Comparison of the Pharmacokinetic Properties of Extended Half-Life and Recombinant Factor VIII Concentrates by In Silico Simulations

Laura H. Bukkems[1] Tim Preijers[1] Max W. F. van Spengler[1] Frank W. G. Leebeek[2] Marjon H. Cnossen[3,*] Ron A. A. Mathôt[1,*]

[1] Hospital Pharmacy-Clinical Pharmacology, Amsterdam University Medical Center, Amsterdam, The Netherlands
[2] Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands
[3] Department of Pediatric Hematology, Erasmus University Medical Center—Sophia Children's Hospital Rotterdam, Rotterdam, The Netherlands

Address for correspondence Ron A. A. Mathôt, PharmD, PhD, Hospital Pharmacy-Clinical Pharmacology, Amsterdam University Medical Center, University of Amsterdam, Meibergdreef 9, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands (e-mail: r.mathot@amsterdamumc.nl).

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Abstract

Background The pharmacokinetic (PK) properties of extended half-life (EHL) factor VIII (FVIII) concentrates differ, leading to variation in the optimal dosing regimen for the individual patient. The aim of this study was to establish these PK differences for various EHL FVIII concentrates by in silico simulations.

Methods FVIII level over time profiles of rFVIII-SC, BAY 81–8973, rFVIII-Fc, BAX 855, BAY 94–9027, and standard half-life (SHL) rFVIII concentrates were simulated for 1,000 severe hemophilia A patients during steady-state dosing of 40 IU/kg every 72 hours or dosing as advised in the summary of product characteristics (SmPC).

Results Although the elimination half-life values were comparable for rFVIII-FC, BAX 855, and BAY 94–9027, a higher area under the curve (AUC; 2,779 IU/h/dL) for BAY 94–9027 was obtained. During steady-state dosing of 40 IU/kg every 72 hours, 58.5% (rFVIII-SC), 69.3% (BAY 81–8972), 89.0% (rFVIII-Fc), 83.9% (BAX 855), and 93.7% (BAY 94–9027) of the patients maintained a trough level of 1 IU/dL, compared with 56.0% for SHL rFVIII. Following dosing schemes described in the SmPC, between 51.0 and 65.4% or 23.2 and 31.1% of the patients maintained a target trough level of 1 IU/dL or 3 IU/dL, respectively.

Conclusion BAY 94–9027 showed the largest increase of AUC and best target attainment compared with SHL rFVIII, followed closely by BAX 855 and rFVIII-Fc. BAY 81–8973 and rFVIII-SC showed smaller PK improvements. Although our analyses increase insight into the PK of these FVIII concentrates, more studies evaluating the relation between factor levels and bleeding risk are needed.

Keywords
- factor VIII
- hemophilia A
- half-life

* *Both are last authors.*

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Georg Thieme Verlag KG,
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Introduction

Hemophilia A is an inherited X-linked bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) and characterized by severe bleeding mainly in joints and muscles. Mainstay of treatment is still intravenous replacement therapy consisting of FVIII concentrate in case of bleeding or to prevent (perioperative) bleeding. Severe and some moderately affected patients receive prophylactic treatment to prevent spontaneous and frequent bleeding with long-term development of hemophilic arthropathy. When the "low dose" strategy is applied, dosing of factor concentrates is still mainly based on the patients' body weight and is generally adjusted on the basis of bleeding frequency.[1] Currently, pharmacokinetic (PK) guided dosing is increasingly applied to optimize dosing in the individual patient, and may be helpful when introducing a novel factor concentrate.[2–5]

In most countries for a long time, so-called standard half-life (SHL) recombinant FVIII concentrates have been used to treat hemophilia A patients on demand and prophylactically. These FVIII concentrates are characterized by a half-life that ranges from 11 to 16 hours, leading to prophylactic dosing every 24 to 72 hours, which is a burden for patients and families.[6] To extend the terminal half-life of FVIII, modifications of physiological and PK properties have been performed. The benefits of these extended half-life (EHL) concentrates are clear: an EHL FVIII concentrate can hypothetically be administered less frequently without a reduction in efficacy.

Currently, four EHL FVIII concentrates are available in Europe: FVIII coupled to the neonatal Fc receptor, e.g., rFVIII-Fc (Elocta) and three PEGylated recombinant FVIII concentrates, e.g., BAX 855 (Adynovi), BAY 94–9027 (Jivi), and N8-GP (Esperoct). These EHL FVIII concentrates show a 1.4- to 1.7 fold increase in half-life compared with SHL FVIII concentrates.[7–9] These half-life increases are less than those obtained in the EHL FIX concentrates, as FVIII is dependent on von Willebrand factor (VWF) to extend its half-life.[10] Furthermore, two FVIII concentrates with improved PK characteristics based on protein modification that improve FVIII stability have been registered, of which it is debatable if they meet the criteria of the EHL concentrates.[11] One is a single-chain FVIII concentrate (rFVIII-SC, Afstyla) and the other is a FVIII concentrate without extra modifications (BAY 81–8973, Kovaltry).

A typical initial regimen of EHL FVIII concentrate in adults with hemophilia A consists of dosing every third to fifth day. However, both the PK properties of EHL FVIII concentrates and interindividual variability of the PK of a FVIII concentrate will influence the concentrate's prophylactic efficacy when this dosing scheme is applied.[12,13] Therefore, to establish the best dosing regimen, differences in the PK properties of concentrates should be taken into account. In the literature, the PK properties of the factor concentrates observed during clinical studies are reported. However, comparison of these PK properties can be difficult, as different dosing regimens are followed in these clinical studies, influencing for instance the area under the curve (AUC). Furthermore, clinical PK outcomes such as time spent above a target FVIII level are often not presented. Therefore, a direct comparison between factor concentrates can be helpful. Several studies have already compared the PK properties of several EHL FVIII concentrates; however, none have yet described a simultaneous comparison of all currently available FVIII concentrates.[14–16] Fortunately, population PK models of the various FVIII concentrates have been published or are publicly available that describe the PK of the FVIII concentrates in a typical patient as well as the intra- and interindividual variability.[17–21] With these population PK models, Monte Carlo simulations can be performed. In this manner, individual PK profiles of a virtual population are obtained that match the patient characteristics of the population from which the model was constructed, while no costs are made and patients are not exposed to therapeutic interventions. As collection of real-world data is time-consuming, other methods of comparison, such as the Monte Carlo simulations, are an important instrument to gain insight into PK differences to inform the physician and patients which factor concentrate may best fit the requirements of each individual patient. Hence, the aim of this study was to compare the PK characteristics of the currently available EHL FVIII concentrates using Monte Carlo simulations.

