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ORIGINAL RESEARCH



Cost-minimization analysis of recombinant factor VIII Fc versus emicizumab for treating patients with hemophilia A without inhibitors in Europe

Maria Elisa Mancuso^a , Giancarlo Castaman^b , Michal Pochopien^c, Samuel Aballéa^d, Aleksandra Drzewiecka^c , Zalmi Hakimi^e , Jameel Nazir^e and Francis Fatoye^f 

^aCentre for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Rozzano, Italy; ^bCenter for Bleeding Disorders and Coagulation, Careggi University Hospital, Center for Bleeding Disorders, Florence, Italy; ^cCreativ-Ceutical, Krakow, Poland; ^dCreativ-Ceutical, Rotterdam, The Netherlands; ^eSwedish Orphan Biovitrum Ltd, Stockholm, Sweden; ^fFaculty of Health and Education, Manchester Metropolitan University, Manchester, UK

ABSTRACT

Background and objective: A cost-minimization model was developed to compare recombinant factor VIII Fc (rFVIII Fc) and emicizumab as prophylaxis for hemophilia A without inhibitors.

Methods: The model was based on 100 patients from the healthcare payer perspective in the UK, France, Italy, Spain, and Germany (5-year time horizon). Costs included: drug acquisition; emicizumab wastage by bodyweight (manufacturer's dosing recommendations); and additional FVIII for breakthrough bleeds. Scenario analyses (UK only): reduced emicizumab dosing frequency; and emicizumab maximum wastage.

Results: Total incremental 5-year savings for rFVIII Fc rather than emicizumab use range from €89,320,131 to €149,990,408 in adolescents/adults (≥ 12 years) and €173,417,486 to €253,240,465 in children (< 12 years). Emicizumab wastage accounts for 6% of its total cost in adolescents/adults and 26% in children. Reducing the emicizumab dosing frequency reduces the incremental cost savings with rFVIII Fc, but these remain substantial (adolescents/adults, $> €92$ million; children $> €32$ million). Maximum emicizumab wastage increases by 86% and 106%, respectively, increasing the incremental cost savings with rFVIII Fc to €125,352,125 and €105,872,727, respectively.

Conclusion: Based on cost-minimization modeling, rFVIII Fc use for hemophilia A prophylaxis in patients without inhibitors is associated with substantial cost savings in Europe, reflecting not only higher acquisition costs of emicizumab, but also other costs including wastage related to available vial sizes.

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Introduction

Congenital hemophilia A is a bleeding disorder caused by deficiency of factor VIII (FVIII)¹. Worldwide, hemophilia occurs in 1 in 5,000 live male births², but its prevalence varies geographically, being highest in high-income countries³. In Europe, approximately 400 boys with hemophilia are born each year⁴. The condition is associated with spontaneous and traumatic bleeding episodes in joints and muscles, which can lead to synovitis, chronic hemophilic arthropathy, and pseudotumors⁵. These, in turn, cause pain, reduced functioning, and impaired health-related quality of life^{6–8}. It has also been shown that people with hemophilia have an increased mortality risk versus the general population^{9,10}. For example, in an analysis of data collected in Sweden between 1969 and 2008, the hazard ratio for all-cause mortality for patients with hemophilia was 2.2 ($p < 0.001$)¹⁰.

Prophylaxis with FVIII replacement therapy is the standard of care for patients to prevent bleeds in patients with hemophilia A¹¹. These include a recombinant factor VIII Fc fusion protein (rFVIII Fc; efmoroctocog alfa), which consists of a single molecule of rFVIII fused to the Fc domain of immunoglobulin G1¹². In Europe, it is the only extended half-life rFVIII product approved for the treatment and prophylaxis of bleeding in patients with hemophilia A of all ages (other products are approved for patients aged > 12 years only)¹³. In phase 3 and long-term extension studies in children, adolescents, and adults with severe hemophilia A, a low annualized bleed rate (ABR) was maintained for up to 4 years with extended-interval prophylactic dosing^{14–16}. In a recently conducted matching-adjusted indirect comparison of individualized prophylaxis with rFVIII Fc or prophylaxis with pegylated rFVIII (BAY 94-9027) according to their approved dosing regimens, rFVIII Fc provided a statistically significant lower ABR¹⁷. Furthermore, in a cost–utility analysis

