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ORIGINAL ARTICLE

Long-term outcomes of prophylaxis with a recombinant factor VIII Fc or recombinant factor IX Fc in patients with hemophilia previously treated on demand

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Abstract

Background: Prophylactic factor replacement therapy is recommended over on-demand treatment for preserving long-term joint health in hemophilia. Extended half-life products, including efmoroctocog alfa/eftrenonacog alfa (recombinant factor VIII [FVIII]/FIX Fc fusion proteins; herein rFVIIIFc/rFIXFc), have the potential to reduce treatment burden with less frequent administration and improve bleed prevention.

Objectives: We report post hoc data from patients with hemophilia A or B (HA/HB) who switched from prestudy on-demand FVIII/FIX to rFVIIIFc/rFIXFc prophylaxis at the start of A-LONG/B-LONG or start of/during ASPIRE/B-YOND phase 3 studies.

Methods: Patients with ≥6 months rFVIIIFc/rFIXFc prophylaxis were enrolled. Treatment exposure, dosing, annualized bleeding rates, joint health, and health-related quality of life (HRQoL) outcomes were assessed. Results were also stratified by age.

Results: Sixty-seven patients with HA and 50 with HB were analyzed; ≥60% were from regions outside Europe/North America, predominately those aged 12 to 25 years. No subjects returned to on-demand treatment postswitch. After switch to rFVIIIFc/rFIXFc prophylaxis, median annualized bleeding rates were reduced and sustained at low levels with stable factor usage across age groups (median treatment duration: 4.8/3.6 years). HRQoL outcomes improved for all ages; most pronounced changes were in the sports and leisure and physical health domains. After switch to rFVIIIFc prophylaxis, total modified Hemophilia Joint Health Score and joints with pain decreased in 64.6% and 29.2% of patients with HA. Insufficient data from patients with HB limited joint health evaluation of rFIXFc.

Conclusions: Findings add to existing evidence and demonstrate the clinical and HRQoL benefits of switching patients from on-demand treatment to rFVIIIFc/rFIXFc prophylaxis.

Some data in this article have previously been presented at the XXVII Congress of the International Society on Thrombosis and Haemostasis (ISTH), Melbourne, Australia, 6-10 July 2019.

KEYWORDS
factor IX, factor VIII, hemophilia, prophylaxis, recombinant fusion proteins

Essentials

- Prophylactic factor replacement is recommended to preserve long-term joint health in hemophilia.
- One hundred seventeen patients switched from on-demand therapy to extended half-life factor VIII/IX prophylaxis.
- Postswitch, bleed protection, and health-related quality of life improved across all ages.
- Joint health outcomes improved in patients with hemophilia A, with limited data for hemophilia B.

1 | INTRODUCTION

Regular prophylactic replacement therapy with coagulation factor VIII (FVIII) or FIX is the standard of care for patients with severe hemophilia A (HA) or hemophilia B (HB), respectively, including patients with moderate disease and a severe phenotype [1]. For preservation of long-term joint health, prophylactic regimens are recommended over on-demand replacement therapy, which is only administered after a bleed has occurred and therefore does not significantly alter the bleeding profile, allowing musculoskeletal damage to occur [1–3]. Despite this, there is considerable variation in the use of prophylaxis among patients with HA and HB, as well as those with different levels of severity, with many individuals remaining undertreated or still receiving on-demand therapy [4–8].

Although prophylaxis is the standard of care in most regions, there remain countries with estimated prophylaxis rates <40%, highlighting an unmet need in hemophilia, particularly in resource-constrained countries [6–9]. Even in North American, Australasian, and Western European countries, where long-term prophylaxis is routinely used in children, the frequency of prophylaxis use ranges from 29% to 100% for adults with severe HA and 12% to 100% for adults with severe HB [6].

Compared with their standard half-life (SHL) counterparts, extended half-life (EHL) replacement products, including efmoroctocog alfa and eftrenonacog alfa (recombinant FVIII/FIX Fc fusion proteins, herein referred to as rFVIIIFc/rFIXFc), have the potential to reduce treatment burden with less frequent administration and improved bleed protection [1]. rFVIIIFc and rFIXFc are approved in the United States, Europe, and other regions of the world for the treatment and prophylaxis of bleeding in patients with HA and HB [10–19], based on the long-term safety and efficacy outcomes of phase 3 pivotal (A-LONG, Kids A-LONG, B-LONG, and Kids B-LONG) [20–23] and extension (ASPIRE and B-YOND) studies [24,25]. Longitudinal analyses of data from the extension studies showed no inhibitor development, safety profiles consistent with prior studies, and sustained low annualized bleeding rates (ABRs) in previously treated subjects receiving up to 5 years of rFVIIIFc/rFIXFc prophylaxis with extended dosing intervals [24,25].

