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A French Real-World Evidence Study Evaluating the Efficacy, Safety, and Pharmacokinetic Parameters of rVIII-SingleChain in Patients with Hemophilia A Receiving Prophylaxis

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Abstract

Background rVIII-SingleChain is a recombinant factor VIII (FVIII) with increased binding affinity to von Willebrand factor compared with other FVIII products. rVIII-SingleChain is indicated for the treatment and prevention of bleeding episodes in patients with hemophilia A.

Objectives To collect real-world evidence data from patients treated with rVIII-SingleChain to confirm the efficacy and safety established in the clinical trial program and carry out a population pharmacokinetic (PK) analysis.

Methods This interim analysis includes data, collected between January 2018 — September 2021, from patients treated with rVIII-SingleChain prophylaxis at French Hemophilia Treatment centers. Data on annualized bleeding rates, dosing frequency,

Keywords
- factor VIII
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- pharmacokinetic
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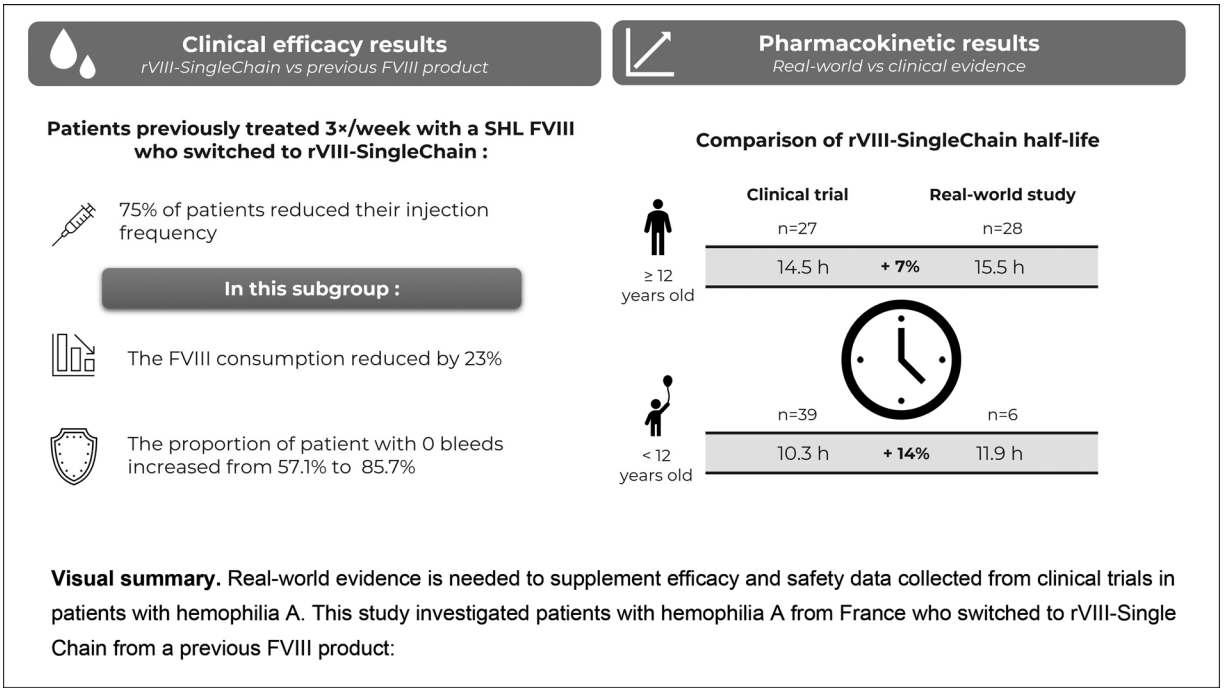

and consumption before and after switching to rVIII-SingleChain were recorded. A population PK analysis was also conducted to estimate PK parameters.

Results Overall, 43 patients switched to prophylaxis with rVIII-SingleChain either from a previous prophylaxis regimen or from on-demand treatment. Following the switch to rVIII-SingleChain, patients maintained excellent bleed control. After switching to rVIII-SingleChain, most patients maintained or reduced their regimen. Interestingly, a majority of patients treated $>2\times$/weekly with a standard half-life FVIII reduced both injection frequency and FVIII consumption with rVIII-SingleChain. A PK analysis revealed a lower clearance of rVIII-SingleChain (1.9 vs. 2.1 dL/h) and a longer half-life both in adolescents/adults ($n = 28$) and pediatric ($n = 6$) patients (15.5 and 11.9 hours, respectively vs. 14.5 and 10.3 hours) than previously reported.

Conclusions Patients who switched to rVIII-SingleChain prophylaxis demonstrated excellent bleed control and a reduction in infusion frequency. A population PK analysis revealed improved PK parameters compared with those reported in the clinical trial.

Introduction

Hemophilia A is an X-linked bleeding disorder caused by a deficiency or absence of functional coagulation factor VIII (FVIII).[1] It represents 80 to 85% of the hemophilia population with an estimated frequency of 1 in 10,000 births.[1] The primary aim of hemophilia A treatment is to prevent and treat bleeding episodes using factor replacement[1,2] or non-factor replacement products.[3,4] FVIII has a relatively short half-life of 8 to 12 hours, which means frequent infusions with FVIII concentrates to prevent and control bleeding episodes.[1] This creates a high treatment burden for patients and can lead to poor adherence to the prescribed treatment regimen.[5] Extended half-life (EHL) FVIII products offer the opportunity of less frequent infusions and potentially improved compliance, while retaining good bleed control, compared with standard half-life (SHL) FVIII products.[6–10]

rVIII-SingleChain (AFSTYLA®; CSL Behring, Marburg, Germany) is a recombinant FVIII (rFVIII) with increased binding affinity to von Willebrand factor (VWF) compared with SHL FVIII concentrates and enhanced molecular stability.[11,12] The AFFINITY clinical trial program has established

the efficacy and safety of rVIII-SingleChain in previously treated adolescent/adult and pediatric patients with hemophilia A.[13,14] In two phase III studies with adolescent/adult and pediatric patients, at least 30% of patients were able to reduce their frequency of infusion with rVIII-SingleChain, compared with their prior SHL FVIII concentrate.[13,14]

