PharmacoEconomics - Open (2022) 6:735–743
https://doi.org/10.1007/s41669-022-00341-7

ORIGINAL RESEARCH ARTICLE

Budget Impact of Intravenous Iron Therapy with Ferric Carboxymaltose in Patients with Chronic Heart Failure with Reduced Ejection Fraction (HFrEF) and Iron Deficiency in Switzerland

Elisabeth Brock[1] · Giorgio Moschovitis[2] · Micha T. Maeder[3] · Otmar Pfister[4]

Accepted: 18 May 2022 / Published online: 10 June 2022

Abstract

Aims A budget impact analysis compared treating patients with heart failure (HF) and reduced ejection fraction (HFrEF) and iron deficiency (ID) in Switzerland with intravenous ferric carboxymaltose (FCM) or placebo.

Methods Clinical data from four international randomized trials showed that FCM versus placebo treatment was associated with a reduced hospitalization rate due to HF. The budget impact of this was modelled over 1 year. Hospital treatment costs for HFrEF, FCM drug costs, and estimated patient numbers were based on published data, official tariffs, specially commissioned analyses of SwissDRG data, and clinical and diagnosis-related groups (DRG) coding expert opinion. The original cost year was 2015. Sensitivity analyses were conducted including updated unit costs from 2019/2020.

Results FCM treatment was associated with average cost savings of Swiss Francs (SFr) 503 per patient per year from the perspective of the Swiss mandatory health insurance system. Extrapolating across all eligible HFrEF patients with ID in Switzerland, this amounted to estimated savings of SFr 23,336,873. Sensitivity analyses showed these results to be robust in the face of changes to input parameters like treatment costs, different hospital settings, updated unit costs, and including outpatient treatment and patient co-payments in the analysis.

Conclusions The present analysis shows that using FCM to treat HFrEF patients with ID in line with current guideline recommendations resulted not only in medical benefits but also in significant cost savings. The analysis also provides an example of the pitfalls of transferring economic evaluation results, even between countries with similar hospital reimbursement systems.

1 Introduction

Chronic heart failure (CHF) leads to considerable morbidity, mortality, and health care resource consumption [1]. Frequent re-hospitalizations due to worsening heart failure (HF) are an important driver of health care costs in this condition. An estimated 1–2% of the population of industrialized countries suffer from CHF [2]. A recent systematic

Key Points for Decision Makers

Treating patients with chronic heart failure with reduced ejection fraction and iron deficiency with the intravenous iron preparation ferric carboxymaltose in line with current guideline recommendations resulted in medical benefits for patients, including a reduction in hospitalization rates due to chronic heart failure.

Our model showed this to be associated with substantial cost savings to the mandatory health insurance system in Switzerland.

The analysis also provides an example of the pitfalls of transferring economic evaluation results, even between countries with similar hospital reimbursement systems.

✉ Elisabeth Brock
ebrock@healthecon.com

1 Market Access Switzerland/Health Economics Europe, HealthEcon AG, Steinentorstrasse 19, 4051 Basel, Switzerland

2 Division of Cardiology, Regional Hospital of Lugano, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland

3 Cardiology Department, Kantonsspital St. Gallen, St. Gallen, Switzerland

4 Cardiology Department, University Hospital Basel, Basel, Switzerland

review of cost-of-illness studies showed that HF poses a considerable and growing economic burden on health care systems with total annual costs estimated at USD25,532 in Germany (approx. equivalent to €23,992 or Swiss Francs (SFr) 24 on 3 May, 2022) and lifetime costs at USD126,819 (approx. €119,776 or SFr123,154) per patient [1]. Costs rise as patients' severity of disease worsens [1].

Approximately one in two patients with CHF has iron deficiency (ID), which is associated with increased mortality, increased hospitalization rate, reduced exercise capacity, and reduced quality of life (QoL) [3]. Recent clinical trials have demonstrated that intravenous iron substitution with ferric carboxymaltose (FCM) can reduce symptoms and HF-associated hospitalizations and improve QoL and exercise capacity in patients with heart failure and reduced ejection fraction (HFrEF) with ID [4–7]. Therefore, the European Society of Cardiology 2016 guidelines on acute and chronic HF recommended screening for ID in HFrEF patients, and if present, to consider FCM treatment (class IIa indication) [2].

