EE105

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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INTRODUCTION

- Both standard half-life recombinant coagulation factor IX (rFIX)[1] and extended half-life recombinant coagulation factor IX Fc fusion protein (rFIXFc)[2] are indicated to prevent and treat bleeding episodes in patients with haemophilia B
- Differences exist in the treatment strategies and regimen (on-demand and prophylaxis) in terms of cost and efficacy

OBJECTIVE

- To estimate the cost-effectiveness of prophylaxis with rFIXFc compared to on-demand treatment with rFIX in patients with haemophilia B without inhibitors

METHODS

Model overview

- A model was designed to compare lifetime costs and health outcomes between rFIXFc prophylaxis (once weekly and individualised interval) and on-demand rFIX treatment, in a patient population based on the B-LONG study (ClinicalTrials.gov identifier: NCT01027364) presented in Powell, et al., 2013[3] — adolescent and adult males (≥12 years) with severe haemophilia B (FIX ≤2 IU/dL) without inhibitors
- The model used a Markov process in which the natural history of haemophilia was captured in terms of three pre-defined health states, 'No bleeds', 'Any bleeds' and 'Death', with transitions between these
  - Patients entered the model through the 'No bleeds' or 'Any bleeds' states and could transition from 'Any bleeds' to 'No bleeds' in subsequent cycles; transition to 'Death', an absorbing state, was also possible
- To capture all differences between treatment arms, a life-long time horizon of 67 years was implemented, while the cycle length within the model was 6 months

Model assumptions and inputs

- Patient characteristics (mean age and weight) were sourced from the B-LONG study[3], using patient-level data for those on prophylaxis (once weekly and individualised interval) but, as the modelling was for a European population, mean body weight was calculated with the exclusion of body weight data for patients from the United States
- Published results from the B-LONG study[3] were used to obtain annualised bleeding rate (ABR) data associated with receipt of rFIXFc prophylaxis, while the ABR associated with rFIX on-demand treatment was obtained from a multicentre, open-label study reported by Kavakli, et al., 2016[4] comparing rFIX on-demand treatment with rFIX once weekly prophylaxis in adult and adolescent patients (ClinicalTrials.gov identifier: NCT01335061)
- As both studies provided ABR values for their total populations (i.e., patients with and without bleeding events) and reported the proportions of patients with no bleeding events, ABRs for populations with at least one bleeding event, which were assumed to be constant over time, could be calculated according to:

$$ABR_{bleed} = \frac{ABR}{1 - P_{no\ bleed}}$$

  - ABR_{bleed} = ABR for a population with at least one bleeding event
  - ABR = ABR for population including patients with and without bleeding events
  - $P_{no\ bleed}$ = proportion of patients with no bleeding events
- In the B-LONG study[3], the median rFIXFc dose used for once weekly prophylaxis decreased over time, with an overall median of 45.2 IU/kg, and medians of 40.7 and 40.5 IU/kg, during the last 6 and 3 months of the study, respectively, a base case value of 45.2 IU/kg was a conservative assumption of the prophylactic dose; for individualised prophylaxis with rFIXFc, after a starting dose of 100 IU/kg at 10 day intervals, the overall median weekly dose was 56.0 IU/kg (median dosing interval of 12.5 days), and this was assumed in the base case analysis of additional modelling for this regimen
- Base-case inputs for modelling comparison of once weekly rFIXFc prophylaxis and on-demand rFIX treatment are summarised in **Table 1**
- The costs used in the model were reported from the perspective of the Italian National Health Service, with total costs accounting for prophylactic treatment, bleeding management (drugs and procedures), and surgery
- The frequency of usage during bleed management was defined in the model and a median dose to treat each bleeding event was specified
  - For rFIXFc, each bleed was assumed to require an average of 1.123 injections for resolution, based on data from the B-LONG study,[3] with a median rFIXFc dose per injection of 46.07 IU/kg
  - For rFIX, dosage reported by Kavakli, et al., 2016[4] may have underestimated usage, as this related to on-demand treatment in patients receiving on-demand therapy or additional dosing for breakthrough bleeds during prophylaxis; therefore, the rFIX dose to manage on-demand bleeding was based on Lambert, et al., 2007:[5] 77.90 IU/kg multiplied by 1.308 administrations per episode
- Modelling the impact of bleeding on quality of life (QoL), no data for the length of bleeding management (days until bleed resolution) were available, therefore this was assumed to be the same for rFIXFc and rFIX
  - This assumption is conservative as the number of rFIX administrations is higher, which may be associated with a longer time of treatment
- As no utilities were identified for the health states included in the model for patients with haemophilia B, values for haemophilia A obtained from post hoc analysis of data from the A-LONG (ClinicalTrials.gov identifier: NCT01181128)[6] and ASPIRE (ClinicalTrials.gov identifier: NCT01454739)[7] studies were used, based on European Quality of Life Five Dimension (EQ-5D) questionnaire results (**Table 2**)
- Costs used in the analysis are summarised in **Table 3**

