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ORIGINAL RESEARCH

Cost-Effectiveness of Recombinant Factor IX Fc Prophylaxis and Recombinant Factor IX On-Demand Treatment in Patients with Haemophilia B Without Inhibitors

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ABSTRACT

Introduction: Recombinant factor IX (rFIX) and recombinant FIX Fc fusion protein (rFIXFc) are standard half-life and extended half-life FIX replacement therapies, respectively, and represent established treatment options indicated for adults and children with haemophilia B. These FIX replacement therapies can be administered as prophylaxis (to prevent bleeding) or 'on-demand' (to stop bleeding). This analysis aimed to estimate the cost-effectiveness of once-weekly prophylaxis with rFIXFc versus on-demand treatment with rFIX in patients with haemophilia B without inhibitors in the Italian healthcare setting.

Methods: A Markov model was developed to assess a hypothetical cohort of adolescent or adult male patients (≥ 12 years) with haemophilia B (FIX level of ≤ 2 IU/dL) without inhibitors. Model inputs were derived from the pivotal phase 3 clinical studies for rFIXFc and rFIX, published literature and assumptions when published data were unavailable. The model employed a lifelong time horizon with 6-monthly transitions between health states, and it estimated total costs, total quality-adjusted life years (QALYs), number of bleeds, number of surgeries and incremental cost-effectiveness ratio.

Results: rFIXFc prophylaxis was associated with lower total costs per patient (€5,308,625 versus €6,564,510) and greater total QALYs per patient (15.936 versus 11.943) compared with rFIX on-demand; rFIXFc prophylaxis was therefore the dominant treatment strategy. The model also demonstrated that rFIXFc prophylaxis was associated with fewer incremental bleeds (− 682.29) and surgeries (− 0.39) compared with rFIX on-demand.

Conclusions: rFIXFc prophylaxis provides improved health outcomes and lower costs, and represents a cost-effective treatment option compared with rFIX on-demand for adolescent and adult male patients with haemophilia B.

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This comparative assessment of cost-effectiveness should help to inform both clinicians and healthcare policy makers when making treatment decisions for patients with haemophilia B.

Keywords: Cost-effectiveness analysis; Factor IX; Haemophilia B; Haemorrhage; Primary prevention; Quality-adjusted life years; Recombinant fusion proteins

Key Summary Points

Why carry out this study?

Recombinant coagulation factor IX Fc fusion protein (rFIXFc) is approved for the treatment and prophylaxis of bleeding in patients with haemophilia B on the basis of the results from clinical trials, which demonstrated significantly lower rates of bleeding with rFIXFc prophylaxis compared with on-demand treatment.

Cost-effectiveness is an important consideration for the management of haemophilia B because of the requirement of lifelong treatment with prophylaxis or on-demand strategies.

This study aimed to evaluate the cost-effectiveness of rFIXFc when used as prophylaxis for patients with haemophilia B without inhibitors from an Italian healthcare perspective.

What was learned from the study?

Over a lifelong time horizon, rFIXFc prophylaxis dominated rFIX on-demand on the basis of greater total quality-adjusted life years (incremental, 3.993 per patient) and lower total costs (incremental, − €1,255,885 per patient).

The improved health outcomes and lower costs associated with rFIXFc prophylaxis were underscored by estimated fewer bleeds and surgeries, as well as lower costs for bleeding management, surgery and workdays lost compared with rFIX on-demand.

This comparative assessment of cost-effectiveness should help to inform both clinicians and healthcare policy makers regarding the optimal treatment strategy for patients with haemophilia B.

INTRODUCTION

Haemophilia B is a rare bleeding disorder characterised by the deficiency of functional coagulation factor IX (FIX) [1]. Haemophilia B is less common than haemophilia A, and estimated to account for 15–20% of all haemophilia cases in Italy [2] and globally [1]. Patients with severe haemophilia B (clotting factor level < 1 IU/dL or $< 1\%$ of normal) may experience spontaneous or recurrent bleeding into muscles and joints [1, 3], which may lead to acute/chronic pain, haemophilic arthropathy, and impaired health-related quality of life (HRQoL) [3].

Treatment for haemophilia principally comprises intravenous clotting factor replacement therapy, which is administered as prophylaxis for the prevention of bleeding episodes and joint damage or 'on-demand' for treatment of episodic bleeds [1, 3]. Prophylaxis is demonstrated to significantly reduce bleeding episodes in patients with haemophilia B (FIX activity ≤ 2 IU/dL) compared with on-demand treatment [4–8]. Reducing bleeding episodes with prophylaxis appears to translate into improved long-term joint function, reduced hospitalisations, and improved HRQoL, including an ability to perform physical activities, compared with on-demand therapy in patients with severe haemophilia A or B [3, 6, 7, 9–13]. Prophylaxis is the standard of care for patients with severe haemophilia without inhibitors (and those with moderate haemophilia [clotting factor level 1–5 IU/dL] associated with a severe bleeding phenotype), as advocated by the World Federation of Hemophilia [1] and the Italian Association of Haemophilia Centres (AICE) Working Party [14].