Methods

Comparison of the FVIII concentrates was performed by generation of FVIII level versus time profiles in silico by Monte Carlo simulations using the NONMEM v7.4.1 (ICON Development Solutions, Ellicott City, Maryland, United States) software. Profiles were created for the following EHL concentrates: rFVIII-Fc (Elocta, Swedish Orphan Biovitrum AB, Sweden), BAX 855 (Adynovi, Takeda Pharmaceutical Company Limited, Japan), and BAY 94–9027 (Jivi, Bayer AG, Germany). rFVIII-SC (Afstyla, CSL Behring GmbH, Germany) and BAY 81–8973 (Kovaltry, Bayer AG, Germany) were also included in this analysis. The different EHL FVIII concentrates were compared with SHL rFVIII concentrates such as Advate (Takeda Pharmaceutical Company Limited, Japan) and Kogenate (Bayer AG, Germany). No population PK model for N8-GP has been published. Therefore, this concentrate was not included in this analysis.

Virtual Study Population

A virtual population of 1,000 patients with severe hemophilia A was simulated with R software (version 3.4.1; R-core team 2017). The virtual patients were given different total body weight, lean body weight, fat-free mass, age, and VWF levels, as these patients' characteristics have been described in the population PK models of the examined FVIII concentrates. The ranges of these characteristics were set to corresponding values that were found in every population used for model building. As a result, age ranged from 12 to 60 years, total body weight ranged from 42 to 106 kg, and VWF from 53 to 290 U/dL. Moreover, the physiological relationship between these patient characteristics was taken into account. Using expert knowledge, a relation between age and weight was simulated with the use of the tmvtnorm package in R. Many studies observed an age-related increase in VWF levels.[22–27] In type 1 VWD patients, a VWF increase between 1.81 and 3.68 IU/dL

per decade was observed, while in a healthy population an average rise of 11 to 18 IU/dL every decade was observed.[24,28–30] Since unfortunately no publication was found in which the VWF increase was described in hemophilia patients of all ages, the age-related increase in VWF levels of the healthy population was adopted. This relation plus extra random noise with a standard deviation of 55.3 U/dL, as described in the publication of the population PK model of BAY 94–9027, was included in the simulation of the VWF levels so that the VWF ranged between 53 and 260 U/dL.[21] Lean body weight was calculated using total body weight with the formula of Janmahasatian et al.[31] The fat-free mass was estimated with the equation of Deurenberg et al for body-fat percentage.[32] For the sake of simplicity, we assumed that all subjects in the simulations were severe hemophilia patients and had no endogenous FVIII, as is characteristic for severe hemophilia A patients on prophylaxis.

Monte Carlo Simulations

Individual PK parameters and subsequent FVIII level versus time profiles per virtual patient were obtained by Monte Carlo simulations. This method takes the distribution of PK parameters, such as clearance and volume of distribution, into account and takes random samples from these distributions in a repeated process (for instance 1,000 times), creating different sets of PK parameters. The Monte Carlo procedure allows for interindividual variability to be taken into account. As a result, virtual patients with the same characteristics had different clearance values. Population PK models of the concentrates published in the literature were used by the Monte Carlo method to simulate the FVIII level versus time profiles.[12,17–21] The PK parameters and equations used in the population PK models are presented in ►**Supplementary Tables S1** to **S4** (available in the online version).

Importantly, the applied population PK models were based on FVIII levels measured by different assays. The data used for the SHL rFVIII population PK model were based on the one-stage assay (OSA), while the models for BAY 81–8973 and rFVIII-SC were based on chromogenic assays (CSAs). The population PK models of the EHL concentrates (rFVIII-Fc, BAX 855, and BAY 94–9027) were all based on FVIII levels measured by both OSA and CSA. Additional information on the population PK models can be found in the Supplementary Methods section (**Supplementary Material**, available in the online version).

FVIII Concentrate Dosing

To compare the PK properties of the described FVIII concentrates, two dosing scenarios were simulated. In clinical practice, FVIII replacement therapy is often applied as prophylaxis in severe hemophilia A patients. Therefore, steady-state dosing scenarios were evaluated. A dosing regimen of 40 IU/kg every 72 hours was chosen for direct comparison of the FVIII concentrates, as this regimen corresponds most to the varying regimens described in the summary of product characteristics (SmPC) of the examined FVIII concentrates.[33–38] This regimen is only used for theoretical comparison of the FVIII concentrates. Recommended dosing regimens described in the SmPC were used to compare implications of the PK differences of these concentrates in clinical practice. Since the SmPCs describe a range of recommended dosing schemes, the middle of these advised dosing schemes was chosen when possible (►**Supplementary Table S6**, available in the online version). In all cases, the dose was based on the total body weight of the virtual patients and rounded to the closest whole FVIII concentrate vial of 250 IU, reflecting a real-life clinical situation.

Comparison of Pharmacokinetic Properties

For the virtual patients, individual clearance and volume of distribution values were generated using Monte Carlo simulation. Therefrom, other PK characteristics such as the elimination half-life, area under the activity versus time profile (AUC), in vivo recovery (IVR), and the time patients spent per week above 1 IU/dL, 3 IU/dL, and 5 IU/dL were calculated. Additionally, individual doses were calculated, based on individual PK parameters of each virtual patient, to maintain trough levels >1 IU/dL, 3 IU/dL, and 5 IU/dL during steady-state dosing using the dosing interval of 72 hours or the dosing interval described in the SmPC of the concentrate.

