

# Recombinant factor VIII Fc for the treatment of haemophilia A

Cedric Hermans<sup>1</sup>  | Maria Elisa Mancuso<sup>2</sup> | Beatrice Nolan<sup>3</sup> | K. John Pasi<sup>4</sup>

<sup>1</sup>Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium

<sup>2</sup>Center for Thrombosis and Hemorrhagic Diseases, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy

<sup>3</sup>Children's Health Ireland at Crumlin, Dublin, Ireland

<sup>4</sup>Royal London Haemophilia Centre, Barts and the London School of Medicine and Dentistry, London, UK

## Correspondence

Cedric Hermans, Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium.  
Email: hermans.cedric@gmail.com

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## Abstract

Prophylaxis with factor VIII (FVIII) is the current therapeutic approach for people with haemophilia A. However, standard half-life (SHL) FVIII products must be injected frequently, imposing a substantial burden on the individual and making it difficult to tailor therapy according to patient need and lifestyle, which could impact adherence. Recombinant FVIII Fc fusion protein (rFVIII Fc; Elocta<sup>®</sup>, Sobi; Eloctate<sup>®</sup>, Sanofi) is a recombinant fusion protein that undergoes slower clearance from the body than SHL FVIII products. This pharmacokinetic property of rFVIII Fc allows prophylactic administration every 3-5 days, or once weekly in selected patients, with doses adjusted to patient needs and clinical outcomes. Higher FVIII levels can be achieved maintaining dosing frequency similar to that usually applied with SHL FVIII. This review provides a summary of recent data from the A-LONG, Kids A-LONG, ASPIRE and PUPs A-LONG studies and recently published real-world experience relevant to rFVIII Fc use in individualised regimens. The review also introduces ongoing studies of rFVIII Fc, including its use for induction of immune tolerance, and discusses some aspects to consider when switching patients to rFVIII Fc and managing ongoing treatment. In summary, rFVIII Fc is suitable for individualised prophylaxis regimens that can be tailored according to patient clinical needs and lifestyle.

## KEYWORDS

factor VIII, factor VIII-Fc fusion protein, haemophilia A, half-life, immune tolerance, prophylaxis, recombinant fusion proteins, rFVIII Fc, surgical haemostasis

## 1 | INTRODUCTION

Routine prophylaxis with factor VIII (FVIII) is the current therapeutic approach for people with severe haemophilia A (PwHA),<sup>1,2</sup> as it reduces the frequency of bleeding episodes, prevents joint damage and improves health-related quality of life (HRQoL).<sup>3,4</sup> However, owing to the half-life of standard half-life (SHL) FVIII, PwHA must inject themselves frequently (on average three times per week) to maintain plasma trough FVIII levels  $\geq 1\%$ . This represents a substantial burden and offers limited options to tailor prophylaxis to an individual patient's needs, which may impact adherence.<sup>5-7</sup> Furthermore,

complete prevention (abolition) of joint bleeding, the key to successful long-term outcomes, is difficult using SHL FVIII products.<sup>6</sup>

Altering the molecular structure of FVIII to modify its pharmacokinetics (PK) can overcome the main drawbacks of SHL FVIII products caused by their short half-life. In particular, the high frequency of injections may impact adherence which in turn impacts FVIII levels, with subsequent increased risk of breakthrough bleeds, especially in patients with more rapid clearance, very active lifestyle and/or pre-existing joint damage.<sup>6,8,9</sup>

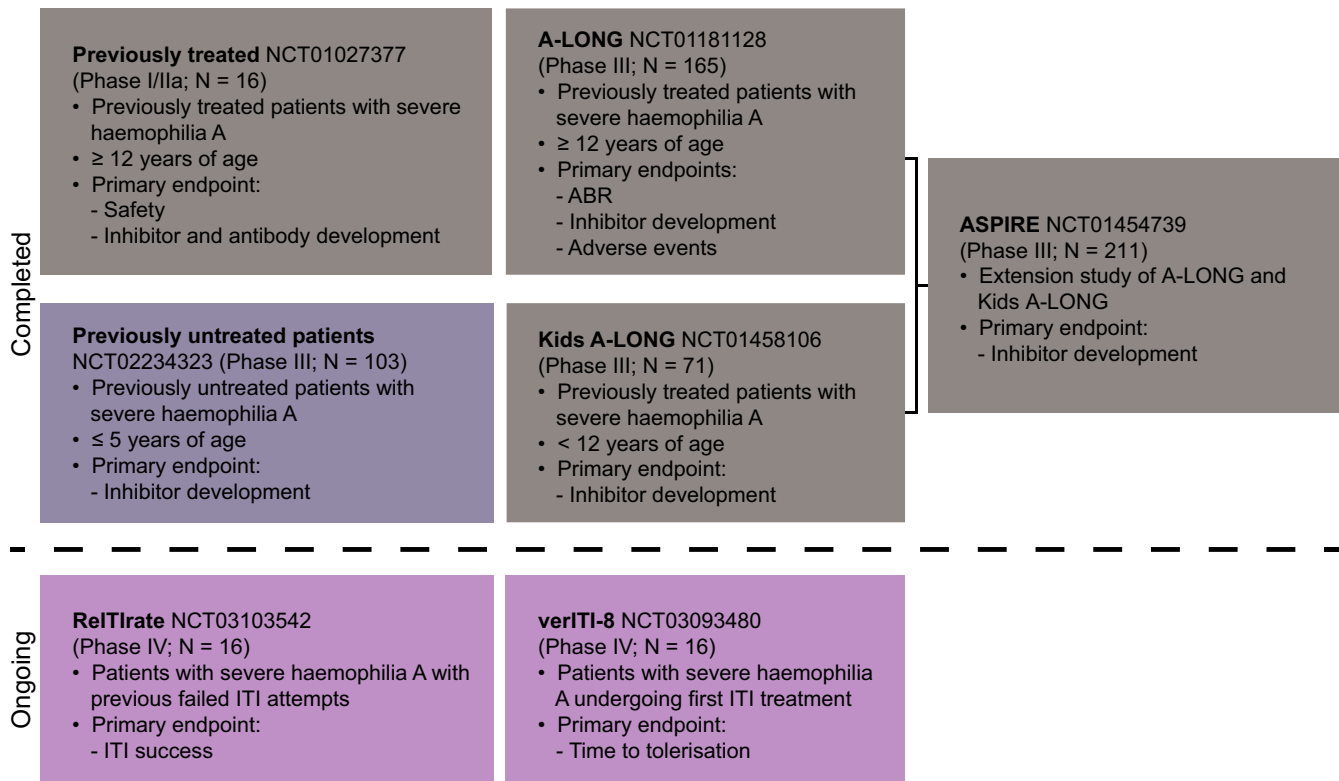
Recombinant FVIII Fc fusion protein (rFVIII Fc; Elocta<sup>®</sup>, Sobi; Eloctate<sup>®</sup>, Sanofi) has an extended half-life relative to native FVIII

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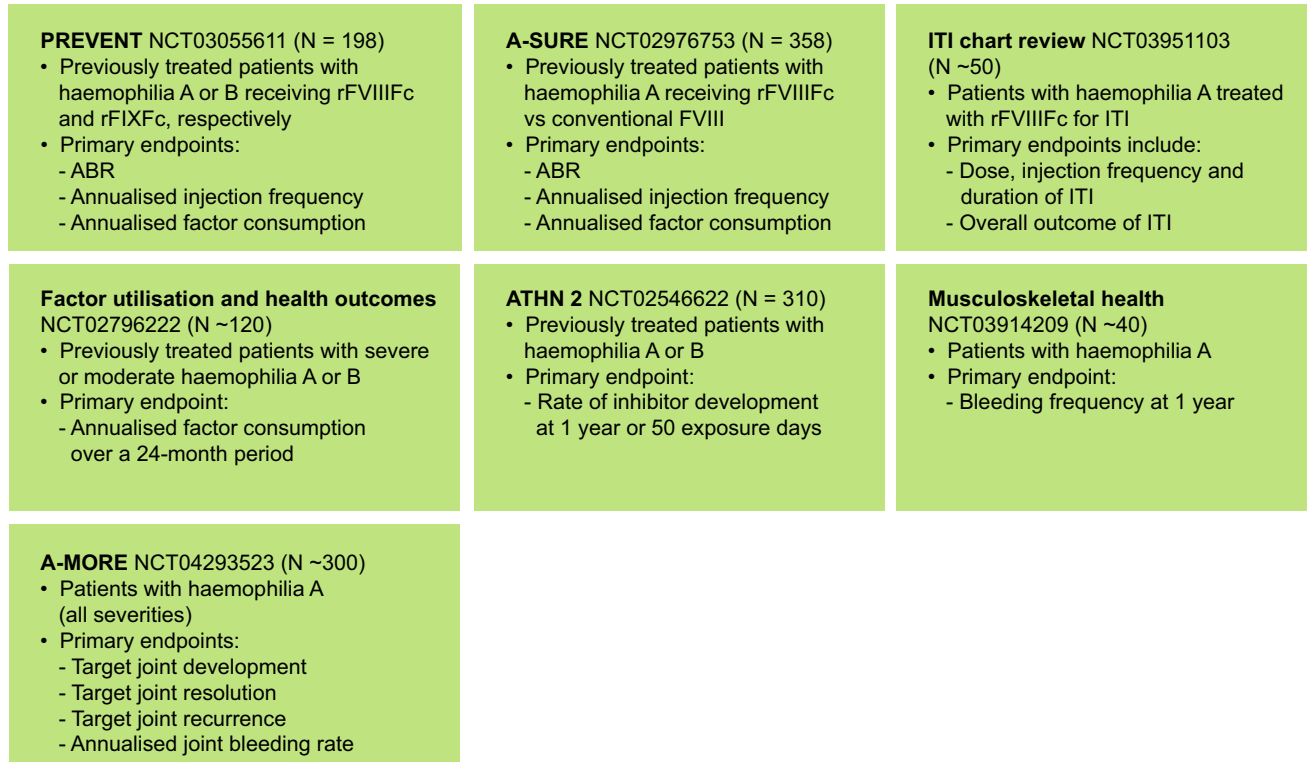
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## Clinical trials



