Received: 9 January 2023 | Revised: 28 June 2023 | Accepted: 13 July 2023

https://doi.org/10.1016/j.rpth.2023.102180

ORIGINAL ARTICLE

Prophylaxis with a recombinant factor VIII Fc in hemophilia A: long-term follow-up on joint health, efficacy, and safety from phase 3 studies in children and adults

Barbara A. Konkle[1,2] | Johannes Oldenburg[3] | John Pasi[4] | Roshni Kulkarni[5] | Beatrice Nolan[6] | Johnny Mahlangu[7] | Guy Young[8] | Simon A. Brown[9] | Ingrid Pabinger[10] | Amy Shapiro[11] | Claude Négrier[12] | Victor Blanchette[13] | Margaret V. Ragni[14] | Jennifer Dumont[15] | Stefan Lethagen[16,17]

[1]Washington Center for Bleeding Disorders, Seattle, Washington, USA

[2]Division of Hematology, University of Washington, Seattle, Washington, USA

[3]Institute of Experimental Hematology and Transfusion Medicine University Clinic Bonn, Bonn, Germany

[4]Royal London Haemophilia Centre, Barts and the London School of Medicine and Dentistry, London, UK

[5]Department of Pediatrics and Human Development, Michigan State University, East Lansing, Michigan, USA

[6]Children's Health Ireland at Crumlin, Dublin, Ireland

[7]Hemophilia Comprehensive Care Centre, Department of Molecular Medicine and Hematology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa

[8]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, California, USA

[9]Queensland Children's Hospital, Brisbane, QLD, Australia

[10]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[11]Indiana Hemophilia & Thrombosis Center, Indianapolis, Indiana, USA

[12]Division of Hematology, University Claude Bernard Lyon I, Lyon, France

[13]Department of Pediatrics and Child Health Evaluative Sciences, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[14]Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[15]Sanofi, Waltham, Massachusetts, USA

[16]Swedish Orphan Biovitrum AB, Stockholm, Sweden

[17]Copenhagen University, Copenhagen, Denmark

Correspondence
Stefan Lethagen, Swedish Orphan Biovitrum AB, SE-112 76, Stockholm, Sweden.
Email: stefan.lethagen@sobi.com

Handling Editor: Dr Suely Rezende

Abstract

Background: Recurrent joint bleeds are a major cause of morbidity in severe hemophilia. Prophylaxis with efmoroctocog alfa (a recombinant factor VIII Fc fusion protein, [rFVIIIFc]) has demonstrated benefits beyond bleed control, including joint health maintenance.

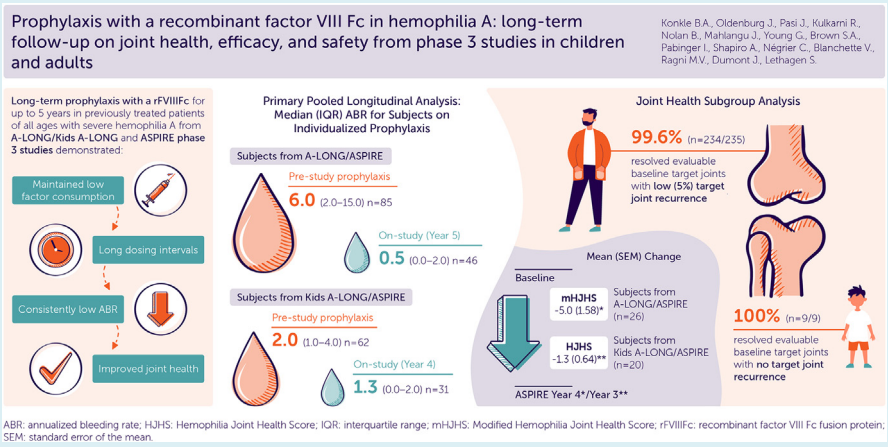
Objectives: To assess long-term efficacy and safety of rFVIIIFc prophylaxis in severe hemophilia A in phase 3 pivotal (A-LONG/Kids A-LONG) and extension (ASPIRE) studies.

Methods: Longitudinal analysis included pooled data from A-LONG/Kids A-LONG and ASPIRE. Subgroup analyses investigated outcomes in modified Hemophilia Joint Health

Score or Hemophilia Joint Health Score and target joints in subjects with 4 to 5 years follow-up on individualized prophylaxis (IP), and those with the highest annualized bleeding rate (ABR) quartile during Year 1 of IP.

Results: Overall, rFVIIIFc consumption remained stable and low ABRs were maintained, with a median treatment duration of 4.2/3.4 years in subjects from A-LONG/Kids A-LONG, respectively. Median overall ABR also remained low (1.0-2.0) in subjects on IP for 4 to 5 years. Sustained improvements in modified Hemophilia Joint Health Score or Hemophilia Joint Health Score were demonstrated over a median follow-up of 3.7 years. In subjects from A-LONG/Kids A-LONG, 99.6% (n = 234)/100% (n = 9) of evaluable baseline target joints were resolved, with no recurrence in 95%/100% of target joints. In IP subjects within the highest ABR quartile in Year 1, continued improvements were observed over a median follow-up of 4.3 years in ABR and joint health, without increased factor consumption. No inhibitors or treatment-related serious adverse events were reported.

Conclusion: Previously treated subjects of all ages receiving long-term prophylaxis with rFVIIIFc had sustained clinical benefits, including improved joint health and low ABR.



KEYWORDS
factor VIII, hemophilia A, joints, recombinant fusion protein, rFVIIIFc

Essentials

- Recombinant factor VIII Fc fusion protein (rFVIIIFc) can improve joint health in hemophilia A.
- Long-term (4-5 years) efficacy and safety of a rFVIIIFc was evaluated using phase 3 trial data.
- rFVIIIFc achieved low annualized bleeds, stable factor consumption, and improved joint health.
- rFVIIIFc (efmoroctocog alfa) prophylaxis demonstrated an acceptable long-term safety profile.

1 | INTRODUCTION

Patients with hemophilia have a tendency to bleed, with bleeding severity inversely correlated with the level of clotting factor [1]. Those with severe hemophilia (<1 International Units (IU)/dL [<1%] endogenous factor activity) are more susceptible to spontaneous bleed events, particularly into the knee, elbow, and ankle joints, compared with patients with moderate or mild hemophilia [1]. Recurrent joint bleeds are a major cause of morbidity in hemophilia and, if inadequately managed, can lead to long-term joint disease, increased pain, and reduced quality of life [2,3].

Prophylaxis with hemostatic agents, such as replacement factor VIII (FVIII), is the current standard of care in hemophilia A, which aims to prevent bleeding and joint destruction and thereby preserve musculoskeletal health [1,3]. It is often difficult to achieve satisfactory joint protection in people with severe hemophilia A treated with

standard half-life (SHL) FVIII prophylaxis, due to the high injection frequency required with these products [4–6].

Extended half-life (EHL) FVIII replacement products may offer a greater potential for treatment personalization compared with SHL therapies, which may help to achieve improved joint protection [5]. Depending on the needs of each individual, EHL products may offer less frequent dosing, increased treatment flexibility, and/or the possibility to maintain higher FVIII levels and, therefore, increased protection against breakthrough bleeds [5–9].

Efmoroctocog alfa (a recombinant factor VIII Fc fusion protein, referred to herein as rFVIIIFc) was the first EHL recombinant FVIII (rFVIII) product to receive Food and Drug Administration and European Medicines Agency approval for use in the USA and Europe [10,11]. Phase 3 pivotal (A-LONG/Kids A-LONG) and extension (ASPIRE) studies have demonstrated the safety, efficacy, and pharmacokinetics of EHL rFVIIIFc in previously treated adults, adolescents, and children [12–14]. The safety and efficacy of rFVIIIFc have also been demonstrated in previously untreated pediatric patients [15]. Moreover, previously published data suggest that patients treated with rFVIIIFc prophylaxis experience additional benefits beyond the immediate prevention of bleeds, including improved joint health [16].