Studies on the cost effectiveness and budget impact of treating HFrEF patients with ID with FCM were carried out in several European countries with divergent results, some showing additional costs and some showing costs savings [8–12]. The impact of treating HFrEF patients with ID with FCM on health care costs in Switzerland is still unclear. Hence, this study sought to explore the impact of intravenous FCM therapy versus placebo in HFrEF patients presenting with ID with or without anemia (ID/IDA) on health care costs in Switzerland using Swiss data.

2 Materials and Methods

ISPOR's good practice guide for budget impact analysis was used as a basis for conducting and reporting the present analysis [13].

2.1 Model Structure

The perspective of the analysis was that of the Swiss mandatory health insurance system. The budget impact associated with treating HFrEF patients with ID in Switzerland with FCM versus placebo was assessed based on a model originally developed for Germany [8]. HFrEF was defined as left ventricular ejection fraction < 45%. ID was defined as serum ferritin level < 100 ng/mL, or between 100 and 300 ng/mL if transferrin saturation (TSAT) was < 20%. The model used clinical trial data to predict New York Heart Association (NYHA) class changes over time, rates of hospitalizations due to worsening HF, and average length of hospital stay for NYHA classes I–IV [8]. Due to a lack of available data for Switzerland, model results presented here are only based on changes in hospitalization costs and FCM drug costs due to the changes in NYHA class over time due to FCM treatment, without taking into consideration any cost differences which might be due to changes in average length of hospital stay. Placebo is the relevant comparator for Switzerland, as registry data showed that iron status was only determined in 62% of patients participating in a heart failure registry focusing on iron deficiency, only 8.5% of iron-deficient HF patients were treated with iron therapy, and only 2.6% were treated with intravenous iron therapy [14]. The use of oral iron supplementation in this patient population was further not recommended by Swiss practitioners as the dose typically required to achieve iron repletion in this patient population would require treatment with oral iron over a period of > 6 months [15].

The timeframe of the budget impact model was 1 year. The cost year of the base case was 2015 in line with a specially commissioned data analysis described in the following section. Updated unit costs for 2019/2020 were used as part of sensitivity analyses.

In line with available efficacy data from clinical trials, all patients were in NYHA classes II and III at the start of the model. Patients were able to stay in the same NYHA class they were in at the start of the model or move to any of NYHA classes I–IV during the course of 1 year as observed in the relevant clinical trials.

At baseline, the average age of the pooled trial dataset was 68.1 years (standard deviation [SD] 10.1). Males comprised 50.9% of the patients. The mean hemoglobin of the pooled trial dataset was 12.1 g/dL (SD 1.3) with 67.1% classified as NYHA class III and 32.9% as NYHA class II. As the distribution of NYHA classes in the eligible Swiss population was considered to differ from that of the pooled trial dataset based on clinical expert opinion, this was changed for the Swiss model adaptation.

Clinical expert opinion was sought from three medical specialists working in a range of hospital settings and different language regions of Switzerland, covering a large university hospital and two medium-sized regional hospitals in the German and Italian-speaking regions. Input values for the base-case and sensitivity analyses were decided by consensus. The same three medical specialists were consulted for all aspects of clinical expert opinion described in the Methods section and co-authored this manuscript.

2.2 Epidemiology and Cost Inputs

A structured literature review was carried out to identify sources of published data to populate the budget impact model with cost and epidemiological data specific to Switzerland. This is described in detail in the Online

Appendix (see electronic supplementary material [ESM]). The searches did not identify any publicly available data suitable to populate the budget impact model with Swiss epidemiological or cost data. Publicly available cost data were not suitable for use in the Swiss budget impact model as they did not reflect causality (i.e. costs being incurred "due to worsening of CHF") and did not allow hospitalization costs to be distinguished by NYHA class. Publicly available epidemiological data were not specific to Switzerland but reflected pooled data from both Germany and Switzerland.

As a result, an analysis of SwissDRG data was specifically commissioned to obtain cost data suitable for use in the Swiss budget impact model, supplemented by expert advice from a diagnosis-related groups (DRG) coding specialist (cs healthcare consult). In addition, Swiss clinical expert opinion was sought regarding epidemiology, cost, and Swiss treatment patterns (e.g. whether patients would be treated at university hospitals or non-university hospitals and which treatments patients in a specific NYHA class might typically receive).

2.3 Base-Case Model Inputs

Base case model input parameters and associated values are summarized in Table 1.

2.4 Number of Eligible Heart Failure Patients

The overall number of HF patients in Switzerland was estimated based on a prevalence of 175,000 per year (Table 2) [16]. This point estimate was validated by Swiss clinical expert opinion (range 150,000–180,000). Among those, 50% (range 75,000–90,000) were estimated to have HFrEF [17].