### Ongoing non-interventional real-world Phase IV post-marketing studies



**FIGURE 1** Overview of key interventional clinical trials and prospective, non-interventional, real-world studies. Abbreviations: ABR, annualised bleeding rate; ITI, immune tolerance induction; N, study sample size (according to clinicaltrials.gov); FVIII, factor VIII; rFIX Fc, recombinant factor IX Fc; rFVIII Fc, recombinant factor VIII Fc [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



and is approved for the prophylaxis and treatment of bleeding in PwHA of all age groups.<sup>10</sup> For long-term prophylaxis, the recommended dose of rFVIIIc is 50 IU/kg every 3-5 days, with the dose adjusted in the range of 25-65 IU/kg based on the patient's response and/or needs, although higher dose or frequency may be required in paediatric patients.<sup>10</sup>

This review covers three main topics on rFVIIIc for PwHA: structural and PK properties of rFVIIIc; published and ongoing trials and real-world experience outside clinical trials (Figure 1); and the potential benefits of rFVIIIc therapy and considerations for treatment.

## 2 | PHARMACOLOGICAL PROFILE OF RFVIIIc

### 2.1 | Fusion protein characteristics

rFVIIIc is a recombinant fusion protein comprising a single molecule of B-domain-deleted rFVIII covalently fused to the Fc domain of human immunoglobulin (Ig) G1 without a linker sequence (Figure 2).<sup>7,8,11</sup> rFVIIIc, as a single protein, is produced in a human cell line (human embryonic kidney cells, HEK293) using recombinant DNA technology.<sup>7,12</sup> rFVIIIc manufacture does not use any animal-derived components and involves multistep purification with a novel affinity chromatography adsorbent and 15 nm pore size virus removal nanofilter.<sup>12</sup> The Fc portion of rFVIIIc binds to the endogenous neonatal Fc receptor and uses the naturally (physiologically) occurring IgG recycling pathway, delaying lysosomal degradation of Fc-containing proteins by recycling them back into the circulation, thereby resulting in an improved PK profile and extended terminal half-life.<sup>7,12</sup>

The FVIII component of rFVIIIc is structurally and functionally comparable to native FVIII, allowing rFVIIIc to bind to von Willebrand factor (VWF) and phospholipids.<sup>11</sup> B-domain-deleted

FVIII contains six glycosylated sites, of which four are conserved in rFVIII products and rFVIIIc.<sup>13</sup>

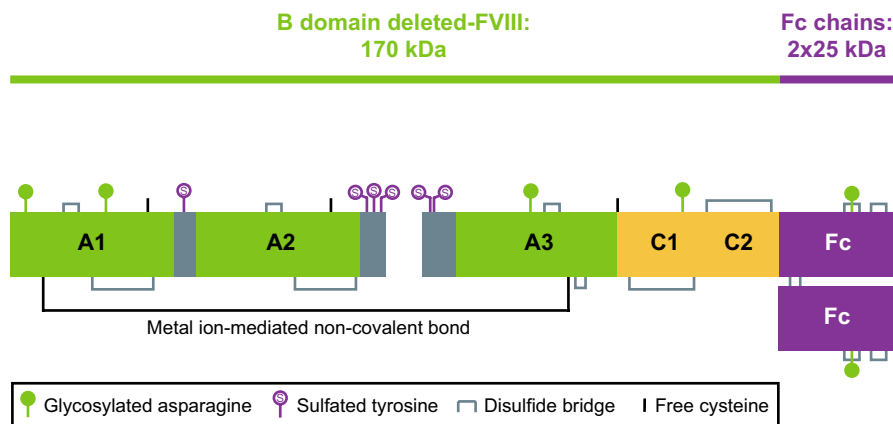
Several other Fc fusion proteins have been developed using a similar strategy and are approved for the treatment of several chronic diseases.<sup>14</sup> In contrast to other modified FVIII molecules such as certain PEGylated FVIII molecules, the rFVIII component of rFVIIIc is fused with the endogenous Fc protein.<sup>7,15</sup>

### 2.2 | Pharmacokinetic properties

One-stage clotting assays or chromogenic substrate assays can be used to assess the PK properties of rFVIIIc.<sup>8,16</sup> A comparative study of 30 laboratories found the two approaches to be similarly accurate, with marginally higher estimates of plasma rFVIIIc levels using the chromogenic assay and neither assay requiring a product-specific rFVIIIc laboratory standard.<sup>17</sup>

PK studies show that rFVIIIc has reduced clearance compared with rFVIII, but similar incremental recovery and volume of distribution.<sup>8,16</sup> Consequently, the terminal half-life of rFVIIIc is, on average, 1.5 times longer than that of an SHL rFVIII product (19.0 vs 12.4 hours for Advate<sup>®</sup>, Takeda;  $P < .001$ ).<sup>16</sup> The dose-normalised area under the concentration-time curve was 51.2 (95% confidence interval [CI] 45.0, 58.4) and 32.9 (95% CI 29.3, 36.9) IU·h/dL per IU/kg for rFVIIIc and Advate, respectively ( $P < .001$ ).<sup>16</sup> VWF plays a role in extending FVIII survival by protecting it from proteolytic degradation and preventing its binding to FVIII clearance receptors; however, through formation of the VWF/FVIII complex, it also limits the potential for FVIII half-life extension.<sup>8,16</sup> Indeed, the half-life and clearance of both rFVIIIc and rFVIII are highly correlated with VWF levels in individual patients, with faster clearance and shorter terminal half-life of rFVIII/rFVIIIc in patients with low VWF levels, suggesting that the Fc moiety of rFVIIIc does not alter the role of VWF in protecting FVIII from clearance.<sup>8</sup> Comparative PK analyses have demonstrated the half-life of rFVIIIc to be longer than that of rFVIII in individual patients.<sup>16</sup>

**FIGURE 2** Structural components of rFVIIIc.<sup>12,13</sup> Adapted from McCue J, et al. *Biologicals*. 2015;43:213-219. <https://doi.org/10.1016/j.biologics.2015.05.012> [wileyonlinelibrary.com]. Copyright © 2015 Biogen. Published by Elsevier Ltd.; published under the terms of the Creative Commons CC-BY 4.0 licence available at: <https://creativecommons.org/licenses/by/4.0/>. Abbreviations: FVIII, factor VIII; rFVIIIc, recombinant factor VIII Fc [Colour figure can be viewed at [wileyonlinelibrary.com](https://wileyonlinelibrary.com)]





Consequently, rFVIIIc may be administered less frequently than rFVIII to maintain similar FVIII exposure (area under curve), or administered as frequently as rFVIII to attain and maintain higher FVIII levels.<sup>18</sup> This offers dosing flexibility and allows treatment to be tailored to the individual patient: a standard treatment schedule to maintain higher FVIII levels in more physically active patients or in those with joint damage, and less frequent dosing in patients with venous access problems or difficulty with adherence.<sup>16,18,19</sup>

As for all FVIII products, age also has an impact on the PK of rFVIIIc, because the clearance of all FVIII products is greater in younger patients and VWF levels tend to increase with age.<sup>20-22</sup> The half-life of rFVIIIc is 12.7 hours in patients aged < 6 years and 14.9 hours in patients aged 6 to < 12 years (but still, on average, 1.5-fold longer than for rFVIII).<sup>23</sup> For this reason, shorter dosing intervals or higher doses may be needed in children compared with older patients, as already demonstrated for SHL products.<sup>10,23</sup>

Clinical trial experience and clinical practice have also revealed that patients may be switched from SHL rFVIII products to rFVIIIc without the need for extensive PK analyses.<sup>19</sup> However, PK analysis could be of value to confirm improved PK with rFVIIIc.

### 3 | SAFETY AND EFFICACY IN PREVIOUSLY TREATED PATIENTS

Two Phase III studies have investigated the safety and efficacy of rFVIIIc in previously treated patients: A-LONG (NCT01181128)<sup>16</sup> and Kids A-LONG (NCT01458106).<sup>23</sup> Patients in both studies were eligible for enrolment in the long-term ASPIRE extension study (NCT01454739).<sup>24</sup>

A-LONG<sup>16</sup> was a partially randomised, open-label, multicentre trial of 165 previously treated patients aged  $\geq 12$  years with severe haemophilia A who were being treated prophylactically or on demand. Patients who were previously receiving on-demand therapy were eligible for the study if they had experienced  $\geq 12$  bleeding events in the 12 months prior to the study. The study comprised three treatment arms: individualised prophylaxis, weekly prophylaxis and on-demand treatment. All patients previously on a prophylaxis regimen were enrolled to the individualised prophylaxis arm. Patients who previously received on-demand treatment could choose to be either enrolled to the individualised prophylaxis arm or randomised to either weekly prophylaxis or on-demand treatment. Randomisation was stratified based on individual bleeding episodes in the preceding 12 months. The primary efficacy endpoints were as follows: (i) difference in the per-patient annualised bleeding rate (ABR) between the individualised prophylaxis arm and on-demand arm; and (ii) assessment of FVIII activity based on PK parameters. The primary safety end points were inhibitor development and adverse events (AEs). A surgery subgroup included patients from any arm who required major surgery.