CONTACT Giancarlo Castaman  castaman@aou-careggi.toscana.it  Center for Bleeding Disorders, Careggi University Hospital, Largo Piero Palagi, 1, Florence 50139, Italy

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evaluating life-long prophylaxis with rFVIIIc versus rFVIII products in patients with severe hemophilia A in Sweden, rFVIIIc was cost-effective, generating greater quality of life and reduced costs¹⁸. Similar results were obtained in the cost-effectiveness analysis of lifelong prophylaxis with rFVIIIc or rFVIII products from an Italian healthcare perspective¹⁹.

Emicizumab is a bispecific monoclonal antibody, which mimics the function of activated FVIII by bridging activated factor IX and factor X to induce coagulation at the site of bleeding^{20,21}. In Europe, it is approved for routine prophylaxis of bleeding episodes in patients with hemophilia A with FVIII inhibitors and in patients with severe hemophilia A without inhibitors²². The recommended dose is 3 mg/kg subcutaneously once weekly (Q1W) for the first 4 weeks (loading dose), followed by maintenance doses of 1.5 mg/kg Q1W, 3 mg/kg every 2 weeks (Q2W), or 6 mg/kg every 4 weeks (Q4W)²².

To date, there are no direct comparative studies of rFVIIIc and emicizumab and a lack of data on their relative economic impact. In a matching-adjusted indirect comparison using data from phase 3 trials, individualized prophylaxis with rFVIIIc was more efficacious than emicizumab administered Q4W for the proportion of patients with zero bleeds, whilst its efficacy in terms of mean ABR was similar to that of emicizumab administered Q1W, Q2W, and Q4W, with trends in favor of rFVIIIc²³. There are several factors that differentiate rFVIIIc and emicizumab and impact on the direct costs of treatment, including possible emicizumab wastage as a result of vial size availability relative to the weight-based dosing schedule²⁴ and the need for additional FVIII to treat bleeds (or prior to physical exercise) in emicizumab-treated patients^{25,26}. Cost-minimization modeling provides a simple analysis with few assumptions for drugs with equivalent/similar efficacy; therefore, the present study used this approach to evaluate the economic impact of rFVIIIc²⁷. One of the assumptions underlying cost-minimization analyses is that the products being evaluated have equivalent efficacy and safety, which has been shown previously in the matching-adjusted indirect comparison²³.

The aim of the current analysis was, therefore, to use a cost-minimization model to compare rFVIIIc with emicizumab when used as prophylactic treatment for patients with hemophilia A without inhibitors in Europe.

Materials and methods

Targeted literature review

A targeted literature review was conducted to identify resources and costs associated with rFVIIIc and emicizumab treatment; the focus was to identify publications on resource use, hospitalization (including length of stay), and healthcare costs associated with the treatment of people with hemophilia A. A search was performed using PubMed on 5 December 2019 (see [Supplementary Table S1](#) for the search strategy). The websites of hemophilia associations and the grey literature (e.g. reports on burden associated with hemophilia A) were also evaluated ([Supplementary Table S2](#)).

Overall, 610 abstracts were screened and 591 were excluded, mainly because they were non-clinical or related

to studies with populations, outcomes, or study designs that were not relevant. The full text of the remaining 19 publications was evaluated^{7,18,19,28–43}. These included literature reviews ($n=3$), cost-utility or cost-effectiveness analyses ($n=8$), burden of disease reports ($n=6$), and budget impact analyses ($n=2$), most of which concerned the USA and Italy, although Portugal, India, Sweden, Thailand, Colombia, Mexico, Iran and Europe were also covered. A small number of publications considered costs according to age (child vs adult) or hemophilia severity (mild, moderate, severe). Four of the 19 publications concerned rFVIIIc ($n=3$) or emicizumab ($n=1$; [Supplementary Table S3](#)). The most common direct costs considered were those associated with prophylactic treatment, treatment of bleeding episodes, hospitalization, and medical visits.