FIX replacement therapy is available as standard half-life (SHL) and extended half-life

(EHL) products, with EHL products providing a half-life that is up to five times longer, and therefore longer infusion dosing intervals compared with SHL FIX [15, 16]. Consequently, prophylaxis with EHL products is less treatment intensive than SHL products, which is expected to provide patient and healthcare system benefits, such as reduced burden of treatment and improved HRQoL and adherence [15–19]. Additional potential benefits provided by prophylaxis with EHL products include better protection from breakthrough bleeds, supporting a more active lifestyle and maintaining long-term joint health [18, 19].

Treatments indicated for the management of patients with haemophilia B in Italy include recombinant FIX (rFIX) and recombinant FIX Fc fusion protein (rFIXFc), which are SHL and EHL FIX replacement therapies, respectively [20, 21]. Clinical trials have demonstrated the safety and efficacy of rFIX in previously treated haemophilia B (baseline clotting factor level $\leq$ 2 IU/dL or $<$ 1–5 IU/dL) and previously untreated haemophilia B (baseline clotting factor level $<$ 1–3 IU/dL) [5, 22, 23]. Correspondingly, rFIXFc prophylaxis has been shown to be effective and well tolerated in patients with haemophilia B (endogenous FIX $\leq$ 2 IU/dL) who were previously treated (aged $<$ 12 years [Kids B-LONG] or $\geq$ 12 years [B-LONG]) [8, 24], or previously untreated (aged $<$ 18 years [PUPs B-LONG]) [25]. Long-term extension (B-YOND) and real-world evidence studies have confirmed the efficacy and safety of rFIXFc for up to 5 years [26, 27], and additional analyses of the phase III trials indicate rFIXFc prophylaxis contributes to an overall improvement in HRQoL including pain, physical functioning and physical activity [28–30].

National registry data for haemophilia in Italy indicate that 707 patients had haemophilia B in 2020, including 593 (84%) aged $>$ 12 years and 387 (55%) with moderate/severe disease [2]. Among those with moderate/severe haemophilia B receiving treatment, only 82% received prophylaxis and 81% of these patients received prophylaxis with EHL [2]. Given the reported benefits of prophylaxis versus on-demand and EHL versus SHL, these data may suggest an unmet need in Italian real-world clinical practice. Pharmacoeconomic analyses providing the comparative value of different treatment options may be an important factor in treatment decision-making processes [31], particularly for patients with severe haemophilia when prophylaxis is recommended to be continued lifelong [1]. This study aimed to estimate the cost-effectiveness of treatment using prophylaxis with rFIXFc versus on-demand treatment with rFIX in patients with haemophilia B without inhibitors in the Italian healthcare setting.

METHODS

Model Overview

A cost-utility model was developed in Microsoft Excel to simulate the natural history of haemophilia B and its therapeutic management. The model estimated the incremental cost-effectiveness ratio (ICER) of rFIXFc prophylaxis compared with rFIX on-demand treatment for a hypothetical cohort of 1000 adolescent or adult male patients ($\geq$ 12 years) with haemophilia B (FIX $\leq$ 2 IU/dL) without inhibitors. The model was conducted from the perspective of the Italian National Health Service (NHS) and considered direct costs (e.g. drug acquisition) and indirect costs (i.e. unpaid time due to missed work) associated with the management of patients. The model base-case had a lifelong time horizon to reflect the lifetime healthcare needs for patients with haemophilia B. Outcomes evaluated in the model were total costs, total quality-adjusted life years (QALYs; a measure of overall health in terms of additional quality and quantity of life gained from a treatment), total life years (LYs; a measure of additional years of life gained from a treatment), number of bleeds and number of joint surgeries. A discount rate of 3.5% per year was applied to costs and health outcomes to reflect that the values of future outcomes will be lower than the present ones. Model inputs for clinical effectiveness (i.e. annualised bleeding rate [ABR]), health-state utilities (a measure of quality/quantity of life for a given health state), healthcare resource utilisation and costs were

extracted from published sources where available (further described below). The model base-case analysis estimated results based on the most valid set of inputs and assumptions, and the robustness of the base-case model results were assessed using sensitivity analyses.

Treatment Pathway

At model entry, patients were assigned to either rFIXFc prophylaxis (once-weekly [base-case] or individualised interval [scenario analysis]) or rFIX on-demand treatment. The base-case model included three pre-defined health states and patients entered the model through the 'No bleeds' or 'Any bleeds' states (Fig. 1). In the base-case analysis, patients could transition from 'Any bleeds' to 'No bleeds' in subsequent cycles; transition to 'Death', an absorbing state, was possible from either of the remaining two states. It was assumed that patients remained in the 'Any bleeds' or 'No bleeds' states for the whole time horizon, unless they died according to the applied probability of death. It was also assumed that patients continued to receive their baseline treatment for the remainder of the analysis (i.e. no treatment switching). The model used a 6-month cycle to determine bleeding status; this aligns with the duration of treatment for the assessment of efficacy in the phase 3 trials of rFIXFc and rFIX. The model included utility values for the 'No bleeds' and 'Any bleeds' states, and short-term disutilities due to bleeding events and joint (hip/knee) surgery.