Patients in the individualised prophylaxis arm initially received rFVIIIc twice weekly (25 IU/kg on Day 1 and 50 IU/kg on Day 4), then 25-65 IU/kg every 3-5 days to achieve a target trough FVIII

level of 1-3 IU/dL ( $n = 118$ ). Patients in the weekly prophylaxis arm received once-weekly rFVIIIc 65 IU/kg ( $n = 24$ ). Patients in the on-demand arm received on-demand treatment with rFVIIIc at a dose of 10-50 IU/kg, depending on bleeding severity ( $n = 23$ ). The median (min-max) duration of treatment was 32.1 (9-54), 28.0 (< 1-38) and 28.9 (15-32) weeks in the individualised prophylaxis, weekly prophylaxis and on-demand treatment arms, respectively.

Kids A-LONG<sup>23</sup> was an open-label, multicentre trial involving 71 previously treated patients aged < 12 years with severe haemophilia A and at least 50 exposure days to any recombinant or plasma-derived FVIII product, including cryoprecipitate. The primary end point was the development of inhibitors. Secondary end points included FVIII activity, ABR and location of bleeding. Overall, 69 patients received prophylaxis with twice-weekly rFVIIIc administered at a dose of 25 IU/kg on Day 1 and 50 IU/kg on Day 4. The dose was subsequently adjusted to a maximum of 80 IU/kg with a minimum administration interval of every 2 days based on bleeding patterns and available PK data. The median time on study was 26.3 weeks.

To evaluate the longer-term safety and efficacy of rFVIIIc, patients who completed A-LONG or Kids A-LONG were eligible to enter ASPIRE (NCT01454739), a long-term extension study.<sup>24</sup> This was a non-randomised, open-label extension study that was completed in October 2017. The primary end point was the development of inhibitors. Secondary end points included ABR and rFVIIIc exposure days. A total of 211 patients (150 from A-LONG and 61 from Kids A-LONG) entered ASPIRE. ASPIRE included four treatment arms (patients aged < 12 years could only participate in the individualised and modified prophylaxis treatment arms) based on the treatment received in A-LONG or Kids A-LONG, with most patients continuing the same treatment regimen in ASPIRE:

- On-demand treatment with rFVIIIc dosing based on the type and severity of bleeding episodes.
- Individualised prophylaxis with rFVIIIc 25-65 IU/kg every 3-5 days or twice-weekly rFVIIIc (20-65 IU/kg on Day 1 and 40-65 IU/kg on Day 4), aiming for a trough level of 1-3 IU/dL. In patients aged < 12 years, the dose could be adjusted to a maximum of 80 IU/kg, with a minimum dosing interval of 2 days.
- Weekly prophylaxis with rFVIIIc 65 IU/kg.
- Modified prophylaxis if optimal treatment could not be achieved with individualised or weekly prophylaxis; modified prophylaxis involved further personalised dosing to meet patient needs (eg dosing less frequently, adding "prevention" doses prior to strenuous activity, and targeting a trough FVIII level of > 3 IU/dL).

The modified prophylaxis arm offered the potential for more flexible dosing, taking into consideration the patient's lifestyle and clinical condition.

Although switching treatment regimens was permitted in ASPIRE, most patients continued the same regimen throughout, with the majority remaining on, or switching to, individualised prophylaxis. For subjects from A-LONG, the cumulative duration of



rFVIII Fc treatment (median [range]) from the beginning of A-LONG to the end of ASPIRE was 4.5 (0.7-5.9) years. For Kids A-LONG to the end of ASPIRE, the cumulative duration of rFVIII Fc treatment (median [range]) was 3.5 (0.4-4.4) years.<sup>24</sup>

### 3.1 | Inhibitor development

The development of inhibitors, defined as a Nijmegen-modified Bethesda assay titre of  $\geq 0.6$  BU/mL (confirmed by a second sample within 2-4 weeks), was the primary safety end point in A-LONG and the primary end point in Kids A-LONG and ASPIRE. In these studies of patients with prior prophylactic or on-demand treatment, there were no cases of inhibitor development in A-LONG,<sup>16</sup> Kids A-LONG<sup>23</sup> or ASPIRE.<sup>24</sup>

### 3.2 | Adverse events

rFVIII Fc was generally well tolerated in A-LONG<sup>16</sup> and Kids A-LONG,<sup>23</sup> and during longer-term treatment in ASPIRE.<sup>24</sup> AEs were similar to those expected in the general and paediatric haemophilia populations and were consistent across settings (eg in patients receiving rFVIII Fc prophylaxis, in patients receiving on-demand treatment with rFVIII Fc and in patients undergoing surgery). AEs related to rFVIII Fc occurred in 10 patients in A-LONG,<sup>16</sup> 2 patients in Kids A-LONG and 2 patients in ASPIRE.<sup>23</sup> There were no serious AEs related to rFVIII Fc in these three trials,<sup>16,23,24</sup> These data indicate that rFVIII Fc is well tolerated by children and adults, and that drug-related AEs are rare in patients with  $\geq 100$  exposure days from the start of treatment. Finally, there were no reports of serious allergic

reactions or anaphylaxis to rFVIII Fc, or vascular thrombotic events associated with rFVIII Fc, in any of the studies.<sup>16,23,24</sup>

## 3.3 | Prophylactic dosing regimens

### 3.3.1 | A-LONG and ASPIRE

rFVIII Fc consumption was relatively stable throughout A-LONG and ASPIRE, with no change in median weekly factor consumption from the end of A-LONG to the end of ASPIRE.<sup>24</sup>

Among patients in the individualised prophylaxis arm in A-LONG, the median dosing interval was 3.5 days in the last 3 months of the study, and 99% received rFVIII Fc at least every 3 days.<sup>16</sup> The median (min, max) weekly total dose was 77.9 (54.0, 141.5) IU/kg/week among patients who administered rFVIII Fc every 3-5 days in the individualised prophylaxis arm and 65.6 (59.4, 70.7) IU/kg/week in the weekly prophylaxis arm.<sup>16</sup> Almost all (98.8%) of the patients in the individualised prophylaxis arm who were previously on FVIII prophylaxis decreased their injection frequency compared with their prestudy regimen (Table 1).<sup>19</sup>

From the end of A-LONG to the end of ASPIRE, the dosing interval was maintained in 71%, increased in 21% and shortened in 8% of patients.<sup>24</sup>

### 3.3.2 | Kids A-LONG and ASPIRE

In Kids A-LONG, the median (interquartile range [IQR]) rFVIII Fc dosing interval was 3.5 (3.5-3.5) days and the median (IQR) weekly dose was 88 (80-103) IU/kg.<sup>23</sup> In total, 59 children completed at least 24 weeks on study, and their median (IQR) dosing interval and

**TABLE 1** Dosing frequency of FVIII (prestudy) and rFVIII Fc (last on study) among patients in the individualised prophylactic dosing subgroup in A-LONG (arm 1, n = 80)<sup>19</sup>

FVIII prestudy injection frequency	N	Number of annual injections, prestudy estimate	rFVIII Fc dosing interval, last on study	Number of annual injections, on-study estimate		Approximate change in annual injections (%)
				n (%) <sup>a</sup>		
Twice weekly	9	104	Every 5 d	8 (88.9)	73	-29.8
			Every 3 d <sup>b</sup>	1 (11.1)	122	+17.3
Three times weekly	65	156	Every 3 d	24 (36.9)	122	-21.8
			Twice weekly	22 (33.8)	104	-33.3
			Every 4 d	4 (6.2)	91	-41.7
			Every 5 d	15 (23.1)	73	-53.2
Four times weekly	5	208	Every 3 d	4 (80.0)	122	-41.3
			Twice weekly	1 (20.0)	104	-50.0
Five times weekly	1	260	Every 5 d	1 (100.0)	73	-71.9

Abbreviations: ABR, annualised bleeding rate; FVIII, factor VIII; rFVIII Fc, recombinant factor VIII Fc.

<sup>a</sup>Percentages refer to the proportion of subjects from each prestudy dosing group who converted to the specified on-study regimen.

<sup>b</sup>Examination of prestudy and on-study bleeding rates indicated that the patient was not dosed appropriately prestudy to manage breakthrough bleeds since the prestudy bleeding rate was 42.0, overall on-study ABR was 7.5, and ABR in the last 3 mo on study was 0.0.



weekly dose in the last 3 months were 3.5 (3.5-3.5) days and 93 (80-109) IU/kg, respectively. Although the median dose was slightly higher in children aged < 6 years, the median dosing interval was 3.5 days in all children (< 6 and 6-12 years). Overall, 46 out of 62 patients (74.2%) had a reduced dosing frequency with rFVIIIc compared with their previous FVIII prophylaxis regimen.<sup>23</sup> From the end of Kids A-LONG to the end of ASPIRE, dosing interval was maintained in 89%, increased in 7% and shortened in 5% of patients.<sup>24</sup>

### 3.4 | Efficacy

ABR was the primary efficacy end point in A-LONG (difference in per-patient ABR between the individualised prophylaxis arm and on-demand arm)<sup>16</sup> and a secondary end point in Kids A-LONG.<sup>23</sup> ABR was also assessed over long-term treatment in ASPIRE.<sup>24</sup>

In A-LONG, ABR was significantly reduced by 92% and 76% in patients receiving prophylaxis with rFVIIIc in the individualised prophylaxis and weekly prophylaxis arms, respectively, compared with that in patients receiving on-demand treatment.<sup>16</sup>

Among 72 patients in the individualised prophylaxis arm and 21 patients in the weekly prophylaxis arm who had target joints (defined as major joints with history of  $\geq 3$  bleeding episodes into the same joint in a 6-month period)<sup>25</sup> at entry into A-LONG, the median (IQR) target joint ABR during rFVIIIc prophylaxis was 0.0 (0.0-3.0) and 0.0 (0.0-1.9), respectively.<sup>26</sup>

Overall, spontaneous, traumatic and joint ABRs in A-LONG and ASPIRE are summarised in Table 2 and demonstrate the consistently low ABRs among patients on rFVIIIc prophylaxis, including a median spontaneous joint ABR of zero with individualised prophylaxis both in A-LONG and ASPIRE.

