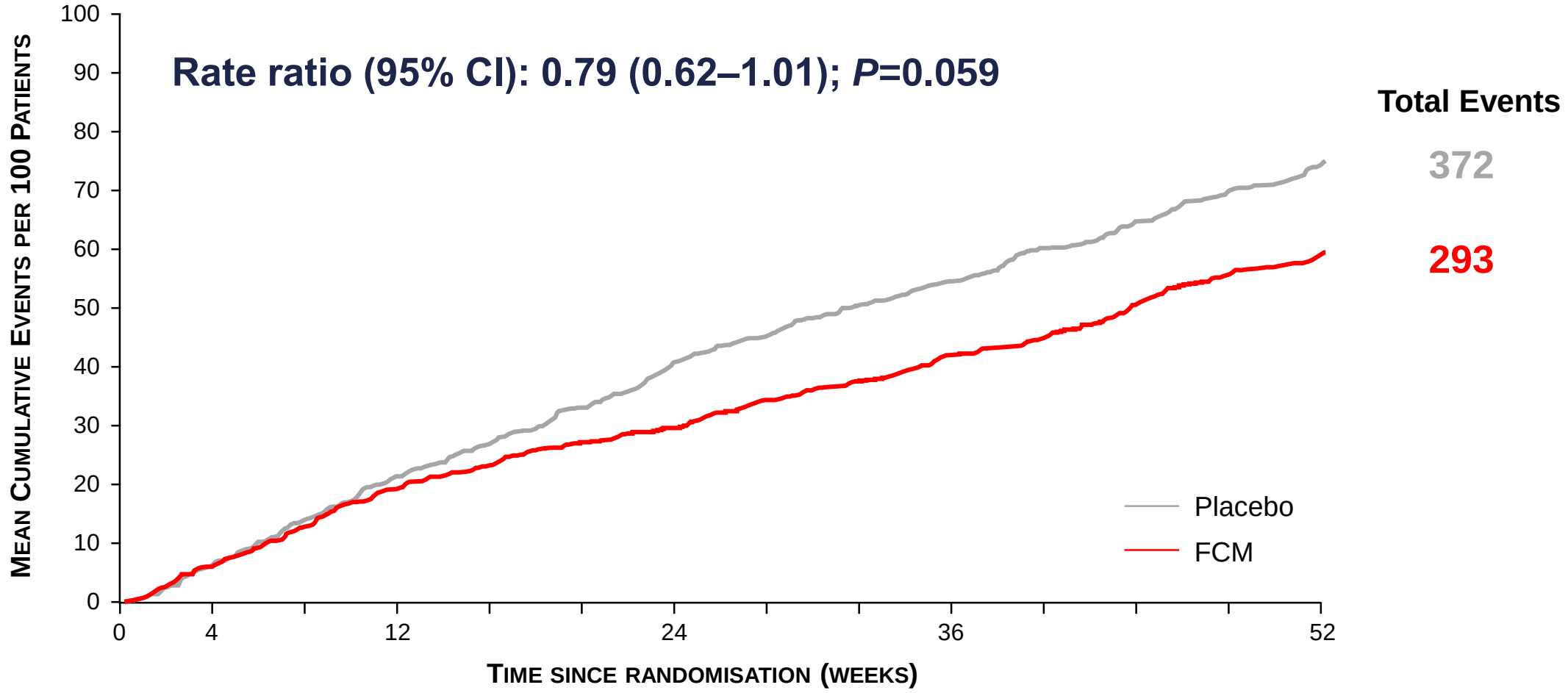
Laboratory test results	FCM (N=558)	Placebo (N=550)
NT-proBNP, pg/mL, median (IQR)	4743 (2781, 8128)	4684 (2785, 8695)
BNP, pg/mL, median (IQR)	1068 (802, 1715)	1204 (803, 1955)
Haemoglobin, g/dL	12.3 ± 1.6	12.1 ± 1.6
Anaemia, %	52	57
Ferritin, ng/mL	83.9 ± 62.2	88.5 ± 68.6
Ferritin <100 ng/mL, %	73	69
TSAT (%)	15.2 ± 8.3	14.2 ± 7.5
TSAT <20%, %	82	85
eGFR, mL/min/1.73 m^2	55.3 ± 21.3	55.7 ± 23.1
eGFR <60 mL/min/1.73 m^2, %	52	52

