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

Dirk J. van Veldhuisen, Piotr Ponikowski, Marco Metra, Michael Böhm, Peter van der Meer, Artem Doletsky, Adriaan A. Voors, Iain MacDougall, Bernard Roubert, Stefan D. Anker, Alain Cohen Solal for the EFFECT-HF Investigators.

Sponsor: Vifor Pharma Ltd.

Dept. of Cardiology, University Medical Center Groningen
Groningen, The Netherlands
Iron deficiency: A therapeutic target in heart failure?

- Iron deficiency is frequent co-morbidity in patients with stable chronic HF and in patients admitted to hospital with acute HF\(^1,2\)
- HF complicated with iron deficiency is associated with impaired functional capacity, poor quality of life and increased mortality\(^1,3,4\)
- Deleterious consequences of iron deficiency in HF irrespective of presence of anaemia\(^1,3,4\)
- Iron deficiency: a therapeutic target in HF\(^5,6\)

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

Defective oxygen delivery (erythropoiesis)

- Iron deficiency
  - Hb
  - Mitochondrion
  - O₂ delivery
  - pVO₂

Defective oxygen utilization (energy metabolism)

- Iron deficiency
  - Aerobic enzymes
  - O₂ utilization
  - ATP synthesis
  - ATP
  - O₂

Haas JD, et al. Nutr 2001;131:676S-90S.
Benefits of Ferric CarboxyMaltose (FCM, iv iron) in CHF: FAIR-HF and CONFIRM-HF studies

Patient Global Assessment

NYHA functional class

6MWT

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

Rationale for EFFECT-HF

- Exercise intolerance (dyspnea and fatigue) is a key symptom of HF\textsuperscript{1}
- Cardiopulmonary exercise testing defines maximum exercise capacity through measurement of peak oxygen uptake (peak VO\textsubscript{2})\textsuperscript{1}
- Peak VO\textsubscript{2} is a powerful predictor of prognosis in HF, is objective, reproducible, and used to evaluate cardiac transplantation and LVAD\textsuperscript{2}
- Even a modest increase in peak VO\textsubscript{2} has been associated with a more favorable outcome in HF patients\textsuperscript{2}

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

**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

**ClinicalTrials.gov identifier:** NCT01394562
Primary and key secondary endpoints

- **Primary endpoint**
  - Change in weight-adjusted peak VO\textsubscript{2} from baseline to Week 24

- **Key secondary endpoints**
  - Change in peak VO\textsubscript{2} (mL/kg/min) from baseline to Week 12
  - Change in other exercise parameters (VE-VCO\textsubscript{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 assessment; QoL, quality of life
The primary efficacy analysis of peak VO₂ at 24 weeks was an ITT analysis in which missing peak VO₂ values were imputed using last observation carried forward (LOCF).

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.

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.

The safety analysis was performed on the safety population, which consisted of all randomized subjects who received ≥1 dose of study medication.
**Patient disposition**

**N=525 screened**

**N=174 randomized to treatment**

**FCM**
- *n=2* excluded from the full analysis set (lack of any post-baseline efficacy assessment)
- *n=86* full analysis set

**Standard of Care**
- *n=0* excluded from the full analysis set (lack of any post-baseline efficacy assessment)
- *n=86* full analysis set

<table>
<thead>
<tr>
<th>Country (N=9)</th>
<th>No. of study sites (N=41)</th>
<th>Patients randomized (N=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3 sites</td>
<td><em>n=4</em></td>
</tr>
<tr>
<td>Belgium</td>
<td>1 site</td>
<td><em>n=8</em></td>
</tr>
<tr>
<td>France</td>
<td>2 sites</td>
<td><em>n=10</em></td>
</tr>
<tr>
<td>Germany</td>
<td>3 sites</td>
<td><em>n=24</em></td>
</tr>
<tr>
<td>Italy</td>
<td>4 sites</td>
<td><em>n=18</em></td>
</tr>
<tr>
<td>Netherlands</td>
<td>2 sites</td>
<td><em>n=22</em></td>
</tr>
<tr>
<td>Poland</td>
<td>1 site</td>
<td><em>n=36</em></td>
</tr>
<tr>
<td>Russia</td>
<td>10 sites</td>
<td><em>n=42</em></td>
</tr>
<tr>
<td>Spain</td>
<td>2 sites</td>
<td><em>n=10</em></td>
</tr>
</tbody>
</table>
## Baseline characteristics – (1/2)

<table>
<thead>
<tr>
<th></th>
<th>FCM (N=86)</th>
<th>SoC (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age years</strong></td>
<td>62.7 (11.56)</td>
<td>64.4 (11.42)</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>26 (30.2)</td>
<td>17 (19.8)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II n (%)</td>
<td>61 (70.9)</td>
<td>54 (62.8)</td>
</tr>
<tr>
<td>III n (%)</td>
<td>25 (29.1)</td>
<td>32 (37.2)</td>
</tr>
<tr>
<td><strong>LVEF %</strong></td>
<td>32.5 (8.7)</td>
<td>31.0 (7.5)</td>
</tr>
<tr>
<td><strong>Ischemic etiology n (%)</strong></td>
<td>60 (69.8)</td>
<td>64 (74.4)</td>
</tr>
<tr>
<td><strong>Peak VO$_2$ ml/min/kg</strong></td>
<td>13.55 (2.28)</td>
<td>13.36 (2.42)</td>
</tr>
</tbody>
</table>