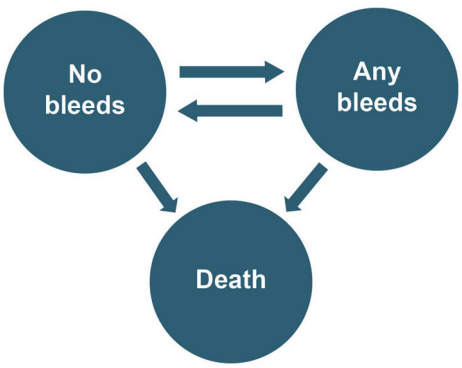

Fig. 1 Markov mode structure

MODEL INPUTS

Key Data Sources

Model inputs were sourced or adapted from key clinical studies for rFIXFc and rFIX where possible; other model inputs were obtained from the published literature or based on assumptions when published data were unavailable. B-LONG (NCT01027364) was a phase 3, non-randomised, open-label study of rFIXFc in previously treated male patients aged $\geq$ 12 years with haemophilia B (FIX level of $\leq$ 2 IU/dL) and without prior inhibitors [8]. B-LONG included four rFIXFc treatment groups: group 1 received weekly dose-adjusted prophylaxis (50 IU/kg); group 2 received interval-adjusted prophylaxis (100 IU/kg starting every 10 days); group 3 received episodic (on-demand) treatment (20–100 IU/kg); and group 4 received treatment in the perioperative period (40–100 IU/kg). The dose of rFIXFc in the once-weekly and individualised-interval groups were adjusted as needed during the study to maintain a trough level of 1–3 IU/dL above baseline, or higher, while the dose in the on-demand group was adjusted according to bleeding severity. The key study for rFIX was a phase 3, open-label study of previously treated male patients aged 12–65 years with haemophilia B (FIX level of $\leq$ 2 IU/dL) and without prior or current inhibitors (NCT 01335061) [5]. In this trial, patients initially received on-demand rFIX treatment for 6 months (dosing was at the investigator's discretion according to the prescribing information) followed by prophylaxis for approximately 12 months (once-weekly regimen of 100 IU/kg).

Patient Characteristics

Patient-level data for those who received rFIXFc prophylaxis (once weekly or individualised interval) in the B-LONG study were used to define the haemophilia B patient population with a mean age of 33.6 years and mean body weight of 72.1 kg (Table 1). To provide a European perspective, the calculations for mean body weight excluded data from patients in the USA.

Table 1 Model inputs: setting, population, efficacy and probability of events

	Base-case value	Sensitivity analysis values	Source
Settings and population			
Age, years	33.6	31.0–36.1	Analysis of patient-level data from B-LONG
Weight, kg	72.1	55.7–86.6	Analysis of patient-level data from B-LONG
Discount rate for health outcomes and costs	3.5%	0–5.0%	Assumption
Probability of events			
Proportion of patients without bleed in the first cycle			
rFIXFc Q1W PPX	23.0%	20.7–25.5%	[8]
rFIX on-demand	0	0	[5]
Transition probabilities, subsequent cycles			
No bleeds → No bleeds	100%	–	Assumption
Any bleeds → No bleeds	0%	0%	Assumption
Annual joint (hip/knee) surgery rate			
rFIXFc Q1W PPX	0.61%	0.55–0.67%	[5], [8]*,†, [32]
rFIX on-demand	2.30%	2.07–2.53%	[32]
Number of workdays lost per year for hospitalisation			
PPX	0.78	0–22	[32], [33]*
On-demand	3.12	1.30–10.60	[32], [33]*
ICH bleeds, incidence rate per 1000 patient years			
rFIXFc Q1W PPX	0.00195	0.00156–0.00234	[34]*
rFIX on-demand	0.00390	0.00312–0.00468	[34]*
Median/mean ABR for any bleeding—all patients			
rFIXFc Q1W PPX	3.12	2.46–3.95	[8]
rFIX on-demand	32.90	0–67.00	[5]

ABR annualised bleeding rate, *ICH* intracranial haemorrhage, *PPX* prophylaxis, *Q1W* once weekly, *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX Fc fusion protein

*Calculation based on data from the source reference(s)

†Assumption based on general data for haemophilia B PPX

Treatment Dosing

The average (median) doses for rFIXFc were 45.2 IU/kg/week for once-weekly prophylaxis and 56.0 IU/kg/week for individualised prophylaxis (calculated using the mean dosing interval of 12.5 days and starting dose of 100 IU/kg every 7 days), based on the B-LONG study [8]. The average (mean) dose for rFIX on-demand was 77.9 IU/kg [35] (Table 2).