The number of HF patients eligible for FCM treatment in Switzerland per year was estimated based on the prevalence of ID in HFrEF patients. As the only published data for the relevant Swiss HF disease registry (EVITA-RAID) was pooled data for German and Swiss patients [14], Swiss clinical expert opinion was sought that estimated the prevalence of ID in HFrEF patients in Switzerland at 53% (range 50–55%). Combining the number of HFrEF patients per year (175,000 total, of which 87,500 have HFrEF) with the clinical expert's estimate of 53% with ID resulted in an estimate of the number of eligible patients in Switzerland of 46,375 as a point estimate for the base-case model adaptation (range 39,750–47,700). Patient numbers were based solely on prevalent patients due to the model time horizon of 1 year.

2.5 Proportion of Patients with NYHA class II

According to the EVITA-RAID Registry, 30% of HFrEF patients were in NYHA class II (Table 2) with a lower

Table 1 Base-case model input parameter values

Model parameter	Value (base case)	Source
Hospitalization cost, per case, NYHA I	SFr 15,444	Specially commissioned analysis of SwissDRG data [18]
Hospitalization cost, per case, NYHA II	SFr 15,519	Specially commissioned analysis of SwissDRG data [18]
Hospitalization cost, per case, NYHA III	SFr 13,951	Specially commissioned analysis of SwissDRG data [18]
Hospitalization cost, per case, NYHA IV	SFr 12,263	Specially commissioned analysis of SwissDRG data [18]
Number of eligible heart failure patients per year	46,375 patients	Derived from published sources [16, 17] and Swiss clinical expert opinion based on EVITA-RAID register
Proportion of heart failure patients with NYHA class II	35%	Swiss clinical expert opinion based on the international literature [16]
FCM drug costs for 500 mg (10 mL)[a]	SFr 164.29	Published price in positive list of reimbursed drugs (http://www.xn--spezialittenliste-yqb.ch/)
FCM drug costs for 1000 mg (20 mL)[a]	SFr 338.40	Published price in positive list of reimbursed drugs (http://www.xn--spezialittenliste-yqb.ch/)
Probability to be in specific NYHA class I–IV or death over time	See Online Appendix Table S4 in the ESM	[8]
Rate of hospitalization due to worsening of CHF	Placebo 0.0026 per patient-week FCM 0.0010 per patient-week	[8]

CHF chronic heart failure, *ESM* electronic supplementary material, *FCM* ferric carboxymaltose, *NYHA* New York Heart Association functional class, *SFr* Swiss Francs

[a]Calculated on basis of the most economical package size

Table 2 Number of eligible heart failure patients

Description of patient population	Estimate (range)	Source
Total population Switzerland	8.08 million	[16]
Prevalent patients with HF	175,000 (range 150,000–180,000)	[16]
Prevalent patients with HFrEF	50% = 87,500 (range 75,000–90,000)	[17]
Prevalent patients with HFrEF with ID	53% (range 50–55%) = 46,375 (range 39,750–47,700)	Swiss clinical expert opinion based on EVITA-RAID registry
Prevalent patients with HFrEF with ID and NYHA class II	35%	Swiss clinical expert opinion based on the international literature [16]

HF heart failure, *HFrEF* heart failure with reduced ejection fraction, *ID* iron deficiency, *NYHA* New York Heart Association

proportion of NYHA class II HFrEF patients with ID than without ID (25% vs 33%) [14]. At the advice of Swiss clinical expert opinion familiar with the data of the EVITA-RAID Registry, the base-case model adaptation was based on a proportion of 35% of CHF patients in NYHA class II, in line with international published data [16].

2.6 Ferric Carboxymaltose Cost in Switzerland

Drug costs associated with FCM treatment in Switzerland for 1 year were estimated as the public price in the Swiss positive list of reimbursed drugs, the List of Specialties, for the most economical pack sizes on 16 June, 2020 (i.e. SFr 164.29 for 500 mg (10 mL) and SFr 338.40 for 1000 mg (20 mL). FCM costs in 2020 are the same as in 2015 as the original cost year of the original data analysis commissioned to estimate hospital costs. The model estimates the cost of FCM for 1 year for the mean cumulative dose of 1679 mg based on the pooled data set of the relevant clinical trials [8]. Swiss expert opinion stated that there is no drug wastage as the dose administered per application in practice is adjusted in such a way as to avoid waste. Due to the two available dosage strengths, these dose adjustments are relatively small relative to the mean cumulative dose predicted by the model based on pooled clinical trial data.