As in adults, the overall ABR was low in patients aged < 12 years who received rFVIIIc prophylaxis in Kids A-LONG, with a median (IQR) of 1.96 (0.0-3.96) for all children, 0.00 (0.0-3.96) in children aged < 6 years and 2.01 (0.0-4.04) in children aged 6 to < 12 years. In both age groups, the median (IQR) spontaneous joint ABR was 0.0 (0.0-0.0).<sup>23</sup> Among children with  $\geq 1$  target joint (also defined as major joints with history of  $\geq 3$  bleeding episodes into the same joint in a 6-month period), the median (IQR) overall ABR was lower on study compared with the prestudy value (0.0 [0.0-5.8] vs 8.0 [4.0-11.0];  $n = 13$ ). In children with no target joints, the median ABR remained constant from the prestudy value to the on-study value ( $n = 56$ ; Figure 3).

During longer-term treatment, ASPIRE showed that ABR in adults and children of all ages remained low, consistent with the initial reports of A-LONG and Kids ALONG.<sup>24</sup>

In A-LONG, 45% of patients in the individualised prophylaxis arm did not experience any bleeding episodes, versus 17% in the weekly prophylaxis arm.<sup>16</sup> In Kids A-LONG, 46% of children did not experience any bleeding episodes during the study.<sup>23</sup>

Most bleeding episodes in A-LONG, Kids A-LONG and ASPIRE were resolved with one or two rFVIIIc injections (Figure 4). In A-LONG, 87% of bleeding episodes involving target joints were resolved with one rFVIIIc injection, and 98% of bleeding episodes involving target joints were resolved with up to two rFVIIIc injections.<sup>26</sup> In ASPIRE, more than 75% of acute bleeding episodes were controlled by one injection of rFVIIIc, and more than 93% of bleeds with two or less injections.<sup>24</sup>

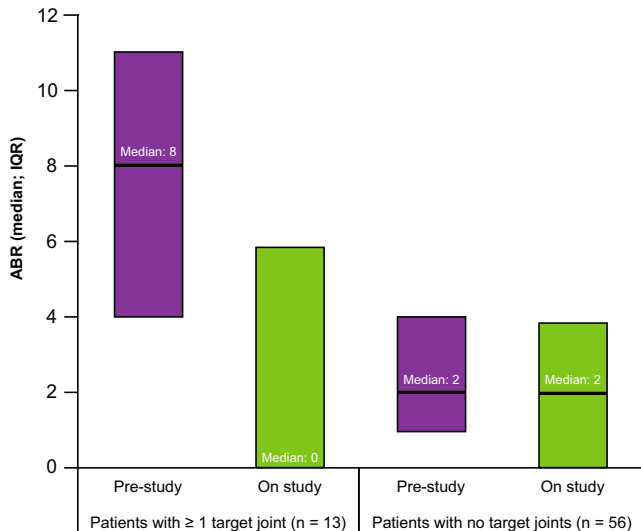
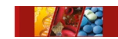
In adults and adolescents in A-LONG, the median dose of rFVIIIc needed to treat a bleeding episode was 27 IU/kg, and among patients who received individualised prophylaxis, weekly prophylaxis and on-demand treatment, the median dose was 33, 30 and 27 IU/kg,

**TABLE 2** ABRs in A-LONG and ASPIRE

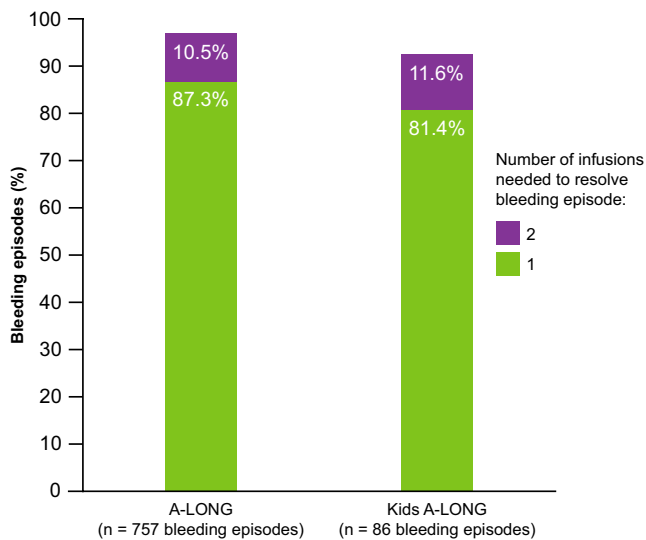
Median (IQR) ABR	Individualised prophylaxis	Weekly prophylaxis	Modified prophylaxis
A-LONG <sup>16</sup>	$n = 117$	$n = 23$	$n/a$
Overall	1.6 (0.0-4.7)	3.6 (1.9-8.4)	$n/a$
Spontaneous	0.0 (0.0-2.0)	1.9 (0.0-4.8)	$n/a$
Traumatic	0.0 (0.0-1.8)	1.7 (0.0-3.3)	$n/a$
Spontaneous joint	0.0 (0.0-1.7)	0.0 (0.0-3.8)	$n/a$
Traumatic joint	0.0 (0.0-1.2)	0.0 (0.0-2.0)	$n/a$
Spontaneous muscle	0.0 (0.0-0.0)	0.0 (0.0-0.0)	$n/a$
Traumatic muscle	0.0 (0.0-0.0)	0.0 (0.0-0.0)	$n/a$
ASPIRE <sup>a 24</sup>	$n = 110$	$n = 27$	$n = 21$
Overall	0.7 (0.0-2.7)	2.2 (0.4-5.1)	4.1 (1.2-8.8)
Spontaneous	0.1 (0.0-1.1)	1.5 (0.0-2.7)	1.4 (0.4-3.9)
Traumatic	0.2 (0.0-1.1)	0.5 (0.2-1.0)	0.9 (0.2-3.0)
Joint	0.5 (0.0-1.7)	1.7 (0.4-3.6)	1.7 (0.6-7.6)
Spontaneous joint	0.0 (0.0-0.7)	1.0 (0.0-2.5)	1.0 (0.0-2.8)

Abbreviations: ABR, annualised bleeding rate;  $n/a$ , not applicable.

<sup>a</sup>ABRs in subjects from the A-LONG parent study.



**FIGURE 3** ABR in children in Kids A-LONG<sup>23</sup> divided according to whether they had at least one target joint or no target joints at baseline. Abbreviations: ABR, annualised bleeding rate; IQR, interquartile range [Colour figure can be viewed at [wileyonlinelibrary.com](#)]

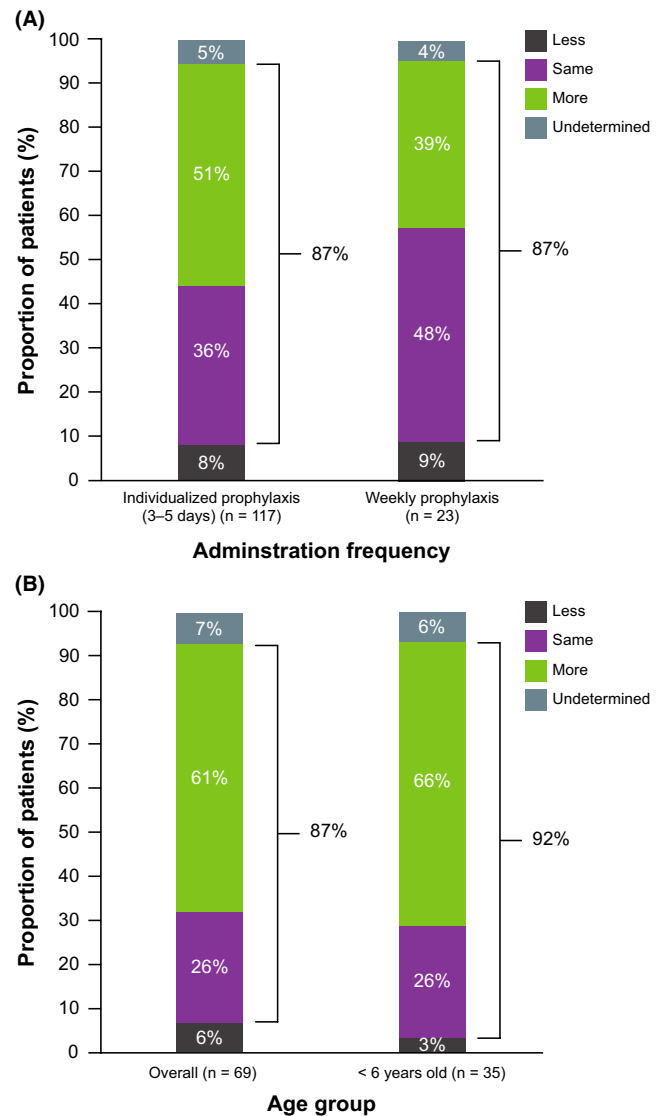


**FIGURE 4** Proportion of bleeding episodes resolved with use of either one or two injections of rFVIII Fc among patients in A-LONG<sup>16</sup> and children in Kids ALONG.<sup>23</sup> Abbreviation: rFVIII Fc, recombinant factor VIII Fc [Colour figure can be viewed at [wileyonlinelibrary.com](#)]

respectively.<sup>26</sup> In Kids A-LONG, a higher median dose of 50 IU/kg was needed per bleeding episode.<sup>23</sup>