Efficacy

ABR data associated with the use of rFIXFc once-weekly prophylaxis and rFIX on-demand treatment were obtained from published data from B-LONG and the open-label study of rFIX [5, 8]

Table 2 Treatment dosage and resource utilisation

	Base-case value		Sensitivity analysis values		
	rFIXFc Q1W PPX	rFIX on-demand	rFIXFc Q1W PPX	rFIX on-demand	Source
PPX					
Median/mean dose, IU/kg	45.20	0	36.16–54.24	0	[8]*, [35]
Bleeding management					
ICH bleed					
Mean dose, IU/kg	46.07	77.90	36.56–55.28	62.32–93.48	[8], [35]
Doses, *n*	1.12	1.31	0.90–1.35	1.05–1.57	[8]*, [35]*
Length of bleeding management, days	10.00	10.00	8.00–12.00	8.00–12.00	Assumption
Other bleed					
Median/mean dose, IU/kg	46.07	77.90	36.56–55.28	62.32–93.48	[8], [35]
Doses, *n*	1.12	1.31	0.90–1.35	1.05–1.57	[8]*, [35]*
Length of bleeding management, days	3.00	3.00	2.40–3.60	2.40–3.60	Assumption
ER visits, *n*	0.11	0.11	0.09–0.13	0.09–0.13	[36]*
Specialist visits, *n*	1.15	1.15	0.92–1.38	0.92–1.38	[36]*
Nurse visits, *n*	0	0	0	0	[36]*
Hospitalisations, *n*	0.83	0.83	0.66–1.00	0.66–1.00	[36]*
Joint (hip/knee) surgery management					
Mean weekly dose, IU/kg	83.17	83.17	66.54–99.81	66.54–99.81	[37]*; Assumption
Doses, *n*	10.00	10.00	8.00–12.00	8.00–12.00	[37]*; Assumption

ER emergency room, *ICH* intracranial haemorrhage, *IU* international unit, *PPX* prophylaxis, *Q1W* once weekly, *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX Fc fusion protein
*Calculation based on data from the source reference

(Table 1). Both studies reported ABR values for their total populations (i.e. patients with and without bleeding events) and the proportion of patients with no bleeding events. Consequently, ABRs for populations with at least one bleeding event, which were assumed to be constant over time, were estimated (using the formula shown in Fig. S1) to be 4.05 and 32.90 for rFIXFc prophylaxis and rFIX on-demand, respectively. The model assumed that all (100%) bleeds were treated.

Probability of Events

The probability of events (and the source of values), including the proportion of patients without a bleed in the first cycle, and rates for hip/knee surgery and intracranial haemorrhage (ICH), are reported in Table 1. The use of drugs for bleed management in the model was defined as the dose and number of injections to treat each bleeding event: mean 46.07 IU/kg per injection and mean of 1.12 injections with rFIXFc prophylaxis [8], and mean of 77.90 IU/kg per injection and mean of 1.31 injections for rFIX on-demand [35]. The rFIX data on management of bleeding were based on Lambert et al. [35], because the mean infusion dose per bleeding event reported by Kavakli et al. [5] may represent underestimated usage, as on-demand treatment data were related to patients receiving on-demand therapy or additional dosing for breakthrough bleeds during prophylaxis. The model assumed a length of bleeding management of 10 days for ICH and 3 days for other types of bleeding. The length of bleeding management (days until bleed resolution) was assumed to be the same for both FIX treatments as no published data were available. However, this assumption is conservative as the higher number of rFIX administrations (relative to rFIXFc) may be associated with a longer time of treatment. The rate of surgery was related to the annual number of bleeds for each treatment; surgery resulted in additional costs and lower HRQoL for 5 days.

Health-State Utilities

As no utilities were identified in literature for the health states included in the model for patients with haemophilia B, health-state utilities were derived from EuroQol five dimension (EQ-5D) data collected for patients with haemophilia A from unpublished post hoc analyses of two studies: A-LONG (NCT01181128) [38] and ASPIRE (NCT01454739) [39] (Table 3). The model also included disutilities (a reduction in utility) associated with bleeding events and surgery, which were assumed to be the same for rFIXFc prophylaxis and rFIX on-demand treatment (Table 3). Patients in the model were assumed to have an annual probability of death identical to male individuals from the Italian general population [40].

Resource Use and Costs

Costs in the model included those associated with the resources required for all primary and secondary care and hospital-based management. Costs were derived predominantly from the Italian NHS and were considered over the whole model period. Direct costs included those associated with drug acquisition and bleeding management (healthcare professional [HCP] time, hospital visits, ICH-specific costs and joint [hip/knee] surgery), while an indirect cost was the mean daily wage for men (applied to the number of workdays lost per year for hospitalisation) (Table 4). The model did not include costs associated with the administration of drugs or the management of adverse events (AEs), as the drugs are usually self-administered at home without HCP supervision and the literature indicated AEs do not generate significant additional costs.

