Budget impact of intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency in France

Sandrine Bourguignon¹, Mathilde Faller¹*, François-Olivier Champs¹, Hélène Moutier¹, Karine Levesque², Gilbert Caranhac³ and Alain Cohen-Solal⁴

¹IQVIA, Courbevoie, France; ²Vifor Pharma France, Paris, France; ³Hox-Com Analytiques, Vincennes, France; ⁴INSERM UMRS-942, Sorbonne Paris Cite, Lariboisière Hospital—AP-HP, Paris, France

Abstract

Aims This analysis aims to evaluate the budget impact of intravenous iron therapy with ferric carboxymaltose for patients with systolic chronic heart failure and iron deficiency, from the perspective of the French public health insurance.

Methods and results A budget impact model was adapted to forecast the budget impact over 5 years, according to two scenarios: one where patients receive ferric carboxymaltose according to market share forecast and another where patients are not treated for iron deficiency. Clinical data were extrapolated from pooled data from four randomized controlled trials. The time horizon was extended to 5 years by applying transition probabilities estimated from the CONFIRM-HF trial. Epidemiological parameters for France were derived from the literature. Cost parameters were derived from national available databases. In the base case analysis, the modelled 5 year cost difference between the scenarios with ferric carboxymaltose vs. no iron deficiency treatment in a population of 189 334 prevalent and incident patients led to €0.8m savings. The cumulative savings resulted from a reduction in the hospitalization costs associated with worsening heart failure (€−35.8m) as well as a reduction in the follow-up costs (€−2.9m). These cost savings outweighed the costs of ferric carboxymaltose treatment (€37.7m). Sensitivity analyses showed that the budget impact varied from €−34m to €+146m. Parameters with the most impact on the budget were the hospitalization rate for patients not treated for iron deficiency, the number of ambulatory sessions needed, the absence of hospitalization cost differentiation between New York Heart Association classes, and administration settings costs.

Conclusions Iron deficiency treatment with ferric carboxymaltose in systolic chronic heart failure patients results in an improvement of New York Heart Association class and thereby increases the well-being of the patients, while providing an overall cost saving for the French national health insurance.

Keywords Iron deficiency; Chronic heart failure; Cost; Budget impact; Ferric carboxymaltose

Introduction

Chronic heart failure (CHF) is a chronic disease in which the heart is unable to pump efficiently, resulting in a limited ability to deliver oxygen to the body. It affects more than a million patients in France,¹ with an estimated prevalence of 2.2% in the overall French population² and up to 15% among individuals aged 85 years or more.³ Cardiovascular diseases represent the second cause of death in France.⁴ In 2013, over 165 000 hospitalizations for heart failure were reported in France, 20% of whom were re-hospitalized for heart failure within the same year.⁵ In 2015, the cost of CHF to the national health insurance was more than €1.2bn, reflecting an annual increase of 4.6%.⁶ A major proportion of healthcare spending for CHF is attributed to hospitalizations,⁷ while other costs are associated with medications, as well as medical and paramedical visits.⁷
Iron deficiency (ID) is observed in approximately half of all patients who experience CHF and is defined as a ferritin level <100 μg/L or ferritin 100–299 μg/L with a transferrin saturation <20%. It can be the consequence of insufficient iron storage (absolute ID) or may arise from a deficit in the transport and use of iron (functional ID). Studies have shown that ID in the context of CHF is associated with disease severity in terms of New York Heart Association (NYHA) score and is also associated with an increased number of hospitalizations and an increased risk of death. Recent guidelines published by the European Society of Cardiology in 2016 for the diagnosis and treatment of heart failure state that ID is a common comorbidity and recommend that treatment with ferric carboxymaltose (FCM) should be considered in symptomatic patients with systolic CHF and ID.