Cost-minimization model

The model was based on a population of 100 people with hemophilia A without inhibitors who were treated with prophylaxis. Children were defined as those aged ≤ 12 years, and adults and adolescents as those aged >12 years. The time horizon of the model was 5 years (with Year 1 set as 2020) and the analysis was from a healthcare payer perspective in the UK, France, Italy, Spain, and Germany.

The cost of prophylaxis treatment with rFVIIIc or emicizumab was based on each product's list price. The rFVIIIc doses used in the model were 85.4 IU/kg/week for adolescents and adults and 88.11 IU/kg/week for children (based on data from the phase 3 A-LONG [NCT01181128]¹⁴ and Kids A-LONG [NCT01458106]¹⁶ studies). For emicizumab, a loading dose of 3 mg/kg per week was administered for 4 weeks (as recommended in the Summary of Product Characteristics²²) followed by maintenance treatment with 1.5 mg/kg per week (based on that used in the HAVEN 3 study [NCT02847637]²⁵). The bodyweights of adolescents/adults and children were based on data from the A-LONG¹⁴ and Kids A-LONG studies¹⁶, respectively.

Other costs included in the model were those associated with emicizumab wastage according to bodyweight, based on the manufacturer's recommendations on the most appropriate number of injections using the various available vial strengths²⁴; cost of additional FVIII for treatment of bleeds (additional rFVIIIc in those treated with rFVIIIc, and octocog alfa for those treated with emicizumab); and cost of wasted on-demand FVIII due to expired shelf life (both products). For the emicizumab group, it was assumed that patients would have a single dose of octocog alfa available at home to treat breakthrough bleeds and it would be wasted if not used within 2 years (the shelf life)⁴⁴. Bleeding rates were based on the ABR for rFVIIIc and emicizumab, plus a proportion of patients without bleeds for emicizumab. These model inputs were selected based on parameters commonly considered in the literature and factors that differentiate rFVIIIc and emicizumab. Further information on the data sources used to quantify these inputs are summarized in [Table 1](#). The manufacturer's recommendations regarding the

Table 1. Model and scenario analyses inputs.

Input	Value	Source
Population size	100 Patients	Assumption
Time horizon	5 Years	–
Country	UK, France, Italy, Spain, and Germany	–
Mean (SD) bodyweight male adolescents/adults (≥ 12 years), kg	73.51 (14.95)	A-LONG trial ¹⁴
Mean (SD) bodyweight male children (<12 years), kg	24.99 (11.85)	Kids A-LONG trial ¹⁶
Wastage	As recommended by manufacturer	Emicizumab dosing calculator ²⁴
rFVIIIc dose – prophylaxis (adolescents/adults)	85.4 IU/kg/week	A-LONG trial ^{14a}
rFVIIIc dose – prophylaxis (children)	88.11 IU/kg/week	Kids A-LONG trial ¹⁶
Emicizumab dose – prophylaxis (loading)	3 mg/kg Q1W	Summary of Product Characteristics ²²
Emicizumab dose – prophylaxis (maintenance)	1.5 mg/kg Q1W	HAVEN 3 ²⁵
FVIII dose to treat breakthrough bleeds	44.53 IU/kg	A-LONG trial ¹⁴
ABR rFVIIIc	2.9	A-LONG trial ¹⁴ (individualized prophylaxis)
ABR emicizumab	1.56	HAVEN 3 ²⁵
		(1.5 mg/kg QW)
Proportion of emicizumab-treated patients without bleeds	55.8%	HAVEN 3 ²⁵
		(1.5 mg/kg QW)
Proportion of emicizumab-treated patients requiring dose up-titration	0%	HAVEN 3 ²⁵
rFVIIIc list price (€ per IU)	UK: 0.89 France: 0.65 Italy: 0.65 Spain: 0.59 Germany: 0.53	SOBI data
Emicizumab list price (€ per mg)	UK: 80.51 France: 77.13 Italy: 55.07 Spain: 76.70 Germany: 64.66	SOBI data
Octocog alfa list price (per IU)	UK: €0.84 France: €0.65 Italy: €0.63 Spain: €0.56 Germany: €1.08	UK: MIMS data Other countries: Sobi data

^aMean dose from individualized prophylaxis arm in A-LONG.