Here, we report long-term outcomes of switching from on-demand treatment to prophylaxis with rFVIIIFc/rFIXFc in a subset of patients who switched treatment at the start of A-LONG/B-LONG or at the start of or during ASPIRE/B-YOND studies.

2 | METHODS

2.1 | Study design and participants

We report a post hoc analysis of data from a subset of subjects enrolled in open-label, phase 3 pivotal (A-LONG or B-LONG) and extension (ASPIRE or B-YOND) studies.

Previously treated adults and adolescents (≥12 years of age and ≥150 exposure days to FVIII/FIX products) with severe HA (<1 international units [IU]/dL [<1%] endogenous FVIII activity) or HB (≤2 IU/dL [≤2%] endogenous FIX activity) were enrolled in the phase 3 studies. The analysis reported here included subjects who received prestudy on-demand treatment with SHL FVIII/FIX and switched to rFVIIIFc/rFIXFc prophylaxis at the start of A-LONG/B-LONG or at the start of or during ASPIRE/B-YOND, with ≥6 months of efficacy on prophylaxis. Subjects who switched to prophylactic treatment in ASPIRE/B-YOND initially received rFVIIIFc/rFIXFc on demand in A-LONG/B-LONG. Prior to prophylaxis, on-demand treatment data (with SHL FVIII/FIX and rFVIIIFc/rFIXFc) were collected for a median duration of 1 year.

At A-LONG enrolment, subjects were assigned to one of 3 treatment regimens: individualized prophylaxis (IP) (25-65 IU/kg every 3-5 days with doses adjusted during the study to maintain a trough level of 1-3 IU/dL above baseline, or higher), weekly prophylaxis (WP) (fixed dose of 65 IU/kg every 7 days with no dose or interval adjustment), or on-demand treatment (10-50 IU/kg, depending on bleeding severity) [20]. Following entry into the ASPIRE extension study, subjects could also receive modified prophylaxis (MP) (personalized dosing by the investigator for subjects in whom optimal prophylaxis could not be achieved with IP or WP) [24]. During ASPIRE, subjects could switch between eligible regimens at any time.

B-LONG subjects included in this analysis were assigned to one of the following treatment regimens at pivotal study entry: dose-adjusted WP (50 IU/kg starting dose every 7 days with doses adjusted during the study to maintain a trough level of 1-3 IU/dL above baseline or higher), interval-adjusted prophylaxis (100 IU/kg

starting dose every 10 days with dosing intervals adjusted during the study to maintain a trough level of 1-3 IU/dL above baseline or higher), or on-demand treatment (20-100 IU/kg, depending on bleeding severity) [22]. At B-YOND enrolment, subjects could also receive MP (personalized dosing for subjects in whom optimal prophylaxis could not be achieved using either WP or interval-adjusted prophylaxis). During B-YOND, subjects could switch between eligible treatment regimens at any time.

Full details on study design and treatment regimens have been published previously [20,22,24–26].

2.2 | Outcome measures

Assessed endpoints included cumulative treatment duration and exposure to rFVIIIFc/rFIXFc prophylaxis, prophylactic dose and dosing interval, factor consumption, and ABR (including overall, joint annualized bleeding rate [AJBR], and spontaneous joint annualized bleeding rate [AJSBR]).

Additional endpoints included changes in joint health outcomes, measured using modified Hemophilia Joint Health Score (mHJHS) by the total score and the number of joints with pain from the last assessment on each regimen, and health-related quality of life (HRQoL), measured using the Haemophilia Quality of Life Questionnaire for adults (Haem-A-QoL) (≥17 years old in HA and ≥18 years old in HB). Insufficient Haemo-QoL data were available from children or adolescents (<17 years old). The mean change in Haem-A-QoL total score and subdomain scores were measured from the last assessment during on-demand treatment to the last assessment on prophylaxis. A meaningful change in Haem-A-QoL has previously been defined as a change of −7.1 points in the total score and −10 points in the physical health and sports and leisure domains [27]. Target joints in the rFVIIIFc studies were defined as major joints with ≥3 bleeding episodes into the same joint in a 6-month period [28]. In rFIXFc studies, target joints were defined as major joints with ≥3 bleeding episodes into the same joint in a consecutive 3-month period.