Heart failure with a reduced ejection fraction occurs when the heart muscle loses its ability to efficiently circulate blood. Four randomized placebo-controlled trials (RCTs), conducted prior to 2014, measuring the efficacy of FCM, demonstrated a clinical improvement associated with the correction of ID in CHF patients with a reduced ejection fraction. The FAIR-HF study was conducted in 75 centres over 24 weeks and recruited 459 ambulatory patients suffering from symptomatic CHF with NYHA II or III and ID. CONFIRM-HF enrolled 304 patients with CHF with NYHA II or III and ID in 42 centres over 52 weeks. FAIR-HF and CONFIRM-HF were combined with data from two smaller studies (FER-CARS-01 and EFFICACY-HF) to conduct a pooled analysis, which showed significant improvements in functional capacity, symptoms, and quality of life for patients taking FCM compared with placebo. The objective of this study was to measure the budget impact of treatment with FCM in patients with CHF and ID and a reduced ejection fraction, in the context of the French national health insurance, using a 5 year time horizon.

Methods

To estimate the budget impact of FCM treatment, we adapted a decision analytic model previously used to assess the budget impact of FCM in Germany, to the French setting. The adaptation was made to meet the French guidelines on budget impact analysis from the national health authorities (Haute Autorité de Santé). The characteristics common to both the current model and that on which the adaptation is based are the clinical data and the method used to convert them into transition probabilities. Other parameters, specifically the perspective, objective of the model, and the scenarios modelled, costs, number of patients, and patient characteristics, differed. Two scenarios were considered: in the first, FCM is administered to increasing market shares of patients with CHF and ID (8, 15, 20, 25, and 35% over 5 years); in the second scenario, patients are not treated for ID. Thus, Scenario 1 combines treated and untreated patients, with different market shares, while Scenario 2 only considers untreated patients. A 5 year time horizon was used, in accordance with guidelines from the French health authority, and the perspective used was the national health insurance. Three outputs were measured: (i) healthcare cost differences between the two scenarios (2017, Euro based), (ii) avoided hospitalizations due to CHF worsening, and (iii) avoided days of hospitalizations due to CHF worsening.

Patient population and treatment

The simulated target population consisted of patients suffering from CHF with a reduced ejection fraction and ID. The model sample size was based on French epidemiological publications, with a reported prevalence of 540 000 patients being managed for CHF and an incidence of CHF of 120 000. Considering that approximately 50% of CHF patients have a reduced ejection fraction, among whom approximately 74% are symptomatic and 50% have ID, a population of 100 000 prevalent patients with CHF and ID was used in the model. Overall, 22 200 incident cases were considered and which were considered to be increasing at the rate of national population growth of 0.4%.

The baseline population characteristics were based on national studies. The mean age (78 years) and mean serum haemoglobin level (11.9 g/dL) used in the model were extracted from a prospective study of patients hospitalized for decompensation heart failure assessed during the 72 h after hospital admission. The proportion of women (51%) was derived from a national survey. Patients included in the four RCTs had NYHA Class II or III at inclusion, which this was thus used for patients at model entry. In the pooled analysis of RCTs, the NYHA distribution was 29% NYHA II and 70% NYHA III for the FCM arm. However, the model allows for adjustment on the proportion of patients in NYHA Classes II and III. In order to represent the population of interest, we used the proportion of patients in the NYHA classes according to a French publication of hospitalized CHF patients, resulting in 35% of patients entering the model with NYHA Class II and 65% entering with NYHA Class III. The model incorporates a transition period between assessment times (from 4 to 16 weeks): 4 weeks after entering the model, patients transition in all NYHA classes or die. The method used to calculate transition probabilities is described in the following section. Patients treated with FCM receive an annual administration in an outpatient setting. In the scenario without FCM, patients did not receive any treatment for ID.
Clinical parameters

The clinical data used in the present study were derived from the pooled analysis used in the initial model up to Week 52. This analysis combined the four RCTs comparing FCM with placebo in CHF patients (FER-CARS-01, FAIR-HF, EFFICACY-HF, and CONFIRM-HF). In the initial model, RCT data were used to develop statistical models predicting the NYHA class distribution over time, rates of hospitalization, and mean length of stay for all NYHA classes (I to IV). In the RCTs, patients hospitalized at the time of assessment were assumed to have an NYHA score of IV. The budget impact model compares treatment with FCM using data from the FCM arm of the pooled dataset, with data for patients receiving no iron treatment taken from the placebo arm (Table 1).