Abbreviations: ABR, annualized bleed rate; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; Q1W, once weekly; SD, standard deviation.

appropriate number of injections are designed to minimize emicizumab wastage (see [Supplementary Figure S1](#)).

Assumptions of the model were: the population size was constant in consecutive years of the analysis; rFVIIIc and emicizumab have the same market share; there was no switching between treatments or discontinuation of prophylactic treatment; and all emicizumab-treated patients received the loading dose at the start of therapy.

Scenario analyses

Scenario analyses were conducted to evaluate the effect of the following on incremental costs (from a UK perspective): reduced dosing frequency for emicizumab (3 mg Q2W and 6 mg Q4W); emicizumab wastage according to patients' bodyweight evaluated based on potential maximum wastage rather than the manufacturer's recommendations (which are designed to minimize wastage; see [Supplementary Figure S1](#)); maximal emicizumab wastage according to bodyweight (set at 81 kg for adolescents/adults and 41 kg for children); up-titration of emicizumab dose (8% of those treated, based on data from the HAVEN 3 study²⁵).

Results

Base-case analysis

In adolescents and adults, total 5-year costs across the five countries ranged from €89,320,131 to €149,990,408 for rFVIIIc

and €173,417,486 to €253,240,465 for emicizumab; most of the costs were accounted for by the cost of administered drug (97% for rFVIIIc and 93% for emicizumab; [Figure 1a](#)). Total incremental 5-year savings associated with using rFVIIIc rather than emicizumab ranged from €84,097,355 to €103,250,057.

In children, total 5-year costs across the five countries ranged from €31,304,879 to €52,568,571 for rFVIIIc and €75,111,853 to €109,712,238 for emicizumab ([Figure 1b](#)); as in adults and adolescents, most of the costs were accounted for by the drug acquisition costs (97% for rFVIIIc and 73% for emicizumab), but in emicizumab-treated patients, the contribution of wastage was higher in children (26%) than in adolescents and adults (6%). Total incremental 5-year savings associated with using rFVIIIc rather than emicizumab ranged from €43,806,974 to €57,143,667.

Scenario analyses

Total and incremental costs for the scenario analyses are summarized in [Figure 2](#). Reducing the dosing frequency of emicizumab reduced its costs ([Figure 2a](#)), but the incremental cost savings associated with using rFVIIIc remained. In adolescents/adults, cost savings with rFVIIIc were €94,168,828 versus emicizumab Q2W and €92,520,460 versus emicizumab Q4W; corresponding savings in children were €38,832,812 and €32,481,446, respectively.

When emicizumab wastage was based on potential maximum wastage rather than the manufacturer's