2.3 | Statistical analysis

Data for endpoints were pooled across pivotal and extension studies but analyzed separately for subjects from A-LONG/ASPIRE and B-LONG/B-YOND. Depending on the time of switch, retrospective preswitch and baseline data were combined with prospective data for analyses of on-demand treatment outcomes. Results were summarized using descriptive statistics. Results were stratified by age and are presented by 3 different age groups (12-25 years, 26-40 years, and ≥41 years).

2.4 | Ethics statement

Study protocols were approved by institutional review boards and/or ethics committees at participating institutions. Subjects provided written informed consent prior to participation in the studies. All studies included in this analysis were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice [29] and ethical principles that comply with the Declaration of Helsinki [30] and are registered with ClinicalTrials.gov (Identifiers: NCT01181128, NCT01454739, NCT01027364, and NCT01425723).

3 | RESULTS

3.1 | Switch from on-demand treatment to rFVIIIFc prophylaxis (A-LONG/ASPIRE)

3.1.1 | Study population and rFVIIIFc dosing

Of the 70 subjects with severe HA who switched from on-demand treatment to rFVIIIFc prophylaxis in A-LONG/ASPIRE, 67 (96%) received prophylaxis for ≥6 months and were included in the analysis, with a median (IQR) prophylactic treatment duration of 4.8 (3.3-5.4) years. Prior to prophylaxis, on-demand treatment data were available for a median (IQR) duration of 1.0 (1.0–1.0) year. Fifty-one subjects switched from on-demand SHL FVIII treatment at A-LONG entry and 16 subjects switched from on-demand rFVIIIFc treatment at the start of or during ASPIRE (Figure 1A).

Subjects who switched to rFVIIIFc prophylaxis were aged between 13 and 64 years with a median of 1.0 target joint at A-LONG entry, regardless of when the switch to prophylaxis occurred (Table 1). The group aged 12 to 25 years had the highest proportion of subjects with ≥1 target joints at baseline (Supplementary Table S1). Most subjects (67.2%) in the analysis were from regions outside Europe and North America, predominately consisting of subjects in the 12 to 25 years age group.

In the first 6 months of prophylaxis, 39 subjects received IP, 24 received WP (n = 1 subject was excluded due to <6 months on WP but then switched to IP and had a total of >6 months on prophylaxis) and 3 received MP. Most subjects who received IP in the first 6 months were in the ≥41 years age group (46.2%), followed by those in the 12 to 25 years age group (28.2%). Subjects who received WP largely consisted of those in the 26 to 40 years age group (41.7%). All 3 subjects who received MP were aged 26 to 40 years. No subjects switched back to on-demand treatment.

Between the start and end of rFVIIIFc prophylaxis for the overall population, median weekly factor consumption remained stable (first and last prophylactic doses, 75.0 IU/kg and 70.0 IU/kg), while the median (IQR) dosing interval was lengthened from 3.5 (3.5-7.0) days to 5.0 (3.5-7.0) days (Supplementary Table S2). When stratified by age, both the 26 to 40 years and ≥41 years groups experienced a decrease in median weekly dose and dosing frequency from first to last prophylactic dose; corresponding values were maintained for subjects aged 12 to 25 years.