### 3.5 | Effects on physical activity and HRQoL

In A-LONG and Kids A-LONG, 87% of patients on prophylaxis reported being able to maintain the same level of activity or increase their activity level during the study compared with their prestudy activity level (Figure 5).<sup>27</sup>

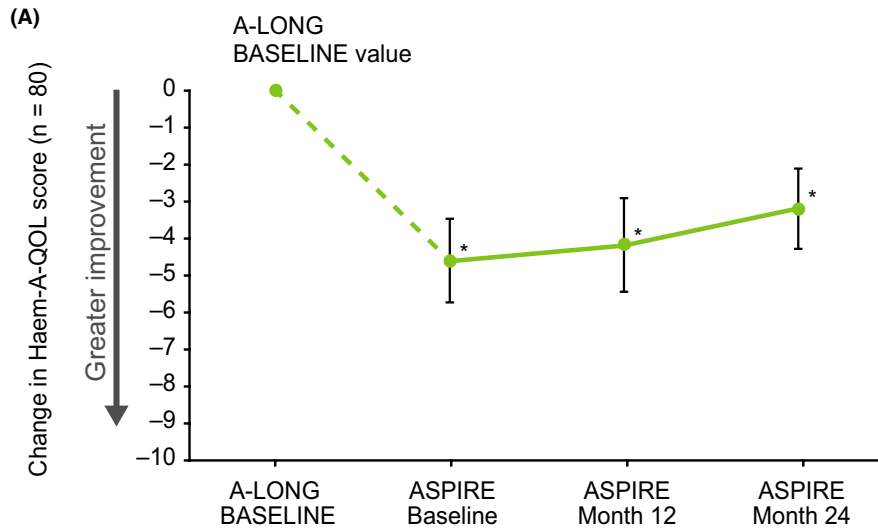


**FIGURE 5** Overall change in physical activity among patients receiving prophylaxis in (A) A-LONG and (B) Kids A-LONG<sup>27</sup> [Colour figure can be viewed at [wileyonlinelibrary.com](#)]

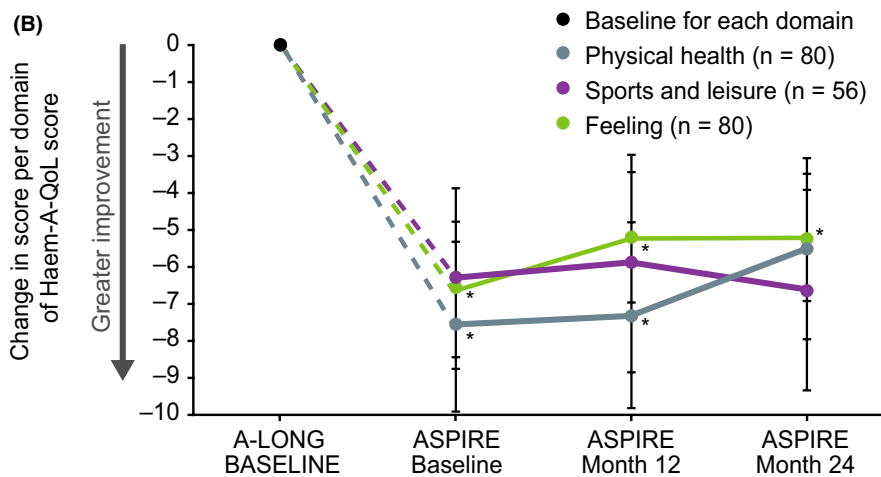
The impact of rFVIII Fc on HRQoL was assessed in 67 patients who completed the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), including 57 on individualised prophylaxis, three on weekly prophylaxis and seven on on-demand treatment.<sup>28</sup> Among patients who received individualised prophylaxis, 24%, 47% and 36% were classified as responders in terms of their improvements in total score, the physical health domain, and the sports and leisure domain, respectively, defined as a 7-point reduction in total score or a 10-point reduction in the physical health and sports and leisure domains. The mean (standard deviation) changes from baseline to Week 28 in the A-LONG study for patients receiving individual prophylaxis were  $-3.2 \pm 9.9$  ( $n = 46$ ;  $P = .034$ ) for total score,  $-7.0 \pm 22.2$  ( $n = 57$ ;  $P = .02$ ) for the physical health domain and  $-4.5 \pm 20.8$  ( $n = 39$ ) for the sports and leisure domain. There were no significant differences in any of these scores (total, physical health, and sports and leisure) for patients who had received weekly prophylaxis or on-demand treatment, although these groups only

included small populations. Evaluation of patients receiving individual prophylaxis by prestudy treatment showed that those receiving prestudy on-demand treatment had larger reductions than those receiving prestudy prophylaxis. In the third interim data analysis of the open-label extension study ASPIRE, HRQoL was evaluated in a population of 80 adult patients from the A-LONG study who enrolled in the ASPIRE study and had total change scores from baseline to

Month 24 in the ASPIRE study. The improvements in HRQoL scores reported in patients in the ALONG study were maintained during longer-term treatment, with the mean total Haem-A-QoL score showing a significant reduction versus A-LONG baseline at all time points (Figure 6A). Similar findings were reported for the individual domains of physical health, sports and leisure, and feeling, with some significant differences being reported (Figure 6).<sup>29</sup>



Domain	A-LONG BASELINE		ASPIRE Baseline		ASPIRE Month 12		ASPIRE Month 24	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Total Haem-A-QoL score	80	29.3 ± 15.7	78	-4.6 ± 9.9*	79	-4.2 ± 11.3*	80	-3.2 ± 9.8*



Domain	A-LONG BASELINE		ASPIRE Baseline		ASPIRE Month 12		ASPIRE Month 24	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Physical health	80	38.8 ± 22.4	79	-7.6 ± 20.3*	80	-7.3 ± 22.4*	80	-5.5 ± 21.8
Sports and leisure	56	51.6 ± 26.7	54	-6.3 ± 17.8	56	-5.9 ± 21.9	56	-6.6 ± 20.1
Feeling	80	21.3 ± 20.3	79	-6.6 ± 16.3*	79	-5.2 ± 15.6*	79	-5.2 ± 15.3*

**FIGURE 6** Mean changes in Haem-A-QoL scores (A and B) from baseline in A-LONG to Mo 24 of ASPIRE.<sup>29</sup> (A) Mean (standard error) change in Haem-A-QoL score in the individualised prophylaxis arm in ASPIRE; (B) Mean (standard error) changes in the physical health, sports and leisure, and feeling domains in the individualised prophylaxis arm in ASPIRE. (A/B): \* $P \leq .01$  compared with A-LONG baseline score. NB. Data presented in graphs are mean (standard error) while data in the supporting tables for (A) and (B) are mean (standard deviation). Abbreviations: Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; n, number of observations at ASPIRE Mo 24 [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]





### 3.6 | Effects on joint health

Spontaneous musculoskeletal bleeding is a common symptom in patients with severe haemophilia, and intra-articular bleeding can result in synovial hypertrophy and haemophilic arthropathy.<sup>30,31</sup> The primary aim of prophylaxis is to prevent joint damage;<sup>31</sup> therefore, it is important to investigate the effects of FVIII prophylaxis on joint health in patients with haemophilia A.

Rates of target joint resolution were assessed in 111 patients in A-LONG and in 13 patients in Kids A-LONG, with evaluable target joints who subsequently enrolled in ASPIRE.<sup>32</sup> During the studies, resolution (defined as  $\leq 2$  spontaneous bleeding episodes in the target joint over 12 consecutive months for all three studies)<sup>25</sup> was achieved in 99.6% of evaluable target joints in A-LONG and 100% of evaluable target joints in Kids A-LONG.

From A-LONG baseline through to ASPIRE Year 2, joint health was also assessed in 47 patients using a modified version of the Haemophilia Joint Health Score (mHJHS).<sup>33</sup> This modified version of the HJHS was developed for adult patients and differs from the original HJHS version 2.1 (primarily designed for children aged 4-18 years) in terms of crepitus of motion (HJHS vs mHJHS: 0-2 vs 0-1), joint pain (0-2 vs 0-1) and global gait (0-4 vs 0-2) scores. Moreover, a score for instability has been added (0-1). Consequently, the total score range is also different (0-124 vs 0-116). Higher scores indicate worse disease. Up to now, this modified version has not been validated.

These post hoc analyses revealed a significant ( $P = .001$ ) improvement from A-LONG baseline to ASPIRE Year 2 among 47 evaluable patients (24 of whom had target joints at baseline) receiving treatment with rFVIIIc. When the data were stratified by previous treatment, the magnitude of improvement in mHJHS was also significant in the group previously receiving on-demand treatment ( $n = 17$ ,  $P = .003$ ), but not in those previously receiving prophylaxis ( $n = 30$ ,  $P = .09$ ).