As such, the more time spent with FVIII trough levels below 1 IU/dL correlates significantly with a greater risk of breakthrough bleeds.[1,15] The International Society of Thrombosis and Haemostasis (ISTH) recommendations recognize activity over time, such as the time to reach 1 IU/dL, as the most clinically meaningful pharmacokinetic (PK) parameter.[16] A population PK analysis based on the AFFINITY clinical trial program demonstrated that following the administration of rVIII-SingleChain the time taken for FVIII activity to fall to 1 IU/dL was 5.1 days, which was comparable to the time observed with other EHL FVIII products, such as rFVIIIFc (4.9 days).[17]

The growing number of FVIII concentrates available on the market and the need to understand their individual PK properties mean that there is currently a large amount of PK data available. However, many factors can influence the analysis of PK data and bias can be introduced due to a lack of standardization.[17] One method to overcome this bias is by using a population PK analysis, which is a powerful approach to estimate PK parameters even when sampling time-points are sparse. This method can also handle data below the limit of quantification and can consider different quantification methods and their analytical performance.[17]

Data from clinical trials are robust; however, the controlled nature of trial conditions and the limited selection of patients can mean the results cannot be generalizable to the wider patient population. Real-world clinical experience data are required to assess the clinical utility of a product in a broader patient population.[18–20] However, the PK parameters calculated in a real-world clinical setting and the pivotal clinical trials do not always align due to the differences in the methodology in the protocols and the complexity of the data.[17]

The Observational register of Patients with haEmophilia A tReated with AFSTYLA® (OPERA; clinicaltrials.gov: NCT04675541) is a national, noninterventional, longitudinal, multicenter, cohort study of hemophilia A patients who have been treated with rVIII-SingleChain in France. The objective of this study was to collect real-life data from patients with hemophilia A treated with rVIII-SingleChain to confirm the efficacy and safety findings established in the AFFINITY clinical trial program. This interim analysis also aimed to conduct a population PK analysis on the real-world usage of rVIII-SingleChain.

Methods

Study Population

Enrolled patients had hemophilia A and were being treated or had been treated with rVIII-SingleChain at French Hemophilia Treatment centers (HTCs). This interim analysis includes patients who were recruited between January 2018 — September 2021 and had been treated in prophylaxis with rVIII-SingleChain. All patients had received previous treatment with FVIII prior to enrolment. Data on patients' previous treatment regimen were collected retrospectively for the year preceding the switch to rVIII-SingleChain. A prophylactic regimen was defined as at least one injection per week for at least 3 months. Patients had no active FVIII inhibitors and/or were not undergoing treatment for immune tolerance induction at the time of inclusion in the study. All patients gave written informed consent prior to participation. Data on rVIII-SingleChain usage were collected for 2 years after inclusion in the study. This postmarketing study did not change the usual medical management of participating patients and did not require any additional visits or investigations. As a result, follow-up visits were completed according to the patients' real-world consultations, without any constraints.

Primary Outcome Measures

Data on the annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR), dosing frequency, and consumption were collected, where possible, on the patient's treatment regimen before and after switching to rVIII-SingleChain.

Population Pharmacokinetic Analysis

FVIII trough levels following the switch to rVIII-SingleChain were also collected during the study visits and were used to carry out a population PK analysis. FVIII levels were determined with either chromogenic or chronometric assays. According to the Summary of Product Characteristics of rVIII-SingleChain and French recommendations, FVIII activity measured by chronometric assay are underestimated by approximately 45%, compared with the chromogenic assay. To account for this underestimation, chronometric assay results were adjusted by multiplying by a conversion factor of 2 to determine the patient's FVIII activity level.[21,22]

Population PK analysis was used to estimate individual PK parameters from time–concentration data. Due to data sparseness issues, the dataset did not allow the estimation of the parameters of the suitable model. For that, two strategies were used to stabilize parameter estimation: (1) either to fix them to their previous estimated values or (2) to use prior information based to their previous estimated values. For that, the model of Zhang[23] developed from 130 patients included in phase II/III studies was used. Briefly, this model consists of a two-compartment model with first-order elimination from the central compartment, zero-order input in the central compartment and a parameter for basal FVIII level (baseline). A part of the interindividual PK variability was explained by bodyweight and VWF level.

Data were analyzed using MONOLIX®, a nonlinear mixed-effects modelling software[24] utilizing the SAEM algorithm. The lower limit of quantification (LLOQ) for FVIII levels was 1 IU/dL. Data below the LLOQ were simulated in a right-truncated Gaussian distribution using the SAEM algorithm.[25] Model evaluation was based on visual inspection of the goodness-of-fit plots and distribution of individual parameters.

From the variance-covariance matrix of the estimated PK parameters, Monte Carlo simulations were performed using

Simulx® software. A total of 1,000 PK profiles were generated according to the patient's characteristic (bodyweight) of the study of Zhang.[23] In the simulation, all patients received steady state dose of 50 IU/kg or 20 IU/kg of rVIII-SingleChain every 3.5 days (similarly to Zhang et al[23]). For the simulations, 90% of the prediction interval of the model were superimposed to patients <12 or ≥12 years of age.

Statistical Analysis

The descriptive statistics using percentages, mean, standard deviation (SD), median, and range were performed when appropriate.

Differences in number of injections per week, factor consumption, and ABR/AsBR were evaluated for a population of <30 patients with available datapoints both pre- and post-switch, using Wilcoxon signed-rank tests for matched pairs. A p-value <0.05 was considered statistically significant.

When considering the full population (≥30 patients), the same analyses were performed using paired Student's t-tests.

Patients with incomplete datasets were excluded from analyses requiring the respective missing variable; however, they were still included in analyses for which they had applicable data.