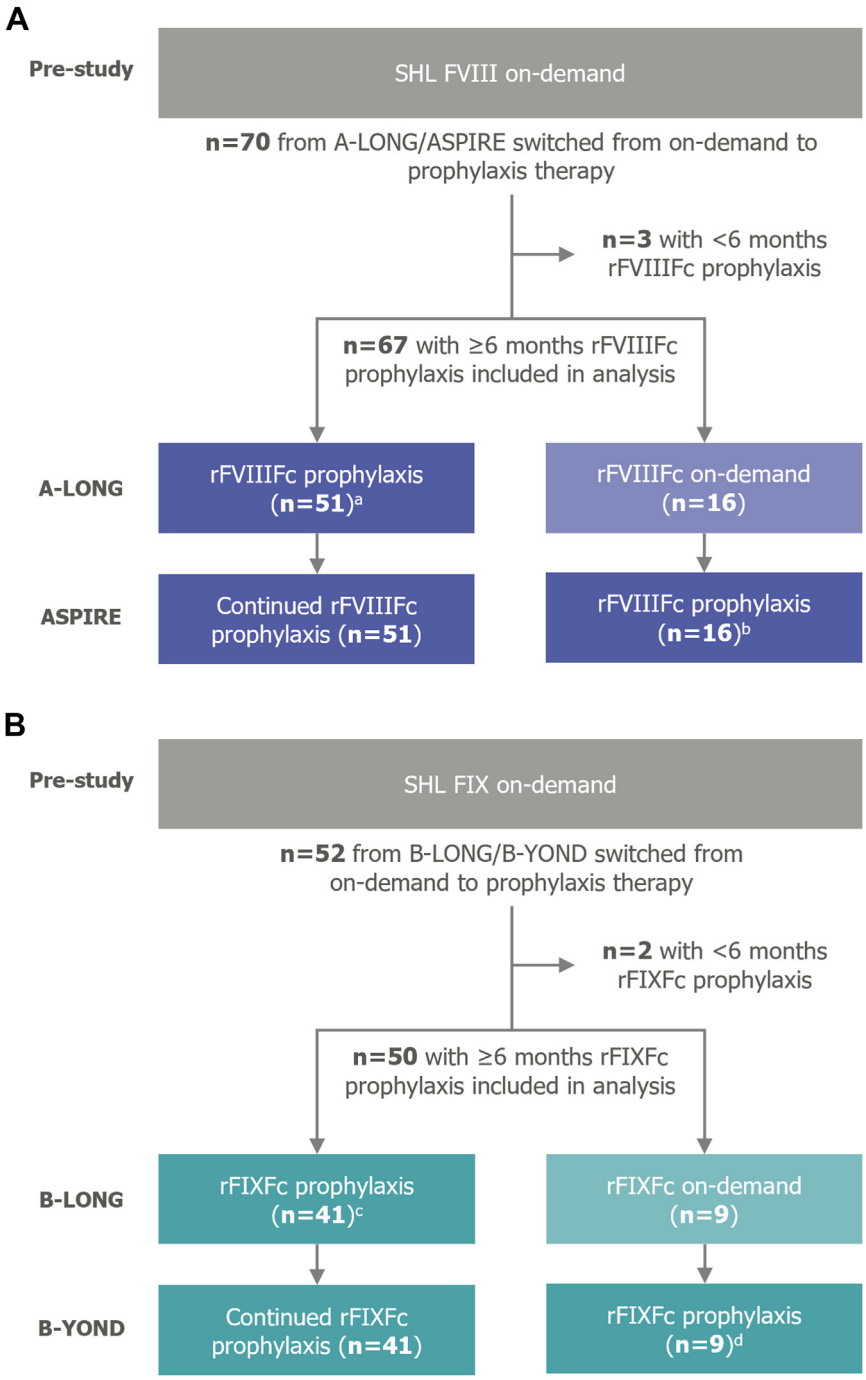


FIGURE 1 **Subject disposition for (A) A-LONG/ASPIRE and (B) B-LONG/B-YOND studies.** [a]Subjects switched from SHL FVIII on-demand treatment to rFVIIIFc prophylaxis at start of A-LONG. [b]Subjects switched from rFVIIIFc on-demand treatment to rFVIIIFc prophylaxis at start of or during ASPIRE. [c]Subjects switched from SHL FIX on-demand treatment to rFIXFc prophylaxis at start of B-LONG. [d]Subjects switched from rFIXFc on-demand treatment to rFIXFc prophylaxis at start of or during B-YOND. No subjects switched back to on-demand treatment. FVIII, factor VIII; FIX, factor IX; rFVIIIFc, recombinant factor VIII Fc fusion protein; rFIXFc, recombinant factor IX Fc fusion protein; SHL, standard half-life.

3.1.2 | ABR

Overall, subjects experienced a reduction in median (IQR) ABRs after switching from on-demand treatment to prophylaxis with rFVIIIFc (overall ABR: 30.0 [18.0-42.0] to 1.5 [0.4-3.5]; AJBR: 21.2 [13.0-33.0] to 1.2 [0.3-2.0]; and AJSBR: 14.0 [7.0-28.0] to 0.4 [0.0-1.6]) (Figure 2A). There were substantial reductions in ABRs from on-demand to prophylactic treatment across all age groups (Supplementary Table S3).