Results presented as mean ± SD unless otherwise noted.
mITT population.
eGFR, estimated glomerular filtration rate.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

TOTAL HF HOSPITALISATIONS AND CV DEATH

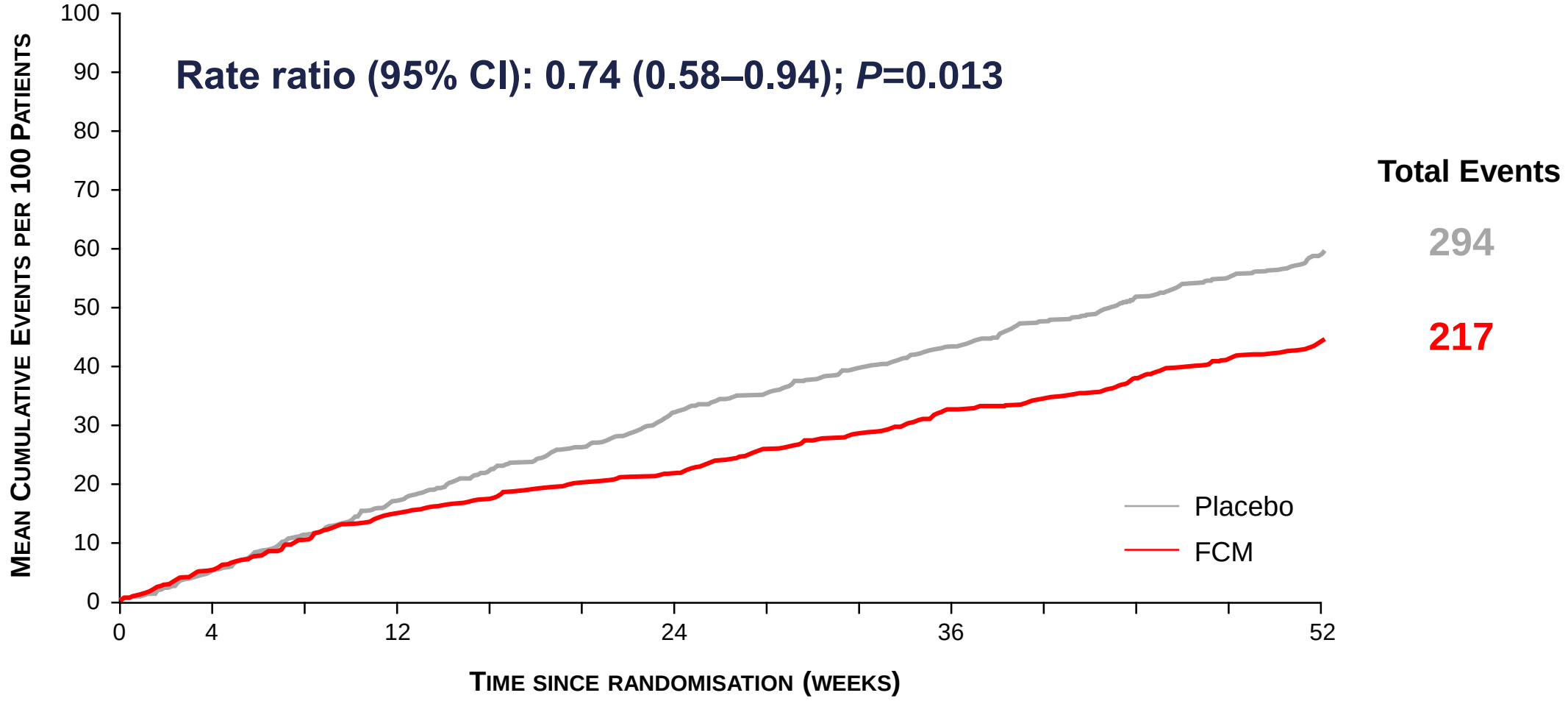
PRIMARY ENDPOINT



mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

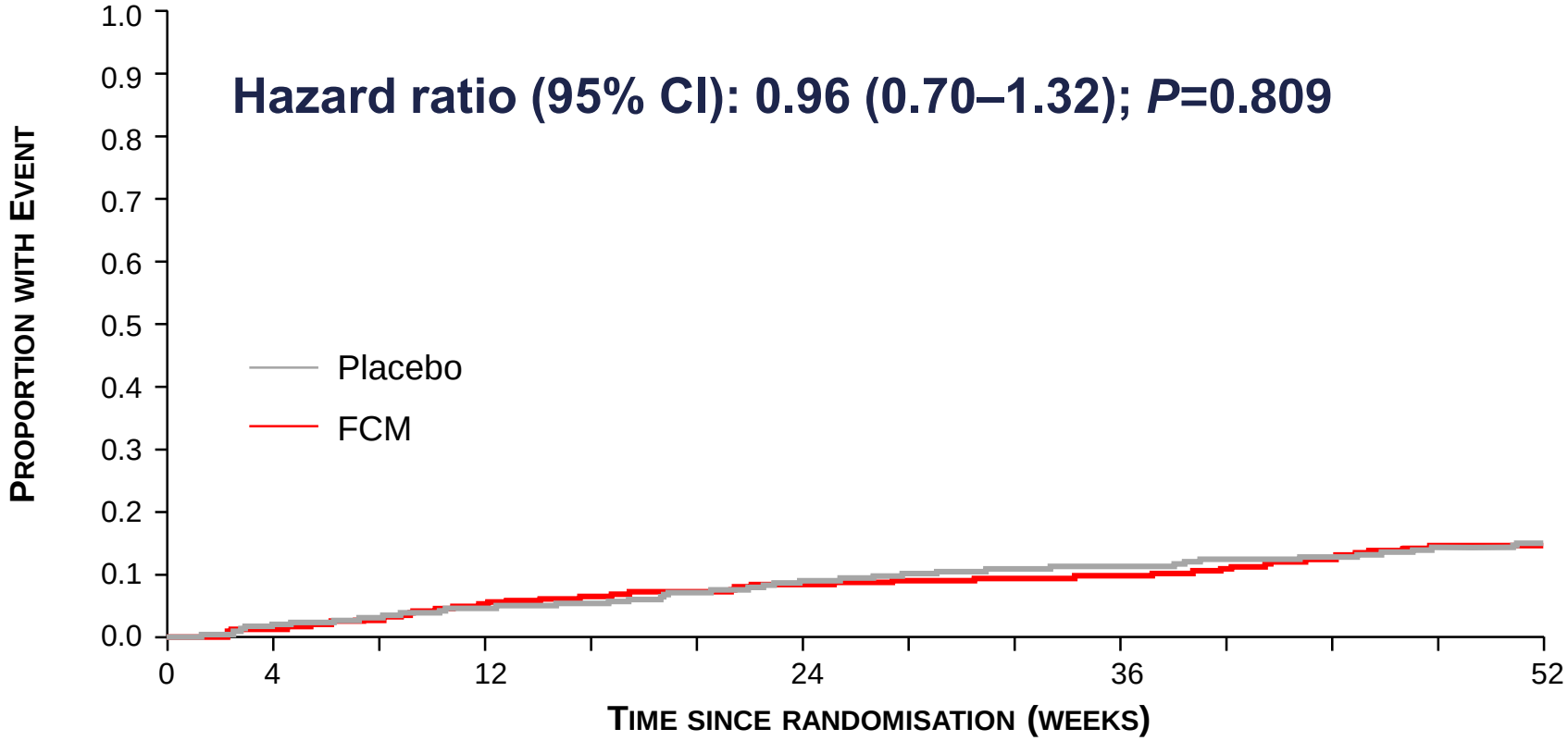
TOTAL HF HOSPITALISATIONS
COMPONENT OF PRIMARY ENDPOINT



mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

CV DEATH
COMPONENT OF PRIMARY ENDPOINT



CV Deaths

78

77

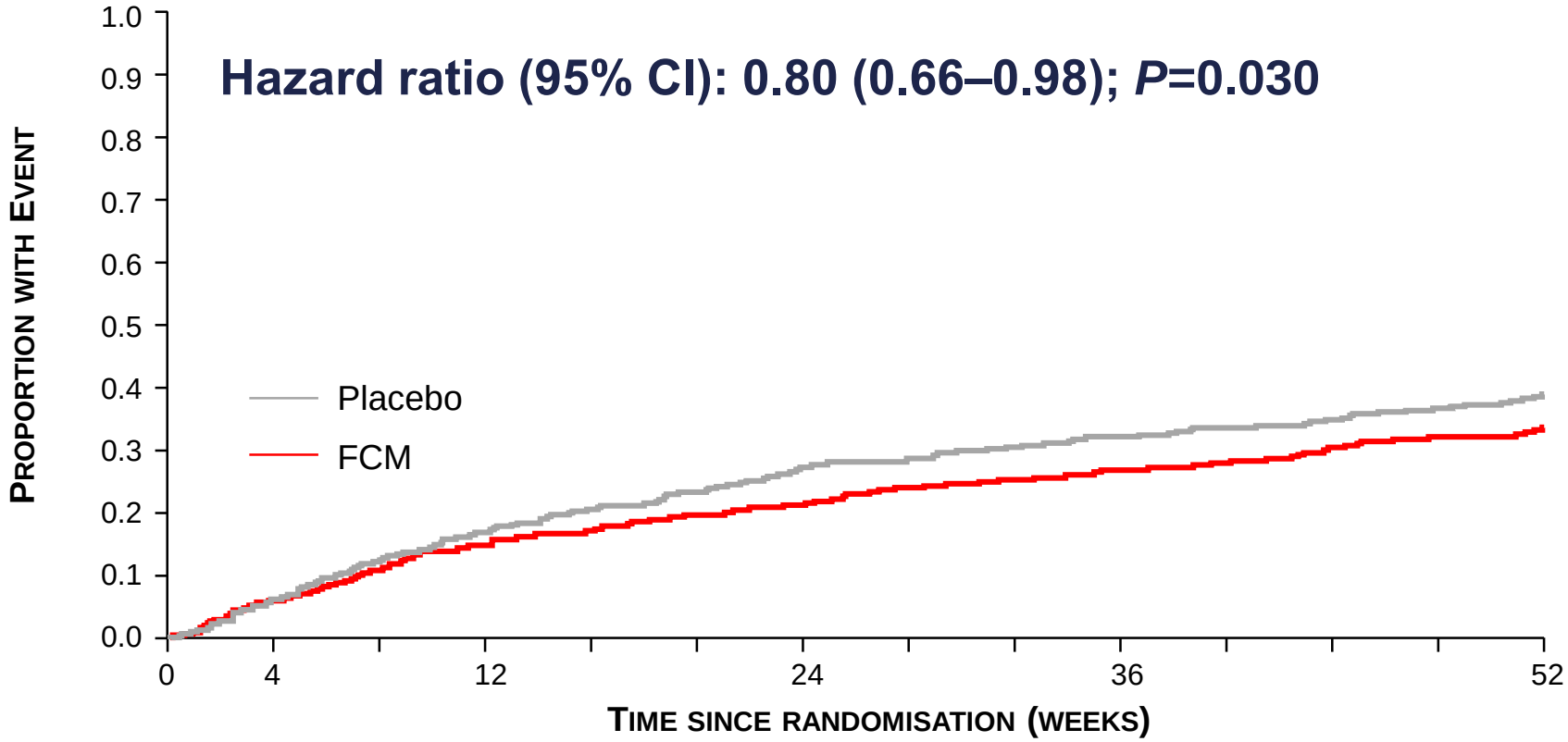