Statistical analyses were performed using GraphPad Prism 7.05 (GraphPad Software, Inc).

Results

Study Population

A total of 58 patients treated with rVIII-SingleChain were included from 14 HTCs in this interim analysis (►**Fig. 1**). All patients were male and had a median (range) age of 29 (5–81) years. Among these patients were 6 pediatric patients aged <12 years and 10 patients aged 12 to 17 years. Forty-five patients had severe hemophilia A, 8 had moderate hemophilia A, and 5 had mild hemophilia A. Eleven (19%) had a history of FVIII inhibitors; of which, all of them had tolerized the inhibitor following the ISTH criteria.[16]

Prior to rVIII-SingleChain initiation, 16/58 patients were treated on-demand with another FVIII product, and 42/58 patients were treated with prophylaxis (►**Fig. 1**). Of these, 36/42 patients were treated with another FVIII product, and 6/42 patients were treated with rVIII-SingleChain as part of the AFFINITY clinical trial program. To be included in this analysis, data needed to be available for 1 year prior to the initiation of rVIII-SingleChain; the six patients who participated in the clinical trial program were not included in this analysis because they had been receiving the drug for 5 years prior to inclusion in the OPERA study. All six patients remained satisfied with their treatment with rVIII-SingleChain and continued treatment once the clinical trial program had ended. For the 52 remaining patients, switched to rVIII-SingleChain, 11 were still treated on-demand and 41 were treated with prophylaxis (►**Fig. 1**). For patients who were previously treated on-demand ($n = 5$), the mean ± SD dosing frequency on rVIII-SingleChain prophylaxis was 1.8 ± 0.3 infusions a week (80% of patients were treated with ≤2 infusions/week). After their switch to rVIII-SingleChain prophylaxis, four out of five patients had experienced zero bleeds at the first follow-up visit (mean ± SD time to follow-up was 22 ± 14 weeks).

Prophylaxis Comparison before/after Switch with rVIII-SingleChain

This interim analysis focuses on the 36 patients who were treated on a secondary prophylactic regimen before and after the switch with rVIII-SingleChain (►**Table 1**). Of these 36 patients, 32 had severe hemophilia A, 3 had moderate hemophilia A, and 1 had mild hemophilia A. The 36 patients had a median (range) age of 28 (5–70) years; 2 patients were aged <12 years, 7 were aged 12–17 years, 23 were aged 18–49 years, and 4 were aged ≥50 years. Hemophilic arthropathy was reported in 19 (53%) patients in the prophylaxis group, with all of these patients being ≥12 years of age.

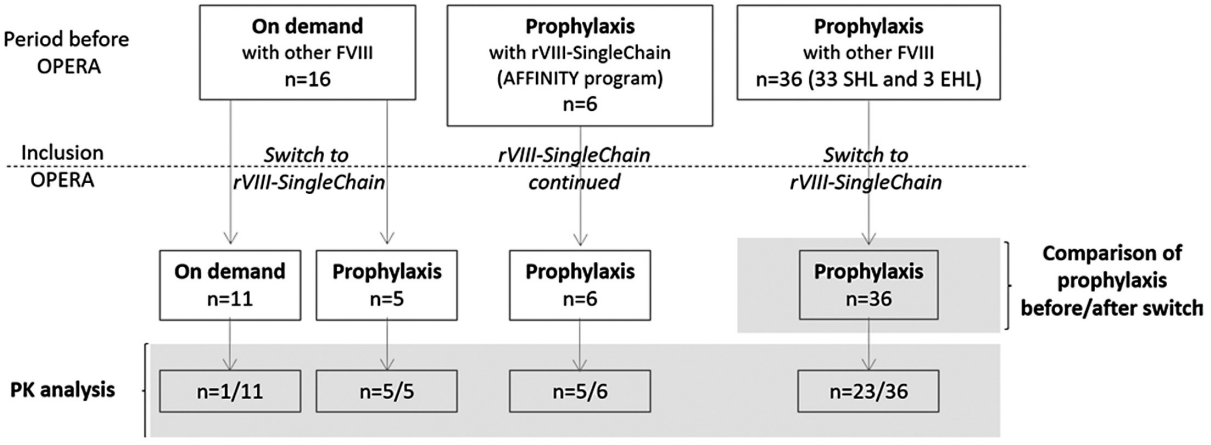

Fig. 1 Flow chart of the OPERA study. A total of 60 patients were included in the OPERA study; however, two were excluded for the interim analyses because eCRF not completed. PK analysis data were collected in $n = 39$ patients. Five patients were excluded from analysis due to FVIII activity lower than the 1% threshold or FVIII activity values were considered as an outlier. A total of 34 patients were included in the PK analysis. EHL, extended half-life; FVIII, factor VIII; PK, pharmacokinetic; SHL, standard half-life.

Table 1 Patient demographics for the prophylaxis group

	<12 y (*n* = 2)	≥12 y (*n* = 34)	Total (*n* = 36)
Age, median (range)	7 (5–9)	29 (12–70)	28 (5–70)
Hemophilia severity, *n* (%)			
Mild	0 (0)	1 (3)	1 (3)
Moderate	1 (50)	2 (6)	3 (8)
Severe	1 (50)	31 (91)	32 (89)
Type O blood group, *n* (%)	0/1 (0)[a]	11/27 (41)[b]	11/28 (39)[c]
Male, *n* (%)	2 (100)	34 (100)	36 (100)
Weight (kg), median (range)	28 (18–37)	70 (42–110)	67 (18–110)
Comorbidities, *n* (%)			
Hemophilic arthropathy[d]	NA	19/32 (59)[e]	19/32 (59)[d, e]
Hepatitis C (active)	0/2 (0)	1/33 (3)[a]	1/35 (3)[a]
Hepatitis B (active)	0/2 (0)	2/33 (6)[a]	2/35 (6)[a]
HIV	0/2 (0)	4/33 (12)[a]	4/35 (11)[a]
Previous FVIII, *n* (%)			
SHL FVIII	2 (100)	31 (91)	33 (92)
EHL FVIII	0 (0)	3 (9)	3 (8)

Abbreviations: EHL, extended half-life; FVIII, factor VIII; HIV, human immunodeficiency virus; NA, not applicable; SHL, standard half-life.
[a]Missing data for 1 patient.
[b]Missing data for 7 patients.
[c]Missing data for 8 patients.
[d]Only for patients ≥12 years.
[e]Missing data for 2 patients.