Results

A dataset of 1,000 virtual patients was created. Patients were given different total body weight, lean body weight, fat free mass, age, VWF and hematocrit levels. In ►**Fig. 1**, the relationship between all simulated patient characteristics is displayed. This dataset was used to perform Monte Carlo simulations, from which individual PK parameters and subsequent FVIII level over time profiles were obtained. In the results described below, PK parameters of BAX 855, rFVIII-Fc, and BAY 94–9027 are presented based on population PK models constructed using data obtained with the OSA method. In ►**Supplementary Table S5** and ►**Supplementary Fig. S1** (available in the online version), additional results based on the CSA method can be found.

Comparison with Similar Dosing Regimen

To compare the FVIII concentrates, the PK differences during steady-state dosing of 40 IU/kg every 72 hours were evaluated. In ►**Fig. 2**, the individually predicted FVIII level over time curves are presented that were obtained with this dosing scheme. To compare the FVIII level over time curves more easily, curves are combined in ►**Supplementary Fig. S1** (available in the online version). The figures show that dosing of BAY 94–9027 produces the highest median FVIII trough levels. The FVIII level over time curves of BAX 855 and rFVIII-Fc appear to be approximately similar. In ►**Supplementary Fig. S2** (available in the online version) the FVIII level over time curves are displayed on a non-log scale, which provides a better representation of the achieved peak levels.

The FVIII level over time curves were used to calculate the elimination half-life, AUC, and IVR. The median elimination half-life was prolonged from 12.6 hours for SHL rFVIII, to 13.9 hours for BAY 81–8973, 15.2 hours for BAX 855, 17.3 hours for rFVIII-Fc, and 17.2 hours for BAY 94–9027

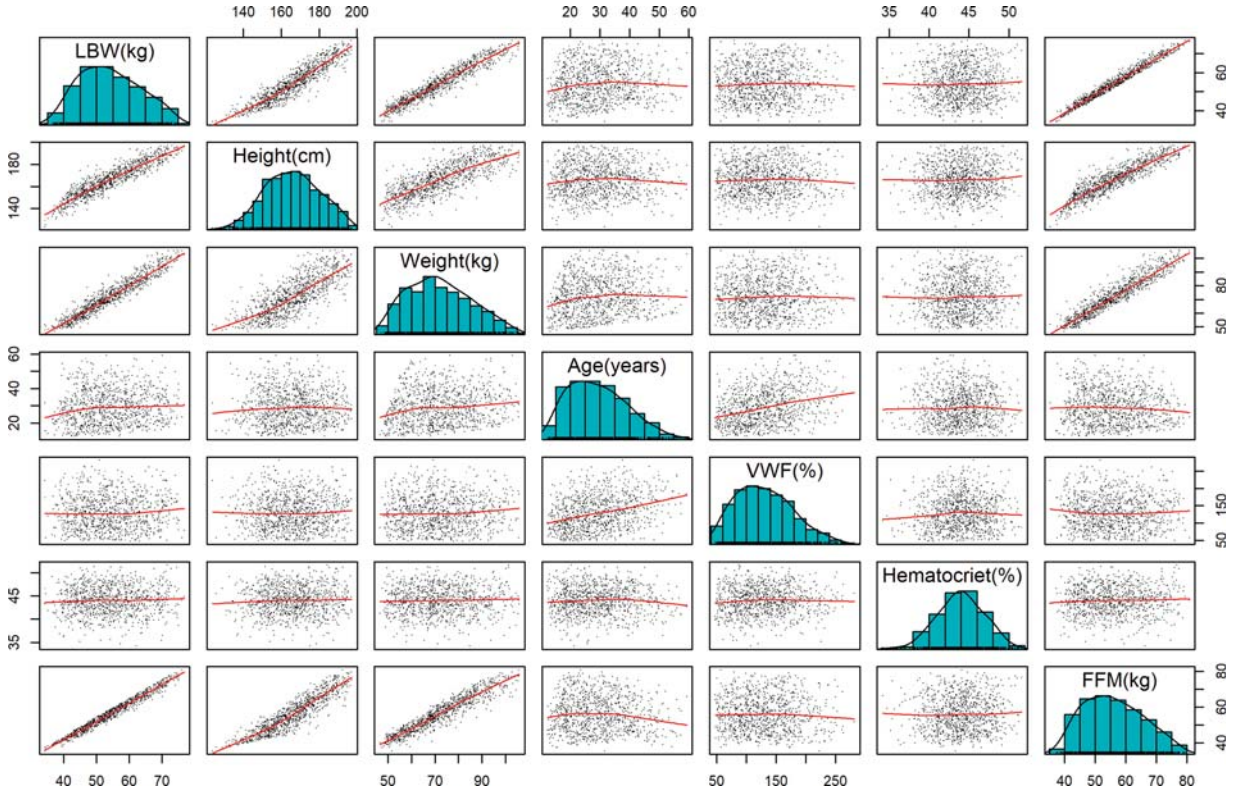

Fig. 1 Relationships between the various simulated patient characteristics of the 1,000 virtual study patients. FFM, fat free mass; LBW, lean body weight; VWF: von Willebrand factor.