Here, we report pooled longitudinal and secondary analyses of final data from phase 3 pivotal studies (A-LONG/Kids A-LONG) and the ASPIRE extension study. These analyses aimed to evaluate the long-term safety and efficacy of rFVIIIFc prophylaxis with individualized dosing regimens over time in subjects of all ages who had severe hemophilia A, with a focus on long-term joint health outcomes.

2 | METHODS

2.1 | Study design and participants

A *post hoc* analysis of final data from phase 3 pivotal (A-LONG and Kids A-LONG) and extension (ASPIRE) studies in subjects with severe hemophilia A treated with rFVIIIFc was conducted.

Eligible subjects for A-LONG (≥12 years of age) and Kids A-LONG (<12 years) studies were male with severe hemophilia A (<1 IU/dL [<1%] endogenous FVIII activity). Enrolled subjects had ≥150 (A-LONG) or ≥50 (Kids A-LONG) prior exposure days to any FVIII product and no history of a positive test for anti-FVIII antibodies (inhibitors).

At A-LONG entry, subjects received one of 3 rFVIIIFc treatment regimens (Supplementary Table S1). Subjects on a prestudy prophylactic FVIII regimen (≥2 times a week) or prestudy on-demand regimen with FVIII with ≥12 bleeding episodes in the 12 months prior to study start date were enrolled to receive individualized prophylaxis (IP) with rFVIIIFc in A-LONG. For entry into the weekly prophylaxis (WP) and on-demand treatment arms, A-LONG subjects were required to have received on-demand treatment with ≥12 bleeding episodes in the 12 months prior to study start. Subjects continuing into ASPIRE study could switch between eligible treatment regimens at enrollment. All subjects enrolled in Kids A-LONG received IP; IP was given twice weekly and then adjusted as needed. A-LONG/Kids A-LONG subjects who did not achieve optimal prophylaxis on IP or WP during the pivotal studies were enrolled to receive modified prophylaxis during ASPIRE. Full details of study design and treatment regimens have been reported previously [12–14].

Study protocols were approved by institutional review boards and/or ethics committees at participating institutions. Subjects, or their guardians, provided written informed consent prior to participation in the studies; if appropriate, adolescent or pediatric subjects also provided assent. All studies included in this analysis were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice [17] and ethical principles that comply with the Declaration of Helsinki [18], and are registered with ClinicalTrials.gov (ClinicalTrials.gov identifiers: NCT01181128, NCT01458106, NCT01454739).

2.2 | Outcome measures

2.2.1 | Longitudinal analysis

Data from the start of A-LONG/Kids A-LONG to the end of ASPIRE were analyzed and the following outcome measures were reported: annualized prophylactic consumption with rFVIIIFc, dosing interval, treatment compliance (dose compliance defined as administered dose within 80%–125% of the prescribed dose, and interval compliance as injection within ±1 day of the prescribed interval), annualized bleeding rate (ABR; including zero bleed rate, spontaneous, traumatic, and joint bleeds), and bleed resolution (defined as the number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode). Zero bleed rates were reported for A-LONG/Kids A-LONG subjects with ≥24 months of efficacy follow-up. Safety data, including development of FVIII inhibitors and high-level data on adverse events (AEs), were also reported.

For subjects who switched from one regimen to another during ASPIRE, the start date/time on each treatment was used as time zero. Observed ABR and consumption data are summarized by year (Years 1-5) from the start time point for that regimen.

Data from subjects originally enrolled in either A-LONG or Kids A-LONG are analyzed separately.

2.2.2 | Post hoc sub analyses

The long-term safety and efficacy of rFVIIIFc were investigated in all subjects remaining on IP in the pivotal and extension studies for 5 years in A-LONG and 4 years in Kids A-LONG (with at least a 6-month efficacy period for each year). The efficacy period began with the first prophylactic dose of rFVIIIFc and ended with the last dose, excluding surgery and rehabilitation periods. For this analysis, ABR and annualized consumption by year, as well as dosing interval, were assessed.

Joint health analyses included subjects with modified Hemophilia Joint Health Score (mHJHS) (A-LONG subjects) or Hemophilia Joint

Health Score (HJHS) (Kids A-LONG subjects) data at pivotal study baseline and at least one additional major time point during ASPIRE (baseline, Year 1, Year 2, Year 3, and/or Year 4). The following outcomes were assessed: change in mHJHS/HJHS from baseline to last available mHJHS/HJHS score, change from baseline to major time point(s), and for A-LONG subjects, joint score subdomains and number of joints with and without pain. The mHJHS was developed due to the lack of validated joint scoring tools in adults and was based on recommendations from the literature [16,19]. The mHJHS ranged from 0 (normal) to 116 (most severe disease) due to simplification of the response scales in the HJHS (version 2.1; range, 0-124); a scoring comparison between HJHS (version 2.1) and mHJHS has been described previously [16].

An additional analysis evaluated subjects with target joints at baseline, defined as a single major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeds had occurred within a consecutive 6-month period [20]. ABRs were assessed in subjects with a target joint at pivotal study baseline and with an efficacy period (as defined above). Target joint resolution (≤2 spontaneous bleeds in the target joint over a consecutive 12-month period) and target joint recurrence (≥3 spontaneous bleeds in a single joint within a consecutive 6-month period after target joint resolution) were also assessed for evaluable target joints [20]. Evaluable target joints were defined as target joints from subjects who were on prophylaxis and had ≥12-month consecutive follow-up and with no surgical intervention during ≥12 months follow-up. Evaluable resolved target joints were target joints with ≥6 months follow-up post-resolution.

A further analysis was conducted to investigate long-term outcomes in subjects who remained on IP throughout A-LONG and ASPIRE, and had ABRs in the highest quartile of all IP-treated subjects during the first year of treatment in A-LONG (n = 122), which corresponded to an ABR of ≥4. Eligible subjects also had available data beyond Year 1. ABR, annualized consumption, and joint health data are reported.

2.3 | Statistical analysis

Outcome measures were summarized using descriptive statistics; mean, median, and IQR were calculated for continuous variables. Categorical variables are reported using absolute counts and proportions. Change in mHJHS subdomains from baseline to last mHJHS assessment in ASPIRE was analyzed using a paired t-test, which after Bonferroni correction was considered to be statistically significant at $P < .00625$.

3 | RESULTS

3.1 | Pooled longitudinal analysis of subjects in A-LONG/Kids A-LONG/ASPIRE

3.1.1 | Subjects

A total of 165 and 71 previously treated subjects enrolled in A-LONG and Kids A-LONG [12,14]. Of the total enrolled population, 164 subjects in A-LONG and 69 subjects in Kids A-LONG received ≥1 rFVIIIFc dose, respectively. Of these, 150 subjects from A-LONG and 61 subjects from Kids A-LONG enrolled in ASPIRE (Table 1). Moreover, 132 subjects from A-LONG and 54 subjects from Kids A-LONG completed ASPIRE [13].

3.1.2 | rFVIIIFc consumption and exposure

In the pooled analysis of subjects from A-LONG/ASPIRE, median (IQR; range) cumulative number of exposure days during the studies was 309 (213-458; 1-735) days, and duration of treatment was 4.2 (2.8-5.3; 0.0-5.9) years. In the pooled Kids A-LONG/ASPIRE analysis population, median (IQR; range) cumulative number of exposure days and duration of treatment during the studies were 358 (162-440; 5-529) days and 3.4 (1.5-4.2; 0.04-4.4) years, respectively.