2.7 Hospitalization Cost, Per Case, by NYHA Class

Hospitalization costs per case for NYHA classes I–IV were based on a specially commissioned data analysis of Swiss-DRG data [18]. This was combined with publicly available SwissDRG Datenspiegel data based on SwissDRG system 6.0 relating to the same year as that of the specially commissioned data analysis (https://www.swissdrg.org/de/akutsomatik/swissdrg-system-1102022/datenspiegel). The specially commissioned SwissDRG data analysis is based on a data pool of 288,955 inpatient cases treated at five university and six non-university hospitals in Switzerland in 2015, representing 24% of all Swiss inpatient cases overall. A total of 1553 cases with heart failure were identified (ICD codes I50.11, I 50.12, I50.13, I50.14), of which 17 cases/patients were in NYHA class I, 173 in NYHA class II, 418 in NYHA class III, and 945 in NYHA class IV.

Less than 5% of these cases ($n = 72$) had a secondary diagnosis of ID/IDA (ICD-10 code D50, D50.0, D50.1, D50.8, D50.9 or E61.1) with none of these patients being classified as NYHA class I, two patients being classified as NYHA class II, 16 patients as NYHA class III, and 54 patients as NYHA class IV. These numbers were too small to be able to yield a reliable and representative estimate of the costs associated with the hospitalization of these patients due to worsening HF. Hence, estimates of hospitalization costs by NYHA class were based on the data of 1553 HF patients [18], including HF patients with and without a diagnosis of ID.

To estimate case-weighted average costs associated with inpatient treatment due to worsening of HF for the individual NYHA classes, the most frequently coded DRG codes for each NYHA class were identified in these 1553 patients [18] and combined with publicly available data of the average costs (reimbursement) associated with these DRG codes in 2015 based on SwissDRG Datenspiegel data (see Online Appendix Tables S1, S2, and S3 in the ESM). This resulted in weighted average hospitalization costs per case of SFr 15,444 for NYHA class I, SFr 15,519 for NYHA class II, SFr 13,951 for NYHA class III and SFr 12,263 for NYHA class IV (Table 1).

2.8 Estimated Costs During 52 Weeks of Follow-Up

Estimated costs during 52 weeks of follow-up were calculated for the base case as the sum of FCM costs and the difference between the costs associated with hospitalizations due to worsening HF with and without FCM treatment.

2.9 Efficacy Inputs

The budget impact model was based on clinical data from four international randomized trials showing that treatment with FCM was associated with reductions in the rate of cardiovascular hospitalizations compared with placebo. Data from four randomized controlled trials (FAIR-HF [4], EFFICACY-HF [7], CONFIRM-HF [19], and FER-CARS-01 [6]) examining the safety and efficacy of FCM treatment in patients with CHF and ID/IDA were pooled on a patient level [8]. All studies were completed up to December 2014. For the model population, baseline information from 833 eligible patients with HFrEF and ID and baseline NYHA functional class II/III participating in the trials were included in the analysis. The baseline characteristics of the trial patients are described in section 2.1. The budget impact model compared treatment of FCM with no iron treatment (placebo), based on the pooled randomized controlled trial data. Trial data were used to develop statistical models predicting NYHA class changes over time, as well as rates of hospitalization due to worsening HF for all NYHA classes I–IV [8]. Base-case model efficacy input values are summarized in Table 1 and Table S4 (see ESM). The underlying calculations for arriving at the efficacy input values were described in detail in a previous publication [8]. Due to different follow-up times in the included trials, the pooled dataset was limited to 24 weeks of follow-up. To extend the time horizon to 52 weeks, CONFIRM-trial data were used to model the clinical outcomes from week 24 to week 52 using logistic regression models [8]. In the base-case analysis, a single HF patient with ID without intravenous FCM was hospitalized 0.13 times due to worsening heart failure and an HF patient treated with FCM was hospitalized on average 0.05 times.

2.10 Sensitivity Analysis

Univariate sensitivity analyses (SA) were carried out to assess how changes in key parameters and parameter values affected the results of the analysis. This was considered to be the most transparent way of assessing uncertainty given the specific characteristics of the input values associated with different model parameters. Several scenario analyses were conducted (see Online Appendix in the ESM for details):

SA 1—no difference in costs associated with NYHA classes II and III.