ABRs remained low between the first and last 6 months of rFVIIIFc prophylaxis (Table 2). In the first 6 months of prophylaxis, subjects who received IP (n = 39) and WP (n = 24) had a median ABR of 0.0 across all ABR categories. Corresponding median ABRs were higher for the 3 subjects who received MP (all of whom were in the 26-40 years age group).

3.1.3 | Joint health

Joint health scores improved after switch to rFVIIIFc prophylaxis with a mean (SD) change in mHJHS of −4.6 (10.6; n = 48); mean (SD)

TABLE 1 Demographic and baseline characteristics of subjects who switched from on-demand treatment to prophylaxis with rFVIIIFc/rFIXFc in A-LONG/ASPIRE or B-LONG/B-YOND, respectively.

	Subjects in A-LONG/ASPIRE (rFVIIIFc)			Subjects in B-LONG/B-YOND (rFIXFc)		
Demographic/characteristic	Total population (*N* = 67)	Subjects switching at A-LONG entry (*n* = 51)	Subjects switching at entry or during ASPIRE (*n* = 16)	Total population (*N* = 50)	Subjects switching at B-LONG entry (*n* = 41)	Subjects switching at entry or during B-YOND (*n* = 9)
Age (years)						
Overall, median (range)	35.0 (13.0-64.0)	36.0 (16.0-64.0)	30.0 (13.0-62.0)	29.5 (12.0-68.0)	29.0 (12.0-68.0)	36.0 (14.0-61.0)
12-25 y, *n* (%)	19 (28.4)	12 (23.5)	7 (43.8)	21 (42.0)	17 (41.5)	4 (44.4)
26-40 y, *n* (%)	23 (34.3)	18 (35.3)	5 (31.3)	17 (34.0)	14 (34.1)	3 (33.3)
≥41 y, *n* (%)	25 (37.3)	21 (41.2)	4 (25.0)	12 (24.0)	10 (24.4)	2 (22.2)
Weight (kg)						
Median (IQR)	75.0 (62.0-82.5)	75.3 (62.0-85.5)	68.8 (61.5-79.1)	70.0 (59.1-83.0)	70.0 (61.0-82.3)	58.7 (50.5-84.0)
BMI (kg/m^2)						
Median (IQR)	23.3 (20.8-27.9)	24.2 (21.1-28.5)	22.2 (20.6-25.6)	24.5 (20.8-26.6)	24.6 (21.4-26.6)	19.2 (17.5-26.6)
Region, *n* (%)						
Europe	8 (11.9)	6 (11.8)	2 (12.5)	10 (20.0)	9 (22.0)	1 (11.1)
North America	14 (20.9)	12 (23.5)	2 (12.5)	10 (20.0)	9 (22.0)	1 (11.1)
Other[a]	45 (67.2)	33 (64.7)	12 (75.0)	30 (60.0)	23 (56.1)	7 (77.8)
Race, *n* (%)						
White	37 (55.2)	28 (54.9)	9 (56.3)	26 (52.0)	24 (58.5)	2 (22.2)
Black	7 (10.4)	5 (9.8)	2 (12.5)	4 (8.0)	4 (9.8)	0 (0.0)
Asian	23 (34.3)	18 (35.3)	5 (31.3)	16 (32.0)	9 (22.0)	7 (77.8)
Other[b]	-	-	-	4 (8.0)	4 (9.8)	0 (0.0)
Number of target joints at A-LONG/B-LONG entry						
Median (IQR)	1.0 (1.0-3.0)	1.0 (1.0-3.0)	1.0 (0.5-2.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	4.0 (1.0-5.0)
Target joints, *n* (%)[c]						
≥1	56 (83.6)	44 (86.3)	12 (75.0)	35 (70.0)	28 (68.3)	7 (77.8)

Percentages may not sum to 100 due to rounding.

BMI, body mass index; IQR, interquartile range; kg, kilogram; rFVIIIFc, recombinant factor VIII Fc fusion protein; rFIXFc, recombinant factor IX Fc fusion protein.

[a]Other regions included Australia, Brazil, China, India, Israel, Japan, New Zealand, and South Africa.

[b]Other races/ethnic groups included Native American/American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Hispanic or Latino, North African, Afghan, and mixed races.

[c]Target joints in the rFVIIIFc studies were defined as major joints with ≥3 bleeding episodes into the same joint in a 6-month period whereas in the rFIXFc studies, target joints were defined as major joints with ≥3 bleeding episodes into the same joint in a consecutive 3-month period.

mHJHS was 23.3 (15.7) at the last assessment during on-demand treatment vs 18.7 (14.1) at the last assessment on prophylaxis (Supplementary Table S4).

