**Supplementary Methods**

FVIII concentration-time profiles for all patients for prophylactic treatment with BAY 81-8973 and rAHF-PFM were simulated according to Shah et al. [10], who studied PK data in an intra-individual cross-over study comparing the PK of BAY 81-8973 and rAHF-PFM in adult patients with severe hemophilia A by means of a population approach. Each subject was treated with a 25 IU/kg every 3 days, as per regimens recommended by Chinese guidelines (1). The PK profile of both compounds were described using a two-compartment model; within a patient, the only PK parameters that differed between BAY 81-8973 and rAHF-PFM were the elimination (CL) and peripheral volume of distribution (V2) (**Table S1**) (2). A 2x2 matrix was included in the simulation. 10,000 patients were simulated in the PK part of the model for one year and then patient results were grouped into categories by the number of bleeds: 0-2, 2-4, 4-6,6-8,8-10,10-12,12+. The average number of bleeding events per category per year was determined, with the proportion of patients in each category over time. Joint bleeds were accumulated within each bleeding category per year, separately.The bleeding rate at a given time was then calculated in the model based on FVIII concentration and cumulative risk. For each simulation subject the instantaneous bleeding risk as function of the FVIII concentration was simulated over time (3). Based on standard principles of time-to-event analysis, the bleeding risk was translated into an expected yearly bleeding rate. Abrantes et al. then studied the association between patients’ FVIII concentration and observed bleeding events based on the clinical development program of BAY 81-8973 (4)by means of an repeated-time-to-event approach (3). It was found that the instantaneous bleeding risk is significantly associated with the FVIII level and the bleeding risk increases with decreasing concentration of FVIII, as described by the following formula:

Where h(t) is the instantaneous risk of bleeding, is the basal risk in absence of FVIII concentrations, FVIII(t) is the FVIII concentration at time t, IFVIII50 is the FVIII concentration at which the risk-to-bleed is halved.

The association between bleeding risk and FVIII concentration was assumed to be time invariant and identical independent of the FVIII product. Hence, differences in bleeding between BAY 81-8973 and rAHF-PFM were only due to differences in FVIII concentration time profiles. The proportions of different types of bleeds was taken from the existing literature. In the base case analysis, it was assumed that 38% of all spontaneous and traumatic bleeds occurred in the joints (5) and that 0.20% of all bleeds were major (i.e. life-threatening and required hospitalisation) (6). Patients in each bleeding per-year category accumulated joint bleeds over time, and based on the cumulative value, the Pettersson score was determined.

**Table S1. BAY 81-8973** **and rAHF-PFM PK parameters(7)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Units** | **Estimate** | **Description** |
| **CLBAY** | dL/h | 1.51 | Clearance of BAY 81-8973 |
| **V1BAY;rAHF-PFM** | dL | 23.6 | Central volume of distribution BAY 81-8973 and rAHF-PFM |
| **QBAY;fAHF-PFM** | dL/h | 1.59 | Intercompartmental clearance of BAY 81-8973 and rAHF-PFM |
| **V2BAY** | dL | 5.35 | Peripheral volume of distribution of BAY 81-8973 |
| **IIVCl** | % | 27.2 | Intraindividual variability in clearance |
| **IIVV1** | % | 8.0 | Intraindividual variability in central volume of distribution |
| **ΔCLrAHF-PFM** | % | 47.8 | Change in clearance for rAHF-PFM compared with BAY 81-8973 |
| **ΔV2rAHF-PFM** | % | 86.6 | Change in peripheral volume of distribution for rAHF-PFMcompared with BAY 81-8973 |

rAHF-PFM: antihemophilic factor (recombinant) plasma/albumin-free method

**Figure S1. Cost-effectiveness scatterplot**

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