SA 2—university versus non-university hospital costs.

SA 3—input values based on a specially commissioned analysis of single-center data from one university hospital in Switzerland [20].

SA 4—including outpatient costs in the analysis.

SA 5—including patients' co-payments in the analysis.

SA 6—varying the number of eligible patients.

SA 7—varying the proportion of patients in NYHA class II at baseline.

SA 8—updated unit costs based on latest available data (2019).

3 Results

3.1 Base Case

In the base-case analysis, a single HF patient with ID without intravenous FCM hospitalized 0.13 times due to worsening HF incurred hospitalization costs of SFr 1835 on average per year. If this HF patient was treated with FCM, this patient was hospitalized on average 0.05 times, that is, less than half as much, incurring hospitalization costs of SFr 763 per year. Hence, treating one single HFrEF patient with ID with FCM versus not treating them with FCM was associated with average cost savings of SFr 503 per HFrEF patient per year ($n = 1$) in Switzerland after FCM therapy costs are subtracted due to a reduction in the number of hospitalizations (Table 3).

Extrapolating the results of the base-case analysis to the total estimated number of eligible patients in Switzerland ($n = 46{,}375$), that is, assuming 100% uptake of FCM, showed that treatment with FCM was associated with cost savings of SFr 23,336,873 per year in Switzerland due to a reduction in the number of hospitalizations as a result of worsening heart failure (Table 4).

3.2 Sensitivity Analyses

The results of the sensitivity analyses confirmed the results of the base-case analysis: treatment with FCM was cost saving in this patient population also in the face of the changes in input values described (Table 5).

4 Discussion

This study provides the first estimate of the budget impact of treating HFrEF patients with iron deficiency (ID) with FCM in Switzerland. Treatment with FCM in this patient population was estimated to result in net cost savings.

A budget impact model for France demonstrated net cost savings with FCM treatment [12]. In contrast, a budget impact model for Germany showed that FCM treatment was associated with a small additional cost of €40 per patient from the perspective of the statutory health insurance system [8]. The reason for this difference in results between Germany and Switzerland might have been due to relatively larger differences in hospitalization costs compared with differences in FCM drug costs between the two countries.

Table 3 Results of the base-case analysis per year per one individual patent ($n = 1$)

	Predicted resource use and cost savings due to avoided hospitalizations during 52 weeks of follow-up[a]		
	No FCM therapy	FCM therapy	Difference
Number of hospitalizations	0.13	0.05	−0.08
Estimated costs during 52 weeks of follow-up			
Hospitalizations due to worsening of HF	SFr 1835	SFr 763	−SFr 1071
Total cost of FCM therapy			SFr 568
Total cost savings during 52 weeks			SFr 503

FCM ferric carboxymaltose, *HF* heart failure

[a]Discrepancies due to rounding

Table 4 Results of the base-case analysis per year for all patients in Switzerland ($n = 46{,}375$)

	Predicted resource use and cost savings due to avoided hospitalizations during the 52 weeks of follow-up[a]		
	No FCM therapy	FCM therapy	Difference
Number of hospitalizations	5852	2357	− 3495
Estimated costs during 52 weeks of follow-up			
Hospitalizations due to worsening of HF	SFr 85,079,890	SFr 35,393,967	− SFr 49,685,924
Total cost of FCM therapy			SFr 26,349,051
Total cost savings during 52 weeks			SFr 23,336,873

FCM ferric carboxymaltose, *HF* heart failure

[a]Discrepancies due to rounding

Table 5 Summary of the results of the sensitivity analyses

Sensitivity analysis	Description (see ESM for further detail)	Total cost savings per year ($n = 1$ [results per individual patient], unless stated otherwise)
SA 1	No difference in costs associated with NYHA classes II and III	SFr 524
SA 2	Costs induced by university vs non-university hospital	University hospital costs: SFr 532 Non-university hospital costs: SFr 450
SA 3	Input values based on specially commissioned analysis of single-center data from one university hospital	SFr 234
SA 4	Including outpatient costs in the analysis	SFr 778
SA 5	Including patients' co-payments in the analysis	SFr 428
SA 6	Varying the number of eligible patients	For $n = 39{,}750$: SFr 20,003,034 For $n = 47{,}700$: SFr 24,003,641
SA 7	Varying proportion of patients in NYHA class II at baseline	SFr 606
SA 8	Updated input unit costs for hospitalization by NYHA class for 2019/2020	SFr 741

ESM electronic supplementary material, *NYHA* New York Heart Association functional class, *SFr* Swiss Francs

Cost-effectiveness analyses performed for the UK and Spain showed FCM treatment to be cost effective given usual willingness-to-pay thresholds [9, 10]. This means that FCM treatment in HFrEF patients with ID in Spain and the UK was associated with additional costs, as well as increased efficacy. In contrast, a cost-effectiveness analysis performed for the Nordic countries showed that FCM treatment was associated not only with increased efficacy but also with cost savings [11].