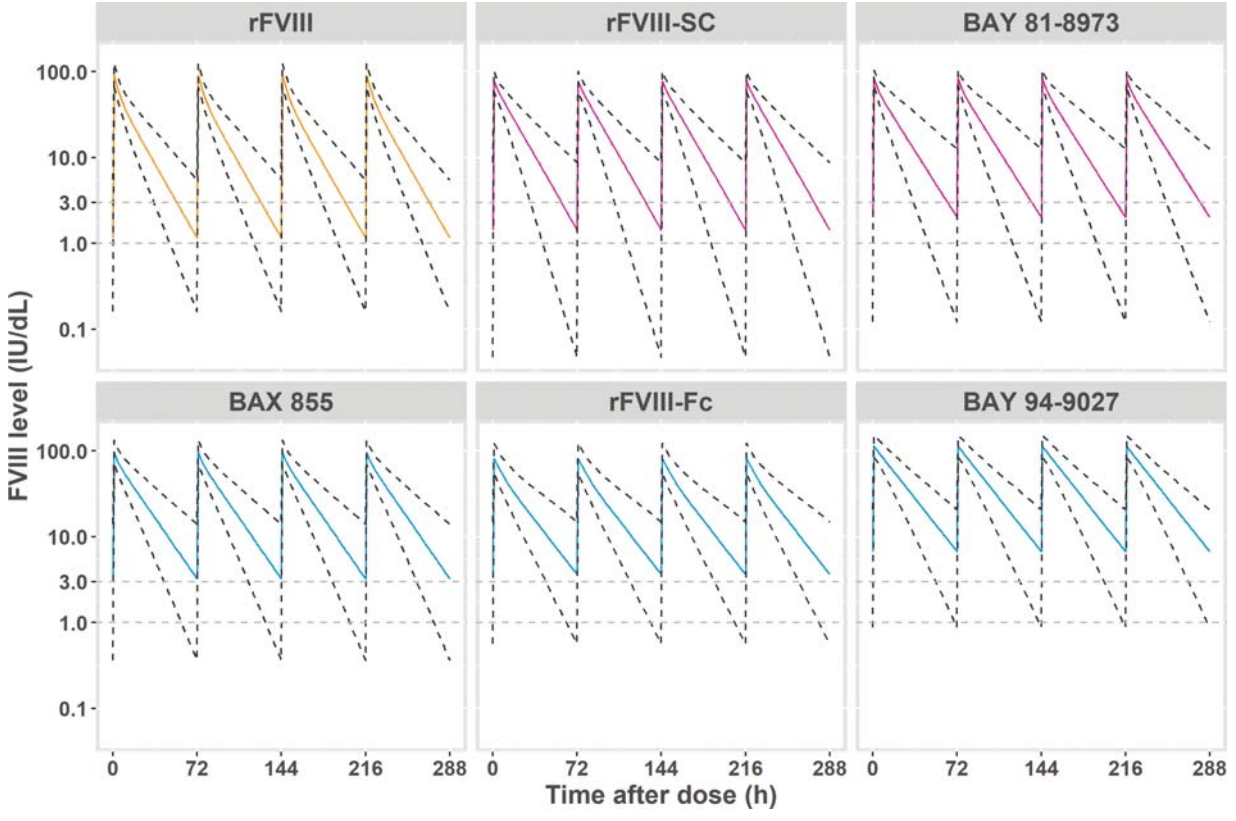

Fig. 2 FVIII level over time curves of FVIII concentrates after steady-state dosing of 40 IU/kg per 72 hours on a logarithmic scale. *Colored solid lines* represent the median and the *dotted lines* the 2.5th and the 97.5th percentiles. For rFVIII, BAX 855, rFVIII-FC, and BAY 94–9027, the one-stage assay was applied to obtain the FVIII level. The curves of rFVIII-SC and BAY 81–8973 are based on FVIII levels obtained with a chromogenic assay.

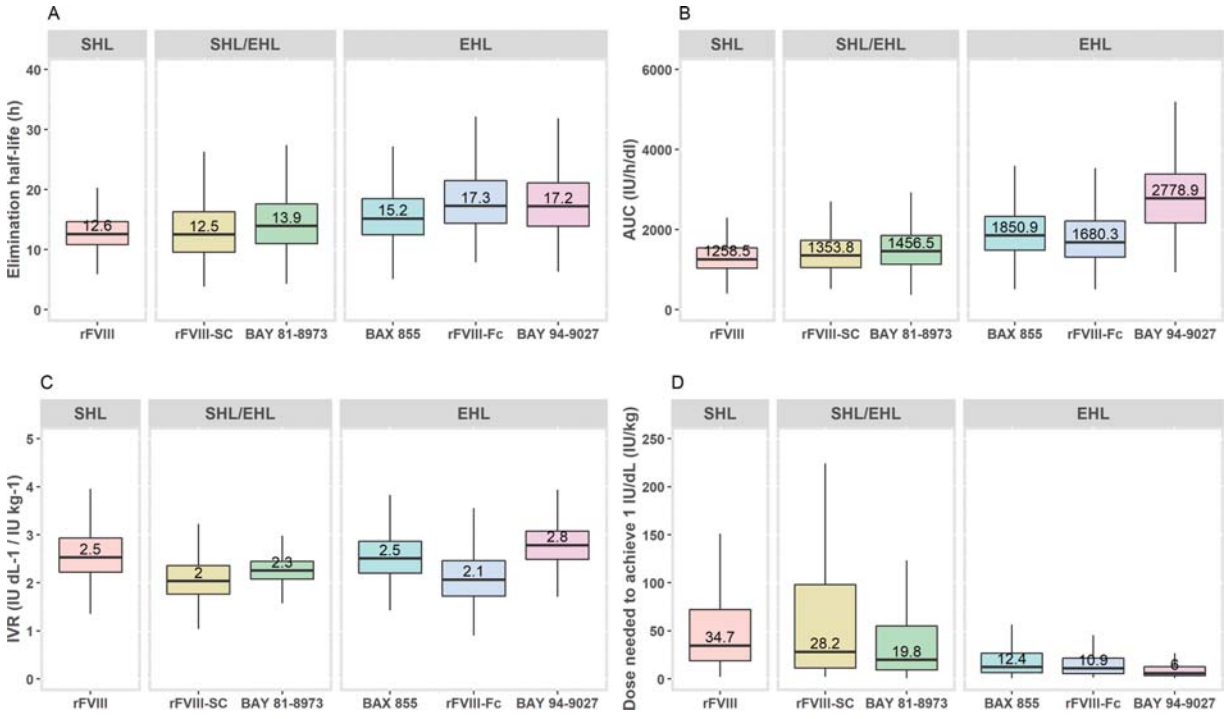

Fig. 3 Pharmacokinetic parameters of the 1,000 simulated patients obtained with steady-state dosing of 40 IU/kg every 72 hours. The (**A**) elimination half-life, (**B**) area under the curve (AUC), (**C**) in vivo recovery (IVR), and (**D**) dose needed to achieve trough level of 1 IU/dL when dosing every 72 hours of the examined FVIII concentrates are displayed. The lower and upper hinges of the colored boxes illustrate the 25th and 75th percentiles (interquartile range, IQR) and the whiskers extend to 1.5 × IQR. Outliers are not shown. For rFVIII, BAX 855, rFVIII-FC, and BAY 94–9027, the one-stage assay was applied to obtain FVIII levels. The curves of rFVIII-SC and BAY 81–8973 are based on FVIII levels obtained with a chromogenic assay.