However, these findings may be limited by the small sample size, short duration of follow-up, inter-observer variability and the fact that the mHJHS has not yet been validated for clinical use.

### 3.7 | Use in peri-operative management

In an analysis of surgeries occurring in subjects enrolled in A-LONG, Kids A-LONG and ASPIRE, 46 major surgeries were performed in 32 patients and in 90 minor surgeries in 70 patients. A total of 44 major surgeries had information on rFVIIIc administration on the day of surgery (33 orthopaedic and 11 non-orthopaedic).<sup>34</sup>

Most major surgeries (87%) required  $\leq 1$  injection of rFVIIIc (including loading dose) to maintain haemostasis during surgery (loading dose was defined as the first dose used on the day of surgery, or the dose used 1 day prior if there was no dose on the day of surgery). The haemostatic responses were rated as excellent or good in all the 42 evaluable major surgeries (excellent:  $n = 39$ , ie haemostasis comparable to what could be expected for individuals

without haemophilia; good:  $n = 3$ , ie prolonged time to haemostasis with somewhat increased bleeding compared with individuals without haemophilia).<sup>34</sup> For major surgery, median (range) rFVIIIc total dose on the day of surgery to maintain haemostasis was 81 (39-158) IU/kg in patients from A-LONG and 38-66 IU/kg in two patients from Kids A-LONG; on the day of minor surgery in patients from A-LONG and Kids A-LONG, median (range) total consumption was 52 (25-112) and 88 (53-216) IU/kg, respectively. Continuous infusion was not permitted.

Eighty-nine percent of minor surgeries required  $\leq 1$  injection of rFVIIIc (including loading dose) to maintain haemostasis during surgery. The haemostatic response was rated as excellent (85%) or good in all evaluable minor surgeries (excellent:  $n = 55$ ; good:  $n = 10$ , as previously defined).

## 4 | RFVIIIc IN CLINICAL PRACTICE

There is growing clinical experience supporting the efficacy and safety of rFVIIIc in patients with haemophilia A. Numerous observational studies and case series have now been published, which consistently show a reduced frequency of dosing or a reduction in FVIII consumption, with the same or decreased bleeding following a switch to rFVIIIc.<sup>35-45</sup> Switching to rFVIIIc was generally well tolerated. Notably, in line with clinical trial data, in publications that reported inhibitor outcomes, no previously treated patients without previous inhibitors developed inhibitors to rFVIIIc.<sup>35-40,46-48</sup> In addition, emerging data on the use of rFVIIIc in patients previously tolerised on another FVIII product showed no recurrence of inhibitor after switch to rFVIIIc.<sup>49</sup> Although no major concerns exist for patients who switched from other FVIII products, lifelong surveillance for inhibitor development is recommended in all previously tolerised patients irrespective of factor concentrate used.<sup>50</sup>

Finally, some observational studies and case reports have investigated the outcomes of using rFVIIIc in patients with haemophilia A undergoing major surgery.<sup>51-57</sup> The authors reported that rFVIIIc provided effective haemostasis in major surgery without significant bleeding; data are summarised in Table 3.

### 4.1 | Ongoing studies in real-world clinical practice

To provide further insight into the safety and efficacy of rFVIIIc in clinical practice, several non-interventional, observational studies have been started in Europe, North America and Japan, as detailed in Table 4.

## 5 | PREVIOUSLY UNTREATED PATIENTS

The A-LONG,<sup>16</sup> Kids A-LONG<sup>23</sup> and ASPIRE<sup>24</sup> studies enrolled patients with previously treated haemophilia A who switched from

TABLE 3 Outcomes with rFVIII-Fc in patients with haemophilia A undergoing major surgery from observational studies and case reports from clinical practice

First author	Study type	Patient(s)	FVIII levels/dosing	Outcomes
Heilal M <sup>53</sup>	Case study	64-y-old with severe haemophilia A undergoing ankle fusion surgery	6000 IU (64 IU/kg) rFVIII-Fc 1 h presurgery Peak FVIII level postinjection: 129 IU/dL FVIII level 6 h post-treatment: 112 IU/dL	No breakthrough/postoperative bleeding was reported
Abraham A <sup>51</sup>	Observational cohort	21 patients with haemophilia A undergoing major surgery (16 orthopaedic surgeries)	Median (range) total rFVIII-Fc used: 151 (123-563) IU/kg (once daily); 388.5 (182-707) IU/kg (twice daily)	9 patients required 1 transfusion of packed red cells each, in accordance with expected blood loss in those surgeries No other blood product transfusion was required
Apte S <sup>52</sup>	Observational cohort	24 patients with severe haemophilia A undergoing total knee replacement surgery	Presurgery: 50 IU/kg Postsurgery: 40-50 IU/kg once daily until D 5, then 30 IU/kg once daily until D 15	23 patients had no significant intra- or postoperative bleeding, and no transfusion support was needed 1 patient also undergoing pseudo-tumour excision required an extra 50 IU/kg rFVIII-Fc and 8 transfusions of packed red cells and 10 of cryoprecipitate for a total blood loss of 2200 mL, as expected; he experienced no postoperative bleeding before discharge
Kremer H <sup>54</sup>	Case study	3-y-old patient with severe haemophilia A undergoing central venous catheter replacement	60 IU/kg bolus presurgery and continuous infusion of 4 IU/kg/h To maintain FVIII levels 80-100 IU/dL on D 1 and 2 postsurgery and 50-80 IU/dL on D 3-5: total dose of rFVIII-Fc used during surgery period was 472 IU/kg (over 7 d; average of 67 IU/kg/d)	No haemorrhage or complications occurred during continuous infusion <sup>a</sup>
Lienhart A <sup>55</sup>	Observational cohort	13 patients with haemophilia A undergoing surgery (8 major, 5 minor)	Average total FVIII-Fc consumption on the day of surgery was 84.5 IU/kg for major surgeries and 44.5 IU/kg for minor surgeries; in the postoperative wk, it was 44 IU/kg/d for major surgeries and 17 IU/kg/d for minor surgeries	Blood loss was as expected for these surgeries
Okamoto A <sup>56</sup>	Case study	28-y-old patient with haemophilia A undergoing cranial surgery	4000 IU (50 IU/kg) rFVIII-Fc 1 h presurgery (D 0); then 45 IU/kg on D 1, 30 IU/kg on D 2, 25 IU/kg/d on D 3-7 and 15 IU/kg/d on D 8-12	150 mL blood loss, as expected for this surgery; two occurrences of mild nasal bleeding; patient was discharged on schedule
Fujii T <sup>57</sup>	Case studies	2 patients with severe haemophilia A each with 2 surgeries, 1 managed with SHL-FVIII and 1 with rFVIII-Fc. Patient 1 had 2 orthopaedic surgeries (knee and hip arthroplasty); patient 2 had hepatectomies	Patient 1: Total factor consumption during perioperative period was 600 IU/kg for SHL-FVIII and 242 IU/kg for rFVIII-Fc Patient 2: 780.7 IU/kg for SHL-FVIII and 487.7 IU/kg for rFVIII-Fc	There was less total blood loss with rFVIII-Fc than with SHL-FVIII for patient 2

Abbreviations: FVIII, factor VIII; FVIII-Fc, factor VIII Fc; h, hour; rFVIII-Fc, recombinant factor VIII Fc; SHL-FVIII, standard half-life factor VIII.

<sup>a</sup>Dosing guidance for continuous infusion is not included within the label.



TABLE 4 Ongoing real-world studies of rFVIII Fc

Study name (ClinicalTrials.gov identifier)	Design	Patient population	Location	Therapy	Primary objective	Status
PREVENT (NCT03055611)	Prospective, non-interventional, multicentre, 24-mo study	198 previously treated patients with haemophilia A or B	Germany	Prophylaxis with rFVIII Fc or rFIX Fc	To describe the real-world usage and effectiveness of rFVIII Fc and rFIX Fc treatment over a 24-mo period	Active, not recruiting
A-SURE <sup>58</sup> (NCT02976753)	Prospective, non-interventional, Phase IV, 24-mo study	358 previously treated patients with haemophilia A receiving FVIII prophylaxis	Europe	Patients prescribed prophylaxis with rFVIII Fc matched with patients receiving SHL FVIII products	To compare the effectiveness of prophylaxis with rFVIII Fc vs SHL FVIII products in patients with haemophilia A over a 24-mo period	Active, not recruiting
Factor utilisation and health outcomes study (NCT02796222)	Prospective, non-interventional, 24-mo study	~120 patients with haemophilia A or B switching from rFVIII or rFIX to rFVIII Fc or rFIX Fc, and patients who remain on rFVIII or rFIX	Canada	On-demand treatment/prophylaxis with rFVIII Fc or on-demand treatment/prophylaxis with rFVIII or rFIX	Annualised factor consumption over a 24-mo period	Recruiting, started April 2016
ATHN 2: factor-switching study (NCT02546622)	Prospective and retrospective arms, non-interventional, 12-mo study	310 patients with haemophilia A or B switching to a newly approved coagulation factor replacement product, or who have recently switched factor products	USA	rFVIII or rFIX replacement products for haemophilia	To determine the rate of inhibitor development at 1 y or 50 exposure days (whichever comes first)	Completed, final results not yet reported
Musculoskeletal health study (NCT03914209)	Prospective, non-interventional, 12-mo study	~40 patients with haemophilia A	Spain	Prophylaxis with rFVIII Fc	Bleeding frequency over 12 mo	Not yet recruiting
A-MORE (NCT04293523)	Prospective, non-interventional, 48-mo study	~300 patients with haemophilia A	Europe	Prophylaxis with rFVIII Fc	To evaluate the long-term effectiveness of rFVIII Fc prophylaxis on joint health over a 48-mo period	Recruiting

Abbreviations: FVIII, factor VIII; rFIX, recombinant factor IX; rFIX Fc, recombinant factor IX Fc; rFVIII, recombinant factor VIII; rFVIII Fc, recombinant factor VIII Fc; SHL, standard half-life.