Prestudy FVIII prophylaxis consumption data were available for 90 subjects in A-LONG/ASPIRE who had at least a half-year efficacy period. Of these, 80 subjects subsequently received on-study IP, while the remaining 10 subjects received on-study WP. The median (IQR) prestudy annualized prophylactic factor consumption in these subjects was 4,070 (3,131-5,218) IU/kg and 3,574 (3,131-4,696) IU/kg, respectively. Median (IQR) prestudy annualized prophylactic factor consumption for the 54 subjects in Kids A-LONG who received on-study IP was 5,218 (4,070-6,392) IU/kg.

Pooled data for on-study annualized prophylactic factor consumption of rFVIIIFc from Years 1 to 5 (Years 1-4 Kids A-LONG) are shown in Table 2. Factor consumption remained stable throughout the follow-up period for subjects of all ages receiving IP and WP during the pivotal and extension studies. As previously described, median (IQR) weekly prophylactic factor consumption was maintained from 75 (70-91) IU/kg at the end of A-LONG to 75 (70-97) IU/kg at the end of ASPIRE (n = 128). Kids A-LONG subjects (n = 61) in ASPIRE had a higher median (IQR) weekly factor consumption (95 [75-116] IU/kg) than at the end of Kids A-LONG (75 [75-105] IU/kg) [13].

3.1.3 | Dosing intervals and compliance

For the 86 subjects from A-LONG and 62 subjects from Kids A-LONG who received on-study IP and a prestudy FVIII prophylactic regimen, median (IQR) prestudy FVIII dosing intervals were 2.3 (2.3-2.3) and 2.3 (2.0-2.3) days, respectively.

The initial median (IQR) dosing interval for 128 subjects in A-LONG/ASPIRE and 69 subjects in Kids A-LONG/ASPIRE who received on-study IP was 3.5 (3.5-3.5) days. From the start to end of follow-up (defined as the end of follow-up in the pivotal study for subjects who did not enter into ASPIRE or the end of follow-up in ASPIRE), the median change (IQR) in rFVIIIFc dosing interval was 0.0 (0.0-0.5) days for A-LONG subjects and 0.0 (0.0-0.0) for Kids A-LONG subjects. During ASPIRE, the majority of subjects from A-LONG (71%) and Kids A-LONG (89%) receiving prophylaxis maintained the dosing intervals achieved during the parent studies, as reported previously [13].

TABLE 1 Demographic and baseline characteristics of subjects enrolled in A-LONG, KIDS A-LONG, and ASPIRE.

			ASPIRE	
	A-LONG (n = 165[a])	Kids A-LONG (n = 71[b])	From A-LONG (n = 150)	From Kids A-LONG (n = 61)
Age at enrollment in pivotal or extension study (y), median (range)	30 (12-65)	5 (1-11)	31 (13-66)	6 (2-12)
Race, n (%)				
White	107 (64.8)	48 (67.6)	98 (65.3)	42 (68.9)
Black or African American	10 (6.1)	9 (12.7)	8 (5.3)	8 (13.1)
Asian	43 (26.1)	5 (7.0)	39 (26.0)	4 (6.6)
Other	5 (3.0)	9 (12.7)	5 (3.3)	7 (11.5)
Region, n (%)				
Europe	41 (24.8)	32 (45.1)	36 (24.0)	32 (52.5)
North America	56 (33.9)	20 (28.2)	51 (34.0)	11 (18.0)
Other	68 (41.2)	19 (26.8)	63 (42.0)	18 (29.5)
Weight (kg), median (range)	71.6 (42.0-127.4)	21.3 (13.0-59.6)	73.3[e] (44.0-125.4)	23.6 (14.2-65.2)
Prestudy ABR[c], n; median (IQR)				
Prior on-demand regimen	n = 78; 27.0 (18.0-40.0)	n = 8; 12.0 (10.5-15.5)	-	-
Prior prophylactic regimen	n = 86; 6.0 (2.0-15.0)	n = 63; 2.0 (1.0-4.0)	-	-
rFVIIIFc regimen, n[d]				
Individualized prophylaxis	118	71	110	59
Weekly prophylaxis	24	-	27	-
Modified prophylaxis	-	-	21	3
On-demand treatment	23	-	13	-

ABR, annualized bleeding rate; rFVIIIFc, recombinant factor VIII Fc fusion protein.
[a]Of 165 enrolled subjects, 164 were exposed to rFVIIIFc.
[b]Of 71 enrolled subjects, 69 were exposed to rFVIIIFc.
[c]One A-LONG subject had missing prestudy ABR data.
[d]Subjects in ASPIRE were permitted to switch treatment regimens at any time upon enrollment and may appear in ≥1 treatment regimen.
[e]Rounding errors may have occurred for some statistics due to rounding from 2 to 1 decimal place.

Pooled A-LONG/Kids A-LONG and ASPIRE compliance with prophylactic regimens was very high; median (IQR) dose and interval compliance rates were 99.1% (97.9%-99.7%) and 98.0% (95.0%-99.1%) for A-LONG subjects, respectively, and 96.4% (86.1%-99.4%) and 95.9% (91.9%-99.2%) for Kids A-LONG subjects, respectively.

3.1.4 | ABR and control of acute bleed episodes

Prestudy ABR for subjects receiving IP or WP, stratified by prestudy FVIII regimen, are reported in Supplementary Table S2. For subjects from A-LONG who received on-study IP and a prestudy prophylactic regimen (n = 85), median (IQR) prestudy ABR was 6.0 (2.0-15.0); for corresponding subjects who received on-study WP (n = 11), median (IQR) prestudy ABR was 2.0 (0.0-28.0). The median (IQR) prestudy ABR for subjects from Kids A-LONG on prestudy prophylaxis (n = 62) was 2.0 (1.0-4.0).

On-study ABRs were low and remained low in subjects from A-LONG and Kids A-LONG for all categories of bleeds receiving prophylactic rFVIIIFc during Years 1 to 5 and 1 to 4, respectively (Table 3). The median ABR for subjects from A-LONG on IP was 1.2 at Year 1 and 0.5 at Year 5. For Kids A-LONG subjects on IP, median ABR was 1.8 at Year 1 and 1.3 at Year 4. Subjects from both A-LONG and Kids A-LONG who received on-study IP maintained a median spontaneous joint ABR of 0.0 throughout Years 1 to 5 and 1 to 4, respectively.

Overall, 96.3% and 93.3% of bleeds treated during the pivotal and extension studies were resolved by ≤2 injections in subjects from A-LONG and Kids A-LONG, respectively.

3.1.5 | Proportion of subjects with zero bleeds during each 6-month efficacy period

The proportions of A-LONG subjects on IP with zero overall bleeds during each 6-month efficacy period for Months 1 to 6 and Months 55 to 60 were 52% and 67%, respectively. For Kids A-LONG subjects on IP, zero overall bleeds at Months 1 to 6 and Months 43 to 48 were 40% and 43%, respectively (Supplementary Table S3).

TABLE 2 Annualized factor consumption for subjects receiving individualized and weekly prophylaxis during A-LONG, Kids A-LONG and ASPIRE[a,b].