Dosing Frequency and Consumption

The median (range) duration of prophylaxis with rVIII-SingleChain was 681 (80–1,082) days. ►**Table 1** describes the previous treatment regimen for the 36 analyzed patients. The majority of patients were previously treated with a SHL FVIII product (33/36, 92%). While the frequency of the previous prophylaxis with SHL was ≤2 infusions/week, for 21 patients (64%) this rate increased after switching to rVIII-SingleChain (25/33, 76%) (►**Fig. 2**). For the three patients who previously received an EHL rFVIII, the rate of prophylaxis ≤2 infusions/week increased after switching to rVIII-SingleChain from 1/3 to 2/3 .

Adolescent/adult patients (≥12 years old) who switched to rVIII-SingleChain prophylaxis from an SHL FVIII product maintained their mean ± SD weekly factor consumption (80.4 ± 27.7 vs. 79.3 ± 30.3 IU/kg, respectively with the previous SHL FVIII vs. with rVIII-SingleChain). For the two pediatric patients (<12 years old), the mean ± SD weekly factor consumptions were 76.0 ± 15.6 versus 93.0 ± 24.0 IU/kg, respectively with the previous FVIII versus with rVIII-SingleChain. For patients who switched from a regimen with >2 infusions/week with an SHL FVIII product to a regimen with ≤2 infusions/week with rVIII-SingleChain, the mean ± SD weekly FVIII consumption was significantly reduced by 23% (94.4 ± 15.1 and 72.4 ± 14.7 IU/kg, respectively, $n = 9$, $p < 0.01$). The three adults who switched from an EHL FVIII product to rVIII-SingleChain prophylaxis slightly reduced their mean ± SD weekly factor consumption (88.8 ± 9.8 vs. 83.5 ± 23.7 IU/kg, respectively).

Of the 33 patients who switched to rVIII-SingleChain prophylaxis from a previous SHL FVIII product, 23/33 had reached follow-up visit 1 (mean ± SD time to follow-up was 31.6 ± 18.8 weeks) and 17/33 had reached follow-up visit 2 (mean ± SD time to follow-up = 36.4 ± 18.4 weeks).

Bleeding Rates

The ABR at follow-up visits 1 and 2 was similar to the previous regimen with SHL rFVIII (►**Fig. 3**). However, the AsBR progressively decreased from the previous regimen with SHL-rFVIII to visit 1 then 2 (1.0, 0.9, then 0.4, respectively). The number of patients who reported zero bleeds slightly increased following the switch to rVIII-SingleChain: 49% ($n = 17/35$) versus 48% ($n = 11/23$) at follow-up visit 1 and 60% ($n = 9/15$) at follow-up visit 2, although this increase was not statistically significant when tested with an analysis of variance ($p = 0.71$; $F = 0.34$).

Nine patients switched from a regimen with >2 infusions/week with their previous SHL product to a regimen with 2 infusions/week with rVIII-SingleChain. Of these, almost half experienced some bleeds in the year prior to switching to rVIII-SingleChain ($n = 3/7$); following the switch to rVIII-SingleChain, only one patient ($n = 1/7$) experienced bleeding at the first follow-up visit (median [range] = 157 [10–246] days).

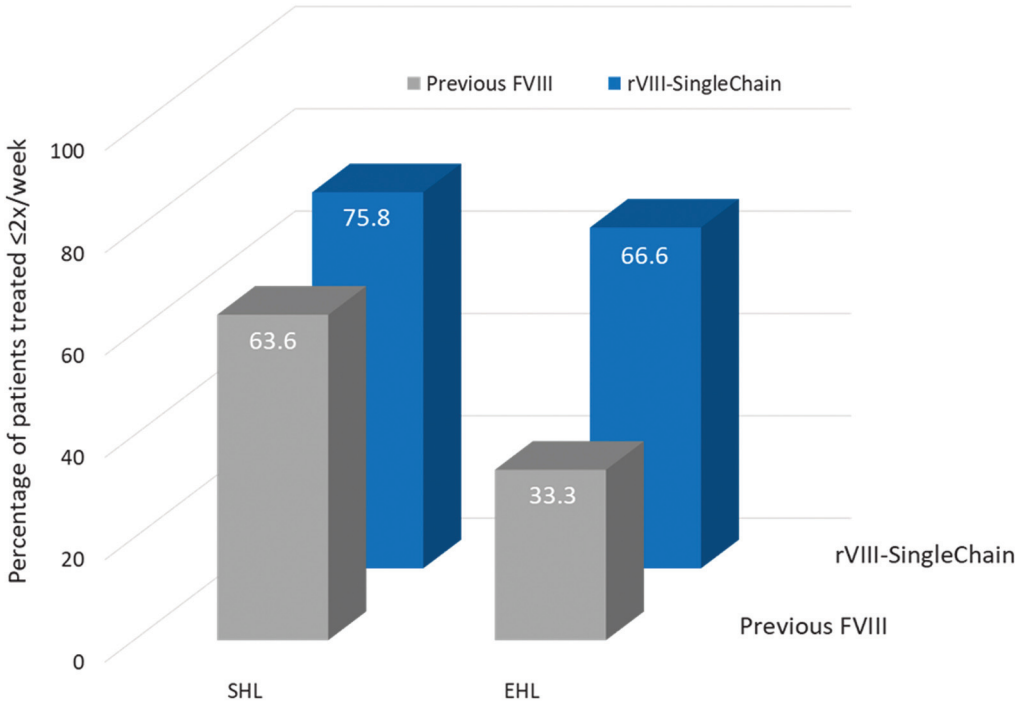

Fig. 2 Prophylaxis regimen with two or less infusions per week before/after the switch to rVIII-SingleChain. EHL, extended half-life; SHL, standard half-life.