TABLE 5 Ongoing studies of ITI with rFVIII Fc

Study name (ClinicalTrials.gov identifier)	Study design	Patient population	Location	Therapy	Primary objective	Status
verITI-8 (NCT03093480)	Open-label, single-arm, interventional, multicentre, Phase IV study	16 patients with severe haemophilia A undergoing their first ITI treatment	Europe, North America and Japan (10 countries)	rFVIII Fc 200 IU/kg/d during ITI period, then 50 or 100 IU/kg/d during tapering period	To describe the time to tolerisation with ITI performed with rFVIII Fc in patients who have not previously undergone ITI	Active, not recruiting
ReITrate (NCT03103542)	Open-label, single-arm, interventional, multicentre, Phase IV study	16 patients with severe haemophilia A who have had previous failed ITI attempts	Europe and North America (9 countries)	rFVIII Fc 200 IU/kg/d during ITI period, then adjusted according to investigator judgement	To describe the outcome of ITI performed with rFVIII Fc, within a time frame of 60 wk, in patients who have had previous failed attempts at tolerisation (including use of immunosuppressants)	Active, not recruiting
ITI chart review (NCT03951103)	Non-interventional 5-y retrospective and prospective chart review	~50 patients with haemophilia A	Europe and Middle East	ITI with rFVIII Fc (any dose)	Baseline characteristics, treatment and outcomes. Primary outcome measures include: dose, injection frequency and duration of ITI; overall outcome of ITI	Recruiting

Abbreviations: ITI, immune tolerance induction; rFVIII Fc, recombinant factor VIII Fc.

their prior treatment regimen (prophylaxis or on-demand treatment) to rFVIII Fc. Likewise, the publications describing experience and outcomes with rFVIII Fc in clinical practice involved patients switching to rFVIII Fc.

The open-label, multicentre, Phase III PUPs A-LONG study (NCT02234323) evaluated safety, including inhibitor development, and efficacy of rFVIII Fc in 103 male previously untreated patients aged < 6 years with severe haemophilia A. The study demonstrated that rFVIII Fc was well tolerated and effective in this patient population. The total inhibitor incidence was 31.1% (28/90) in patients with  $\geq 10$  exposure days or who had an inhibitor, in line with expected rates for FVIII products, whereas the incidence of high-titre inhibitors ( $\geq 5$  BU/mL), at 15.6%, was lower than previously reported.<sup>59-61</sup> The median (range) time to inhibitor development was 9 (1-53) exposure days. In 89 patients who received a prophylactic regimen, the median (IQR) weekly dose was 101.44 (62.98, 138.68) IU/kg and median interval (IQR) was 3.87 (3.28, 4.74) days. Median ABRs (IQR) in patients treated with episodic and prophylactic regimens were 2.24 (0.00, 5.94) and 1.49 (0.00, 4.40), respectively.<sup>59</sup>

## 6 | TOLERANCE INDUCTION

About one-third of previously untreated patients with severe haemophilia A develop inhibitors to FVIII products, which have a significant impact on treatment and outcomes, including increased mortality.<sup>60,62,63</sup>

Some patients with low inhibitor titres can be managed by administering higher doses of FVIII, but patients with high titres require bypassing agents such as activated prothrombin complex concentrate or recombinant factor VIIa to control or prevent bleeding episodes, or emicizumab to prevent bleeding episodes.<sup>64,65</sup> Eradication of inhibitors remains the preferred treatment strategy for these patients in order to restore haemostatic efficacy of replacement therapy.<sup>65</sup> This is achieved by immune tolerance induction (ITI) therapy, which involves frequent and regular injections of FVIII concentrates over a period of months to years and is effective in about two-thirds of patients with inhibitors.<sup>65</sup>

Several preclinical studies have indicated that rFVIII Fc may have relatively low immunogenicity and may be able to induce tolerance in animal models,<sup>66,67</sup> and it has been proposed that rFVIII Fc could improve immune tolerance in patients with inhibitors.<sup>65,68</sup> In terms of the likely mechanism, it has been speculated that the IgG Fc component of rFVIII Fc drives the immunomodulatory effects of rFVIII Fc because specific T-cell epitopes in the Fc domain activate a subset of regulatory T cells that tip the resulting immune response towards tolerance.<sup>69</sup>

The use of rFVIII Fc in ITI has been examined in case reports<sup>70,71</sup> and small cohort studies.<sup>72,73</sup> For example, in one case study of three children with severe haemophilia A and inhibitors (one of whom had a failed previous ITI attempt), when treated with rFVIII Fc, all three seemed to respond relatively rapidly and at



lower dose frequency compared with SHL rFVIII ITI, and tolerance was achieved in two patients (the third patient had no detectable anti-FVIII antibody after 2.8 months but a FVIII recovery of 57%, below the predetermined 60% threshold for tolerance).<sup>71</sup> In a retrospective chart review, 9 out of 10 patients undergoing first-time ITI with rFVIII Fc (regimens ranging from 50 IU/kg three times per week to 200 IU/kg once daily) were tolerised, and 10 out of 19 rescue ITI patients reached negative titre, of whom 4 were tolerised (although 1 subsequently relapsed).<sup>74</sup> In a report of interim outcomes for 38 paediatric and adult patients with haemophilia A and inhibitors  $\geq 0.6$  BU/mL who underwent ITI with rFVIII Fc in India (regimens ranging from 50 IU/kg three times per week to 200 IU/kg per day), the median (range) duration of inhibitors prior to ITI was 2 (0.1-20) years. Preliminary data show that 17 patients (45%) achieved a negative inhibitor titre after ITI for a median (range) duration of 23 (10-64) weeks,<sup>72</sup> although negative inhibitor titre does not equate to inhibitor eradication.

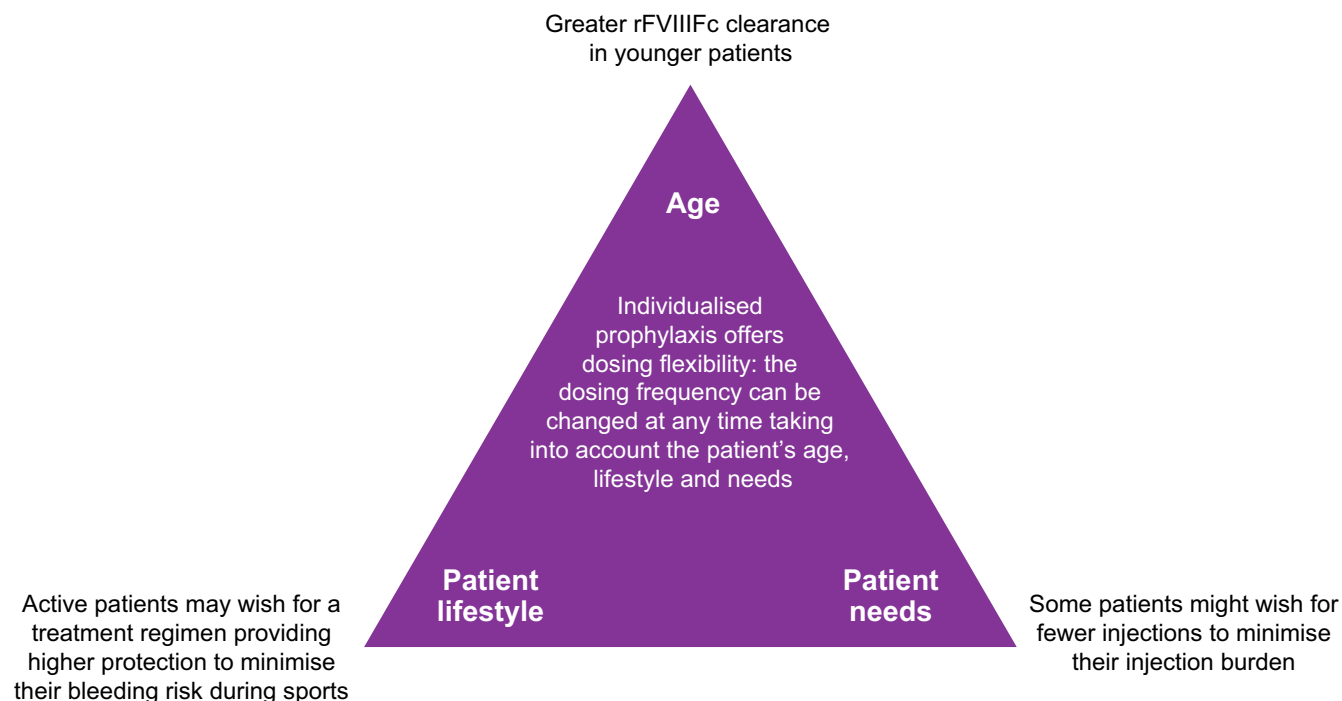
Two prospective, open-label, single-arm, interventional, multi-centre studies are now under way to examine the efficacy of rFVIII Fc in ITI (Table 5). The veriTI-8 study (NCT03093480) is assessing time to tolerisation with rFVIII Fc over a 48-week period in 16 patients undergoing primary ITI treatment.<sup>75</sup> Interim results showed that 6 out of 14 enrolled patients had been successfully tolerised, with a median (range) time to tolerisation of 11.7 (8.1-32.0) weeks. Meanwhile, the RelTIrate study (NCT03103542) will assess the rate of ITI success with rFVIII Fc over a 60-week period in 16 patients undergoing rescue ITI therapy having had at least one previous failed ITI attempt.