Three outcomes were integrated in the analysis: the probability of being in each of the NYHA classes, the probability of experiencing death over time, and the rate of hospitalization due to CHF worsening (0.0013 hospitalizations per patient-week for FCM vs. 0.0033 for placebo) were considered in the calculation of the budget impact. Mean length of hospitalization (11.72 days per hospitalization for FCM vs. 14.73 for placebo) was considered separately and was not part of the calculation of the budget impact. This choice was made because the multivariate statistical models predicting length of stay were not considered robust. Considering that FCM reduces length of stay, this can be regarded as a conservative approach to measuring the budget impact.

To predict these outcomes, multivariate statistical analyses were conducted. The explanatory variables in all regression analyses included baseline age, gender, haemoglobin level, and NYHA class. Geographical region was considered in the analysis and was included as a predictor if the region variable improved model fit or model predictions. Akaike and Bayesian criteria, log-likelihood ratio test, and the clinical credibility of the predictions were used to select variables. To predict the disease status in terms of NYHA class over time, a multinomial logistic regression model was built and implemented into the model.

To calculate the probability of being in each of the NYHA classes, three statistical models were used from the initial model to predict three clinical outcomes: (i) improvement of NYHA class, (ii) worsening of NYHA class, and (iii) death. Because of different follow-up times in the clinical trials, the pooled dataset was limited to 24 weeks of follow-up. In order to extend the time horizon to 52 weeks, data from the CONFIRM-HF trial only were used to model the transition probabilities from Week 24 to Week 52, using repeated measures logistic regression models. No trial data were available beyond 52 weeks. Thus, in this model, transition probability from Week 52 is the same as that calculated for Week 24 to 52 (from the CONFIRM-HF trial).

Rate of hospitalizations and mean length of stay

A log-negative binomial regression analysis from the initial model was used to estimate the hospitalization rate due to CHF worsening. A log-link negative binomial regression was used to estimate the mean length of stay per hospitalization due to CHF worsening. The multivariate analysis used data from all cardiovascular hospitalizations with a variable for reason of hospitalization (other cardiovascular vs. worsening of CHF) included as an additional covariate.

Cost parameters

Direct medical costs covered by the national health insurance were included in the budget impact model. In both modelled scenarios (see first paragraph in section), the integrated costs include outpatient follow-up, other CHF-related medications,

Table 1 Clinical data

| Study                  | Type               | Clinical parameters in the model | Outcomes in the model                                                                 | Extrapolation of clinical data                                                                 |
|-----------------------|--------------------|---------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| FER-CARS-01           | Clinical trial     | Not used directly               | • Probability of being in each of the NYHA classes or experiencing death over time    | Multivariate statistical regression, to allow adjustment on baseline age, gender, haemoglobin level, and NYHA class |
| FAIR-HF               | Clinical trial     |                                 | • Rate of hospitalization due to CHF worsening                                        |                                                                                             |
| EFFICACY-HF           | Clinical trial     |                                 | • Average length of hospitalization                                                   |                                                                                             |
| CONFIRM-HF            | Clinical trial     |                                 |                                                                                      |                                                                                             |
| Iron deficiency in    | Pooled analysis of  | Used in the model                |                                                                                      |                                                                                             |
| chronic heart failure:| RCTs               |                                 |                                                                                      |                                                                                             |
| an international      |                    |                                 |                                                                                      |                                                                                             |
| pooled analysis       |                    |                                 |                                                                                      |                                                                                             |

CHF, chronic heart failure; NYHA, New York Heart Association; RCTs, randomized controlled trials.

*Not considered in the budget impact calculation.
and hospitalizations due to worsening of CHF. Patients treated with FCM were attributed an administration cost for intravenous FCM. Costs of outpatient follow-up were obtained from recommendations of the French health authorities. No follow-up cost was attributed to NYHA Class I due to the absence of limitation in daily activities for these patients. Patients in NYHA Classes II, III, and IV were attributed a weekly cost of €5.17, €8.22, and €8.22, respectively, for follow-up.

Other types of medications for CHF were obtained from national guidelines on management of heart failure patients from 2014 and were reviewed by experts in order to obtain an estimation as close as possible to real-world practice in 2018. The associated prices were extracted from a national database, giving weekly costs of €5.28, €6.19, and €5.07 for NYHA Classes II, II, and IV, respectively.