4.1 Strengths and Limitations

The current study has several limitations which are mainly related to the scarce availability of data for Switzerland. Indeed, a systematic review did not result in identifying suitable Swiss data to populate the model. Despite the existence of disease registries in Switzerland, none was able to furnish relevant data specific enough to the patient population covered in this budget impact analysis, nor did disease

registry data include costs in different sectors of the health care system. The model base case was thus populated with data relating to the inpatient sector only. We explored the inclusion of outpatient costs in one sensitivity analysis based on Swiss clinical expert opinion.

One limitation of the current study is that it does not explicitly take into account FCM administration costs due to the focus on inpatient costs. If FCM were administered in the outpatient sector in line with guideline recommendations [15], administration costs for iron doses up to 1000 mg would be estimated at approximately SFr 51 (approx. €49) (Tarmed tariff position no. 00.1430—15-min intravenous injection or infusion administered by nurse, associated with 57.09 tax points valued at an average of SFr 0.89 per tax point [21–23]). Adverse event costs were not included in the model as serious adverse events are exceedingly rare and the most common adverse events like nausea and minor injection- or infusion-site reactions are self-limiting and would not incur treatment costs in routine clinical practice [23].

The model was further populated with data obtained from HF patients overall, including patients with and without ID because of a lack of data for the specific patient group of interest, namely HF patients with ID. The reason for this appeared to be that treating physicians either did not diagnose and/or code ID despite the literature showing that this condition is present in a sizeable proportion of HF patients and is associated with worse prognosis (quality of life, re-hospitalization) and increased costs in comparison with HF patients without ID. This is in line with the findings of the analysis of registry data described in the Methods section reporting that iron status was only determined in 62% of heart failure patients treated in centers participating in a registry focusing on ID [14]. A separate analysis of the data of a single Swiss university hospital used for one of the sensitivity analyses showed that HF cases with ID coding were more expensive on average for NYHA classes II–IV than HF cases without additional ID coding. However, this was based on very small patient numbers. There were no data available to compare costs for NYHA class I. To account for these limitations, parameter values to populate the budget impact model were chosen conservatively in order to bias against FCM, to avoid overestimating the cost savings associated with FCM treatment (e.g. estimating costs based on a patient without any complications, rather than on a far more costly patient with complications).

There was also uncertainty regarding the number of eligible HFrEF patients. Based on pooled Swiss and German registry data, 54.7% of HFrEF patients were estimated to also have ID [14], with expert opinion suggesting that 53% of Swiss HFrEF patients also have ID. International prevalence rates were found to range widely from 37 to > 70% [14]. Using alternative international data to estimate the prevalence of ID in HFrEF patients resulted in a broadly similar estimate to the Swiss base case estimate of 53% overall, with estimates of ID with or without anemia ranging from 53% in NYHA class I or II patients to 48% in NYHA class III or IV patients [24]. To account for the uncertainty inherent in this estimate, as well as a lack of robust data regarding uptake of FCM in this patient population, the budget impact model was also run for just one patient ($n = 1$), rather than for the whole HFrEF patient population with ID potentially eligible for FCM treatment in Switzerland.

A further limitation of this study, again relating to the availability of data, is that the clinical efficacy model underlying the budget impact model was based on clinical trials including stable HF patients, whereas the cost data available related only to acute HF patients.

The uncertainty relating to the cost differential between NYHA classes II and III, which may be difficult to discern in clinical practice, was explored in a sensitivity analysis as well. In the course of exploring this, we came across an interesting observation relating to the comparison of costs and hence model results across countries.