## 7 | EXPERT OPINION

### 7.1 | Potential benefits of rFVIII Fc therapy and considerations for treatment

rFVIII Fc proved to be effective and well tolerated in previously treated patients with haemophilia A, providing low ABRs, target joint resolution, improved orthopaedic scores and no new cases of inhibitor development. rFVIII Fc was also associated with improvements in HRQoL. These results highlight several possible benefits for patients switching to rFVIII Fc in terms of individualisation of treatment with increased treatment flexibility and treatment tailoring to individual needs compared with SHL FVIII products. We believe that this is important in clinical practice owing to the phenotypic heterogeneity of haemophilia A and varying individual patient lifestyles. Moreover, treatment individualisation from childhood might allow better haemostatic control to avoid joint bleeding, including subclinical bleeds, and to prevent the development of joint damage in the long term. As illustrated in Figure 7, the dosing of rFVIII Fc can be tailored according to the patient's age and lifestyle, desire for increased protection and fewer injections, and clinical factors such as clinical phenotype.

Individualised prophylaxis may permit treatment intensification depending on the patient's needs. For example, highly active patients may benefit from more frequent prophylactic doses to avoid the risk of bleeding during sports or other activities, whereas patients with venous access limitations may prefer fewer injections to maintain minimal trough rFVIII Fc activity levels.



**FIGURE 7** Triad of clinical factors that influence individualised prophylaxis with rFVIII Fc aiming for zero bleeding events in patients with severe haemophilia A. Abbreviation: rFVIII Fc, recombinant factor VIII Fc [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



The Kids A-LONG study demonstrated that rFVIIIc prophylaxis has the potential to reduce administration frequency compared with SHL rFVIII products. rFVIII prophylaxis in children often necessitates insertion of a central venous access device because of the difficulty of injecting the factor concentrate through peripheral veins. As rFVIIIc can be administered less frequently in prophylaxis, it might be possible to avoid central venous access device insertion. Nevertheless, some highly active children may benefit from more frequent rFVIIIc dosing to minimise their bleeding risk during sports or other activities.

By tailoring the administration of rFVIIIc to the individual patient, it may be possible to achieve a very low rate of, or even no, bleeds in a large proportion of patients with severe haemophilia A.

## 7.2 | Strategies for successfully initiating rFVIIIc in patients with severe haemophilia A

A switch from rFVIII to rFVIIIc may benefit patients differently depending on their needs. PK simulations suggest that switching to rFVIIIc at the same dose and dosing frequency as the previous SHL rFVIII prophylaxis will lead to higher trough levels in most patients. Dosing can thereafter be adjusted based on individual needs. If the goal is fewer injections, a conservative approach could be to prescribe a similar total weekly factor dose, but to administer one injection fewer per week.<sup>18</sup> A patient already well controlled on rFVIII prophylaxis could potentially benefit from reduced injection frequency and decreased rFVIIIc consumption. In a patient who is not optimally covered by prophylaxis with SHL rFVIII, it may be possible to keep the injection frequency and dose the same as for prior rFVIII treatment to benefit from improved bleed control.<sup>18</sup>

Assessment of FVIII levels is universally used to guide dosing, which many clinicians do by testing the trough FVIII level and monitoring the patient's clinical response. In some clinics, however, treaters may want to perform more extensive PK testing at the time of switching to rFVIIIc. Given that full dense-sampling PK studies are burdensome, reduced-sampling protocols using population (Bayesian) PK calculation tools such as the WAPPS-Hemo tool (<https://www.wapps-hemo.org/>) can help to predict the PK of rFVIIIc and make informed dosing decisions, and these have already been used for a large number of patients worldwide. A proportion of patients may be treated once weekly, and post hoc analyses have demonstrated a correlation between VWF levels and prolongation of half-life that might be helpful in the identification of patients who may benefit most from the PK characteristics of rFVIIIc.<sup>19</sup>

## 7.3 | Research gaps

In Ireland, rFVIIIc is available for all patients, including those who are previously untreated.<sup>76</sup> The PUPs A-LONG study is the first to evaluate use of an extended half-life rFVIII product in previously untreated patients, and demonstrated rates of inhibitor development,

including high-titre inhibitors, which were consistent with or lower than rates reported for SHL rFVIII products.<sup>59,60</sup> Further data are required to help haematologists determine the optimal strategy, including timing of initiation, for starting rFVIIIc in previously untreated patients.

Data on long-term outcomes in clinical practice such as rFVIII consumption, joint status and quality of life are also needed. The ongoing A-SURE, PREVENT and A-MORE studies include relevant end points (Table 4).<sup>58,77</sup>

The verITI-8 and RelTtrate studies have been designed to investigate the role of rFVIIIc in ITI therapy in both ITI-naïve and -experienced patients. These studies should provide valuable data on the efficacy of rFVIIIc in ITI therapy.

Following the use of rFVIIIc in developing countries as part of the World Federation of Hemophilia Humanitarian Aid Program,<sup>78</sup> some data have been reported that show reduced frequency of dosing or a reduction in rFVIII consumption, with maintained or decreased bleeding, when switching to rFVIIIc,<sup>36,39,41,51,52,72</sup> and further data are anticipated.

Considering that A-LONG and Kids A-LONG enrolled patients with severe haemophilia A, studies of patients with mild and moderate haemophilia A switching from on-demand use of other rFVIII products to rFVIIIc would also be valuable. In Ireland, there has been clinical experience of this in patients with no issues encountered (Nolan B, unpublished observations). Continued follow-up of these patients, including inhibitor development, will help inform clinical practice.

Research is ongoing to further improve the PK profile of rFVIIIc. In this regard, BIVV001 (rFVIIIc-VWF-XTEN), a novel fusion protein comprising a VWF-D'D3 domain fused to rFVIII via immunoglobulin G1 Fc domains and two XTEN<sup>®</sup> polypeptides, has been designed.<sup>79</sup> It has been shown in animal studies not to bind endogenous VWF and to have a four-fold extended half-life compared with SHL rFVIII. Once-weekly prophylaxis may be possible based on data from a Phase I/IIa study in adults with severe haemophilia A in which the half-life of BIVV001 was 37.6 hours (vs 9.1 hours for rFVIII) among patients receiving a single 25 IU/kg dose, and 42.5 hours (vs 13.2 hours for rFVIII) among those receiving a single 65 IU/kg dose.<sup>80</sup> The average residual FVIII level was 5% at 7 days after BIVV001 injection for the 25 IU/kg dose and 17% for 65 IU/kg, with no inhibitors detected for either dose.

## 8 | CONCLUSIONS

Clinical trials and clinical experience demonstrate that rFVIIIc provides effective prophylaxis for previously treated patients with severe haemophilia A and is generally well tolerated. The safety and efficacy of long-term treatment (up to 5.9 years) with rFVIIIc have been demonstrated in the Phase III ASPIRE extension study. The studies also showed that rFVIIIc can be used to manage bleeding events and to maintain peri-operative haemostasis in patients with haemophilia A. Some data suggest that rFVIIIc prophylaxis might



also confer better joint protection than previous rFVIII treatment, although further data are needed to confirm these observations. rFVIII-Fc allows broader treatment flexibility and treatment individualisation compared with SHL FVIII products. The flexibility provided by rFVIII-Fc extends to the ability to adapt the prophylaxis regimen according to the individual patient's activity, joint status and quality of life, with the potential to intensify or even de-escalate the treatment regimen as appropriate for that patient. In this way, it may be possible to address the phenotypic heterogeneity of haemophilia A. In addition, patients using rFVIII-Fc could require fewer injections than with SHL FVIII products, which may reduce the burden of treatment and potentially improve adherence. In summary, rFVIII-Fc is suitable for use in individualised prophylaxis regimens that can be tailored according to the patient's age, clinical needs, lifestyle and wishes.

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## CONFLICT OF INTEREST

CH has received speaker fees or honoraria for consultancy or advisory boards from Takeda, Pfizer, Bayer, Octapharma, LFB, CAF-DCF, Roche, Novo Nordisk, CSL Behring, Sobi, Biogen and Biomarin. MEM has acted as a paid consultant/advisor/speaker for Bayer Healthcare, CSL Behring, Novo Nordisk, Roche, Sobi, Takeda, Octapharma, Pfizer, Kedrion, Grifols, Biomarin, Catalyst and Bioverativ. BN has received speaker fees from Sobi and led sponsored clinical trials for Sanofi, Sobi, Bioverativ, Biogen, CSL Behring and Bayer. KJP has received speaker fees or honoraria for consultancy or advisory boards from Biotest, Takeda, Pfizer, Octapharma, Biomarin, Catalyst Bio, Roche, Novo Nordisk, Sobi, Apcintex and Sanofi.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## ORCID

Cedric Hermans  <https://orcid.org/0000-0001-5429-8437>

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