Hospitalization costs were obtained from the national hospitalization database (Programme de Médicalisation des Systèmes d’Information (PMSI), 2016), using the diagnosis code for CHF (I500, I501, and I509) and iron deficiency or anaemia. This database contains anonymized data of hospitalizations classified by diagnosis-related group (DRG). In total, 288,378 hospitalizations for CHF were identified for the year 2016. The mean cost of hospitalization for CHF and ID or anaemia was €3938.01.

The mean cumulative annual FCM dose used in the RCTs was 1679 mg, and the mean dose per administration was 800 mg. Moreover, a real-world study carried out in Germany reported that annual doses of 925 mg per patient were used. We thus considered that all treated patients received an administration of up to 1000 mg (maximal dose per administration) of FCM in the beginning of each year via one ambulatory consultation before death. We assigned the ambulatory administrations at the beginning of each year in order to simplify the model and to be able to capture patients who transition to the state of death during the first transition period of each year and thus cannot be treated afterwards. We assumed that if an additional dose was needed to reach 1679 mg, it was administered within the DRG for hospitalization for deterioration of CHF, with no extra charge for the national health insurance. In a secondary analysis, two ambulatory sessions were considered for administration of a dose of 1679 mg at the beginning of each year.

Ferric carboxymaltose can currently be administered according to two ambulatory care modalities. The first, included in the base case analysis, is the reimbursement of FCM via a specific DRG (28Z17Z). The public and private hospitalization ratio weighted mean tariff was €338.27 per administration. As of March 2017, a new tariff was created in France for the administration of products in hospital but without formal admission to a hospitalization unit, called AP2. This new administration modality is considered in a secondary analysis. For the perspective of the national health insurance, only DRG tariffs are considered for FCM administration. Cost of FCM vials is considered included in the tariffs and is covered by hospitals. A summary of the costs included in the model is presented in Table 2.

### Secondary analysis

In alignment with French guidelines, in addition to the base case analysis, secondary analyses were conducted. These secondary analyses allowed for the introduction of alternative values for specific parameters. In the first secondary analysis, the cost of two ambulatory administrations was considered for FCM treatment. The second analysis introduced the new administration modality for FCM, resulting in a cost of €40 per administration of FCM. A third analysis allowed for transportation costs, including an extra cost of transportation for each FCM administration and for each hospitalization due to CHF worsening. These costs were extracted from a report of the French National Assembly in 2014 specifying that in 2013, the national insurance paid €52.10 per transportation. After applying the consumer price index in the health sector between 2014 and 2017 a cost of €101.3 was applied for a return trip. In the base case analysis, hospitalization costs are not differentiated by NYHA class. In another secondary analysis, hospitalization costs are differentiated by NYHA class, using the same variation between classes as those used in the initial budget impact model, in the absence of French sources reporting.

### Table 2: Cost parameters considered in the budget impact models

| Cost                      | With FCM     | Without FCM | Source                                      |
|---------------------------|--------------|-------------|---------------------------------------------|
| Cost of administration    | €338.27      | €0          | Hospitalization standard rates              |
| Cost of hospitalization   | €3938.01     |             | National PMSI hospitalization database      |
| Cost of outpatient follow-up |             |             | HAS recommendation recommendations          |
| NYHA I: €0 per week      | HAS recommendations | Costs from medicaments.gouv.fr |
| NYHA II: €5.17 per week  | HAS recommendations | Costs from medicaments.gouv.fr |
| NYHA III and IV: €8.22 per week | HAS recommendations | Costs from medicaments.gouv.fr |
| Cost of other medications |             |             | HAS recommendations and expert recommendations |
| NYHA I: €0 per week      | HAS recommendations | Costs from medicaments.gouv.fr |
| NYHA II: €5.28 per week  | HAS recommendations | Costs from medicaments.gouv.fr |
| NYHA III: €6.19 per week | HAS recommendations | Costs from medicaments.gouv.fr |
| NYHA IV: €5.07 per week  | HAS recommendations | Costs from medicaments.gouv.fr |

FCM, ferric carboxymaltose; HAS, Haute Autorité de Santé; NYHA, New York Heart Association.