	Year 1	Year 2	Year 3	Year 4	Year 5
Subjects from A-LONG					
Individualized prophylaxis (IU/kg)					
n	122	90	87	59	46
Median	4,137	4,167	4,135	4,122	4,136
IQR	3,833-4,861	3,926-4,926	3,868-4,929	3,915-5,142	3,762-4,746
Weekly prophylaxis (IU/kg)[c]					
n	38	34	28	22	13
Median	3,478	3,413	3,415	3,424	3,411
IQR	3,367-3,600	3,272-3,479	3,089-3,515	3,293-3,474	3,384-3,655
Subjects from Kids A-LONG					
Individualized prophylaxis (IU/kg)					
n	61	52	46	31	
Median	4,945	5,241	5,408	5,052	
IQR	4,320-5,621	4,484[d]-6,015	4,484-6,122	4,389-5,867	-

IU, International Unit; kg, kilogram.
[a]For subjects who switched from one regimen to another during ASPIRE, the start date/time on each treatment time is used as zero, and data are summarized by year from the start time point for that regimen.
[b]Sample sizes for years 1 to 5 comprised subjects with at least a half-year efficacy period in the prophylaxis group at the corresponding year.
[c]Subjects on weekly prophylaxis may come from the modified prophylaxis regimen if subjects were on weekly dosing interval without additional doses or with a limited number of additional doses.
[d]Rounding errors may have occurred for some statistics due to rounding from 2 to one decimal place.

For A-LONG subjects on IP, zero spontaneous bleeds were 65% and 78% for Months 1 to 6 and Months 55 to 60, respectively, while zero joint bleeds were 58% (Months 1-6) and 70% (Months 55 to 60). For Kids A-LONG subjects, zero spontaneous bleeds were 77% and 70% for Months 1 to 6 and Months 43 to 48, respectively and 68% (Months 1-6) and 70% (Months 43-48) for zero joint bleeds (Supplementary Table S3).

3.1.6 | Safety

No subject developed inhibitors during A-LONG, Kids A-LONG, or ASPIRE. rFVIIIFc was generally well tolerated with no reports of serious, life-threatening bleeds, treatment-related serious AEs, or vascular thrombotic events [12–14]. There was 1 report of death due to the serious AE of polysubstance overdose and completed suicide; these serious AEs were assessed by the investigator as unrelated to rFVIIIFc treatment during A-LONG [12].

3.2 | Longitudinal analysis of subjects on IP for 5 (A-LONG) and 4 (Kids A-LONG) years

A total of 45 subjects from A-LONG and 31 subjects from Kids A-LONG remained on IP from the start until Year 5 and Year 4, respectively. Demographics and baseline characteristics of this subgroup (Supplementary Table S4) were largely consistent with all subjects enrolled in A-LONG, Kids A-LONG, and ASPIRE (Table 1).

Consistent with the primary pooled analysis, the annualized consumption of rFVIIIFc also remained stable throughout the study period for this subgroup of subjects (Supplementary Table S5). For A-LONG subjects who remained on IP to year 5, median (IQR) annualized rFVIIIFc consumption was 4,077 IU/kg (3,880-4,770) at Year 1 and 4,127 IU/kg (3,743-4,574) at Year 5. Similarly, for Kids A-LONG subjects who remained on IP to Year 4, median (IQR) annualized rFVIIIFc consumption at Year 1 was 4,921 IU/kg (4,320-5,819) and 5,052 IU/kg (4,389-5,867) at Year 4.

The median (IQR) prestudy FVIII dosing interval for the 20 subjects from A-LONG and 25 subjects from Kids A-LONG who received prestudy prophylaxis was 2.3 (2.3-2.3) and 2.3 (2.0-2.3) days, respectively. For subjects receiving IP from the start until Year 5 or 4, respectively, median (IQR) initial dosing interval with rFVIIIFc was 3.5 (3.5-3.5) days each from the start of A-LONG (n = 45) and Kids A-LONG (n = 31). Dosing intervals were maintained, with no change in median dosing interval from the start of both pivotal studies to the end of ASPIRE.

Median prestudy ABRs in A-LONG subjects on prestudy FVIII prophylaxis and on-demand treatment were 7.0 and 24.0, respectively. In Kids A-LONG subjects, corresponding values were 2.0 and 13.5, respectively. During the studies, the median overall ABR remained low (1.0-2.0) in A-LONG and Kids A-LONG subjects from Years 1 to 5 or Years 1 to 4 and was consistent with the primary

TABLE 3 Median (IQR) annualized bleeding rate for subjects receiving individualized and weekly prophylaxis during A-LONG, Kids A-LONG, and ASPIRE[a,b].

Treatment regimen	Type of ABR	Year 1	Year 2	Year 3	Year 4	Year 5
Subjects from A-LONG						
Individualized prophylaxis	*n*	122	90	87	59	46
	Overall	1.2 (0.0-4.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.0 (0.0-3.0)	0.5 (0.0-2.0)
	Spontaneous	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.4)	0.0 (0.0-1.0)
	Traumatic	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
	Joint	1.0 (0.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-1.2[d])
	Spontaneous joint	0.0 (0.0-1.8)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)
Weekly prophylaxis[c]	*n*	38	34	28	22	13
	Overall	2.0 (1.0-5.0)	2.0 (0.0-4.0)	1.3 (0.0-4.0)	2.1 (1.0-6.0)	1.7 (0.0-5.1)
	Spontaneous	1.0 (0.0-3.0)	0.5 (0.0-2.2)	0.5 (0.0-2.0)	1.0 (0.0-5.0)	1.0 (0.0-3.0)
	Traumatic	1.0 (0.0-1.9)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
	Joint	1.5 (0.0-4.0)	1.0 (0.0-3.0)	1.1 (0.0-3.4)	1.5 (0.0-4.4)	1.7 (0.0-4.1)
	Spontaneous joint	1.0 (0.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-4.4)	0.0 (0.0-3.0)
Subjects from Kids A-LONG						-
Individualized prophylaxis	*n*	61	52	46	31	
	Overall	1.8 (1.0-3.0)	2.0 (0.0-4.1)	1.0 (0.0-3.0)	1.3 (0.0-2.0)	
	Spontaneous	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	
	Traumatic	1.0 (0.0-2.0)	1.0 (0.0-2.5)	0.5 (0.0-2.0)	0.0 (0.0-2.0)	
	Joint	0.0 (0.0-1.8)	0.0 (0.0-3.0)	0.0 (0.0-1.6)	0.0 (0.0-1.2)	
	Spontaneous joint	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	

ABR, annualized bleeding rate.

[a]For subjects who switched from one regimen to another during ASPIRE, the start date/time on each treatment time is used as zero, and data are summarized by year from the start time point for that regimen.

[b]Sample sizes for Years 1 to 5 comprised subjects with at least a half-year efficacy period in the prophylaxis group at the corresponding year.

[c]Subjects on weekly prophylaxis may come from the modified prophylaxis regimen if subjects were on weekly dosing interval without additional doses or with a limited number of additional doses.

[d]Rounding errors may have occurred for some statistics due to rounding from 2 to 1 decimal place.

pooled analysis. Spontaneous, traumatic, joint, and spontaneous joint ABR outcomes were also comparable with the primary pooled population (Supplementary Table S5).

3.3 | Joint health analyses

3.3.1 | mHJHS/HJHS analyses

The mHJHS and HJHS analyses included 78 subjects from A-LONG and 42 subjects from Kids A-LONG who received on-study prophylaxis, respectively (demographic and baseline characteristics in Supplementary Table S6).

Results presented in the Figure show a sustained decrease in mHJHS/HJHS from A-LONG and Kids A-LONG baseline to the final assessment in ASPIRE over a median (range) follow-up of 3.7 (0.8-6.0) and 3.7 (0.8-4.5) years, respectively.

Improvement in mHJHS was observed from A-LONG baseline to major time points of the study period (Figure). For A-LONG subjects (n = 78), the mean (SD; SEM) change in mHJHS from baseline to last available ASPIRE assessment was −3.5 (7.48; 0.85; $P < .0001$). An improvement was observed regardless of prestudy regimen, with a mean (SD; SEM) change from baseline in mHJHS of −1.9 (6.69; 0.91) for the 54 subjects on prestudy prophylaxis and −7.0 (8.08; 1.65) for the 24 subjects on prestudy on-demand treatment.

