Supplementary appendix

# Responder analysis of improvement in six-minute walk test with ferric carboxymaltose in iron- deficient heart failure with reduced ejection fraction patients

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**Supplementary Table 1: Key Characteristics of the two included randomized controlled trials in iron-deficient HFrEF patients**

|  |  |  |
| --- | --- | --- |
|  | **FAIR-HF1,2** | **CONFIRM-HF3,4** |
| **Randomization** | 2:1 (FCM:placebo) | 1:1 (FCM:placebo) |
| **Number of patients** | 459 (FCM: 304; placebo: 155) | 301\* (FCM: 150; placebo: 151) |
| **Study duration** | 24 weeks | 52 weeks |
| **Patient population and HF details** | Ambulatory patients with optimallytreated CHF (NYHA class II/III) and iron deficiency | Ambulatory patients with optimallytreated CHF (NYHA class II/III) and iron deficiency |
| **Hemoglobin** | ≥9.5 and ≤13.5 g/dL | <15 g/dL |
| **Primary endpoint** | Change in PGA score and NYHAclass from baseline to week 24 | Change in 6MWT distance frombaseline to week 24 |

**Legend:** \*304 patients were randomized but only 301 received study treatment and had any post-baseline assessment. 6MWT, 6-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; NYHA, New York Heart Association; PGA, Patient Global Assessment.

# Supplementary Table 2: Proportion of patients with 6MWT data available at weeks 12 and 24 in FCM and placebo arms

|  |  |  |
| --- | --- | --- |
| **Number of Patients (%)** | **FCM(N=454)** | **Placebo(N=306)** |
| At week 12 |
| Patient with data available | 408(89.9) | 276(90.2) |
| Patients imputed for death | 6(1.3) | 5(1.6) |
| Patients imputed for hospitalization | 4(0.9) | 8(2.6) |
| Alive and non-hospitalized patients with missing data | 36(7.9) | 17(5.6) |
| At week 24 |
| Patients with data available | 396(87.2) | 264(86.3) |
| Patients imputed for death | 12(2.6) | 9(2.9) |
| Patients imputed for hospitalization | 6(1.3) | 10(3.3) |
| Alive and non-hospitalized patients with missing data | 40(8.8) | 23(7.5) |

# Legend: 6MWT, 6-minute walk test; FCM, ferric carboxymaltose

# Supplementary Table 3: NNT to achieve defined change vs baseline in 6MWT at weeks 12 and 24 (random-effects model)

|  |  |  |
| --- | --- | --- |
|  | **Week 12** | **Week 24** |
| **Improvement** |  |  |
| **≥20 m** | 6 | 6 |
| **≥30 m** | 8 | 7 |
| **≥40 m** | 9 | 8 |
| **Deterioration** |  |  |
| **≥10 m** | 7 | 6 |

**Legend:** ORs from the random-effects responder analysis were converted into NNT using the formula described in Hutton et al.5 and the placebo control response/deterioration proportion.

6MWT, 6-minute walk test; NNT, number needed to treat; OR, odds ratio

**Supplementary Table 4: Changes in KCCQ-OSS score according to 6MWT responder categories from baseline to week 12 and 24 in the FCM and placebo arms.**

|  |  |
| --- | --- |
| 6-Minute Walk Test (6MWT) Responder Categories | Mean(SD) Changes in KCCQ-OSS score from Baseline |
| FCM | Placebo |
| At week 12 |
| Improvement ≥ 20 | 14.2(18.9) | 5.4(11.3) |
| Improvement ≥ 30 | 15.6(19.8) | 4.5(10.2) |
| Improvement ≥ 40 | 17.0(20.2) | 5.0(11.1) |
| Deterioration ≥ 10 | 0.80(14.9) | 1.8(16.2) |
| At week 24 |
| Improvement ≥ 20 | 15.6(19.1) | 8.7(14.5) |
| Improvement ≥ 30 | 16.9(19.5) | 9.0(14.7) |
| Improvement ≥ 40 | 17.5(20.2) | 9.5(13.2) |
| Deterioration ≥ 10 | -0.56(15.1) | -0.2(16.1) |

**Legend:** 6MWT, 6-minute walk test; NNT, FCM, Ferric carboxymaltose; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; SD, Standard deviation

**Supplementary Table 5: Changes in KCCQ-CSS score according to 6MWT responder categories from baseline to week 12 and 24 in the FCM and placebo arms.**

|  |  |
| --- | --- |
| 6-Minute Walk Test (6MWT) Responder Categories | Mean(SD) Changes in KCCQ-CSS score from Baseline |
| FCM | Placebo |
| At week 12 |
| Improvement ≥ 20 | 13.5(18.5) | 5.4(10.6) |
| Improvement ≥ 30 | 14.8(19.5) | 4.6(10.1) |
| Improvement ≥ 40 | 15.6(19.3) | 5.1(11.3) |
| Deterioration ≥ 10 | -0.66(16.4) | 3.0(16.5) |
| At week 24 |
| Improvement ≥ 20 | 14.4(18.7) | 7.6(15.3) |
| Improvement ≥ 30 | 15.4(19.0) | 8.1(15.3) |
| Improvement ≥ 40 | 15.7(19.7) | 9.0(14.2) |
| Deterioration ≥ 10 | -1.0(15.0) | 0.5(15.7) |