Population Pharmacokinetic Profile of rVIII-SingleChain

Population PK data were collected from 39 patients, including 28 adult/adolescent and 6 pediatric patients; patient characteristics are summarized in ►**Supplementary Table S1** (available in the online version). Five patients were excluded from analysis due to FVIII activity lower than the 1 IU/dL threshold or FVIII activity values were considered as an outlier. Of the 34 patients included in the PK analysis, 23 were included in the prophylaxis comparison group, 5 were previously enrolled in the AFFINITY clinical trial program, 6 were previously treated on-demand (5 of whom switched to prophylaxis with rVIII-SingleChain for this study and 1 remained on on-demand treatment) (►**Fig. 1**).

Population PK analysis was performed in 34 patients with a median (range) age of 31 (3–69) years. A total of 76 FVIII levels (19 chromogenic and 57 chronometric) were performed at a median [range] time from rVIII-SingleChain initiation of 21 [0–223] weeks, with a mean of 1.8 samples per patient (minimum 1, maximum 5).

After visual inspection of the goodness-of-fit and individual parameter distribution, a new estimation of population parameter was made based on prior information provided by the model of Zhang et al (►**Supplementary Figs. S1** and **S2** [available in the online version]). The final PK parameter estimation is shown in ►**Table 2**. Briefly, the population clearance of rVIII-SingleChain was estimated to be 1.9 dL/h, which is lower than that estimated by Zhang et al (2.1 dL/h).[23] Consequently, in patients ≥12 years old, the mean ± SD half-life of rVIII-SingleChain was 15.5 ± 5.8 hours. In patients <12 years old, the mean ± SD half-life of rVIII-SingleChain was 11.9 ± 6.4 hours. Overall, 8 patients ≥12 years old had a history of inhibitors, compared with 20 patients who had no history of inhibitors. Patients with a positive inhibitor history had a numerically shorter mean (SD) half-life compared with those without a history of inhibitors; however, this difference was not significant (13.3 [1.9] vs. 16.3 [7.4] hours, $p = 0.50$).

Using the parameters of the final estimated models, simulations were performed to illustrate the effect of new parameters on trough level for patients receiving 20 or 50 IU/kg every 3.5 days. According to the simulated PK profiles, 52.6% and 71.4% of children treated 2 ×/weekly with 20 or 50 IU/kg of rVIII-SingleChain, respectively, would maintain FVIII trough levels higher than 1 IU/dL (►**Fig. 4A**). In adults, the simulation shows a 2 ×/weekly prophylaxis regimen with 20 or 50 IU/kg of rVIII-SingleChain would allow patients to maintain a FVIII trough level higher than 1 IU/dL, respectively in 70.1% and 82.8% of patients (►**Fig. 4B**).

Discussion

Patients with severe hemophilia A in France who receive prophylaxis with a FVIII concentrate use mainly an EHL product. EHL FVIII products provide similar efficacy to SHL FVIII products, but with lower dose and/or a greater proportion of patients able to infuse 2 ×/week or less while meeting the target trough level of 3 to 5%.[1,26] In the OPERA study, prior to switching to rVIII-SingleChain, 64% of patients were treated 2 ×/week or less. After switching to rVIII-SingleChain, 76% were treated 2 ×/week or less. However, for those who

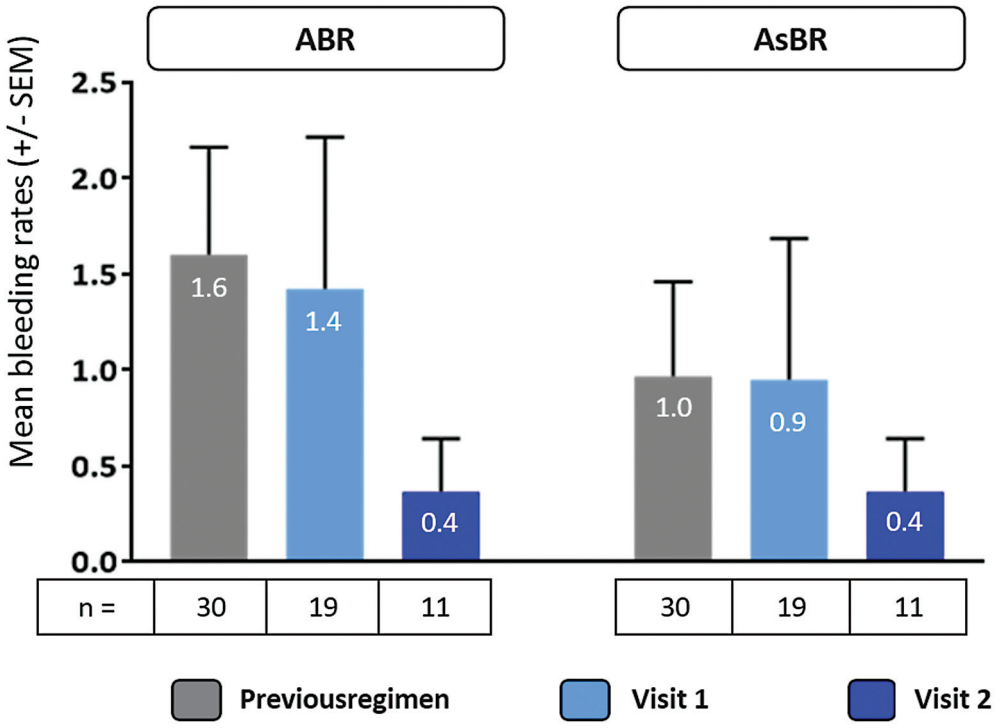

Fig. 3 Comparison of bleeding rates for patients who switched to rVIII-SingleChain prophylaxis from a prophylactic regimen with an SHL FVIII product. Gray bars: prophylaxis with an SHL FVIII; blue bars: first (light blue) and second (dark blue) visits of follow-up during prophylaxis with rVIII-SingleChain. ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; SEM, standard error of the mean; SHL, standard half-life.