For A-LONG subjects with an mHJHS evaluation in ASPIRE Year 4 (n = 26), the mean (SD; SEM) change in mHJHS from baseline to ASPIRE Year 4 was −5.0 (8.06; 1.58). An improvement was observed regardless of prestudy regimen, with a mean (SD; SEM) change from baseline in mHJHS of −3.5 (7.93; 2.39) for the 11 subjects on prestudy prophylaxis with available data for ASPIRE Year 4, and −6.0 (8.26; 2.13) for the 15 subjects on prestudy on-demand treatment.

Overall, the change (decrease) in mHJHS from A-LONG to last available major ASPIRE time points, categorized by joint score

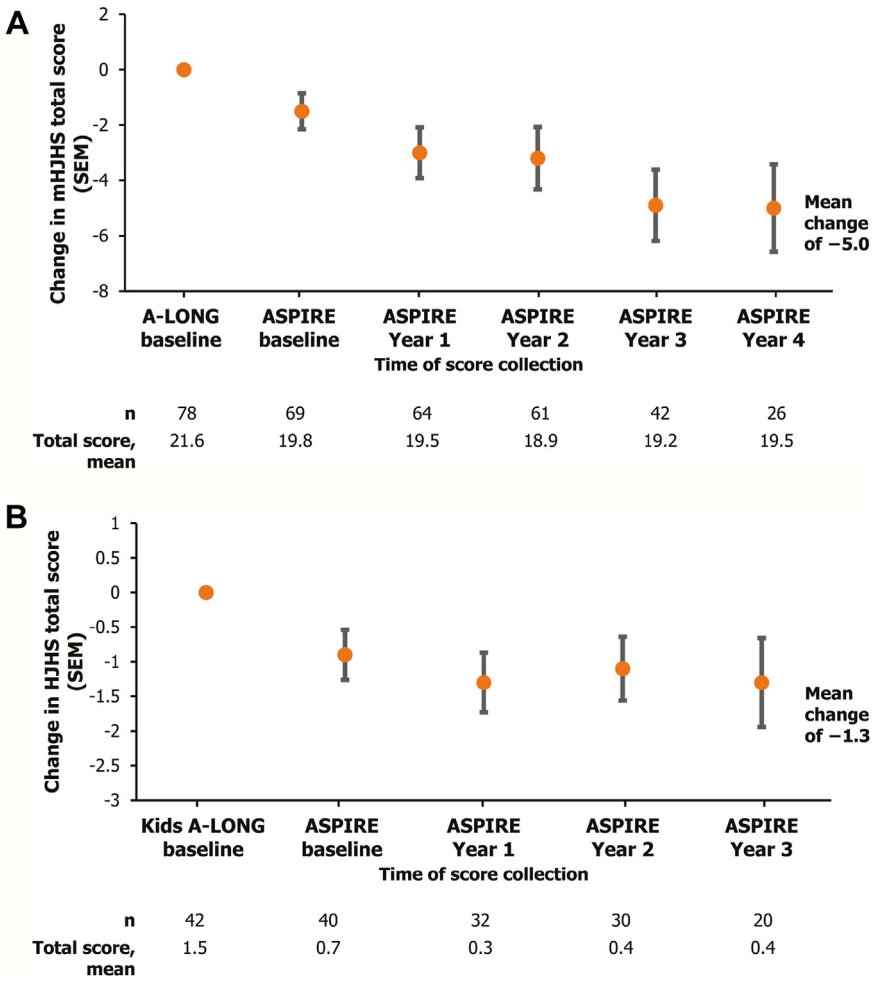


FIGURE Mean (SEM) change in (A) mHJHS total score over time from A-LONG baseline in A-LONG/ASPIRE subjects and (B) HJHS total score over time from Kids A-LONG baseline in Kids A-LONG/ASPIRE subjects. Number of subjects listed were those who were always on prophylaxis and had baseline mHJHS/HJHS from A-LONG/Kids A-LONG and at least one assessment in ASPIRE at a major assessment visit. There were variable follow-up times between A-LONG to ASPIRE baseline (median: 8.3 months) and between Kids A-LONG to ASPIRE baseline (median: 6 months). HJHS, Hemophilia Joint Health Score; mHJHS, modified Hemophilia Joint Health Score.

subdomains, showed statistically significant improvements in swelling for A-LONG subjects (n = 78; −1.45; P < .0001) (Supplementary Table S7). Improvements in swelling were observed regardless of prestudy regimen; however, the decrease in swelling was larger for subjects on prestudy on-demand treatment (−3.04) compared to prestudy prophylaxis (−0.74). Modest improvements, although not statistically significant, were also observed in most other mHJHS subdomains. Limited data also showed that observed improvements in mHJHS increased with age (data not shown).

The initial improvement from baseline in HJHS for Kids A-LONG subjects was maintained throughout the study period (Figure). For Kids A-LONG subjects (n = 42), the mean (SD; SEM) HJHS change from baseline to last ASPIRE assessment was −1.0 (2.50; 0.39; P < .0096). Improvement in HJHS was observed regardless of prestudy regimen. For subjects on prestudy prophylaxis (n = 37), mean (SD; SEM) change in HJHS from Kids A-LONG baseline to ASPIRE last assessment was −0.9 (2.45; 0.4), while for subjects who received prestudy on-demand treatment (n = 5), mean (SD; SEM) change from baseline in HJHS was −1.8 (3.03; 1.36).

For Kids A-LONG subjects with an HJHS evaluation in ASPIRE Year 3 (n = 20), the mean (SD; SEM) HJHS change from baseline to last ASPIRE assessment was −1.3 (2.88; 0.64). Improvement in HJHS was observed regardless of prestudy regimen. For subjects on prestudy prophylaxis with available data for ASPIRE Year 3 (n = 17), mean (SD; SEM) change in HJHS from Kids A-LONG baseline to ASPIRE Year 3 was −1.2 (3.09; 0.75), while for subjects who received prestudy on-demand treatment (n = 3), mean (SD; SEM) change from baseline in HJHS was −1.7 (1.53; 0.88).

Approximately 30% of evaluable subjects experienced a decrease in the number of painful joints from A-LONG baseline to ASPIRE baseline (n = 21/69) or from A-LONG baseline to ASPIRE end of Year 4 (n = 8/26) (Supplementary Table S8).

3.3.2 | Target joint analysis

A total of 111 subjects from A-LONG and 13 subjects from Kids A-LONG had ≥1 target joints at study entry and entered the efficacy period (Supplementary Table S6). For this subgroup, cumulative median (range) duration on rFVIIIFc was 4.3 (0.04-5.85) years and 4.1 (0.4-4.3) years for A-LONG and Kids A-LONG subjects, respectively.

Overall, pooled data demonstrated sustained low target joint spontaneous ABRs in the target joints present at baseline in subjects from A-LONG and Kids A-LONG receiving long-term prophylaxis of rFVIIIFc (Supplementary Table S9). rFVIIIFc prophylaxis resulted in resolution of 99.6% (n = 234/235) of all evaluable baseline target joints in subjects from A-LONG and all (n = 9) evaluable baseline target joints in subjects from Kids A-LONG. Target joint recurrence remained low in the post-resolution period (Table 4); only 5% of evaluable previously resolved target joints in subjects from A-LONG/ASPIRE and no evaluable resolved target joints in pediatric subjects recurred over a median follow-up of 3.7 years.