(►**Fig. 3A**). The median half-life of rFVIII-SC (12.5 hours) was comparable to that of SHL rFVIII (12.6 hours). Larger differences between the examined concentrates are seen when comparing the AUC values obtained during the steady-state dosing (►**Fig. 3B**). BAY 81–8973 and rFVIII-SC demonstrated small increases in median AUC values compared with SHL rFVIII (1,259 IU/h/dL). However, higher AUC values were obtained with the "true" EHL concentrates. BAY 94–9027 had the highest median AUC value of 2,779 IU/h/dL, followed by BAX 855 with a median AUC of 1,851 IU/h/dL and rFVIII-Fc with an AUC of 1,680 IU/h/dL. The median IVR of BAX 855 was similar to that of SHL rFVIII (2.5 IU/dL per IU/kg), while BAY 94–9027 showed a slightly higher median IVR (2.8 IU/dL per IU/kg). rFVIII-Fc, rFVIII-SC, and BAY 81–8973 demonstrated lower median IVR values than SHL rFVIII (►**Fig. 3C**).

To gain more clinical insight into the impact of the differences in PK properties between the FVIII concentrates during steady-state dosing of 40 IU/kg every 72 hours, we evaluated the time patients spent above 1 IU/dL per week (= 168 hours) (►**Fig. 4A**), e.g., when a virtual patient spends 168 hours above 1 IU/dL, the FVIII level never drops below 1 IU/dL. For all of the examined FVIII concentrates, FVIII levels will not drop below 1 IU/dL in at least 50% of the patients. BAY 94–9027 showed the highest percentage of patients maintaining FVIII levels above 1 IU/dL (93.3%), followed by rFVIII-Fc (89.0%) and BAX 855 (83.9%). For rFVIII, rFVIII-SC, and BAY 81–8973, around 25% of the patients spent less than 144 hours above 1 IU/dL, thereby demonstrating a FVIII level under 1 IU/dL around 24 hours per week. In ►**Fig. 5A** the results of the time patients spent above 3 IU/dL per week during steady-state dosing of 40 IU/kg every 72 hours are presented. Only 14.1% of the patients maintain a trough level of 3 IU/dL after SHL rFVIII administration, while this is between 52.8 (BAX 855) and 75.9% (BAY 94–9027) for the "true" EHL concentrates. Results for time patients spent above 5 IU/dL per week can be found in ►**Supplementary Table S5** and ►**Supplementary Fig. S3** (available in the online version).

Additionally, the PK characteristics of the concentrates were compared in an artificial way by calculating the dose needed to achieve specific trough levels when dosing every 72 hours. For a target trough level of 1 IU/dL, median (artificial) doses of 34.7, 28.2, and 19.8 IU/kg every 72 hours can be administrated for rFVIII, rFVIII-SC, and BAY 81–897, respectively (►**Fig. 3D**). Lower (artificial) doses of the "true" EHL concentrates can be administered as only median doses of 12.4, 10.9, and 6.0 IU/kg of BAX 855, rFVIII-Fc, and BAY-9027 every 72 hours are needed to produce FVIII trough levels of 1 IU/dL, respectively. Other PK parameters that were obtained with the Monte Carlo simulations using the dosing regimen of 40 IU/kg every 72 hours, such as clearance, volume of distribution, trough level before administration of the subsequent FVIII concentrate dose, time above a target level, percentage of patients that obtain a trough level above a certain target level, and doses needed to achieve specific trough levels, can be found in ►**Supplementary Table S5** (available in the online version). In this table the parameters discussed above are also presented, including the 95% prediction intervals of the simulated values.