### Medical history

<table>
<thead>
<tr>
<th></th>
<th>FCM (N=86)</th>
<th>SoC (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension n (%)</strong></td>
<td>62 (72.1)</td>
<td>56 (65.1)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation n (%)</strong></td>
<td>35 (40.7)</td>
<td>41 (47.7)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus n (%)</strong></td>
<td>26 (30.2)</td>
<td>32 (37.2)</td>
</tr>
<tr>
<td><strong>Myocardial infarction n (%)</strong></td>
<td>58 (67.4)</td>
<td>55 (64.0)</td>
</tr>
</tbody>
</table>

*mean (standard deviation)

FCM, ferric carboxymaltose; SoC, standard of care
## Baseline characteristics – (2/2)

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>FCM (N=86)</th>
<th>SoC (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics n (%)</td>
<td>80 (93.0)</td>
<td>82 (95.3)</td>
</tr>
<tr>
<td>ACEi/ARB n (%)</td>
<td>81 (94.2)</td>
<td>77 (89.5)</td>
</tr>
<tr>
<td>Beta-blocker n (%)</td>
<td>84 (97.7)</td>
<td>84 (97.7)</td>
</tr>
<tr>
<td>Aldosterone antagonists (MRA) n (%)</td>
<td>58 (67.4)</td>
<td>62 (72.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>FCM (N=86)</th>
<th>SoC (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP pg/mL*</td>
<td>838 (762)</td>
<td>796 (819)</td>
</tr>
<tr>
<td>NT-proBNP pg/mL*</td>
<td>2631 (3141)</td>
<td>2415 (2592)</td>
</tr>
<tr>
<td>Estimated GFR mL/min/1.73m²*</td>
<td>51.5 (13.3)</td>
<td>50.8 (12.3)</td>
</tr>
<tr>
<td>Hb g/dL *</td>
<td>12.93 (1.30)</td>
<td>12.99 (1.46)</td>
</tr>
<tr>
<td>Ferritin ng/mL*</td>
<td>62.06 (60.64)</td>
<td>64.72 (51.44)</td>
</tr>
<tr>
<td>&lt;100 ng/mL n (%)</td>
<td>74 (86.0)</td>
<td>71 (82.6)</td>
</tr>
<tr>
<td>TSAT % *</td>
<td>19.65 (13.71)</td>
<td>20.07 (9.63)</td>
</tr>
<tr>
<td>&lt;20% n (%)</td>
<td>53 (61.6)</td>
<td>46 (53.5)</td>
</tr>
</tbody>
</table>

*mean (standard deviation);

FCM, ferric carboxymaltose; SoC, standard of care
## Results: Iron-related parameters

### Change from baseline to Week 24

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FCM (N=86)</th>
<th>SoC (N=86)</th>
<th>Contrast: FCM – SoC**</th>
<th>P-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 24</td>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>Ferritin  ng/mL*</td>
<td>62.06 (60.64)</td>
<td>283.17 (150.28)</td>
<td>64.72 (51.44)</td>
<td>92.31 *** (65.43)</td>
</tr>
<tr>
<td>TSAT %*</td>
<td>19.65 (13.71)</td>
<td>26.54 (8.25)</td>
<td>20.07 (9.63)</td>
<td>21.90 (10.17)</td>
</tr>
<tr>
<td>Hb g/dL*</td>
<td>12.93 (1.30)</td>
<td>13.90 (1.30)</td>
<td>12.99 (1.46)</td>
<td>13.19 (1.47)</td>
</tr>
</tbody>
</table>

*mean (standard deviation)

**least squares means (standard error)

***29 pts in SoC received oral iron

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)

P = 0.02

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)

P = 0.01

*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: VE/VCO₂ slope and peak work rate

VE/VCO₂ slope

Contrast FCM vs placebo for VE/VCO₂ 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/VCO₂, 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; FCM, ferric carboxymaltose; LOCF, last observation carried forward; SoC, standard of care
Hospitalizations and deaths (safety population)

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

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.
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.

**Parameter** | **FCM (N=88)** | **SoC (N=85)** | **Total (N=173)**
--- | --- | --- | ---
Any AE | n (%) E | n (%) E | n (%) E
--- | --- | --- | ---
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
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 (FCM) over a 24-week period resulted in:
  - A significantly beneficial effect on peak VO$_2$ compared with the SoC arm (irrespective of baseline 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 in patients with HF and iron deficiency

SoC, standard of care

We dedicate this work to our 2 wonderful and inspiring colleagues, and fellow Steering Committee members who died during the study:

Viviane Conraads (Antwerp, Belgium), and
Henry Krum (Melbourne, Australia).