Table 2 Population PK model parameter estimates of FVIII activity

Parameter	Point estimate	RSE (%)
CL (dL/h)	1.90	6.2
WT effect on CL	0.64	15.1
V1 (dL)	31.99	5.2
WT effect on V1	0.87	9.7
Q (dL/h)	1.33	0.1
V2 (dL)	2.6	0.2
BASE (IU/dL)	0.76	–
Interindividual variability[a]		
ω2CL	0.0583	–
ω2V1	0.0388	–
ω2BASE	0.344	–
Residual variability[b]		
σ2prop	0.109	–
σ2add (IU/dL)	1.15	–

Abbreviations: BASE, endogenous FVIII activity; CL, clearance; Q, intercompartmental clearance; RSE, relative standard error of the estimate; V1, volume of central compartment; V2, volume of peripheral compartment; WT, body weight; ω2, variance of random effect; σ^2_{prop}, proportional component of the residual error model; σ^2_{add}, additive component of the residual error model.

[a]Values shown represent the variance of the random effect.

[b]Values shown represent either the proportional or the additive components of the residual error model. The reference population weight for the pharmacokinetic parameters for V1 and V2 is 68 kg.

were previously treated more than 2 ×/week, 75% reduced their frequency to 2 ×/week with rVIII-SingleChain while significantly reducing FVIII consumption and increasing the proportion of patients with zero bleeds.

Furthermore, this study demonstrated that rVIII-SingleChain provided excellent bleed control for patients with hemophilia A, which was comparable to the outcomes with EHL FVIII products. After switching to rVIII-SingleChain prophylaxis, some patients also reported a reduced dosing frequency compared to their previous SHL FVIII product; patients who switched to rVIII-SingleChain from a previous EHL product reported comparable dosing frequencies for the two products. These results align with other real-world evidence studies evaluating rVIII-SingleChain, which demonstrated that patients were able to reduce their infusion frequency without increasing factor consumption or compromising clinical results.[18–20,27] Results from a matching-adjusted indirect comparison of clinical trial data for rFVIIIFc and rVIII-SingleChain showed that patients who were on routine prophylaxis with rVIII-SingleChain were able to maintain a similar ABR, percentage of patients with zero bleeds and annualized FVIII consumption compared with rFVIIIFc.[28]

The correlation between FVIII trough levels and bleeding tendency is well established[1,15]; the time spent below a minimum FVIII level of 1 IU/dL correlates with a greater risk of breakthrough bleeds.[15] Population PK studies often estimate the time to 1 IU/dL, and a review of the literature has shown the time to 1 IU/dL after a single dose of 50 IU/kg of

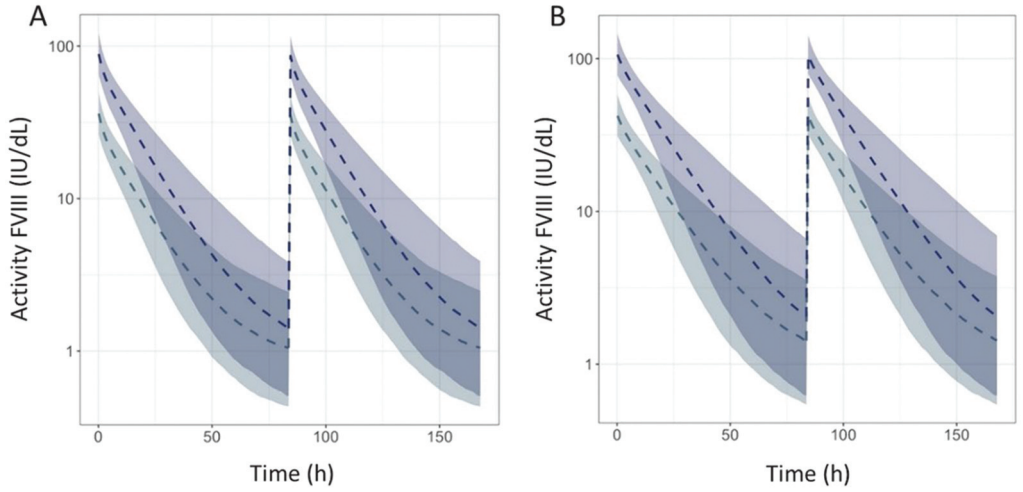

Fig. 4 Predicted steady-state FVIII activity profiles for rVIII-SingleChain at two different dosing schedules: 20 and 50 IU/kg 2 ×/weekly for patients <12 years **(A)** and patients ≥12 years **(B)**. The *y*-axis represents FVIII activity on a logarithmic scale. *Dashed lines*: median-predicted values. *Shaded regions*: 90% prediction intervals. With a prophylactic regimen of 20 IU/kg 2 ×/weekly (gray), the simulation predicts a edian (90% PI) trough level of 1.0 (0.4–2.5) IU/dL in patients <12 years, and 1.4 (0.5–3.7) IU/dL in patients ≥12 years. Using the same prophylactic regimen with 50 IU/kg dosing (purple), the model predicts to reach 1.4 (0.5–3.9) and 2.0 (0.6–6.9) IU/dL respectively, in patients <12 years and ≥12 years. FVIII, factor VIII.