Number at risk

FCM	544	509	483	468	289
Control	537	511	486	465	285

mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

SECONDARY ENDPOINT
FIRST HF HOSPITALISATION OR CV DEATH



First Events

209

181

Number at risk

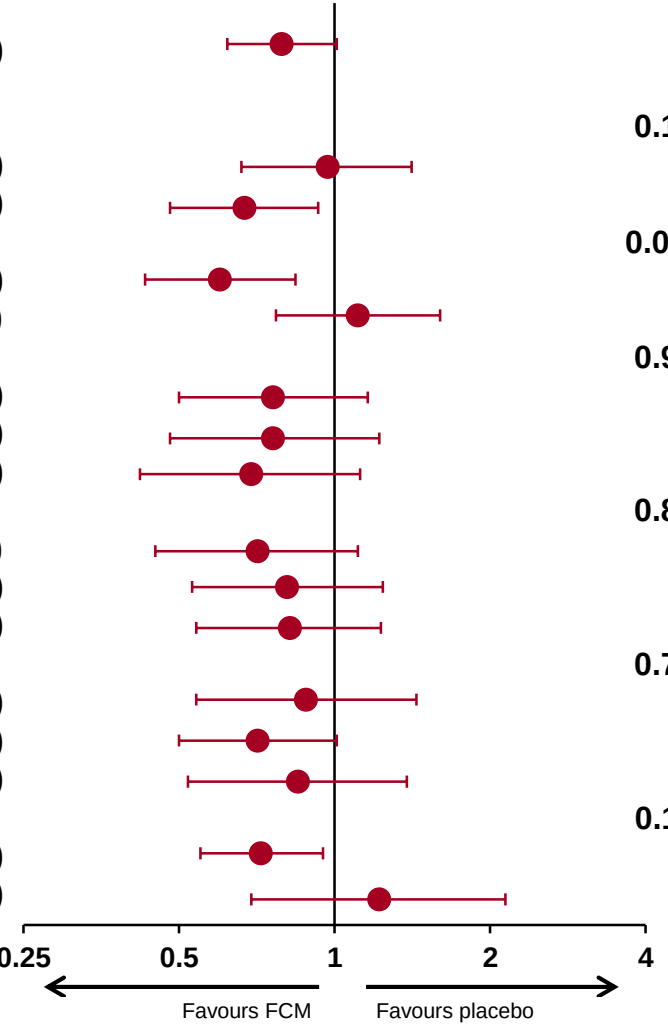
FCM	519	457	416	381	227
Control	514	446	389	358	209

mITT population.

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

PRIMARY ENDPOINT
FOR SELECTED PREDEFINED SUBGROUPS

	FCM Events / Patients	Placebo Events / Patients	Rate Ratio (95% CI)	P for interaction
Overall	293 / 558	372 / 550	**0.79 (0.62–1.01)**	