3.4 | Analysis of subjects within the highest ABR quartile in Year 1

3.4.1 | Subjects

The 23 A-LONG subjects who were enrolled in ASPIRE, remained on IP and were within the highest ABR quartile (which equaled ABR ≥4) during Year 1 were analyzed in a subgroup analysis (Supplementary Table S10). For these subjects, median (range) cumulative duration of treatment during A-LONG and ASPIRE was 4.3 (2.7-5.8) years. Median (range) number of exposure days for this population was 398.0 (197.0-730.0) days, with 405.0 (197.0-741.0) injections.

3.4.2 | Annualized factor consumption and ABR

Median annualized prophylactic consumption was similar during the first year of treatment in A-LONG (n = 23, 4,634 IU/kg), compared to prestudy annualized prophylactic consumption (n = 20, 4,696 IU/kg), and remained stable to the end of ASPIRE (n = 23, 4,666 IU/kg). From first dosing interval in A-LONG to the last dosing interval in ASPIRE, 11 of 23 (47.8%) subjects who remained in the IP arm maintained their twice weekly dosing interval or lengthened their dosing interval to every 4 or 5 days. Twelve subjects reduced their dosing interval slightly, from twice weekly to every 3 days.

Overall ABR (median) decreased at Year 1 of treatment (5.1) compared with prestudy ABR (16.0), and further decreased in the last year of ASPIRE (1.2). Reductions were also observed in the subpopulation of subjects on prestudy prophylaxis (n = 20); the overall ABR (median) was 12.0 prior to A-LONG, 5.6 at Year 1 and 1.1 at the last year of ASPIRE (Supplementary Table S11).

3.4.3 | Joint health

All evaluable pre-existing target joints (n = 55) were resolved from A-LONG baseline to final follow-up. The mHJHS data were only available for 11 subjects at A-LONG baseline. The mean (SD) mHJHS score at baseline for these subjects was 32.9 (20.4), with a mean (SD) improvement of −3.9 (12.1) points (P = .3096) at the last mHJHS assessment.

4 | DISCUSSION

This is an extensive analysis of final data from phase 3 pivotal (A-LONG and Kids A-LONG) and extension (ASPIRE) studies in adult and pediatric subjects who had severe hemophilia A treated with rFVIIIFc for up to 5 years. The longitudinal analysis reported here represents the longest duration of EHL rFVIIIFc follow-up to date, and [21] together with *post hoc* sub analyses, confirms the long-term safety and efficacy of rFVIIIFc prophylaxis for preventing all types of bleeds over time in subjects with severe hemophilia A across all age groups.

The primary pooled longitudinal analysis of subjects from A-LONG and Kids A-LONG demonstrated consistently low ABRs and stable factor consumption with prophylactic rFVIIIFc throughout Years 1 to 5 of treatment. Improvements in ABR over time could be explained by the very high compliance rates and long-term follow-up reported with the prescribed rFVIIIFc prophylactic regimens in this study. Indeed, treatment compliance is paramount to long-term joint health, which may be facilitated by EHL factor replacement products [22–24].

Consistent with the primary pooled analysis, the subgroup that remained on rFVIIIFc IP up to Year 5 (A-LONG) or Year 4 (Kids A-LONG) showed stable on-study median factor consumption and dosing intervals. Median ABR was low and remained low throughout the study period. Interestingly, pharmacokinetic data confirmed a wide variation in baseline half-life within this subgroup. This may have implications for trough factor levels and risk of spontaneous joint bleeds over time among subjects. However, findings from this study indicate variations in rFVIIIFc half-life had minimal or no impact on clinical outcomes described above.

In joint health analyses, sustained improvements in mHJHS/HJHS were demonstrated over a median follow-up of 3.7 years. A-LONG subjects who received prestudy on-demand treatment had a greater change in mHJHS over time compared with those who received prestudy prophylactic treatment. This is an anticipated finding that reflects the difficulty in demonstrating significant changes in joint function over time in a group of subjects on long-term prophylaxis with low ABRs, which requires a large sample size or very long follow-up. The statistically significant improvements in swelling over time observed for the overall population and subpopulation of subjects who received on-demand treatment may be attributed, at least in part, to the improved hemostatic efficacy that rFVIIIFc offers over SHL products in relation to its reduced clearance and thus greater bleed

TABLE 4 Summary of target joint recurrence for evaluable resolved target joints in subjects from A-LONG and Kids A-LONG studies.

Parameter	Total
Subjects from A-LONG	
Resolved target joint with ≥6-mo follow-up post-resolution, *n* (%)[a]	222 (94.9)
Target joint recurrence after resolution, *n* (%)[b]	11 (5.0)
Post-resolution follow-up per target joint (months), median (IQR)	32.5 (22.6-49.7)
Subjects from Kids A-LONG	
Resolved target joint with ≥6 mo follow-up post-resolution, *n* (%)[a]	9 (100)
Target joint recurrence after resolution, *n* (%)[b]	0 (0.0)
Post-resolution follow-up per target joint (mo)	38.7 (37.3-39.0)

[a]Percentage based on number of resolved target joints.
[b]Percentage based on number of resolved target joints evaluable for recurrence. Target joint was defined as a single major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeds had occurred within a consecutive 6-month period. Target joint resolution was ≤2 spontaneous bleeds in the target joint over a consecutive 12-month period. Target joint recurrence was ≥3 spontaneous bleeds in a single joint within a consecutive 6-month period after target joint resolution. Evaluable target joints were target joints with ≥12 months follow-up and no surgical intervention within 12 months since the start of follow-up. Evaluable resolved target joints were target joints with ≥6 months follow-up post-resolution.

protection at similar factor consumption [25]. Although these findings are promising, a question that remains is how to define a clinically important or minimally important difference in HJHS/mHJHS. Such data are often limited in the context of clinical trials, which therefore highlights an important area for future research.

Target joint subgroup analysis showed sustained low target joint ABRs and resolution of almost all target joints present at pivotal study baseline, with 5% and 0% of target joint recurrence of resolved target joints in A-LONG/ASPIRE and Kids A-LONG/ASPIRE subjects, respectively. The development of target joints, which indicates suboptimal protection against joint bleeds, negatively impacts the quality of life in patients with hemophilia A, especially individuals aged ≥45 years [26]. Joint bleeds are understood to be the primary cause of pain experienced in hemophilia and thus prove an important outcome for pain management [27]. The data presented here show that prophylaxis with rFVIIIFc was able to resolve >99% of preexisting target joints in adults (A-LONG), and all target joints in children (Kids A-LONG). Furthermore, over a median follow-up of 3.7 years, target joint recurrence was rare in adults and did not occur in pediatric subjects. As such, rFVIIIFc prophylaxis demonstrated valuable effects that could improve the quality of life for patients with hemophilia, especially pain. Indeed, a *post hoc* analysis of data from A-LONG showed that IP with rFVIIIFc improved pain from baseline to the end of study [27].

The clinical benefits of rFVIIIFc prophylaxis were also observed over time in the subgroup in the highest ABR quartile during Year 1 of rFVIIIFc IP. Continued improvements were observed over a median follow-up of 4.3 years in ABR, target joint resolution, and mHJHS, without increasing factor consumption and injection frequency. Despite most subjects in this population receiving prestudy prophylaxis, substantial improvements in ABRs were observed with rFVIIIFc during Year 1, which were further reduced to levels comparable with the overall study population by the final assessment.