Total mHJHS and joints with pain decreased in 64.6% (*n* = 31; Supplementary Table S4) and 29.2% (*n* = 14; data not shown) of subjects, respectively, after the switch to prophylaxis. Subjects aged 12 to 25 years had the largest reduction in mean mHJHS after switching to prophylaxis (−7.7), followed by subjects aged ≥41 years (−4.7). The ≥41 years age group had the highest percentage of subjects with a reduction in joints with pain (50.0% vs 33.3% for those aged 12 to 25 years and 10.5% for those aged 26-40 years).

3.1.4 | HRQoL

Mean (SD) change in total Haem-A-QoL score was −4.4 (11.5; *n* = 50), from 30.7 (14.7) to 26.3 (15.2) at the last assessment during on-demand treatment and prophylaxis, respectively (Figure 3A). A meaningful change in total score was achieved in 32% of subjects (*n* = 16; Supplementary Table S5). The most pronounced changes in Haem-A-QoL domains were observed in sports & leisure and physical health, with a meaningful change achieved in 51.2% (*n* = 21/41) and 54.7% (*n* = 29/53) of subjects, respectively.

Across age groups, the greatest mean reduction in the physical health domain was observed in subjects aged ≥41 years and a

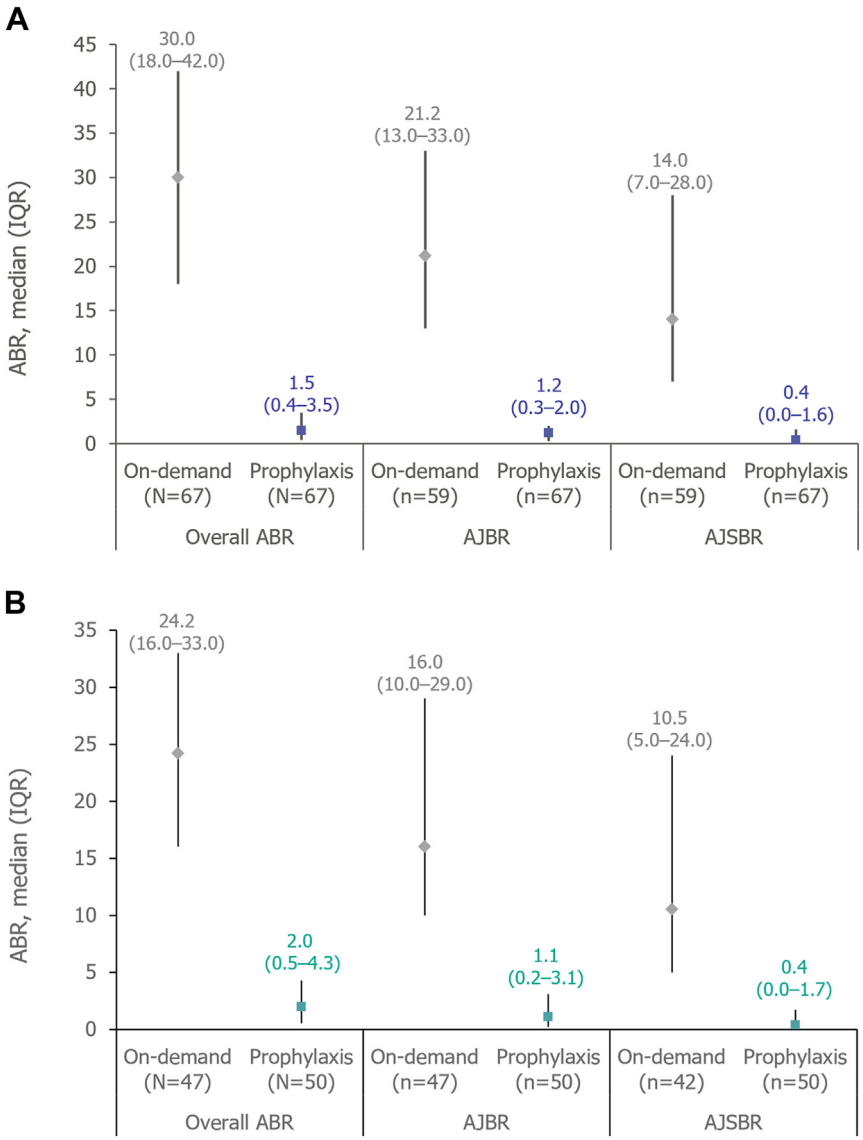


FIGURE 2 **Median annualized bleeding rates of subjects during on-demand treatment vs prophylaxis with (A) rFVIIIFc in A-LONG/ASPIRE and (B) rFIXFc in B-LONG/B-YOND.** ABR, annualized bleeding rate; AJBR, joint annualized bleeding rate; AJSBR, spontaneous joint annualized bleeding rate; IQR, interquartile range; rFVIIIFc, recombinant factor VIII Fc fusion protein; rFIXFc, recombinant factor IX Fc fusion protein.