Model Outputs

The primary outcome measure was estimated ICER, i.e. the cost per QALY gained. Secondary outcome measures were the ICER for cost per bleed avoided, total costs, total QALYs, total LYs gained, and total number of bleeds and

Table 3 Health-state utilities and disutilities

	Base-case value	Sensitivity analysis values	Source
Utilities			
Prophylaxis			
No bleeds	0.866	0.825–0.906	A-LONG and ASPIRE*
Any bleeds	0.837	0.796–0.877	A-LONG and ASPIRE*
On-demand			
No bleeds	0.721	0.680–0.761	A-LONG and ASPIRE*
Any bleeds	0.692	0.651–0.732	A-LONG and ASPIRE*
Disutilities			
Other bleed†	0.039	0.030–0.050	A-LONG and ASPIRE*
ICH bleed‡	0.400	0.320–0.480	[41]§
Change in utility with ≥ 1 year	− 0.008	− 0.010 to − 0.004	A-LONG and ASPIRE*
Joint (hip/knee) surgery	0.010	0.008–0.012	A-LONG and ASPIRE*, [32]§

ICH intracranial haemorrhage
*Unpublished post hoc analyses
†Disutility lasting for 7 days
‡Disutility lasting for 90 days
§Calculation based on data from the source references

surgeries for each treatment strategy. Total cost was subdivided into treatment and bleeding management costs, while estimated QALYs were subdivided into no bleeds and any bleeds states, loss due to bleed, and loss due to surgery.

Sensitivity Analyses

One-way deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were performed to assess the influence of uncertainty on the final model results. In the DSA, all model parameters were systematically and independently varied over plausible ranges determined by 95% confidence intervals (CIs), standard deviations (SDs) or, in the absence of a reported CI/SD, an assumed variation of ± 10% or ± 20% of the point estimate. In the PSA, key parameters were varied according to their statistical distributions; 1000 simulations with different sets of inputs were performed and drawn randomly from pre-specified statistical distributions.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Base-Case Analysis

Over a lifelong time horizon, mean total costs per patient were lower for rFIXFc prophylaxis (once-weekly, €5,308,625) compared with rFIX on-demand (€6,564,510), producing an incremental cost of − €1,255,885 (Table 5). rFIXFc prophylaxis was associated with greater mean total QALYs per patient than rFIX on-demand

Table 4 Direct and indirect costs

	Base-case value	Sensitivity analysis values	Source
Drug acquisition, per IU			
rFIXFc	€1.21	€0.97–1.46	Sobi 2022
rFIX	€0.69	0.55–0.83	Italy tender price 2022
Bleeding management, per unit			
ER visit	€213.52	€170.81–256.22	[42], [43]
Specialist visit	€20.66	€16.53–24.79	[42]*
Nurse time	€23.44	€18.75–28.13	[44]*
Hospitalisation	€3803.62	€3042.90–4564.34	[45], [46]*
ICH-specific cost	€18,878.46	€15,102.77–22,654.16	[45], [46]*
Joint (hip/knee) surgery	€7385.94	€5908.75–8863.12	[45], [46]*
Indirect costs			
Mean daily wage	€132.83	€106.26–159.39	[47], [48]*

ER emergency room, *ICH* intracranial haemorrhage, *IU* international unit, *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX Fc fusion protein
*Calculation based on data from the source references

(15.936 versus 11.943), which represented an incremental gain of 3.993 QALYs. Prophylactic treatment with rFIXFc was also associated with fewer incremental bleeds (− 682.29) and surgeries (− 0.39) compared with rFIX given on-demand, as well as lower bleeding management costs (− €2,188,250), surgery costs (− €14,674) and indirect costs (− €271,920). The ICER demonstrated that rFIXFc prophylaxis was the dominant treatment strategy (i.e. more effective [bleeds avoided and QALY gains] and less costly) compared with rFIX on-demand.

Sensitivity Analyses

Deterministic Sensitivity Analyses

Consistent with the base-case analysis, rFIXFc was the dominant strategy over rFIX across most of the parameters in the DSA. Tornado diagrams show the parameters in the model which had the greatest impact on incremental costs and incremental QALYs (Fig. 2a, b). For costs, the model was most sensitive to variations in ABR (any bleed) and nurse time for managing an ICH bleed, while for QALYs the model was most sensitive to discount rate for health outcomes and utility for any bleed with on-demand treatment.

Probabilistic Sensitivity Analyses

The cost-effectiveness plane for rFIXFc prophylaxis compared with rFIX on-demand is shown in Fig. 3. The probability that rFIXFc once-weekly prophylaxis was the dominant strategy compared with rFIX on-demand was 63%.