Primary data from A-LONG, Kids A-LONG, and ASPIRE showed that rFVIIIFc prophylaxis was well tolerated in previously treated adults and children, with no reports of subjects developing inhibitors or treatment-related serious AEs [12–14]. This is consistent with data that show rFVIIIFc to be well tolerated in previously untreated patients [15]. EHL products aim to provide improved hemostatic protection to patients with hemophilia, with the potential to offer increased treatment flexibility and a reduced dosing frequency to meet individual needs [6,28]. Compared with SHL products, EHL rFVIIIFc can increase protection by providing higher factor trough levels for a longer duration between injections (area under the curve), without increasing the dosing frequency, or equally, achieve similar protection but with fewer injections [7,8,25]. Previously reported data from A-LONG and Kids A-LONG showed that dosing frequency reduced with rFVIIIFc prophylaxis compared with prestudy dosing interval in subjects who received prestudy FVIII prophylaxis [7,14]. Here, we demonstrated that the dosing intervals from the pivotal studies were subsequently maintained throughout the follow-up period. Improved bleed protection was also offered by rFVIIIFc, as evidenced by the much lower on-study vs prestudy ABRs [29].

The Joint Outcome Study and Joint Outcome Continuation study found that even low joint ABRs which are not clinically evident can lead to joint damage [4,30], highlighting the importance of preventing joint bleeds and starting prophylaxis before their occurrence. However, standard prophylaxis does not provide complete joint protection in severe hemophilia A and joint disease may occur in adolescents despite early prophylaxis [1,4]. There is potential for rFVIIIFc prophylaxis to help address this need; this longitudinal analysis clearly demonstrated that prophylaxis with rFVIIIFc provided sustained low target joint ABRs in subjects with severe hemophilia A. For A-LONG subjects, improvement in overall ABRs was observed regardless of prestudy treatment. This was most notable for subjects receiving IP, who experienced very low bleeds across all ABR types. In Kids A-LONG subjects, who had lower ABRs at baseline compared with adult subjects and received on-study IP, there was a similar improvement in ABRs regardless of prestudy treatment. Median spontaneous joint ABRs were also sustained at low levels across IP and WP treatment groups throughout the study period. Notably, at each 6-month efficacy period in A-LONG/Kids A-LONG and ASPIRE, at least 70% of subjects on IP, across all ages, experienced zero spontaneous joint bleeds. It should be noted that comparisons with other EHL FVIII replacement products are limited by heterogenous study designs [31].

A key strength of the *post hoc* analyses reported here includes the ASPIRE study design, which approximated real-world clinical practice with individualized dosing regimens, included the option to switch treatment regimens, and had dosing flexibility across most treatment

groups. Furthermore, data from up to 5 years follow-up are reported. However, the data collection and analyses in this study are subject to several limitations. The study design for A-LONG and Kids A-LONG lacked randomization and blinding, meaning that it was not possible to minimize allocation and experimenter bias. Further, comparison between treatment arms was not permitted by the studies due to discrepancies between patient populations. A-LONG and Kids A-LONG were also not sufficiently powered to detect differences between treatment regimens. Additionally, SHL rFVIII products were not included as a relevant comparator and control.

Given the rarity of hemophilia A, *post hoc* analyses were limited by small sample sizes. Additionally, the analyses were retrospective in nature and were thus limited by the information available from the physician and patient data available. For example, it would be interesting to investigate the characteristics of patients with zero bleeds, such as factor level activity and genotype, compared with those who experienced bleeds during the study. Although such data were not available for the current analysis, this could provide an area of potential future research. Moreover, although HJHS/mHJHS are well studied, future studies could consider supplementing these results with objective outcome measures of joint health, such as musculoskeletal ultrasound (eg, Hemophilia Early Arthropathy Detection with Ultrasound [32]). A further limitation is that while trough FVIII levels were monitored in the IP cohort to guide prophylactic dosing, trough levels were not captured as an endpoint in the pivotal and extension studies and were therefore not available for analysis.

5 | CONCLUSION

Long-term prophylaxis with efmoroctocog alfa (rFVIIIFc) clearly demonstrated sustained clinical benefits, including improved joint health and low ABR with maintained low consumption and long dosing intervals, in previously treated subjects of all ages who had severe hemophilia A and were included in pooled longitudinal and subgroup analyses of phase 3 pivotal and extension studies.

ACKNOWLEDGMENTS

The authors thank the participants, the investigators and their teams who took part in this study. The authors also acknowledge Sabrina Meisgen, PhD and Louise Edvardsson, PhD, from Sobi for publication coordination; Somto Madueke, MPharm, and Abbie Rogers, BSc, from Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction. Further, the authors acknowledge that some data reported in this manuscript have been published previously at international conferences (ISTH 2019 and EAHAD 2019). The present study was funded by Sobi and Sanofi.

FUNDING

This study was sponsored by Sobi and Sanofi. This article was based on data from the A-LONG, Kids A-LONG, and ASPIRE studies (ClinicalTrials.gov identifiers: NCT01181128, NCT01458106, NCT01454739), sponsored by Sobi and Sanofi. Support for third-party writing assistance for this article, provided by Somto Madueke, MPharm, and Abbie Rogers, BSc, Costello Medical, UK, was funded by and Sanofi in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

AUTHOR CONTRIBUTIONS

Substantial contributions to the analysis and interpretation of the data: B.K., J.O., J.P., R.K., B.N., J.M., G.Y., S.B., I.P., A.S., C.N., V.B., M.R., J.D., S.L.; drafting the article or revising it critically for important intellectual content: B.K., J.O., J.P., R.K., B.N., J.M., G.Y., S.B., I.P., A.S., C.N., V.B., M.R., J.D., S.L.; final approval of the version of the article to be published: B.K., J.O., J.P., R.K., B.N., J.M., G.Y., S.B., I.P., A.S., C.N., V.B., M.R., J.D., S.L.

RELATIONSHIP DISCLOSURES

B.K.: Consultancy from BioMarin, CSL Behring, Genentech, Octapharma, and Sanofi; research funding from Bioverativ, a Sanofi company, Takeda, Uniqure; research funding and consultancy from Pfizer and Spark Therapeutics; **J.O.:** Symposia/congresses, honoraria for speaking and honoraria for consulting from Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Sobi; research funding from Bayer, Biotest, CSL Behring, Grifols, Octapharma and Shire; **J.P.:** Honoraria from Alnylam, ApcinteX, BioMarin, Bioverativ, a Sanofi company, Catalyst, Octapharma, and Sobi; research funding from Alnylam, BioMarin, and Bioverativ; speakers' bureau for Bayer, Novo Nordisk, Pfizer, Shire; **R.K.:** Advisory board and honoraria for Bayer, Bioverativ, BPL, Genentech, Kedrion, Novo Nordisk, Octapharma, and Shire; research funding from Bayer, Bioverativ, Novo Nordisk, and Shire; **B.N.:** Research funding from Bayer, Bioverativ, CSL Behring, and Sobi; **J.M.:** Consultancy from Alnylam, Amgen, Catalyst Biosciences, Chugai, CSL Behring, LFB, Novo Nordisk, Roche, Shire, Spark; research funding from Alnylam, Bayer, Biogen, BioMarin, Catalyst Biosciences, CSL Behring, Novo Nordisk, Roche, Shire, Sobi; and speaker bureau from Alnylam, Biogen, BioMarin, CSL Behring, Novo Nordisk, Roche, Sanofi, Shire, Sobi; **G.Y.:** Consultancy and honoraria from Bioverativ, CSL Behring, Genentech/Roche, Novo Nordisk; consultancy from Bayer, Kedrion; honoraria from Sanofi; **S.B.:** Nothing to disclose; **I.P.:** Honoraria for speaking and advisory boards for Bayer, Biotest, CSL Behring, Baxalta/Shire, Novo Nordisk, Pfizer, Roche and Sobi; unrestricted grants to institution from CSL Behring and Novo Nordisk; **A.S.:** Nothing to disclose; **C.N.:** Consultancy from Sobi; research support from Alnylam/Sanofi, CSL Behring, Novo Nordisk, Roche, and Sobi; honoraria from Alnylam (Sanofi), Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, Sobi, and Spark; **V.B.:** Honoraria for education events and advisory boards for Bayer, Bioverativ, Novartis, Novo Nordisk, Pfizer and Shire; research grants from Bioverativ and Shire; member of Data Safety Monitoring Boards for Octapharma and Shire; chair (non-remunerated) of the International Prophylaxis Study Group, which is supported by grants from Bayer, Bioverativ, CSL

Behring, Novo Nordisk, Pfizer and Shire to The Hospital for Sick Children Foundation, Toronto, Ontario, Canada; **M.R.:** Research support from Alnylam (Sanofi), BioMarin, Bioverativ (Sanofi), OPKO Biologics, Sangamo, Shire (Takeda), and Spark Therapeutics; advisory committee for Alnylam (Sanofi), BioMarin, Bioverativ (Sanofi), and Spark Therapeutics; non-financial support from Shire; **J.D.:** Employee of Sanofi; **S.L.:** Shareholder of Sobi; employee of Sobi.