meaningful change above the average percentage was seen in both the 17 to 25 years and ≥41-years age groups (Supplementary Table S5). In the sports & leisure domain, the greatest mean reduction and the highest percentage with a meaningful change was observed in the 17 to 25 years age group.

TABLE 2 Annualized bleeding rates of subjects during the first and last 6 months of rFVIIIFc prophylaxis in A-LONG/ASPIRE and rFIXFc prophylaxis in B-LONG/B-YOND.

	rFVIIIFc prophylaxis in A-LONG/ASPIRE (*N* = 67)		rFIXFc prophylaxis in B-LONG/B-YOND (*N* = 50)	
Median (IQR)	First 6 months	Last 6 months	First 6 months	Last 6 months
Overall ABR	0.0 (0.0-2.0)	0.0 (0.0-2.0)	2.0 (0.0-6.0)	2.0 (0.0-4.0)
AJBR	0.0 (0.0-2.0)	0.0 (0.0-2.0)	1.0 (0.0-4.0)	0.0 (0.0-2.0)
AJSBR	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)

ABR, annualized bleeding rate; AJBR, joint annualized bleeding rate; AJSBR, spontaneous joint annualized bleeding rate; IQR, interquartile range; rFVIIIFc, recombinant factor VIII Fc fusion protein; rFIXFc, recombinant factor IX Fc fusion protein.

3.2 | Switch from on-demand treatment to rFIXFc prophylaxis (B-LONG/B-YOND)

3.2.1 | Study population and rFIXFc dosing

Fifty-two subjects with severe HB switched from on-demand to prophylaxis in B-LONG/B-YOND. Of these, 50 subjects (96%) received rFIXFc prophylaxis for ≥6 months and were included in the analysis, with a median (IQR) treatment duration of 3.6 (1.9-5.9) years. Prior to prophylaxis, on-demand treatment data were available for a median (IQR) duration of 1.0 (1.0-1.0) year. Forty-one subjects switched from on-demand SHL FIX treatment at B-LONG entry, whereas 9 subjects

switched from on-demand rFIXFc treatment at the start of or during B-YOND (Figure 1B).

Subjects who switched to rFIXFc prophylaxis were aged between 12 and 68 years and had a median of 1.0 target joint at B-LONG entry, regardless of when the switch to prophylaxis occurred (Table 1). The proportion of subjects with ≥1 target joints at baseline (vs those with zero target joints) increased with age (Supplementary Table S1). Most subjects (n = 30, 60%) in the analysis were from regions other than Europe or North America and of these, 50% were in the 12 to 25 years age group.

In the first 6 months of prophylaxis, 33 subjects received dose-adjusted WP and 17 subjects received interval-adjusted prophylaxis. The 26 to 40 years age group had the highest percentage of subjects on WP in the first 6 months (76.5%), compared with 61.9% and 58.3% in the 12 to 25 and ≥41 years age groups, respectively. Most subjects who received interval-adjusted prophylaxis in the first 6 months were in the 12 to 25 years age group (47.1%). No subjects switched back to on-demand treatment.

In the overall population, the median weekly dose and dosing interval remained stable from the start of rFIXFc prophylaxis to the end of the follow-up period (50 IU/kg and 7 days, respectively). Subjects aged 26 to 40 years had a slightly lower median last dose than first dose on prophylaxis, whereas subjects aged 12 to 25 years had a maintained weekly dose and those aged ≥41 years had a slightly higher last prophylactic dose than first dose; the median dosing interval was maintained for all ages (Supplementary Table S6).