**Legend:** 6MWT, 6-minute walk test; NNT, FCM, Ferric carboxymaltose; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; SD, Standard deviation

**Supplementary Table 6: Changes in EQ-5D Health State (VAS) score according to 6MWT responder categories from baseline to week 12 and 24 in the FCM and placebo arms.**

|  |  |
| --- | --- |
| 6-Minute Walk Test (6MWT) Responder Categories | Mean(SD) Changes in EQ-5D Health State (VAS) score from Baseline |
| FCM | Placebo |
| At week 12 |
| Improvement ≥ 20 | 8.6(13.9) | 5.3(13.7) |
| Improvement ≥ 30 | 9.0(14.2) | 5.1(12.7) |
| Improvement ≥ 40 | 8.7(14.0) | 4.8(12.9) |
| Deterioration ≥ 10 | -0.4(12.9) | -0.1(13.5) |
| At week 24 |
| Improvement ≥ 20 | 10.6(14.4) | 8.3(13.8) |
| Improvement ≥ 30 | 11.2(14.6) | 6.9(12.9) |
| Improvement ≥ 40 | 11.6(14.8) | 6.0(12.5) |
| Deterioration ≥ 10 | 2.9(12.5) | -1.5(14.3) |

**Legend:** 6MWT, 6-minute walk test; NNT, FCM, Ferric carboxymaltose; VAS, Visual analogue scale; SD, Standard deviation

**Supplementary Table 7: Changes in EQ-5D index score according to 6MWT responder categories from baseline to week 12 and 24 in the FCM and placebo arms.**

|  |  |
| --- | --- |
| 6-Minute Walk Test (6MWT) Responder Categories | Mean (SD) Changes in EQ-5D index score from Baseline |
| FCM | Placebo |
| At week 12 |
| Improvement ≥ 20 | 0.13(0.23) | 0.06(0.17) |
| Improvement ≥ 30 | 0.13(0.23) | 0.04(0.15) |
| Improvement ≥ 40 | 0.14(0.23) | 0.04(0.16) |
| Deterioration ≥ 10 | -0.05(0.21) | -0.02(0.24) |
| At week 24 |
| Improvement ≥ 20 | 0.13(0.23) | 0.07(0.21) |
| Improvement ≥ 30 | 0.15(0.23) | 0.06(0.21) |
| Improvement ≥ 40 | 0.16(0.23) | 0.04(0.19) |
| Deterioration ≥ 10 | 0.03(0.22) | -0.01(0.21) |

**Legend:** 6MWT, 6-minute walk test; NNT, FCM, Ferric carboxymaltose; SD, Standard deviation

**Supplementary Table 8: Changes in NYHA Score according to 6MWT responder categories from baseline to week 12 and 24 in the FCM and placebo arms.**

|  |  |
| --- | --- |
| 6-Minute Walk Test (6MWT) Responder Categories | Mean (SD) Changes in NYHA Score from Baseline |
| FCM | Placebo |
| At week 12 |
| Improvement ≥ 20 | -0.4(0.6) | -0.1(0.3) |
| Improvement ≥ 30 | -0.4(0.6) | 0.0(0.3) |
| Improvement ≥ 40 | -0.5(0.7) | -0.1(0.4) |
| Deterioration ≥ 10 | 0.2(0.7) | 0.3(0.7) |
| At week 24 |
| Improvement ≥ 20 | -0.4(0.6) | -0.2(0.4) |
| Improvement ≥ 30 | -0.5(0.6) | -0.2(0.5) |
| Improvement ≥ 40 | -0.5(0.7) | -0.2(0.5) |
| Deterioration ≥ 10 | 0.4(0.9) | 0.4(0.8) |

**Legend:** 6MWT, 6-minute walk test; NNT, FCM, Ferric carboxymaltose; NYHA, New York Heart Association; SD, Standard deviation

# Supplementary Figure 1: Mean change from baseline in 6MWT with FCM vs placebo at weeks 12 and 24 – random-effects model



**Legend:** LS mean difference based on a random-effects MMRM analysis adjusted for study, baseline 6MWT score, age, estimated glomerular filtration rate, diabetes status, sex, and left ventricular ejection fraction. The random-effects model was an expanded version of the fixed-effects model, including random treatment-by-study interactions. Since only 6 patients are from Latin America and the remainder are from Europe, region was not included in the model. In FCM and placebo groups, patient numbers were 418 and 289, respectively, at week 12 and 415 and 283, respectively, at week 24. 6MWT, 6-minute walk test; CI, confidence interval; FCM, ferric carboxymaltose; LS, least-squares; MMRM, mixed model for repeated measures; SD, standard deviation.

**Supplementary Figure 2: Responder analyses across MCID thresholds for 6MWT**



**Legend:** ORs with CIs and p-values were obtained from logistic regression models, including treatment group, study, and the following baseline factors: 6MWT distance, age, eGFR, diabetes status, sex, and left ventricular ejection fraction. The random-effects model was an expanded version of the fixed-effects model, including random treatment-by-study interactions. Furthermore, the covariate effects were allowed to vary across studies by introducing appropriate interactions. Patients were from Europe and Latin America, but since only six patients were from Latin America, region was not included in the model. Patients who had died or were hospitalised at week 12 and 24 were counted as deteriorated/non-responder at the respective time point. 6MWT, 6-minute walk test; CI, confidence interval; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; MCID, minimal clinically important difference; OR, odds ratio; PBO, placebo.

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