ETHICS APPROVAL

Study protocols were approved by institutional review boards and/or ethics committees at participating institutions. Subjects, or their guardians, provided written informed consent prior to participation in the studies; if appropriate, subjects also provided assent. All studies included in this analysis were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[17] and ethical principles that comply with the Declaration of Helsinki,[18] and are registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01181128, NCT01458106, NCT01454739).

DATA AVAILABILITY

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by European Medicines Agency and/or Food and Drug Administration, while protecting individual participant integrity and compliance with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity and commitment to publication of the results. To request access to study data, a data sharing request form (available on www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at: https://www.sobi.com/en/policies.

REFERENCES

[1] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26:1–158.

[2] Fischer K, de Kleijn P, Negrier C, Mauser-Bunschoten EP, van der Valk PR, van Galen KPM, et al. The association of haemophilic arthropathy with health-related quality of life: a post hoc analysis. *Haemophilia*. 2016;22:833–40.

[3] Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1:51–9.

[4] Warren BB, Thornhill D, Stein J, Fadell M, Ingram JD, Funk S, et al. Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the joint outcome continuation study. *Blood Adv*. 2020;4:2451–9.

[5] Ar MC, Balkan C, Kavaklı K. Extended half-life coagulation factors: a new era in the management of hemophilia patients. *Turk J Haematol*. 2019;36:141–54.

[6] Lambert T, Benson G, Dolan G, Hermans C, Jiménez-Yuste V, Ljung R, et al. Practical aspects of extended half-life products for the treatment of haemophilia. *Ther Adv Hematol*. 2018;9:295–308.

[7] Shapiro AD, Ragni MV, Kulkarni R, Oldenberg J, Srivastava A, Quon DV, et al. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. *J Thromb Haemost*. 2014;12:1788–800.

[8] Oldenburg J, Goldmann G, Marquardt N, Horneff S, Klein C, Albert T, et al. Real-world clinical experience of extended half-life recombinant factor VIII Fc fusion protein (rFVIIIFc) in comparison to conventional factor products in patients with severe hemophilia A. *Curr Med Res Opin*. 2021;4:950–60.

[9] Peyvandi F, Berger K, Seitz R, Hilger A, Hecquet ML, Wierer M, et al. Kreuth V initiative: European consensus proposals for treatment of hemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies. *Haematologica*. 2020;105:2038–43.

[10] European Medicines Agency. Summary of Product Characteristics Elocta. Available at: https://www.ema.europa.eu/en/documents/product-information/elocta-epar-product-information_en.pdf. [accessed May 10, 2021].

[11] Food and Drug Administration. Prescribing Information Eloctate. Available at: https://www.fda.gov/media/88746/download. [accessed May 10, 2021].

[12] Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123:317–25.

[13] Nolan B, Mahlangu J, Pabinger I, Young G, Konkle BA, Barnes C, et al. Recombinant factor VIII Fc fusion protein for the treatment of severe haemophilia A: final results from the ASPIRE extension study. *Haemophilia*. 2020;26:494–502.

[14] Young G, Mahlangu J, Kulkarni R, Nolan B, Liesner R, Pasi J, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Haemost*. 2015;13:967–77.

[15] Königs C, Ozelo MC, Dunn A, Kulkarni R, Nolan B, Brown SA, et al. First study of extended half-life rFVIIIFc in previously untreated patients with hemophilia A: PUPs A-LONG final results. *Blood*. 2022;139:3699–707.

[16] Oldenburg J, Kulkarni R, Srivastava A, Mahlangu JN, Blanchette VS, Tsao E, et al. Improved joint health in subjects with severe haemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein. *Haemophilia*. 2018;24:77–84.

[17] International Conference on Harmonisation. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1). Available at: https://www.ich.org/page/ich-guidelines; 1996. [accessed May 12, 2021].

[18] World Medical Association. WMA Declaration of Helsinki – ethical principles for medical research involving human subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; 1964. [accessed May 12, 2021].

[19] Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res*. 2011;63:223–30.

[20] Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935–9.

[21] Wall C, Scott M, Xiang H, Palmer B, Collins P, Chowdary P, et al. Longitudinal analysis of rFVIIIFc use and efficacy in the UK: a report from the national haemophilia database. *Res Pract Thromb Haemost*. 2020;4:PB0878.

[22] Iorio A, Krishnan S, Myrén KJ, Lethagen S, McCormick N, Yermakov S, et al. Indirect comparisons of efficacy and weekly factor consumption during continuous prophylaxis with recombinant factor VIII Fc fusion protein and conventional recombinant factor VIII products. *Haemophilia*. 2017;23:408–16.

[23] Krishnan S, Vietri J, Furlan R, Duncan N. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. *Haemophilia*. 2015;21:64–70.

[24] Carcao M. Changing paradigm of prophylaxis with longer acting factor concentrates. *Haemophilia*. 2014;20:99–105.

[25] Berntorp E, Negrier C, Gozzi P, Blaas P-M, Lethagen S. Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc. *Haemophilia*. 2016;22:389–96.

[26] Klamroth R, Pollmann H, Hermans C, Faradji A, Yarlas AS, Epstein JD, et al. The relative burden of haemophilia A and the impact of target joint development on health-related quality of life: results from the ADVATE Post-Authorization Safety Surveillance (PASS) study. *Haemophilia*. 2011;17:412–21.

[27] Pasi J, Hermans C, Hakimi Z, Nazir J, Aballéa S, Ezzalfani M, et al. Improvement in pain-related quality of life in patients with haemophilia A treated with rFVIIIFc individualized prophylaxis: post hoc analysis from the A-LONG study. *Ther Adv Hematol*. 2022;13:1–9.

[28] Bentorp E, Dolan G, Hay CRM, Linari S, Santagostino E, Tosetto A, et al. European retrospective study of real-life haemophilia treatment. *Haemophilia*. 2017;23:105–14.

[29] Thornburg CD, Duncan NA. Treatment adherence in hemophilia. *Patient Prefer Adherence*. 2017;11:1677–86.

[30] Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *New Engl J Med*. 2007;357:535–44.

[31] Di Minno MND, D'Angiolella LS, Cortesi PA, Molinari AC, Mantovani LG. Critical review of the pivotal studies of four rFVIII products for the treatment of hemophilia A patients: the role of octocog alfa. *Farmeconomia Health Econ Ther Pathw*. 2020;21:21–34.

[32] Martinoli C, Della Casa Alberighi O, Di Minno G, Graziano E, Molinari AC, Pasta G, et al. Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). *Thromb Haemost*. 2013;109:1170–9.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2023.102180