The data analysis conducted to identify Swiss hospitalization costs associated with different NYHA classes showed a cost gradient, with NYHA class IV being associated with lower hospitalization costs than NYHA class III. This appears counterintuitive in that one would expect the inpatient treatment of patients with higher disease severity (and therefore higher NYHA functional class) to cost more than that of patients with a lower disease severity, in line with the pattern of hospitalization costs observed in Germany [8]. One explanation for the observed counterintuitive cost gradient in the Swiss data might be the very small number of cases identified in the data pool of patients with NYHA class I receiving inpatient hospital treatment ($n = 17$). It has further been suggested by a medical controlling expert (cs healthcare consult) that the counterintuitive gradient with NYHA class IV patients treated in Switzerland incurring lower average hospitalization costs than NYHA class III patients, which was not observed in Germany, might be due to systematic differences in the way patients are assigned DRG codes within the German and the Swiss DRG systems. In Switzerland, patients are assigned a specific DRG code independently of the NYHA class coded as the main diagnosis. Hence, secondary diagnoses, diagnostic and therapeutic procedures which may not all be a direct consequence of heart failure may determine which DRG code is assigned to an individual patient. In contrast, in Germany, patients are usually assigned a specific DRG code depending on the severity of HF, that is, based on NYHA class. This example of HF hospitalization costs thus illustrates the pitfalls of assuming that results from even such a simple economic model as a budget impact analysis can be transferred directly to countries with seemingly similar health care and reimbursement systems.

The strengths of our analysis are that the budget impact model probably underestimated the effect of FCM treatment on overall costs. The main reason for this was that the base case considered only the effect on costs of overall differences in the rate of hospitalization observed with FCM. Differences in length of stay which were also observed with FCM in the randomized clinical trials were not considered in this analysis due to the lack of suitable Swiss data to represent this in the budget impact model. While a budget impact model may represent a relatively simple form of economic comparison from a methodological point of view, the message it conveys is easy to understand and familiar to Swiss decision makers as budget impact is widely used in the Swiss health care system. This analysis adds to existing knowledge by being the first exploration of the rate and cost of potentially avoidable hospitalizations with FCM treatment in HFrEF patients with ID in Switzerland. It further adds to existing knowledge by being the first analysis of the budget impact of FCM treatment in CHF patients with ID in Switzerland. In addition, it is based on a specifically commissioned data analysis of secondary data in an area with a paucity of published data.

5 Conclusion

Intravenous iron substitution is easy to administer and incorporate in clinical practice. The present analysis suggests that FCM treatment of HFrEF patients with ID/IDA in line with guideline recommendations [2] results not only in medical benefits to the affected patients due to a reduction in the number of hospitalizations but also in cost savings for the Swiss mandatory health care system. To our knowledge, this is the first budget impact analysis of iron substitution in symptomatic patients with HFrEF in Switzerland.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-022-00341-7.

Acknowledgements This work was supported by Vifor Pharma Switzerland.

Declarations

Funding This work was supported by Vifor Pharma Switzerland.

Conflict of interest EB is an employee of HealthEcon, who was commissioned by Vifor Pharma Switzerland to conduct the analysis and prepare the first draft of this manuscript. OP reports consultant fees and or research grants from Vifor Pharma, Novartis, Pfizer, MSD, Astra Zeneca, Boehringer Ingelheim, Sanofi, and Bayer. GM reports consultant fees for taking part in advisory boards for Novartis, Bayer, Astra Zeneca, and Boehringer Ingelheim, outside of the submitted work.

Availability of data and material The analysis described in this manuscript is based on efficacy data based on published data, publicly available resource use, cost and epidemiological data, as well as a proprietary analysis of SwissDRG data. These have been described and referenced extensively in the methods section of this manuscript. The authors would be happy to respond to further enquiries regarding the details of the analysis should these not have been answered by the information provided in the methods section. The model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript.

Code availability The authors would be happy to respond to further enquiries regarding the details of the analysis should these not have been answered by the information provided in the methods section.

Author contributions All authors contributed to the conception of the work, validation of the input parameter values and drafting and revision of the manuscript.

Ethics approval Ethics committee approval was not required for this study. In Switzerland, IRBs (i.e. cantonal/ hospital ethics commissions) are tasked with assessing research which falls under the Humanforschungsgesetz (Human Research Act; https://www.fedlex.admin.ch/eli/cc/2013/617/de). KOFAM (kofam.ch) is the Federal Office of Public Health's (FOPH) portal for human research in Switzerland. KOFAM offers on its website the 'categorizer', a tool set up to help researchers ascertain whether their research project needs to be assessed by an ethics committee: https://www.kofam.ch/de/categoriser/. As the work presented here at no point in time touched on any individual or non-anonymized patient data, nor on any of the other topics covered by the Human Research Act, the Human Research Act does not apply to the work presented here, and hence ethics committee approval was not required.