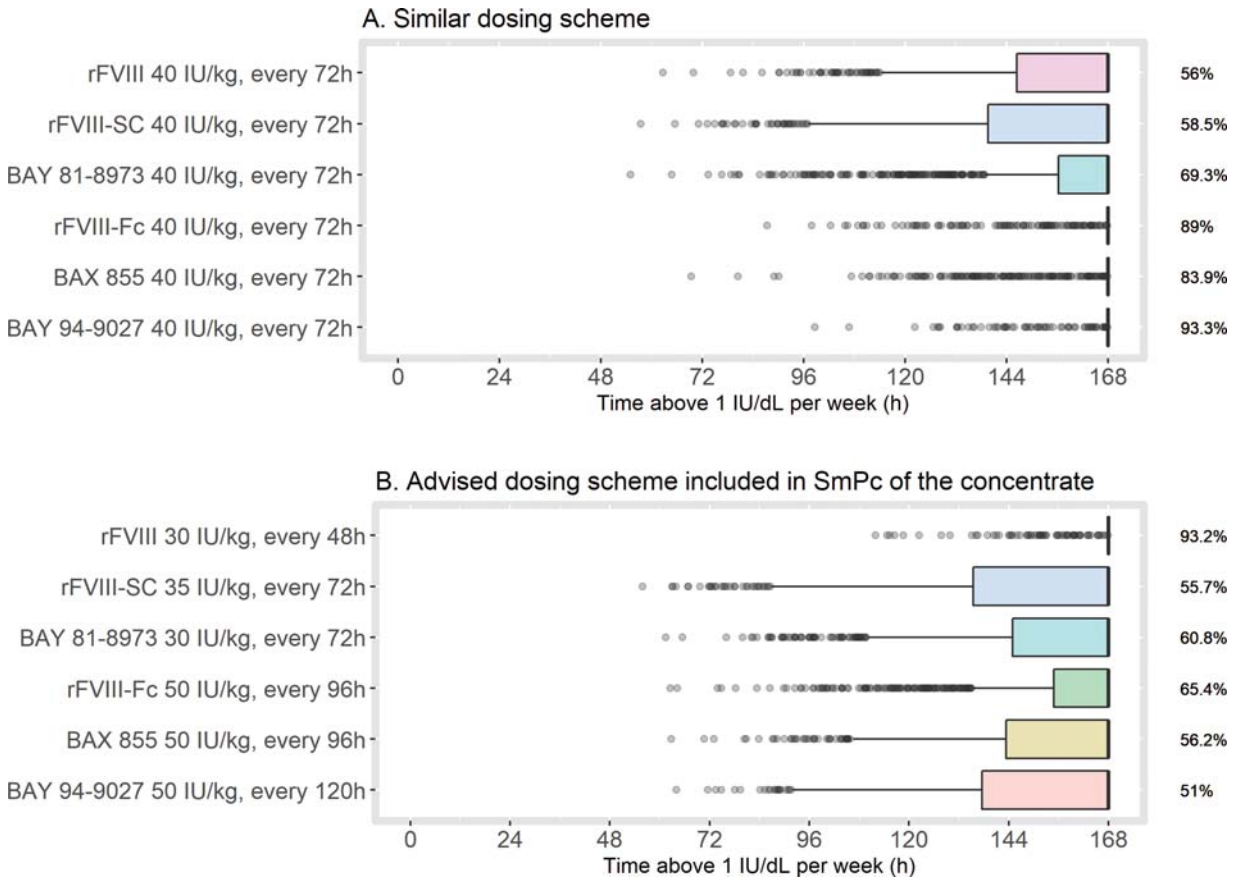

Fig. 4 Boxplot of time patients spend per week above 1 IU/dL during the dosing interval following steady-state dosing of 40 IU/kg every 72 hours (*top*) and the recommended dosing scheme of the SmPC (*bottom*). The lower and upper hinges of the colored boxes illustrate the 25th and 75th percentiles (interquartile range, IQR) and the whiskers extend to 1.5 × IQR. The outliers are visualized as individual points. The numbers on the right of the graph present the percentage of patients never experiencing FVIII levels below 1 IU/dL. SmPC, summary of product characteristics.

Comparison of SmPC Dosing Regimens

To evaluate the dosing schemes commonly used in clinical practice, PK properties based on the dosing regimens described in the SmPCs of the concentrates were compared. ►**Fig. 4B** confirms that the average patient does not spend time below 1 IU/dL when dosing schemes described in the SmPCs are applied, as the median time spend above 1 IU/dL is 168 hours per week, and the number of patients with FVIII levels maintaining FVIII levels above 1 IU/dL is at least 50%. For all FVIII concentrates except SHL rFVIII (93.2%) ,the number of patients not demonstrating FVIII levels under 1 IU/dL is only between 51.0 and 65.4%. Moreover, large interindividual variability is observed, as some patients spend only approximately 72 hours—so only three of the seven weekdays—above a FVIII trough level of 1 IU/dL. When examining the time patients spend above 3 IU/dL per week after administration of the doses described in the SmPC of the concentrate, the median patient spends between 120 and 144 hours above this target for all concentrates except SHL rFVIII (►**Fig. 5B**). Only between 23.2 and 31.3% of the patients maintain a trough FVIII level of 3 IU/dL after administration of the EHL concentrates. Between 12.2 and 16.6% of the patients maintain a target trough level of 5 IU/dL following the dosing scheme of the EHL FVIII concentrates described in the SmPC (►**Supplementary Fig. S3**, available in the online version). The impacts of the evaluated SmPC dosing schemes on weekly concentrate consumption are displayed in ►**Supplementary Table S6** (available in the online version).

Discussion

Monte Carlo simulations were performed for a virtual population of 1,000 patients to compare the PK properties of the FVIII concentrates rFVIII-SC, BAY 81–8973, BAX 855, rFVIII-Fc, and BAY 94–9027 and SHL rFVIII based on reported PK data in earlier studies. Individual PK parameters and FVIII level over time curves were obtained and evaluated after steady-state dosing of 40 IU/kg every 72 hours or dosing corresponding to the SmPCs of the concentrates. The simulations showed the largest AUC and best target attainment—as described by the longest time above a FVIII target level and highest percentage of patients maintaining a FVIII target trough level—for BAY 94–9027 when compared with SHL rFVIII, followed closely by comparable results for BAX 855 and rFVIII-Fc. This is in line with other publications.[14–16] Similar to the conclusions drawn by Mahlangu et al, PK properties of BAY 81–8973 and rFVIII-SC were only slightly better than those of SHL rFVIII in this analysis.[11] This