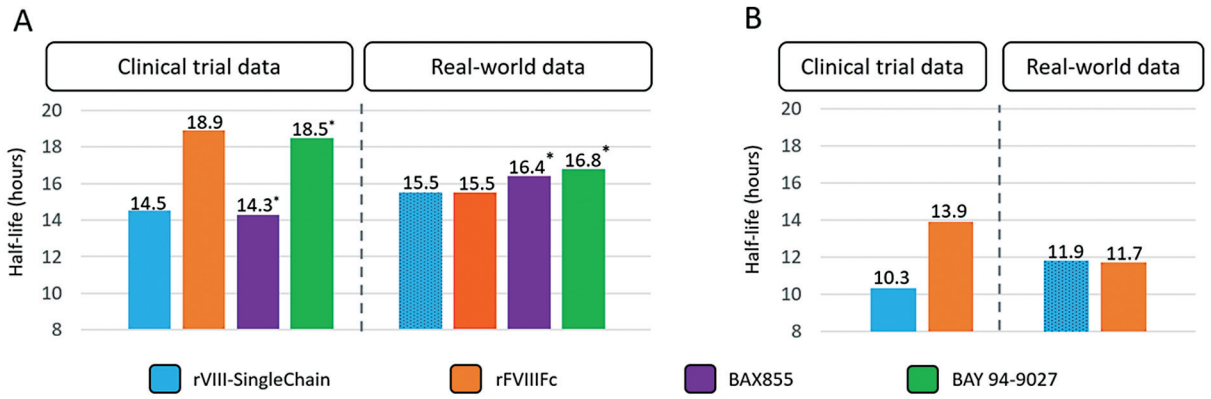

Fig. 5 Comparison of half-life of FVIII products across the clinical trial programs versus real-world evidence studies in **(A)** adolescent/adult patients (≥12 years) and **(B)** pediatric patients (<12 years). For FVIII concentrates with multiple studies, the half-life is represented as mean. *For patients ≥18 years. ►**Fig. 5A** was reproduced from published data. Clinical data: rVIII-SingleChain[34]; rFVIIIFc[6, 42]; BAX855 [43]; BAY 94–9027 [44]. Real-world data: rVIII-SingleChain (OPERA study, dotted blue bar); rFVIIIFc [7, 8, 32]; BAX855 [8, 9]; BAY 94–9027 [9, 31]. ►**Fig. 5B** was reproduced from published data. Clinical data: rVIII-SingleChain [14]; rFVIIIFc [45]). Real-world data: rVIII-SingleChain (OPERA study, dotted blue bar); rFVIIIFc [7].

rVIII-SingleChain is longer than that obtained with SHL FVIII and similar to that obtained with EHL FVIII.[17]

To our knowledge, no phase III studies in hemophilia A have investigated the FVIII steady-state trough levels reached with prophylactic regimens; however, this can be simulated in population PK models. The results from population PK models demonstrate that rVIII-SingleChain can achieve higher trough levels compared to SHL FVIII products[9,25] and rVIII-SingleChain achieves similar trough levels to another EHL product, rFVIIIFc (1.3 vs. 1.2 IU/dL).[23,29] Prophylaxis with rVIII-SingleChain also provides similar clinical efficacy to the EHL FVIII product, rFVIIIFc.[28]

Multiple factors can influence the analysis and interpretation of PK parameters, particularly the half-life. For example, a product's half-life may be wrongly estimated if drug elimination does not occur in a simple, linear fashion, but instead is characterized by slower absorption or multi-compartment distribution.[16,17,30,31] For this reason, the "activity over time" has been defined as the most clinically meaningful PK parameter by the ISTH guidelines.[16] Accurate estimates are of key importance to compare across clinical trial programs and real-world clinical usage, as PK may impact dosing recommendations. Even an increase of 20% of half-life can reduce the dosing frequency from 3 to 2 times per week. Standardization of PK study designs is therefore an important strategy to avoid methodological bias in the future.

Population PK analysis is a powerful approach to estimate PK parameters even when sampling time-points are sparse and can take into account and handle data below the limit of quantification. Population PK analyses have been utilized in

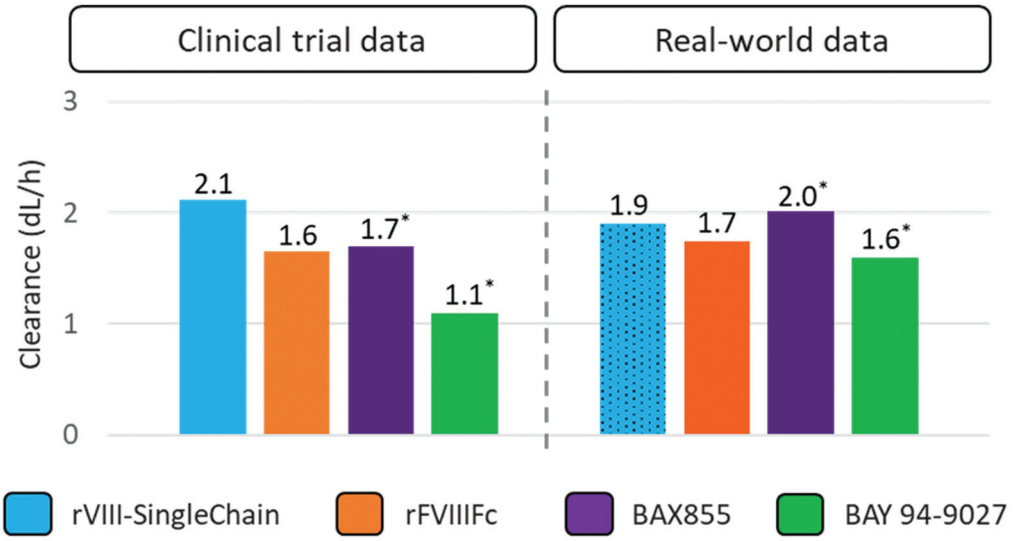

Fig. 6 Comparison of clearance of FVIII products across the clinical trial programs versus real-world evidence studies. Reproduced from published data. Clinical data: rVIII-SingleChain [23]; rFVIIIFc [29]; BAX855 [46]; BAY 94–9027 [9]. Real-world data: rVIII-SingleChain (OPERA study, dotted blue bar); rFVIIIFc [47]; BAX855 and BAY 94–9027 [9]. *For patients ≥18 years.