Table 1: Summary of base case inputs

	Base case	Low value	High value	Source: Base case	Source: Low/high value
SETTINGS AND POPULATION					
Time horizon, years	67			Assumption	
Discount rate for health outcomes	0.035	0	0.05	Assumption	Assumption
Discount rate for costs	0.035	0	0.05	Assumption	Assumption
Age, years	33.6	31.0	36.1	Internal analysis	SD = 14.69
Weight, kg	72.1	57.7	86.6	Internal analysis	±20%
Cohort size	1000			Assumption	
PROBABILITY EVENTS					
Proportion of patients without bleed in the first cycle					
rFIXFc once weekly prophylaxis	23.0%	20.7%	25.2%	Powell 2013[3]	±10%
rFIX on-demand	0	0	0	Kavakli 2016[4]	±10%
Transition probabilities, subsequent cycles					
No bleeds→No bleeds	100%			Assumption	
Any bleeds→No bleeds	0%	0%		Assumption	±10%
Annual surgery rate					
rFIXFc once weekly prophylaxis	0.61%	0.55%	0.67%	Miners 2002,[8] Kavakli 2016[4]*	±10%
rFIX on-demand	2.30%	2.07%	2.53%	Miners 2002[8]	±10%
Different number of days lost per year					
Prophylaxis	0.78	0	22	Zhou 2015[9]	Miners 2002[8]
On-demand	3.12	1.3	10.6	Zhou 2015[9]	Miners 2002[8]
ICH bleeds					
ICH incidence rate per 1000 patient years – prophylaxis	0.00195	0.00156	0.00234	Witmer 2008[10]	±20%
ICH incidence rate per 1000 patient years – on-demand	0.00390	0.00312	0.00468	Witmer 2008[10]	±20%
ABR					
ABR for any bleeding, mean (95% CI) – all patients					
rFIXFc once weekly prophylaxis	3.12	2.46	3.95	Powell 2013[3]	Powell 2013[3]
rFIX on-demand	32.90	0	67.00	Kavakli 2016[4]	Kavakli 2016[4]
Proportion of treated bleeds					
rFIXFc once weekly prophylaxis	100%			Assumption	
rFIX on-demand	100%			Assumption	
DOSAGE, prophylaxis treatment					
rFIXFc once weekly prophylaxis, mean weekly dose, IU/kg	45.20	36.16	54.24	Powell 2013[3]	±20%
rFIX on-demand, mean weekly dose, IU/kg	0	0	0	Lambert 2007[5]	±20%

*Assumption based on general data for haemophilia B prophylaxis.
ABR, annualised bleeding rate; CI, confidence interval; ICH, intracranial haemorrhage; rFIX, recombinant coagulation factor IX; rFIXFc, recombinant coagulation factor IX Fc fusion protein; SD, standard deviation

Table 2. Health state utilities used in the model (based on EQ-5D data)

	Utility	Lower CI	Upper CI
PROPHYLAXIS			
No bleeds	0.866	0.825	0.906
Any bleeds	0.837	0.796	0.877
ON-DEMAND			
No bleeds	0.721	0.680	0.761
Any bleeds	0.692	0.651	0.732

CI, confidence interval; EQ-5D, European Quality of Life Five Dimension questionnaire

Table 3. Costs used in the analysis

	Cost, €	Source
DRUGS, price per IU		
rFIXFc	1.21	Sobi
rFIX	0.69	Italy tender price
BLEEDING MANAGEMENT PROCEDURES AND SURGERY, price per unit		
ER visit	213.52	Official Gazette 2013;[11] University Hospital Federico II Diagnostic Therapeutic Assistance Pathway 2021[12]
Specialist visit	20.66	Official Gazette 2013[11]
Nurse time	23.44	National Collective Labour Agreement for Employees of National Health System[13]
Hospitalisation	3,803.62	Official Gazette 2013;[14] Annual Report on Hospitalisation Activity 2019[15]
ICH-specific cost	18,878.46	Official Gazette 2013;[14] Annual Report on Hospitalisation Activity 2019[15]
Surgery	7,385.94	Official Gazette 2013;[14] Annual Report on Hospitalisation Activity 2019[15]
INDIRECT COSTS		
Male daily wage	132.83	JP Salary Outlook 2021;[16] FTE Methodology[17]

ER, emergency room; FTE, full-time equivalent ; ICH, intracranial haemorrhage; rFIX, recombinant coagulation factor IX; IU, international unit; rFIXFc, recombinant coagulation factor IX Fc fusion protein

Analysis outcomes

- Cost-effectiveness was presented as an incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{\Delta \text{Cost}}{\Delta QALY}$$