Table 5 Cost-effectiveness analysis: base-case scenario (rFIXFc once-weekly prophylaxis)

	rFIXFc prophylaxis	rFIX on-demand	Incremental
Total costs, €	5,308,625	6,564,510	− 1,255,885
Prophylaxis—drug	4,715,315	0	4,715,315
Bleeding management—drug	323,730	3,820,085	− 3,496,355
Bleeding management—HCR	229,888	2,418,138	− 2,188,250
Joint (hip/knee) surgery	11,166	25,840	− 14,674
Indirect	28,526	300,446	− 271,920
Total QALYs	15.936	11.943	3.993
QALYs in no bleeds state	3.788	0	3.788
QALYs in any bleeds state	12.207	12.520	− 0.314
QALY loss due to bleed	0.058	0.572	− 0.514
QALY loss due to surgery	0.001	0.005	− 0.004
Total LYs	22.91	22.91	0
Number of bleeds	71.48	753.77	− 682.29
Number of surgeries	0.14	0.53	− 0.39
ICER (cost/QALY gained)	Dominant		
ICER (cost/bleed avoided)	Dominant		

HCR healthcare resources, *ICER* incremental cost-effectiveness ratio, *LY* life year, *QALY* quality-adjusted life year, *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX Fc fusion protein

Scenario Analysis

Additional modelling was performed to compare the cost-effectiveness of rFIXFc prophylaxis (individualised interval) with rFIX on-demand. The results of this scenario analysis were consistent with the base-case analysis: rFIXFc prophylaxis dominated rFIX on-demand (Table S1).

DISCUSSION

This economic analysis shows that, over a lifelong time horizon, rFIXFc prophylaxis is a dominant strategy (i.e. more effective combined with lower costs) compared with rFIX on-demand in patients with haemophilia B (FIX $\leq$ 2 IU/dL) from an Italian healthcare perspective. rFIXFc prophylaxis was associated with long-term cost savings (approximately − €1.25 million per patient) plus health benefits (fewer bleeds and greater QALYs [indicating better HRQoL]).

The robustness of the model base-case findings was supported by the results of the sensitivity analyses. The DSA showed that the main drivers supporting the dominance of rFIXFc prophylaxis over rFIX on-demand were inputs related to bleeding events and their management. Additionally, the PSA demonstrated a greater than 60% probability of rFIXFc prophylaxis being dominant compared with rFIX on-demand.

Although drug acquisition costs were higher for rFIXFc prophylaxis than rFIX on-demand for patients with haemophilia B, our data indicate that these costs were offset by other treatment and cost benefits. The results of this analysis indicate that rFIXFc prophylaxis is associated with a reduction in the number of bleeds and surgeries, which reflect the observed improvement in HRQoL (QALY gains) compared with