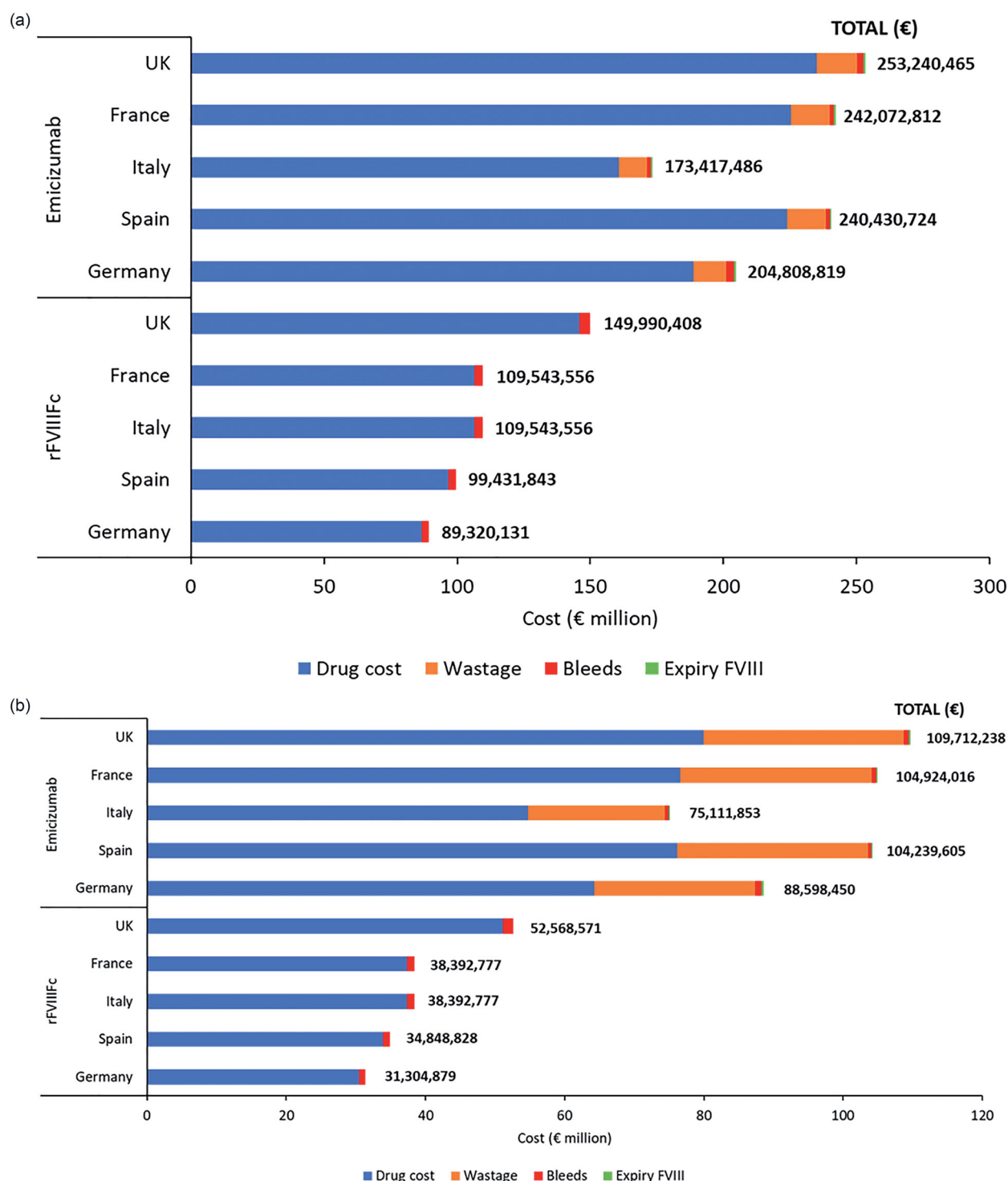


Figure 1. Five-year costs associated with using rFVIII Fc and emicizumab for prophylactic treatment of 100 people with hemophilia A (base-case analysis: recommended wastage; emicizumab 1.5 mg/kg once weekly). (a) Adolescents/adults (≥ 12 years). (b) Children (< 12 years). **Abbreviation:** rFVIII Fc, recombinant factor VIII Fc.

recommendations (which are designed to minimize wastage), incremental cost savings with rFVIII Fc were greater than in the base-case analysis (€125,352,125 for adolescents/adults and €105,872,727 for children) (Figure 2b). Wastage costs increased by 86% (adolescents/adults) and 106% (children) compared with the base-case analysis.

At maximal emicizumab wastage (bodyweight set at 81 kg for adolescents/adults and 41 kg for children), incremental

cost savings with rFVIII Fc were €121,145,014 and €62,665,311, respectively (Figure 2c).