  - $\Delta Cost$ = the difference between the total cost of the intervention (rFIXFc prophylaxis) and the comparator (on-demand rFIX treatment)
  - $\Delta QALY$ = the difference between quality-adjusted life-years (QALYs) for the intervention (rFIXFc prophylaxis) and the comparator on-demand rFIX treatment
- Health outcomes were estimated as QALYs, divided into no bleeds, any bleeds state, loss due to bleed, and loss due to surgery

Sensitivity analyses

- One-way deterministic sensitivity analyses and probabilistic sensitivity analyses were performed
- The impact on the ICER was evaluated, and parameters and assumptions with the greatest impact on the results were identified
- A probabilistic sensitivity analysis (PSA) was performed, and key parameters were varied according to their statistical distributions
- At least 1,000 simulations with different sets of input values were performed and drawn randomly from pre-specified statistical distributions

RESULTS

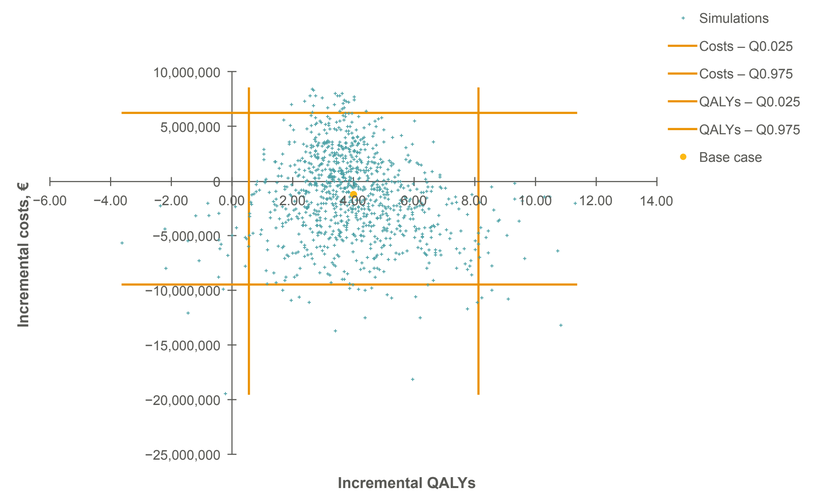
- Prophylaxis with rFIXFc was associated with lower costs and greater number of QALYs than on-demand rFIX treatment (**Table 4**)
- Prophylactic treatment with rFIXFc was also associated with fewer bleeds than rFIX given on-demand
- rFIXFc was the dominant strategy over rFIX across most uncertain parameters, being associated with better QoL and lower costs
- Results are shown for once weekly prophylaxis with rFIXFc; additional modelling for individualised interval prophylaxis with rFIXFc (data not shown) confirmed these benefits
- rFIXFc once weekly was the dominant strategy in 62% of the runs in the probabilistic sensitivity analysis (1,000 simulations; **Figure 1**)

Table 4. Base case results for rFIXFc once weekly prophylaxis versus on-demand treatment with rFIX

	rFIXFc prophylaxis	rFIX on-demand	Incremental
Total costs, €	5,308,625	6,564,510	–1,255,885
Prophylaxis treatment — drug costs	4,715,315	0	4,715,315
Bleeding management — drug costs	323,730	3,820,085	–3,496,355
Bleeding management — procedure costs	229,888	2,418,138	–2,188,250
Surgery cost	11,166	25,840	–14,674
Indirect costs	28,526	300,446	–271,920
Total QALYs	15.936	11.943	3.993
QALYs in no bleeds state	3.7883	0.0000	3.7883
QALYs in any bleeds state	12.2066	12.5203	–0.3137
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	0.00
Number of bleeds	71.48	753.77	–682.29
Number of surgeries	0.14	0.53	–0.39
ICER (cost/QALYG)	Dominant		
ICER (cost/bleed avoided)	Dominant		

ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; QALYG, quality-adjusted life-years gained; rFIX, recombinant coagulation factor IX; rFIXFc, recombinant coagulation factor IX Fc fusion protein

Figure 1. Incremental cost-effectiveness plane



QALY, quality-adjusted life-year

CONCLUSIONS

- Prophylactic rFIXFc is associated with fewer bleeds, lower costs and greater number of QALYs compared to on-demand rFIX treatment
- In comparison with on-demand rFIX treatment, prophylaxis with rFIXFc was the dominant treatment strategy

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DISCLOSURES

Michał Pochopien and Mondher Toumi were previously employees of Creativ-Ceutical, a consultancy company that received funding from Sobi for this research. Anna Tytuła is an employee of Creativ-Ceutical. Aletta Falk, Lorenzo Cioni, Zalmai Hakimi and Daniel Eriksson are employees of Sobi. Aletta Falk is also a shareholder in Sobi.