HAS recommendations were reviewed by a clinician in order to be adapted to real-world practices.
hospitalization costs by NYHA classes. In another secondary analysis, we considered a length of hospital stay extracted from the national PMSI database (mean length of stay). The hypotheses used in the base case and secondary analyses are presented in Table 3. The values of parameters tested in secondary analyses are presented in Table 4.

### Sensitivity analysis

A sensitivity analysis was conducted to measure the parameter’s impact on the result of the base case analysis, to identify the highest impact parameter. Deterministic sensitivity analysis was carried out using minimal and maximal values based on expert opinion concerning age and NYHA distribution or located within the interval $-25$ to $+25\%$ for costs and hospitalization rates. Table 5 presents the values tested in the sensitivity analysis.

### Results

**Predicted New York Heart Association class distributions over time and number of deaths**

In the base case model, 35% of the patient cohort had NYHA Class II disease and 65% had NYHA Class III at model entrance. Following treatment, more patients treated with FCM had improved NYHA class compared with the patients not treated. At Week 52, 4.5% of the patients treated with FCM were in NYHA I, 56.2% in NYHA II, 26.0% in NYHA III, and 2.3% in NYHA IV. In contrast, among patients not treated for ID, more patients were in NYHA Class III (44.1%) or NYHA IV (7.2%), and fewer patients were in NYHA II (30.4%) or NYHA I (0.6%). At Week 52, 11.0% of the patients treated with FCM were predicted to have died, compared with 17.6% of patients not treated. Tables 6 and 7 present the distribution of treated and untreated patients over time in the model.

**Five year model outcomes according to rate of hospitalization and mean length of stay**

Using the modelled 5 year time horizon, the scenario with FCM had 70 848 hospitalizations vs. 80 345 hospitalizations in the scenario without FCM per 189 334 patients (Table 8). This represents a 12% decrease in the number of hospitalizations for worsening of CHF. Predicted mean length of stay in each scenario corresponded to a total of 830 630 days and 1 183 129 days of inpatient care over the 5 year period, representing a 30% decrease for the scenario with FCM.

### Table 3 Hypothesis considered in the base case and secondary analysis

| Base case | Secondary analysis no. 1 | Secondary analysis no. 2 | Secondary analysis no. 3 | Secondary analysis no. 4 | Secondary analysis no. 5 |
|-----------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Clinical data | Pooled analysis | Pooled analysis | Pooled analysis | Pooled analysis | Pooled analysis |
| Administration tariff | Not included | Not included | Included | Included | Included |
| Hospitalization costs | Not included | Not included | Not included | Not included | Not included |
| Transportation costs | Not included | Not included | Not included | Not included | Not included |
| Cost differentiation by NYHA levels | Not differentiated | Not differentiated | Differentiated | Differentiated | Differentiated |
| Length of hospitalization for deterioration of CHF | Pooled analysis using (FCM arm for FCM and placebo arm for no ID treatment) | Pooled analysis using (FCM arm for FCM and placebo arm for no ID treatment) | Pooled analysis using (FCM arm for FCM and placebo arm for no ID treatment) | Pooled analysis using (FCM arm for FCM and placebo arm for no ID treatment) | Pooled analysis using (FCM arm for FCM and placebo arm for no ID treatment) |

CHF, chronic heart failure; DRG, diagnosis-related group; FCM, ferric carboxymaltose; ID, iron deficiency; NYHA, New York Heart Association.
In the base case analysis, the modelled 5 year cost difference between the scenarios with and without FCM in the population of 189 334 prevalent and incident patients with CHF and ID and a reduced ejection fraction was € −0.8m (€ −881 834), representing a saving of €5 per patient. Therefore, the use of FCM according to market shares is expected to be cost saving for the national health insurance, with the extra cost associated with administration of FCM compensated by the reduced costs of hospitalization and follow-up. Costs of the two scenarios are presented in Table 9. Improved disease state (NYHA classes) and fewer hospitalizations, due to FCM therapy, resulted in reduced healthcare costs. The cumulative savings resulted from lower costs for hospitalization due to CHF worsening (€ −35.8m) and follow-up costs (€ −2.9m). These cost savings for CHF therapy outweigh the costs of FCM treatment (€37.7m). Results are presented per year in Table 10.

