# A Cost-effectiveness Analysis of PK-driven Prophylaxis Using myPKFiT vs. Standard Prophylaxis in Haemophilia A

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## INTRODUCTION

- The mainstay of hemophilia A therapy is represented by prophylaxis of bleeding and prevention of arthropathy. Prophylactic FVIII regimens have been shown to be effective in reducing bleeding frequency in patients with severe haemophilia[1]. Results from Swedish studies, as well as those of numerous other studies, have proven the efficacy of a standard regimen of regular infusions with 20–40 IU/kg FVIII concentrates every other day or at least 3 times a week in reducing bleeding episodes, decreasing hospitalization, and improving long term joint function.[1-7]
- Maintaining FVIII levels above 1% and so converting severe hemophilia (with FVIII < 1%) into a more moderate form of the disease was the rationale of these regimens. This target was chosen in order to conveniently optimize budget constraints, frequency of dosing and venous access.[8]
- Despite its effectiveness, probably due to lower-than-expected or insufficient FVIII levels occurring between infusions, a relatively significant number of patients still bleed, as already suggested by early studies comparing weekly dosing frequencies.[9-12]
- Because of the high costs associated with factor concentrates, a generalized increase of dosages would not be sustainable in the great majority of countries. An alternative approach might be to identify individualized optimal treatment regimens, and one of these methodologies is the pharmacokinetic (PK).

## STUDY OBJECTIVES

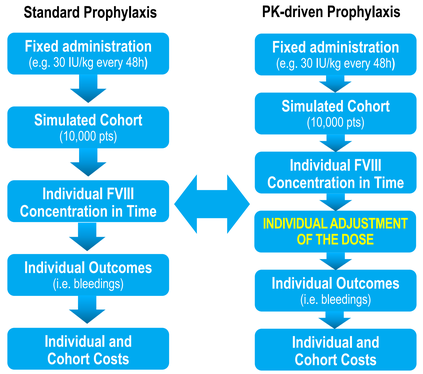
- The aim of this study is to assess the cost-effectiveness profile of rFVIII PK-driven prophylaxis as compared with standard regimens in a virtual population of severe haemophilia A subjects.

## METHODS

- In order to perform an individual simulation over a hypothetical population of severe hemophilia A patients, a microsimulation model was developed and the analysis was performed over a 1-year time horizon in the Italian cost setting.
- Patients of the simulated cohort were assumed to be treated with rFVIII PK-driven prophylaxis or with standard FVIII regimen, and an estimate of the consumption, costs, annual joints bleeding rate (AJBR) and the incremental cost-effectiveness ratio (ICER) expressed as € per joint bleed avoided was carried out .
- The rFVIII PK-driven prophylaxis was based on the population PK model, developed by Bjorkman et al.,[13] which is a two-compartmental model with the primary PK parameters being clearance (CL), volumes of distribution of the central and peripheral compartment (V1, V2), and inter-compartmental clearance (Q).
- An exponential model is applied for individual clearance (ηCL) and plasma volume (ηV1) to account for inter-individual and inter-occasion variance.[11] To obtain the rFVIII concentration curve in time for each simulated patient, the Bjorkman equation was implemented in the microsimulation model.
- A simulated population of 10,000 patients, derived from a previous model that made use of the same PK model in a simulated population of 1,000 severe haemophilia A subjects[14], where each patient from this cohort was replicated 10 times with different ηCL and ηV1 randomly extracted from the covariance matrix reported by Bjorkman et al.[13] creating a population of 10,000 severe haemophilia A patients characterized by age, body weight, ηCL and ηV1 with a mean age of 27.8 years and a mean BW of 73.7 Kg.
- The AJBR was used as efficacy parameter to compare the two prophylaxes. The AJBR for each simulated patient in the two arms was estimated based on the relationship between FVIII concentration and bleeding rate reported by Den Uijl, et al.[15]
- For each simulated patient the number of ABJR is calculated by weighting the percent of time spent in each concentration interval for the bleeding rate associated.