Consent to participate The analysis presented here was not based on individual or non-anonymized patient data. The authors would like to thank patients whose aggregated, anonymized clinical trial, registry, and SwissDRG data served as the basis for deriving the parameter input values for the analysis presented here.

Consent for publication Not applicable.

References

1. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. BMC Cardiovasc Disord. 2018;18(1):74.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 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. Eur J Heart Fail. 2016;18(8):891–975.
3. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol. 2011;8(9):485–93.
4. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361(25):2436–48.
5. Ponikowski P, Filippatos G, Colet JC, Willenheimer R, Dickstein K, Luscher T, et al. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. Eur J Heart Fail. 2015;17(3):329–39.
6. Arutyunov G. The safety of intravenous (IV) ferric carboxymaltose versus IV iron sucrose on patients with chronic heart failure (CHF) and chronic kidney disease (CKD) with iron deficiency (ID). Eur J Heart Fail. 2009;8:ii71.
7. Clinicaltrials.gov. EFfect of ferric carboxymaltose on exercise capacity and cardiac function in patients with iron deficiency and chronic heart failure (EFFICACY-HF). 2019. https://clinicaltrials.gov/ct2/show/results/NCT00821717?term=EFFICACY-HF&rank=1.
8. Theidel U, Vaatainen S, Martikainen J, Soini E, Hardt T, Doehner W. Budget impact of intravenous iron therapy with ferric carboxymaltose in patients with chronic heart failure and iron deficiency in Germany. ESC Heart Fail. 2017;4(3):274–81.
9. Gutzwiller FS, Schwenkglenks M, Blank PR, Braunhofer PG, Mori C, Szucs TD, et al. Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. Eur J Heart Fail. 2012;14(7):782–90.
10. Comin-Colet J, Rubio-Rodriguez D, Rubio-Terres C, Enjuanes-Grau C, Gutzwiller FS, Anker SD, et al. A cost-effectiveness analysis of ferric carboxymaltose in patients with iron deficiency and chronic heart failure in Spain. Rev Esp Cardiol (Engl Ed). 2015;68(10):846–51.
11. Hofmarcher T, Cabrales Alin D, Linde C. Cost effectiveness of implementing ESC guidelines for treatment of iron deficiency in heart failure in the Nordic countries. Scand Cardiovasc J. 2018;52(6):348–55.
12. Bourguignon S, Faller M, Champs FO, Moutier H, Levesque K, Caranhac G, et al. Budget impact of intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency in France. ESC Heart Fail. 2019;6(3):559–69.
13. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014;17(1):5–14.
14. Wienbergen H, Pfister O, Hochadel M, Michel S, Bruder O, Remppis BA, et al. Usefulness of iron deficiency correction in management of patients with heart failure [from the registry analysis of iron deficiency-heart failure (RAID-HF) Registry]. Am J Cardiol. 2016;118(12):1875–80.
15. Gstrein C, Meyer M, Anabitarte P. Iron substitution in the treatment of chronic heart failure. Swiss Med Wkly. 2017;147:w14453.
16. Ruschitzka F. Heart Failure Guidelines 2016. 2017. http://www.swisscardio.ch/public/veranstaltungskalender/veranstaltungsarchiv/2016/jahrestagung16/programm/15.06.2016/Ruschitzka_Frank_20160615_1545_Auditorium_B.pdf.
17. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. JAMA. 2020;324(5):488–504.
18. cs healthcare consult. Specially commissioned analysis based on SwissDRG data. Data on file at Vifor Pharma Switzerland, see online appendix for further detail. 2016.
19. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger. Eur Heart J. 2015;36(11):657–68.
20. Swiss University Hospital. Specifically commissioned single-center data analysis. Data on file at Vifor Pharma Switzerland. 2016.
21. Tarmed. Tarmed Online Browser—Tarifversion: 1.09, gültig ab 1.1.2018. 2022. https://www.tarmed-browser.ch/de.
22. NewIndex AG. Kantonale Taxpunktwerte 2019. 2022. https://www.newindex.ch/wp-content/uploads/2019/02/TPW-DE-2019-2013.pdf.
23. Vifor (International) Inc. Fachinformation FERINJECT Inj Lös 100 mg/2 ml. 2022. https://compendium.ch/product/1080875-ferinject-inj-los-100-mg-2ml/mpro.
24. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013;165(4):575-82 e3.