Table 4 List and values of parameters tested in the secondary analysis

| Parameters | Base case | Value tested | Rationale |
|------------|-----------|--------------|-----------|
| Administration cost | €338.27 | €676.54 | Dose of 1679 mg |
| Transportation costs | €0 | Included | Alternative financing used in France |
| Secondary analysis no. 3 | PMSI extraction (France) | €101.03 per administration and hospitalization | and variation from the German model applied |
| Hospitalization cost NYHA I | €3938.01 | €4141.35 | Possible difference of costs by NYHA classes |
| Hospitalization cost NYHA II | €4287.88 | | |
| Hospitalization cost NYHA III | €4744.28 | | |
| Hospitalization cost NYHA IV | €6104.34 | | |
| Secondary analysis no. 4 | RCTs pooled analysis | PMSI extraction | Source from French database tested |
| Length of hospitalization for deterioration of CHF—FCM | 14.73 days | 9.10 days | |
| Length of hospitalization for deterioration of CHF | 9.10 days | | |

Table 5 List and values of parameters tested in the sensitivity analysis

| Parameters | Base case | Upper value tested | Lower value tested | Rationale |
|------------|-----------|--------------------|--------------------|-----------|
| Average age | 78 | No value tested | 75 | Expert advice |
| Initial NYHA repartition: % of patients in NYHA II | 35% | 76% | No value tested | |
| Initial NYHA repartition: % of patients in NYHA III | 65% | 24% | No value tested | |
| Costs of other medications—NYHA I | €0.00 | €0.00 | €0.00 | ±25% |
| Costs of other medications—NYHA II | €5.28 | €7.60 | €3.96 | ±25% |
| Costs of other medications—NYHA III | €6.19 | €7.74 | €4.64 | ±25% |
| Costs of other medications—NYHA IV | €5.07 | €6.34 | €3.80 | ±25% |
| Costs of follow-up—NYHA I | €0.00 | €0.00 | €0.00 | ±25% |
| Costs of follow-up—NYHA II | €5.17 | €6.46 | €3.88 | ±25% |
| Costs of follow-up—NYHA III | €8.22 | €10.28 | €6.17 | ±25% |
| Costs of follow-up—NYHA IV | €8.22 | €10.28 | €6.17 | ±25% |
| Hospitalization rate of patients treated with FCM | 0.0013 | 0.0016 | 0.0010 | ±25% |
| Hospitalization rate of patients not treated for ID | 0.0033 | 0.0041 | 0.0025 | ±25% |
| DRG tariff | €338 | €423 | €254 | ±25% |

Budget impact

Secondary analyses

Secondary analyses tested alternative values for administration costs, transportation costs, hospitalization costs, and length of hospital stay (Table 4). Table 11 shows the results in terms of budget impact over 5 years for these analysis as the difference in costs between the scenarios with vs. without FCM (i.e. total cost of scenario with FCM − total cost of scenario without FCM).

The secondary analysis with two ambulatory sessions implies that two DRG tariffs are considered. In this analysis, the budget impact was positive, reflecting increased costs (€36.9m). When the length of stay was subtracted from the mean length of stay according to the PMSI database for CHF and ID patients, the budget impact was unchanged, as we did not consider length of stay in the calculation of the budget impact; however, the number of days of hospitalization saved was 86 414 vs. 352 499 in the base case. Costs
of hospitalization for CHF worsening, derived from a PMSI extraction, did not vary depending on NYHA class. When differentiated costs of hospitalization were used, greater savings were anticipated (€12.8m).

### Sensitivity analysis

The results of the deterministic sensitivity analysis are presented as a Tornado diagram (Figure 1), which shows how variations in the seven highest impact inputs affect the budget impact result. The Tornado diagram indicates that the parameter with the greatest impact on the result was the rate of hospitalization due to CHF worsening in patients without FCM, coherent with the weight of the cost of hospitalization in the budget impact. The mean patient age at entrance in the base case of the model comes from a study of patients hospitalized for decompensated heart failure. It is possible that the mean age of the targeted population is lower (e.g. 67.6 years in the ODIN cohort7), which would reduce the budget impact (€3.4m for a mean patient age of 75 years). Overall, in the deterministic sensitivity analysis, the budget impact varied between €16m and €146m (and between €7.5m and €+8.5m if hospitalization rates were excluded).