real-world studies and have demonstrated differences between results based on clinical studies compared with those from real-world evidence, in both adolescent/adult and pediatric patients (►**Fig. 5**). For example, based on real-world data from Bulgaria, Canada, and France, the half-life of the EHL FVIII, rFVIIIFc, in patients ≥12 years old was 15.2, 15.7, and 15.7 hours, respectively[7,8,32]; however, the product label for rFVIIIFc reports a half-life of 19.0–20.9 hours.[33] Similarly, in our study, real-world data from France with rVIII-SingleChain demonstrated a longer half-life than reported in the product label (15.5 vs. 14.2 hours), based on phase I study results.[34] The indirect comparison of real-world data in ►**Fig. 5** highlights that rVIII-SingleChain has a similar half-life compared to EHL FVIII concentrates in adolescent/adult (►**Fig. 5A**) and pediatric patient populations (►**Fig. 5B**).

This real-world study also reports a lower clearance level for rVIII-SingleChain in patients treated with prophylaxis, compared with that reported by Zhang et al.[23] Similarly, there are differences in the clearance levels reported in clinical studies for EHL FVIII concentrates, when indirectly compared to the values reported in real-world evidence (►**Fig. 6**). Furthermore, the clearance rates reported for rVIII-SingleChain in this study and EHL FVIII products in real-world data are similar (1.9 vs. 1.7 dL/h) (►**Fig. 6**).

According to several publications,[22,35–39] real-world evidence shows that rVIII-SingleChain is a full-fledged EHL FVIII.

Randomized clinical trials (RCTs) are recognized as the gold standard for evaluating the efficacy of new products.[40] However, in rare diseases, it has often been impossible to implement RCTs. Therefore, real-world evidence provides really valuable insights.[41] The role of real-world evidence, alongside clinical trials, is key in providing new insights into hemophilia management.[41]

It often happens that in a real-world setting both the characteristics of patients and the way in which products are used can differ from the clinical trial setting.[40] That is what we observed here, mainly when we compared the PK parameters observed in phase I studies to those in real-world evidence. The main explanation is the difference in protocols between phase I studies of EHL FVIII, that can influence results.[17] This point demonstrates the need for standardization of PK analyses in clinical data and reveals the interest in population PK analysis using a Bayesian method.

Conclusions

In summary, the switch to rVIII-SingleChain showed efficient protection against spontaneous bleeds. For most patients previously treated more than 2 ×/week with an SHL FVIII concentrate, treatment with rVIII-SingleChain was associated with a reduction in dosing frequency and of FVIII consumption according to previous studies. In addition, this real-world study from French patients with hemophilia A treated with rVIII-SingleChain prophylaxis demonstrated a lower clearance and a longer half-life than reported in the clinical trial program, comparable to the other EHL FVIII products. This highlights the need for standardization of PK parameters across clinical trial programs and real-world clinical usage to avoid discrepancies between studies.

What is known about this topic?

- rVIII-SingleChain is a recombinant factor VIII (FVIII) for the prevention of bleeding in patients with hemophilia A.
- Data from clinical trials are robust; however, the controlled nature of trial conditions and the limited selection of patients can mean the results cannot be generalizable to the wider patient population.
- Real-world clinical experience data are required to assess the clinical utility of a product in a broader patient population.

What does this paper add?

- Real-world evidence from patients with hemophilia A treated with rVIII-SingleChain in France demonstrated excellent bleed control, and similar pharmacokinetic (PK) parameters compared with extended half-life FVIII products.
- A population PK analysis was conducted in patients treated with rVIII-SingleChain.
- PK results showed a lower clearance level and a longer half-life compared with the clinical trial.

Authors' Contribution

B. Guillet, C. Martin, and H. Catovic designed the study and analyzed data on safety and efficacy. X Delavenne performed the population PK analysis. B. Guillet, A. Hassoun, B. Wibaut, A. Harroche, C. Biron-Andreani, Y. Repesse, R. d'Oiron, B. Tardy, B. Pan Petesch, P. Chamouni, V. Gay, M. Fouassier, C. Pouplard, and X. Delavenne provided and reviewed the patient data. B. Guillet, C. Martin, H. Catovic, and X. Delavenne drafted the initial version of the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

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Conflict of Interest

B.G. has been a consultant for Baxter/Baxalta/Shire/Takeda, CSL Behring, LFB, Novo Nordisk, Octapharma, Roche-Chugaï, and Sobi. Abel H. has been a consultant for Bayer, CSL Behring, and Sobi. B.W. has received consulting fees from SOBI, Roche (fees go to Lille University Hospital or association pour le Développement de la Recherche et de l'Innovation dans le NORD PAS DE CALAIS). Annie H. has been a consultant for CSL Behring, Takeda, Novo Nordisk, LFB, Sobi, and Roche. C.B.-A. has received funding from CSL-Behring, Takeda, Sobi, LFB, and Roche. Y.R. has been a consultant for Baxter/Baxalta/Shire/Takeda, CSL Behring, LFB, Octapharma, Roche-Chugaï, and Sobi. R.d.O. has been a consultant for Bayer, Baxter/Baxalta/Shire/Takeda, Biomarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, and Spark Therapeutics. B.T. has received research funding from CSL Behring, Takeda, Novo Nordisk, LFB, Sobi, Roche, and Octapharma. B.P.P. has been a consultant for Sobi, CSL Behring, Takeda, Biomarin, NovoNordisk, and Roche/Chugai. P.C. has been a consultant for Sobi. V.G. has received honoraria for participation in symposia by NovoNordisk and Sobi. M.F. has been a consultant for CSL Behring, Roche, and SOBI, and has received research funding from SOBI and Novo Nordisk. C.P. has been a consultant for Baxter/Baxalta/Shire/Takeda, CSL Behring, Roche, and Sobi. C.M. and H.C. are employees of CSL Behring. X.D. has received honoraria for participation in symposia by CSL Behring, Shire, Octapharma, and Sobi.

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