Discussion

To our knowledge, this the first study to compare the economic impact of rFVIII Fc with emicizumab when used as

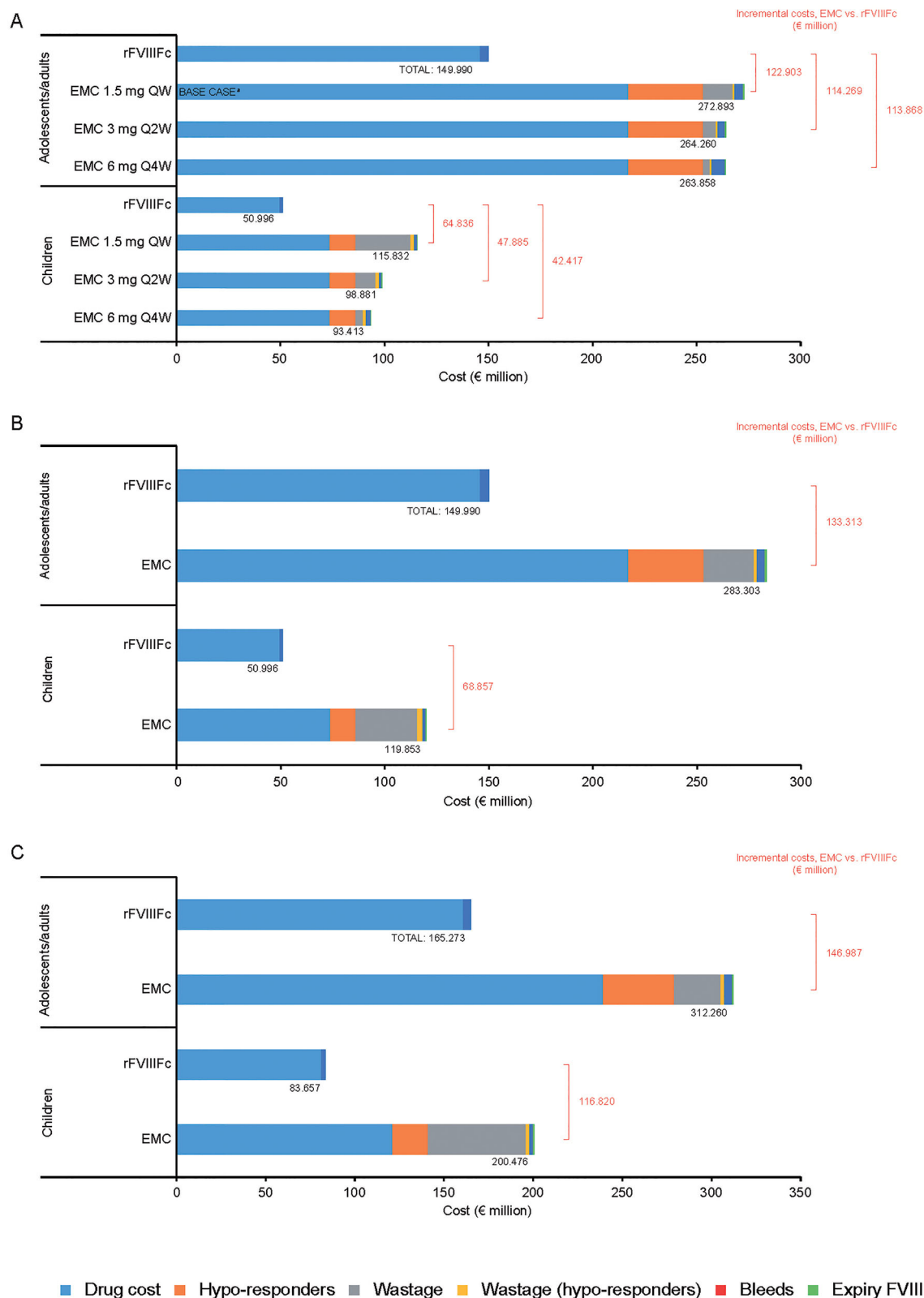


Figure 2. Scenario analyses (UK): 5-year costs associated with using rFVIII Fc and emicizumab for prophylactic treatment of 100 people with hemophilia A, according to (a) Reduced dosing frequency for emicizumab, (b) Emicizumab potential maximum wastage, and (c) Maximal emicizumab wastage according to bodyweight. (a) Base-case dosing interval for emicizumab (1.5 mg every week) included for comparative purposes. (b) Eloquent dose set at 88.11 IU/kg/week. **Abbreviations:** QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; rFVIII Fc, Recombinant factor VIII Fc.