### Discussion

In this analysis, we have estimated the budget impact of treatment for ID using FCM in patients with CHF and a reduced ejection fraction from the French public healthcare
perspective. The use of FCM is expected to be cost saving for the French national insurance over a 5 year period. In the scenario with FCM, the model predicted that patients treated with FCM would have better NYHA status and experience fewer hospitalizations for CHF compared with patients without iron therapy. The cost category estimated to have the highest contribution to the budget impact was hospitalization for worsening of CHF, in both scenarios (with FCM €278m and without FCM €314m), and it had also the highest potential for savings in the budget impact (€−35m). The added cost of FCM treatment of €37m was compensated by savings in hospitalization costs and follow-up costs. In the base case analysis, FCM use is predicted to be cost saving over 5 years of treatment (€−0.8m).

The German budget impact analysis, based on the same pooled RCT data, compared treatment with FCM for all patients vs. no iron treatment, using 1000 patients in each group, from the perspective of the German national health insurance over a 1 year period. It concluded that in the first year, FCM was cost saving (€−198 768) if the dose of FCM was 925 mg and had a limited positive impact if the dose of 1679 mg was used (€40 031). In comparison with this analysis, in our study, we used available data from the RCTs to extrapolate using a 160 week horizon. We also compared our results with two scenarios, which are anticipated to represent the number of patients treated or not treated with FCM in France over 5 years. In Austria, a Markov model was built to evaluate the budget impact of FCM from the perspective of the national health authorities. Another analysis evaluated the impact of FCM for the Swiss healthcare system. The use of FCM in CHF was projected to be cost saving over a 4 year period.

One of the main limitations of our budget impact analysis is that the clinical efficacy data come from the pooled analysis of RCTs conducted in nine countries, which therefore does not necessarily reflect real-life care of CHF and ID patients in France. However, the statistical regressions used to evaluate clinical parameters did not change when the variable ‘region’ was integrated (except for length of stay, where this variable was kept in the regression and does not impact costs).

### Table 9 Costs associated with the two modelled scenarios over a 5 year period in 189 334 patients

| Scenario 1 with FCM (€) | Scenario 2 without FCM (€) | Difference (Scenario 1 vs. Scenario 2) (€) |
|-------------------------|-----------------------------|------------------------------------------|
| Other medications       | 139 047 532                 | 154 871                                   |
| Hospitalizations due to CHF worsening | 278 582 493                   | 314 465 168                               | −35 882 675 |
| Follow-up               | 169 882 867                 | 172 830 523                               | −2 947 656  |
| Total cost of resources other than FCM | 587 512 892                   | 626 188 352                               | −38 675 460 |
| Cost of FCM treatment   | 37 793 627                  | 37 793 627                                | 0           |
| Total cost over 5 years | 881 834                     | −881 834                                  | −5          |

CHF, chronic heart failure; FCM, ferric carboxymaltose.

### Table 10 Annual costs according to different scenarios by year in 189 334 patients

| Scenario 1 with FCM | Scenario 2 without FCM | Difference (Scenario 1 vs. Scenario 2) |
|---------------------|-------------------------|----------------------------------------|
| Resources other than FCM (€) | 116 376 600 | 119 082 760 | −276 160 |
| Treatment costs for FCM (€) | 2 706 160 | 123 356 317 | −120 650 |
| Total Scenario 1 (€) | 119 082 760 | 123 356 317 | −4 273 557 |
| Resources other than FCM (€) | 118 022 422 | 123 356 317 | −5 333 895 |
| Treatment costs for FCM (€) | 5 333 895 | 123 356 317 | −118 022 422 |
| Total Scenario 1 (€) | 118 022 422 | 123 356 317 | −5 333 895 |
| Resources other than FCM (€) | 118 493 032 | 123 356 317 | −4 863 285 |
| Treatment costs for FCM (€) | 7 282 645 | 123 356 317 | −116 073 672 |
| Total Scenario 1 (€) | 118 493 032 | 123 356 317 | −4 863 285 |
| Resources other than FCM (€) | 118 374 998 | 123 356 317 | −4 981 319 |
| Treatment costs for FCM (€) | 9 270 130 | 123 356 317 | −118 084 187 |
| Total Scenario 1 (€) | 118 374 998 | 123 356 317 | −4 981 319 |
| Resources other than FCM (€) | 116 245 839 | 123 356 317 | −7 110 478 |
| Treatment costs for FCM (€) | 13 200 797 | 123 356 317 | −110 155 520 |
| Total Scenario 1 (€) | 116 245 839 | 123 356 317 | −7 110 478 |