Hb level at baseline				**0.15**
<12 g/dL	136 / 228	171 / 236	**0.97 (0.66–1.41)**	
≥12 g/dL	156 / 329	201 / 314	**0.67 (0.48–0.93)**	
Heart Failure aetiology				**0.015**
Ischaemic	149 / 265	236 / 257	**0.60 (0.43–0.84)**	
Non-ischaemic	140 / 282	128 / 275	**1.11 (0.77–1.60)**	
eGFR tertiles (mL/min per 1.73 m²) at baseline				**0.94**
<42.96	115 /157	152 / 165	**0.76 (0.50–1.16)**	
≥42.96 to <64.32	76 /166	83 / 156	**0.76 (0.48–1.22)**	
≥64.32	56 /164	79 / 159	**0.69 (0.42–1.12)**	
NT-pro BNP (pg/mL) or BNP (pg/mL) at baseline				**0.88**
Lower tertile	69 / 187	105 / 177	**0.71 (0.45–1.11)**	
Middle tertile	99 / 191	115 / 183	**0.81 (0.53–1.24)**	
Upper tertile	125 / 179	152 / 189	**0.82 (0.54–1.23)**	
Left ventricular ejection fraction at baseline				**0.74**
<25%	84 / 104	113 / 122	**0.88 (0.54–1.44)**	
25% to <40%	144 / 288	178 / 243	**0.71 (0.50–1.01)**	
40% to <50%	65 / 166	80 / 184	**0.85 (0.52–1.38)**	
Diagnosis of HF				**0.11**
Documented HF prior to index hospitalisation	249 / 405	336 / 385	**0.72 (0.55–0.95)**	
Newly diagnosed at index hospitalisation	44 / 153	36 / 165	**1.22 (0.69–2.14)**	