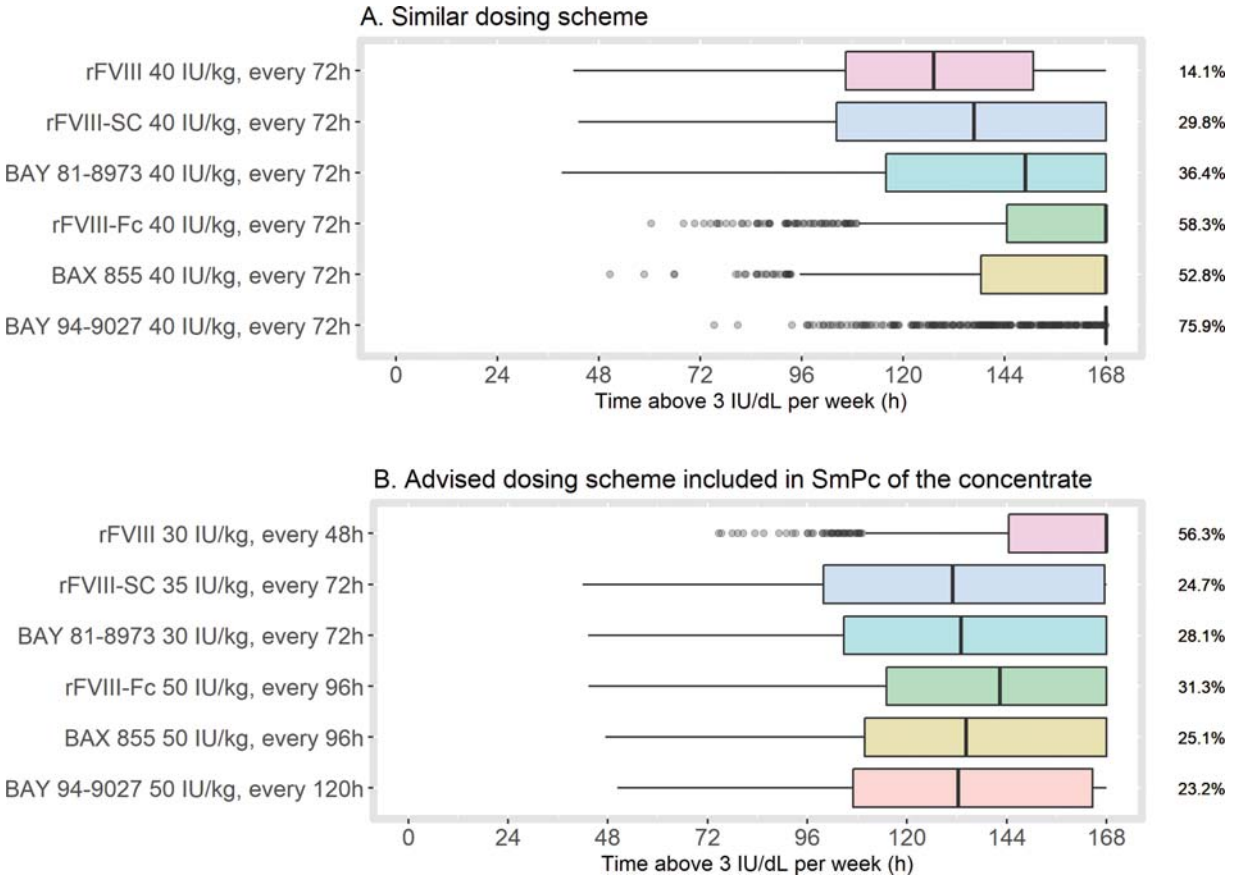

Fig. 5 Boxplot of time patients spend per week above 3 IU/dL during the dosing interval following steady-state dosing of 40 IU/kg every 72 hours (*top*) and the dosing scheme described in the SmPC (*bottom*). The lower and upper hinges of the colored boxes illustrate the 25th and 75th percentiles (interquartile range, IQR) and the whiskers extend to 1.5 × IQR. The outliers are visualized as individual points. The numbers on the right of the graph present the percentage of patients never experiencing FVIII levels below 3 IU/dL. SmPC, summary of product characteristics.

underlines that these FVIII concentrates should not be regarded as EHL concentrates.

Comparison of the PK properties of FVIII concentrates is not straightforward, as many different PK parameters have to be taken into account. For instance, the obtained elimination half-life values for BAX 855, rFVIII-Fc, and BAY 94–9027 were rather similar, while BAY 94–9027 showed a larger AUC than BAX 855 and rFVIII-Fc. Elimination half-life is determined by both clearance and volume of distribution. When both clearance and volume of distribution change with the same proportion, the elimination half-life will remain the same, while a different clearance and thus AUC are obtained. Therefore, these findings indicate that FVIII concentrates should not only be judged based on elimination half-life. In addition, it is important to not only judge the concentrates based on the obtained FVIII trough level, as a certain time above a higher FVIII level may be necessary to safeguard adequate hemostasis, especially during sport activities.[39] For this reason the lower calculated doses for the EHL FVIII concentrates of 6.0 to 12.4 IU/kg to achieve a trough level of 1 IU/dL when dosing every 72 hours obtained do not reflect doses given in clinical practice as the obtained FVIII levels shortly after infusion may not be sufficient to safely participate in physical activities, and should therefore be regarded as artificially obtained doses simulated for comparison. Specifically, these doses only underline that longer dosing intervals are possible for most of the patients receiving these EHL FVIII concentrates or that higher FVIII trough levels can be achieved.

To evaluate dosing schemes that are commonly used in clinical practice, PK properties after administration of doses described in the SmPC were examined. A study by Collins et al demonstrated that a longer time with a FVIII level below 1 IU/dL was associated with a higher number of bleeds and hemarthroses.[40] Therefore, an interesting PK property is the time patients spend above a FVIII level of 1 IU/dL per week. When administrating the dose described in the SmPC, the percentage of patients not demonstrating FVIII levels below 1 IU/dL was more or less similar for the compared FVIII concentrates (between 51.0 and 65.4%), indicating sufficient dosing for around half of the patients. However, a high interindividual variability of the time spent per week above a certain FVIII target level was observed, underlining the need for individual PK-guided dosing in clinical practice. Since the SmPCs report a range of dosing schemes, this percentage will be higher when the upper boundary of the dosing range is adopted instead of the currently evaluated (middle) dosing scheme. Furthermore, the majority of the SmPCs also indicate that the dosing scheme needs to be adjusted based on patient characteristics (►**Supplementary Table S6**, available in the

online version), especially for younger patients who often present with increased clearance and shorter half-life.[12] When the dose described in the SmPC is converted to the needed number of IU/kg per concentrate per week, differences between necessary IU/kg of a concentrate to obtain adequate FVIII levels appear less extreme than those after the artificial comparison of the dose needed to achieve specific trough levels when dosing every 72 hours. For example, according to the evaluated SmPC dosing scheme on a weekly basis, 70 IU/kg would be necessary for BAY 94–9027 and BAY 81–8973 (►**Supplementary Table S6**, available in the online version), while in the artificial comparison a median necessary dose of 6.1 IU/kg for BAY 94–9027 was calculated to maintain a FVIII trough level of 1 IU/dL when dosing every 72 hours compared with a median estimated dose of 17.3 IU/kg for BAY 81–8973. It is important to keep in mind that longer dosing intervals of, for instance, 120 hours, result in less patient burden as dosing frequency is lower.