prophylactic treatment for hemophilia A without inhibitors in Europe. Results of the cost-minimization analysis demonstrate that based on emicizumab and rFVIII Fc list prices in

the UK, France, Italy, Spain, and Germany, prophylactic treatment of hemophilia A is 69% to 94% more expensive with emicizumab than rFVIII Fc in adolescents and adults and

109% to 140% more expensive in children. Cost savings for 100 adolescents/adults treated with rFVIII-Fc instead of emicizumab for 5 years range from €84,097,355 to €103,250,057; respective cost savings for 100 children range from €43,806,974 to €57,143,667. Clearly, the magnitude of the cost savings has important implications for healthcare resource allocation and budgets in general, particularly when one considers the lifelong nature of hemophilia A.

Most of the cost savings associated with rFVIII-Fc reflect the difference in acquisition costs between the two products, but drug wastage also has an impact, particularly in children. At maximum wastage (when adolescents/adults bodyweight is set at 81 kg and children's at 41 kg), cost savings for rFVIII-Fc versus emicizumab increase from €103,250,057 to €121,145,014 and €57,143,667 to €62,665,311, respectively (UK data). Reducing the dosing frequency of emicizumab reduces the incremental costs, but the cost savings associated with using rFVIII-Fc remain substantial (in excess of €92 million in adults and adolescents, and €32 million in children). Conversely, as expected, using a more convenient combination of vial sizes (rather than the combination associated with least wastage) to achieve the appropriate emicizumab dose is associated with greater costs savings for rFVIII-Fc. The extent to which clinicians use the most convenient approach to dosing is not clear, but in view of the impact of wastage on costs, particularly in children, it should be avoided. It is acknowledged that up-titration of the emicizumab dose, as permitted in the HAVEN 3 study²⁵, is not licensed²². Excluding this cost from the model reduces the cost differential between rFVIII-Fc and emicizumab, but the excess cost of the latter remains substantial.

The current study used cost-minimization modeling to evaluate the economic impact of rFVIII-Fc, as it provides a simple analysis with few assumptions for drugs with equivalent/similar efficacy²⁷. Previous studies have used budget impact³⁸, cost-utility¹⁸, and cost-effectiveness analyses¹⁹. The budget impact model evaluated the economic impact of introducing rFVIII-Fc to the market in Italy over a 3-year time horizon. The results showed a potential cost saving of more than €13.3 million compared with the "market mix" at the time (commonly used recombinant or plasma-derived FVIII) for treating hemophilia A³⁸. The cost-utility¹⁸ and cost-effectiveness¹⁹ studies evaluated life-long prophylaxis with rFVIII-Fc versus rFVIII products for severe hemophilia A (from Swedish and Italian healthcare perspectives, respectively) and both showed rFVIII-Fc to dominate rFVIII (i.e. it provided greater quality-adjusted life-years at a lower cost). The authors of the Italian study concluded that the cost-effectiveness of rFVIII-Fc reflected the modeled lower frequency of bleeding, improved joint health, and reduced factor consumption¹⁹. Analyses of the economic impact of emicizumab have also been conducted, but these focus on its cost-effectiveness versus bypassing agents in patients with hemophilia A and inhibitors^{45–47} or the cost impact of delayed inhibitor development versus FVIII prophylaxis in patients with hemophilia A³⁹. The cost-effectiveness analyses showed that emicizumab dominated bypassing agents, and delayed inhibitor

development with emicizumab was associated with cost savings versus FVIII products.