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COVID-19 SENSITIVITY ANALYSIS

	mITT Population RR or HR (95% CI)	Pre-COVID sensitivity analysis RR or HR (95% CI)
Total HF Hospitalisations and CV Death	RR: 0.79 (0.62–1.01) P=0.059	RR: 0.75 (0.59–0.96) P=0.024
Total HF Hospitalisations	RR: 0.74 (0.58–0.94) P=0.013	RR: 0.70 (0.55–0.90) P=0.005
CV Death	HR: 0.96 (0.70–1.32) P=0.81	HR: 0.94 (0.68–1.29) P=0.69
First HF Hospitalisation or CV Death	HR: 0.80 (0.66–0.98) P=0.030	HR: 0.79 (0.65–0.97) P=0.023
Total CV Hospitalisations and CV Death	RR: 0.80 (0.64–1.00) P=0.050	RR: 0.77 (0.62–0.97) P=0.024
Days Lost Due to HF Hospitalisations and CV Death	RR: 0.67 (0.47–0.97) *P*=0.035	N/A

HR, hazard ratio; RR, rate ratio.

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ADVERSE EVENTS OF INTEREST

Adverse events (AE)	FCM (N=559)		Placebo (N=551)	
	Patients n (%)	Total Events (n)	Patients n (%)	Total Events (n)
Cardiac disorders	224 (40.1)	391	244 (44.3)	453
Infections	102 (18.2)	143	121 (22.0)	165
Diarrhea	17 (3.0)	19	14 (2.5)	16
Constipation	10 (1.8)	10	10 (1.8)	12
Hypophosphataemia	1(0.2)	1	1 (0.2)	1
Bone pain	0 (0)	0	1 (0.2)	1
Pruritis	3 (0.5)	3	3 (0.5)	3
Rash	2 (0.4)	2	2 (0.4)	2
Urticaria	1 (0.2)	1	1 (0.2)	1
Neoplasm	9 (1.6)	3	7 (1.3)	9
Drug hypersensitivity	2 (0.4)	2	0 (0)	0
Hypersensitivity	0 (0)	0	1 (0.2)	1

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CONCLUSIONS

- In patients with iron deficiency, stabilised after an episode of acute HF, treatment with FCM relative to placebo:
  - Reduced the risk for the combined endpoint of HF hospitalisations and CV death by 21%. The statistical significance was narrowly missed *(p=0.059)*
  - The result of the primary endpoint, was mainly driven by a 26% reduction in HF re-hospitalisation *(p=0.013)*
  - Statistically significant treatment benefits with FCM were seen on the time to first HF hospitalisation or CV death
- 80% of patients only required 1-2 injections of FCM during the dosing period
- The prespecified COVID-19 sensitivity analyses revealed statistically significant differences in favor of FCM for the primary and secondary outcomes
- Treatment with FCM was well tolerated

Administration of FCM in patients with iron deficiency, LVEF <50%, stabilised after an episode of acute HF reduces the risk of subsequent HF hospitalisations

THANK YOU!

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