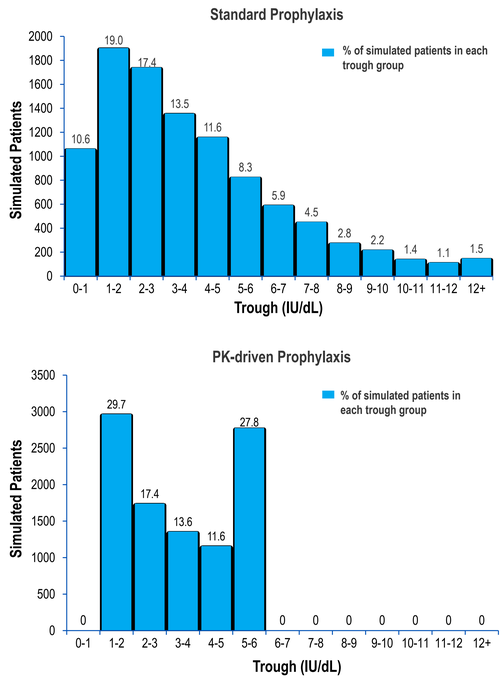
## RESULTS

### Figure 1: Concept of the Microsimulation Model



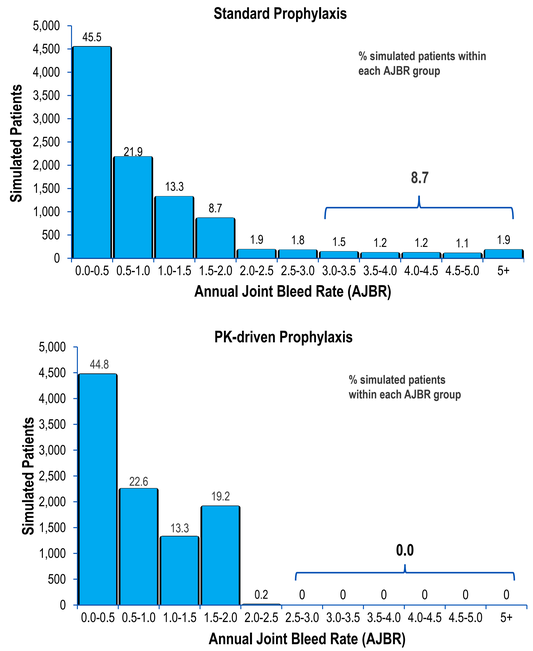

- The simulation showed that 10.6% of simulated patients treated with the standard prophylaxis (30 IU/dL every 48 hours) had a minimum concentration of FVIII below 1 IU/dL and 27.8% above 5 IU/dL (Figure 2).

### Figure 2: Percentage of Simulated Patients According to Trough Levels




- With PK-driven prophylaxis all simulated patient had a minimum FVIIII level in the range 1–5 IU/dL, as a result of the individual dose adjustment. The different distribution of FVIII levels had an impact on bleeding rates with the fraction of patients who had AJBR > 2.5 decreasing from 8.7% (standard prophylaxis) to 0% (PK-driven prophylaxis) (Figure 3).

### Figure 2: Percentage of Simulated Patients According to ABJR




- Overall, during this simulation, with the PK-driven prophylaxis the mean AJBR decreased from 1.012 to 0.845. The mean FVIII dose for PK-driven prophylaxis was 29.64 IU/kg, with a mean reduction of 0.36 IU/kg with respect to standard prophylaxis.
- €260,662 was the average annual cost for FVIIII to cover the prophylaxis and the management of bleedings with PK-driven prophylaxis and €265,859 with standard prophylaxis, with a total saving of €5,197 per patient-year.
- PK-driven prophylaxis, from the cost-effectiveness point of view, resulted dominant over standard prophylaxis (Table 1), as it was less costly and more effective (reduction of AJBR).
- 27.8% of the simulated population had a FVIII level > 5 IU/dl and an ABJR of 0.260 with the standard prophylaxis: 14.6% of them had a FVIII minimum level above 10 IU/dL. With the PK- driven prophylaxis the FVIII dose was adjusted to have the minimum concentration of FVIII equal to 5 IU/dL. An average dose reduction of 8.66 IU/Kg and an increased ABJR of 0.14 were observed. On the other side the dose was increased to simulated patients with a faster pharmacokinetics who had a minimum FVIII concentration < 1IU/dL (10.6%) in order to reach the goal of minimum 1 IU/dL. The dose was increased on the average to 49.23 IU/Kg in these patients with the consequent reduction of 1.932 in the AJBR (Table 2).

### Table 1: Concept of the Microsimulation Model

| | Standard PRO | PK-driven PRO | Difference |
|---|---|---|---|
| **Outcomes** | | | |
| Average annual joint bleeds | 1.01 | 0.85 | -0.167 |
| Average FVIII dose (IU/Kg) | 30.00 | 29.64 | -0.360 |
| **Costs and Cost-effectiveness** | | | |
| Annual prophylaxis cost (€) | 262,289 | 257,653 | -4,635 |
| Annual joint bleeds cost (€) | 3,570 | 3,008 | -561 |
| **Total annual cost (€)** | **265,859** | **260,662** | **-5,197** |
| ICER (€ per bleed avoided) | **-31,205** | | |

PRO = prophylaxis

### Table 2: Outcomes of the Simulation in the Group of Patients that with Standard Prophylaxis had a Minimum FVIII Concentration Below 1 IU/dL (10.6%) and in the Group that had a Minimum FVIII Concentration Above 5 IU/dL (27.8%)

| | % on total cohort | Standard PRO Mean dose (IU/kg) | Standard PRO Mean AJBR | PK-driven PRO Mean dose (IU/kg) | PK-driven PRO Mean AJBR | *Δmean dose (IU/Kg) | *Δannual ABJR |
|---|---|---|---|---|---|---|---|
| Patients with FVIII level > 5 IU/dl using standard PRO | 27.8% | 30.00 | 0.260 | 21.34 | 0.400 | **8.66** | **-0.140** |
| Patients with FVIII level < 1 IU/dl using standard PRO | 10.6% | 30.00 | 3.727 | 49.23 | 1.796 | **-19.23** | **1.932** |

*Δ = standard prophylaxis – PK-driven prophylaxis

## DISCUSSION & CONCLUSION

- Accounting for patients' individual PK characteristics. PK-driven prophylaxis appears to be a promising strategy for optimisation of available resources and improvement of health outcomes in the severe haemophilia A population. myPKFit showed to be able to support the assessment of individual PK in subject with severe haemophilia A in real clinical practice.

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## DISCLOSURES

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