For the FVIII concentrates, different IVR values were obtained and only BAY 855 showed IVR values comparable to those of SHL rFVIII. Furthermore, a large interindividual variability in IVR values was observed as the 95% prediction interval of the IVR value of all concentrates showed approximately a twofold difference between the lower and upper boundaries (►**Fig. 4C** and ►**Supplementary Table S5**, available in the online version). This indicates that dosing in critical situations such as life-threatening bleeding may differ for the various concentrates and for each individual. Therefore, this should preferably be performed based on individual IVR values obtained for each patient separately or monitored closely, as is now standard practice in critical settings.[1,5] It is important to realize that the observed IVR differences may also be due to the application of various assays, activators, and test settings, or a different number of compartments in the population PK models, e.g., one or two compartments, or varying data sampling schemes of the data used for population PK model development. For instance, data of the phase 3 study of rFVIII-Fc showed a smaller IVR difference between SHL rFVIII and rFVIII-Fc (2.4 vs. 2.2 IU/dL per IU/kg) than the results observed in our study (2.52 vs. 2.01 IU/dL per IU/kg).[41]

The differences in PK properties of the EHL FVIII concentrates compared with SHL rFVIII were less extreme than differences observed between the EHL FIX concentrates and SHL rFIX.[10] However, newer FVIII therapies are currently being developed which may further elongate FVIII half-life, such as BIVV001.[42] Overall, in our study, the shapes of the FVIII level over time curves of all FVIII concentrates were rather similar, namely, a short distribution phase followed by a longer elimination phase, as depicted in ►**Fig. 2**. Between the various EHL FIX concentrates, larger differences are seen, as rFIX-Fc shows a rapid decline during the distribution phase, possibly caused by the influence of extravascular reservoir FIX.[43] For FVIII, the extravascular amount does not seem to be clinically relevant, leading to less diversity between the EHL FVIII concentrates. Despite the smaller differences in PK between the EHL FVIII concentrates when compared with EHL FIX concentrates, it is important to realize that it is essential to study the relationships between FVIII dose, PK, and pharmacodynamics (PD; e.g., bleeding) of the EHL FVIII concentrates more extensively, as PK–PD relationships give more insight into the actual hemostatic efficacy of these concentrates.

This study was performed in silico and used the available population PK models of the respective FVIII concentrates to calculate the PK properties of the concentrates. This approach enabled us to compare the different FVIII concentrates in a similar (virtual) population, which in some ways resembles a multiarm crossover study. Importantly, however, the results of this study are based on simulations and should be interpreted with caution, namely, bias may be introduced by the used population PK models since they are based on data obtained from varying populations. To overcome this shortcoming, we only simulated "virtual" patients with characteristics corresponding to values that were found in all datasets of the used population PK models. Therefore, the obtained results only apply to patients with similar characteristics to the population simulated in this study. This means that this study only applies to patients with ages ranging from 12 to 60 years, a bodyweight ranging from 42 to 106 kg, and VWF levels ranging from 53 to 290 U/dL. A difficulty of comparing the PK properties of the FVIII concentrates described in this study was the use of different assays to measure plasma FVIII. Although all population PK models used in this study were based on FVIII levels measured with an assay method that provided valid results according to literature, the use of different assays may have led to discrepancies and contributed to the observed PK differences.[44,45] Notably, the use of varying assay activators for the OSA method could have also introduced variation in FVIII levels.[46] Furthermore, different sampling schemes used for data collection to construct the various population PK models and applied model structures (one- vs. two-compartment models) may have additionally contributed to the observed differences. A full PK comparison (head-to-head comparison) with real-world clinical data, with populations including children and the more obese, is therefore recommended. Lastly, we would like to stress that it is important to base factor concentrate choice not only on PK characteristics, but also on clinical evidence and the safety profile of the factor concentrate.

Conclusion

This in silico study observed important differences between the PK parameters of the EHL FVIII concentrates. BAY 94–9027 showed the largest increase in AUC and best target attainment, followed closely by BAX 855 and rFVIII-Fc. BAY 81–8973 and rFVIII-SC showed only minor PK improvements compared with SHL rFVIII. Since this study was only based on in silico simulations, further studies comparing the PK properties of FVIII concentrates with real-world clinical patient data are obligatory. Additionally, studies defining the relationship among dose, PK, and bleeding events (PD) of the studied FVIII concentrates are essential to ultimately

define the relationship between FVIII levels and bleeding (risk).

What is known about this topic?

- The pharmacokinetic (PK) properties of extended half-life (EHL) factor VIII (FVIII) concentrates differ, leading to variation in the optimal dosing regimen for the individual patient.
- A full simultaneous PK comparison of the available EHL FVIII concentrates has not yet been performed.

What does this paper add?

- Monte Carlo simulations were used to examine the differences in pharmacokinetic properties of EHL FVIII concentrates.
- BAY 94–9027 showed the largest increase of AUC and best target attainment compared with SHL rFVIII, followed closely by BAX 855 and rFVIII-Fc.
- When a dosing scheme advised in the SmPC of the concentrates is applied, only around 50% of the patients maintain a target FVIII level of 1 IU/dL.

Authors' Contributions

L.H.B., T.P., and M.W.F.S. performed the pharmacokinetic analyses. L.H.B. wrote the manuscript. R.A.A.M. and M.H.C. supervised the study, while F.W.G.L. gave critical guidance. All authors contributed substantially to the critical revision of the manuscript and approved the final draft of the manuscript.

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Conflict of Interest

F.W.G.L. reports grants from CSL Behring, Shire, uniQure; consultancy for uniQure, Shire, and Biomarin, for which fees go to the university; travel support from Sobi; and has served as a DSMB member for a study by Roche, outside the submitted work. M.H.C. has received grants from governmental research institutes such as Dutch Research Institute (NWO), ZonMW, and Innovation Fund, and unrestricted investigator initiated research grants as well as educational and travel funding from the following companies over the years: Pfizer, Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi, Biogen, Novo Nordisk, Novartis, and Nordic Pharma, and has served as a member on steering boards of Roche and Bayer; all grants, awards, and fees go to the institution. R.A.A.M. reports grants from Bayer, grants from Shire, grants from Merck Sharpe Dome, grants from CSL Behring, other from Bayer, other from Shire, outside the submitted work. Other authors declare no competing financial interests.

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