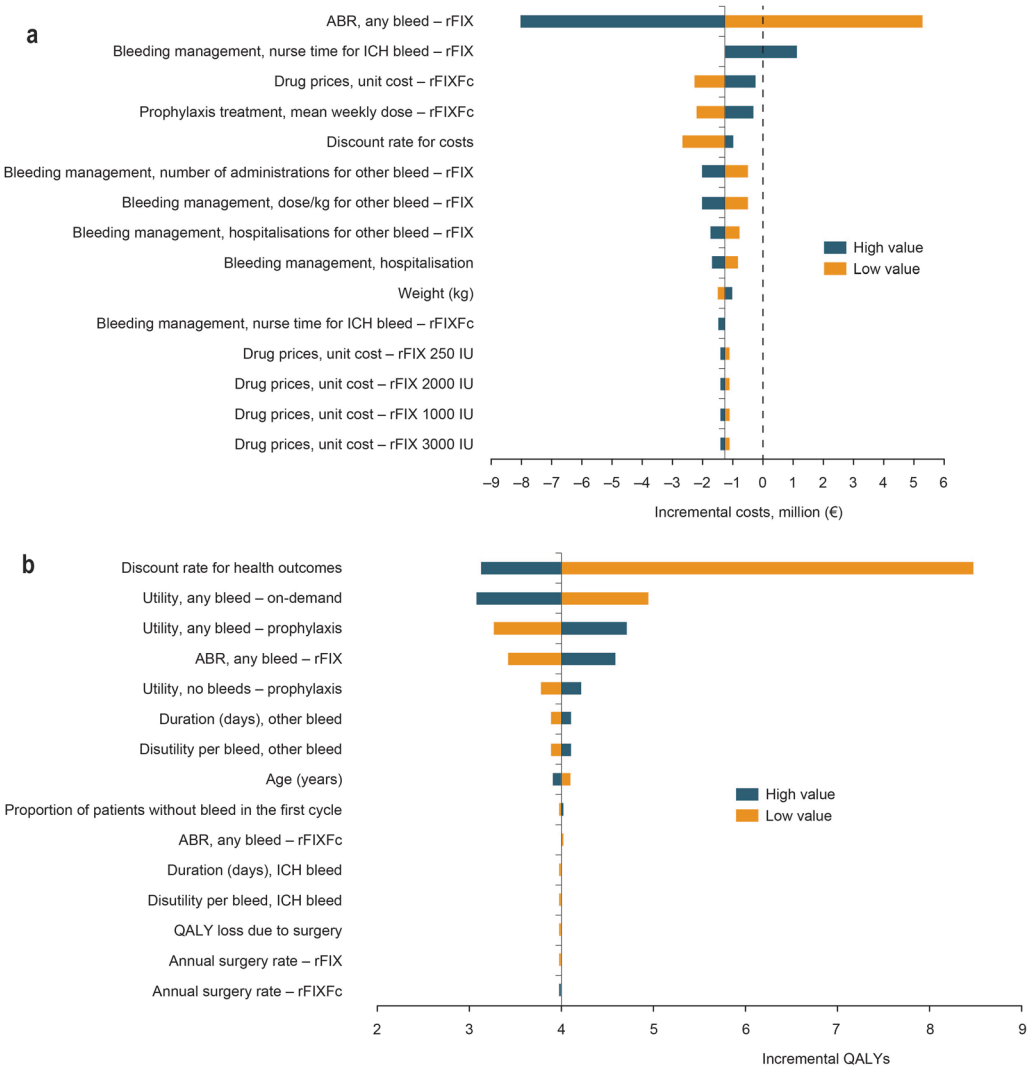

Fig. 2 One-way deterministic sensitivity analysis for incremental costs (**a**) and QALYs (**b**). *ABR* annualised bleeding rate, *ICH* intracranial haemorrhage, *IU* international unit, *QALY* quality-adjusted life year, *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX Fc fusion protein. The solid line represents the base-case incremental value

rFIX on-demand. In addition, when acquisition costs for rFIXFc and rFIX were excluded, the difference in total costs between the two treatment strategies were mainly driven by lower bleeding management costs, surgery costs and indirect costs in favour of rFIXFc prophylaxis.

Drug acquisition represents a key cost driver [49, 50], which may be a barrier to the use of prophylaxis in resource-constrained countries, centres and/or hospitals, where access to regular prophylaxis may be limited [51]. However, our data indicate that prophylaxis with EHL therapies such as rFIXFc may represent the most economical use of their resources. When selecting treatment for haemophilia B, it is important to consider that other direct and indirect non-medication factors, such as recurrent bleeding rates, diminished work productivity and hospitalisation, may convey a disproportionate economic and/or humanistic burden on patients and their caregivers [17, 33, 49, 50]. Other evidence supporting the

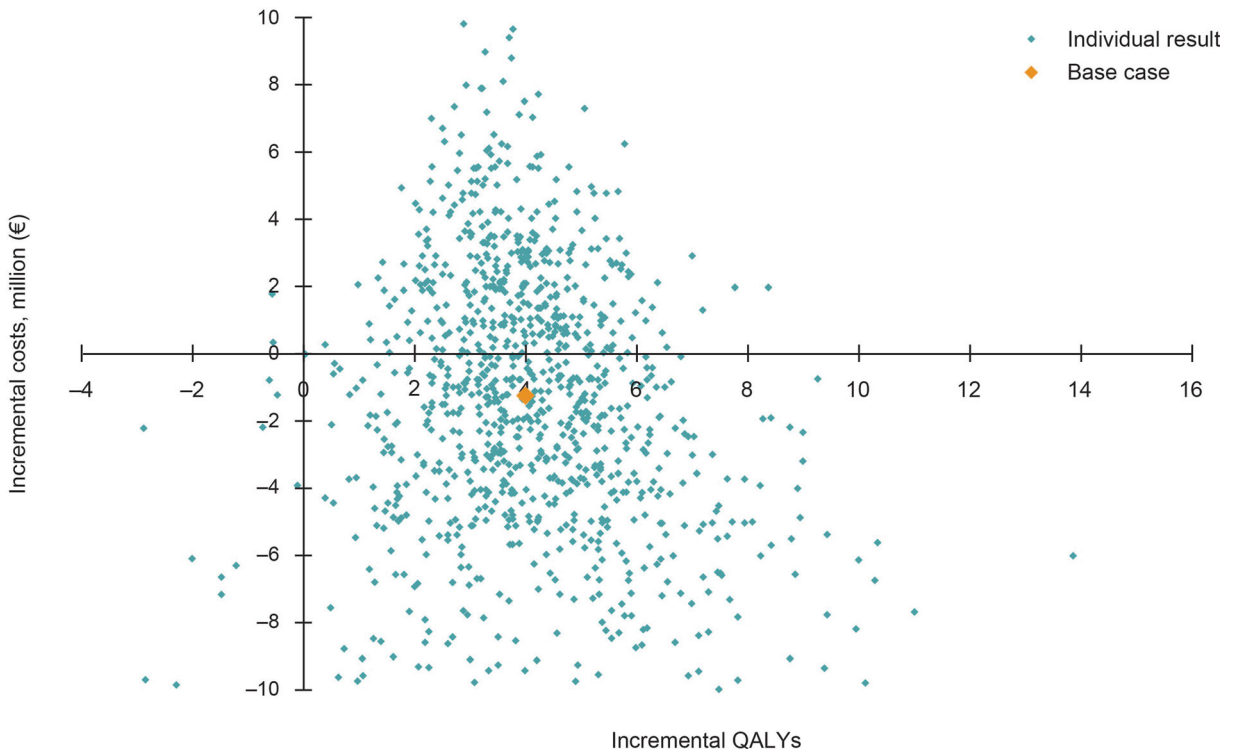

Fig. 3 Probabilistic sensitivity analysis: cost-effectiveness plane. *QALY* quality-adjusted life year

use of EHL FIX prophylaxis compared with SHL FIX on-demand include primary prophylaxis is demonstrated to significantly improve long-term clinical outcomes versus on-demand therapy in patients with severe haemophilia [11, 12, 52]; on-demand therapy may incur higher lifetime healthcare costs versus prophylaxis due to higher non-medication costs (e.g. rehabilitation and surgery) [53]; patients with haemophilia B may have fewer bleed-related hospitalisations when treated with EHL FIX versus SHL FIX [49]; and patients with severe haemophilia B receiving prophylaxis may have higher HRQoL versus those treated with on-demand [54].