One of the assumptions underlying cost-minimization analyses is that the products being evaluated have equivalent efficacy and safety. Although there are no direct comparative trials of rFVIII-Fc and emicizumab, rFVIII-Fc has been shown to be at least as effective as emicizumab, as measured by ABR, in a matching-adjusted indirect comparison²³, a validated method for comparing treatments in the absence of head-to-head studies⁴⁸. However, it is acknowledged that the indirect comparison did not evaluate long-term outcomes, such as joint health. Other potential limitations of the current model include the generalizability of the results outside the five European countries evaluated, and the source of data on ABRs and additional factor required to treat bleeds and patients whose emicizumab dose requires up-titration; these came from clinical trials rather than clinical practice so data from the real-world setting are required to substantiate these cost drivers. Another limitation is that acquisition costs for rFVIII-Fc and emicizumab in this analysis were based on the list price for each country, but, in practice, costs can vary according to national tenders or even regional agreements. In some countries or regions, there is an agreement between the manufacturer and the regulatory authorities ensuring the annual cost for emicizumab prophylaxis is equivalent to the average annual cost of prophylaxis with FVIII concentrates. As such, while there would still be a cost differential between emicizumab and rFVIII-Fc, it is much less than that demonstrated by the model. Finally, it is worth noting that an additional factor may be required before physical activity in some emicizumab-treated patients, as shown in the HAVEN 4 trial²⁶, but this was not included in the model.

In conclusion, when making the decision to use rFVIII-Fc or emicizumab for prophylaxis in people with hemophilia A without inhibitors, payers should consider both the acquisition and other costs associated with their use. Emicizumab has a much higher acquisition cost; this and other factors, such as wastage related to the vial sizes for emicizumab and dose up-titration in some patients, mean that there are substantial cost savings associated with using rFVIII-Fc. Given that rFVIII-Fc appears to be at least as effective as emicizumab, the additional cost of the latter may not be justified as payers need to consider good value for money more closely and the opportunity for potential cost savings. Over the 5-year period evaluated in the current cost-minimization model, these cost savings amount to €840,974 to €1,032,501 per patient for adolescents/adults and €438,070 to €571,437 per patient for children. Therefore, each year, an additional 300 children could be treated considering a twice weekly regimen with 1,000 IU/infusion rFVIII-Fc, and an additional 100 adolescents/adults with a twice weekly regimen of 3,000 IU/infusion. Scaling these costs up to the population level has significant cost implications for healthcare systems in Europe. As well as cost differences, the practicalities of using emicizumab in terms of wastage, particularly in children, are an important consideration. These results may help inform resource allocation decisions to improve overall health outcomes of individuals with hemophilia A without inhibitors in Europe.

Transparency

Declaration of funding

The study was funded by Swedish Orphan Biovitrum AB.

Declaration of financial/other interests

MEM has acted as a paid consultant/speaker/advisor for Bayer Healthcare, Biomarin, CSL Behring, Catalyst Bioscience, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutic, Sobi, Takeda, and UniQure.

GC has acted as a paid consultant/speaker/advisor for Alexion, Bayer Healthcare, Biomarin, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Roche, Sanofi, Takeda, Werfen, and UniQure.

MP, SA, and AD are employees of Creativ-Ceutical, a consultancy company that received funding from Swedish Orphan Biovitrum for this research.

ZH and JN are employees of Swedish Orphan Biovitrum AB.

FF reports grant/research support from Swedish Orphan Biovitrum AB.

Author contributions

All authors were involved in the conception and design of the study. MP, SA, and AD were involved in analyzing the data associated with the study. All authors were involved with drafting and revising the manuscript, and for the final approval of the manuscript. All authors agree to be accountable for all aspects of the work.

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Data availability statement

The data that support the findings of this study are available from the corresponding author [GC], upon reasonable request.

Reviewer disclosures

Peer reviewers on this manuscript have received an honorarium from JME for their review work but have no other relevant financial relationships to disclose.

ORCID

Maria Elisa Mancuso  <http://orcid.org/0000-0002-7113-4028>
 Giancarlo Castaman  <http://orcid.org/0000-0003-4973-1317>
 Aleksandra Drzewiecka  <http://orcid.org/0000-0003-3396-8571>
 Zalmai Hakimi  <http://orcid.org/0000-0001-5835-8599>
 Francis Fatoye  <http://orcid.org/0000-0002-3502-3953>

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