FCM, ferric carboxymaltose.

### Table 11 Secondary analysis of budgetary impact over a 5 year period according to different hypothesis in 189 334 patients per scenario

| Hypothesis variable | 5 year budget impact (€) |
|---------------------|--------------------------|
| Base case           | −881 834                 |
| Dose of 1679 mg FCM | 36 911 793               |
| Administration of FCM through the ‘AP2’ tariff | −34 206 412 |
| Use of €101 reimbursed transportation for each FCM administration and hospitalization for CHF worsening | 8 824 120 |
| Hospitalization costs differentiated by NYHA level | −12 837 897 |

CHF, chronic heart failure; FCM, ferric carboxymaltose; NYHA, New York Heart Association.

ESC Heart Failure 2019; 6: 559–569
DOI: 10.1002/ehf2.12432
Moreover, in the main analysis, we considered that an FCM dose up to 1000 mg was administered in an ambulatory setting and that any dose above 1000 mg was administered within the DRG of hospitalization for deterioration of CHF. The secondary analysis using two ambulatory settings showed that the result was sensitive to the type of administration setting.

Another limitation is the maximal follow-up period of 52 weeks in the clinical trials, compared with the 5 year horizon of our model, requiring extrapolation of the efficacy predictions beyond the available trial data. Furthermore, the available data for hospitalization costs from the French national database, which represent a major cost in the analysis, could not be differentiated by NYHA levels, even though a secondary analysis concluded that the differentiation could lead to more savings. Overall, the translation of this model to the French setting could be improved with more specific and local clinical and cost data. A more robust and specific model would improve the accuracy of the results. The costs included in the model are extracted from guidelines and publications but may not precisely reflect the diversity of patient management in France. For instance, no follow-up cost was attributed to NYHA I, while the management of those patients without symptoms may in fact include follow-up.

In conclusion, ID is a relevant co-morbidity in CHF and is associated with worse symptomatic status and increased hospitalization. Treating this complication by intravenous iron supplementation results in improved symptomatic status and reduced frequency and duration of hospitalization. This study estimates the costs for the national health insurance of increased use of FCM in France, which is recommended by most recent European Society of Cardiology guidelines \(^3\) in the context of treating ID in patients suffering from CHF with a reduced ejection fraction. The analysis compares two scenarios, one where FCM gains an increasing market share and one where FCM is not on the market, over a 5 year time horizon. In both scenarios, 189,334 patients enter the model over 5 years. The base case analysis concludes that FCM is expected to be cost saving (€−0.8m), with the use of FCM reducing the number of hospitalizations for worsening of CHF, which represents the greatest cost associated with CHF in France. Accordingly, the main saving comes from hospitalization costs, and sensitivity analysis showed that the rate of hospitalization has a major impact on the result. Secondary analysis allowed other hypotheses to be considered. The budget impact varied from €−12.6m, when hospitalization costs were differentiated by NYHA levels, to €+36.9m when two ambulatory sessions are considered. In deterministic sensitivity analysis, the budget impact varied between €−16m and €146m. The use of FCM as standard care in CHF and ID patients in France is therefore expected to meet a medical need in this population, with a minimum budget impact on the French national health insurance.

**Conflict of interest**

This study was funded by the Vifor Pharma.

**Funding**

This study was performed by the Stratégique Santé, based on a model developed by Xcenda and Esior, and funded by the Vifor Pharma.
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