In routine clinical practice, prophylaxis with rFIXFc is initiated at 50 IU/kg once weekly or 100 IU/kg once every 10 days for adults/adolescents or 50–60 IU/kg once weekly for children [21]. Patients have the flexibility to continue or extend rFIXFc beyond a weekly prophylaxis regimen on the basis of individual response [21], supported by the B-LONG study where the interval-adjusted prophylaxis group had an average dosing interval of 12.5 days and 54% of patients had a dosing interval of at least 14 days [8]. Additionally, effective bleed prevention with less frequent dosing was observed in the B-YOND study, where most patients (78%) maintained the dosing intervals achieved in the parent studies [27]. Our data showed that rFIXFc prophylaxis was the dominant treatment strategy compared with rFIX on-demand for both once-weekly prophylaxis (base-case analysis) and individualised-interval prophylaxis (scenario analysis).

A cost-effectiveness analysis of lifelong treatment consisting of prophylaxis in childhood and on-demand treatment in adulthood for patients with haemophilia B (FIX $\leq$ 2 IU/dL) in China showed that rFIXFc was the dominant strategy compared with rFIX and the probability of rFIXFc being cost-effective was greater than 90% at willingness to pay thresholds of 1–3 times gross domestic product per capita in 2021 [55]. Also in support of our study findings, several economic evaluation studies across multiple countries have reported that prophylaxis is

more cost-effective than on-demand treatment for patients with severe haemophilia A [56–59]. Comparisons of cost-effectiveness analyses may be limited by differences in model methodology including the time horizon, cycle length, health states, disease severity and treatments assessed [60].

A key strength of our model was the inclusion of utilities based on the EQ-5D instrument, which is the preferred health outcome measure recommended by pharmaceutical reimbursement authorities in 29/34 sampled countries including Europe, North America, South America, Asia and Australia [61]. Another strength was the use of a lifelong time horizon, which is consistent with the recommended treatment duration for prophylaxis in international treatment guidelines [1] and the majority of other cost-effectiveness analyses of prophylaxis versus on-demand treatment in haemophilia [55–59]. Other strengths include the assessment of weekly and individualised prophylaxis regimens; the inclusion of direct and indirect costs, several types of bleeding events, and surgical management; and population demographics from a phase 3 study representative of previously treated male patients aged $\geq$ 12 years with haemophilia B.

Many of the model inputs were based on published literature, but some were based on assumptions or unpublished post hoc analyses. In addition, the inclusion of efficacy data for rFIXFc prophylaxis and rFIX on-demand were not derived from a head-to-head study or an indirect treatment comparison (e.g. network meta-analysis or matched-indirect treatment comparison). The model inputs were largely specific to rFIXFc and rFIX and therefore the results cannot be directly correlated to other comparisons of EHL and SHL therapies. The current analysis included costs associated with ICH and other bleeds, but different severities of bleeds were not considered in the model. Similarly, the model did not assess other potential healthcare factors/resources associated with the management of haemophilia, such as joint health/joint assessments, orthoses, pain medication, treatment switches, and inhibitor development. However, the inclusion of additional elements within the model is reliant on what data are publicly available and it is advantageous to not make models overcomplicated. Furthermore, we estimate that including additional management strategies would likely be neutral across the treatment options and have a negligible effect on the model base-case results; at the very least, the ICER may be more favourable for rFIXFc owing to additional QALY gains.

CONCLUSION

Treatment guidelines recommend prophylaxis for patients with haemophilia B, and our data indicate that rFIXFc prophylaxis represents an efficacious and cost-effective option for the treatment of adolescent and adult male patients ($\geq$ 12 years) with haemophilia B from an Italian healthcare perspective. In comparison with on-demand rFIX treatment, prophylaxis with rFIXFc was the dominant treatment strategy and associated with fewer bleeds, greater QALYs and lower costs compared with on-demand rFIX treatment. This comparative assessment of cost-effectiveness should help to inform both clinicians and healthcare policy makers when making treatment decisions for haemophilia B.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interests. Michał Pochopien, Anna Tytuła and Mondher Toumi were previously employees of Creativ-Ceutical, a consultancy company that received funding from Sobi for this research. Aletta Falk, Nicoletta Martone, Zalmai Hakimi and Daniel Eriksson are employees of and shareholders in Sobi.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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