3.2.2 | ABR

Subjects experienced a reduction in median (IQR) ABRs after switching from on-demand treatment to prophylaxis with rFIXFc (overall ABR: 24.2 [16.0-33.0] to 2.0 [0.5-4.3]; AJBR: 16.0 [10.0-29.0] to 1.1 [0.2-3.1]; and AJSBR: 10.5 [5.0-24.0] to 0.4 [0.0-1.7]; Figure 2B). During prophylactic treatment, the lowest median ABRs were observed in the 26 to 40 years age group despite subjects aged 12 to 25 years having the lowest median ABRs during on-demand treatment (Supplementary Table S7).

ABRs were low and sustained between the first and last 6 months of rFIXFc prophylaxis (Table 2). Subjects aged 26 to 40 years had the lowest median overall ABRs in the first and last 6 months of prophylaxis.

3.2.3 | Joint health

The mean (SD) change for total mHJHS after switch to rFIXFc prophylaxis was −1.3 (2.3; n = 7) with a mean (SD) mHJHS of 18.3 (16.3) at the last assessment during on-demand treatment and 17.0 (16.3) at the last assessment on prophylaxis. Joints with pain decreased after switch to prophylaxis with a mean (SD) change of −0.6 (1.3; n = 11). No further analyses could be conducted as joint health data were only available from a limited number of subjects.

3.2.4 | HRQoL

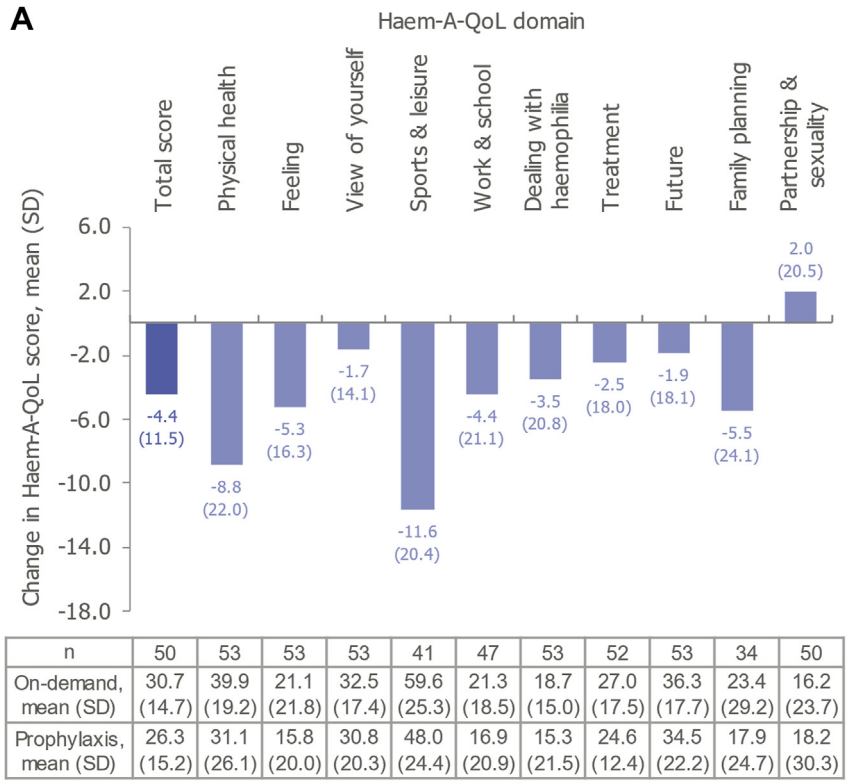
Mean (SD) change for total Haem-A-QoL score was −3.1 (9.5; n = 29) from 34.2 (15.2) at the last assessment during on-demand treatment to 31.1 (17.8) at the last assessment on prophylaxis (Figure 3B). A meaningful change in total score was achieved in 27.6% of subjects (n = 8; Supplementary Table S8). The sports & leisure and physical health Haem-A-QoL domains had the most pronounced changes, with a meaningful change achieved in 72.0% (n = 18/25) and 52.9% (n = 18/34) of subjects, respectively.

Although similar reductions were seen in the mean change in total Haem-A-QoL score across age groups, subjects aged 18 to 25 years generally had the lowest mean score during on-demand treatment and prophylaxis, and subjects aged ≥41 years had the highest mean score across treatment regimens (Supplementary Table S8). In the physical health domain, subjects aged 26 to 40 years had the greatest mean reduction and highest percentage of subjects with a meaningful change. In the sports & leisure domain, the largest mean reduction was seen in subjects aged ≥41 years and the highest percentage of subjects with a meaningful change was in the 26 to 40 years age group.

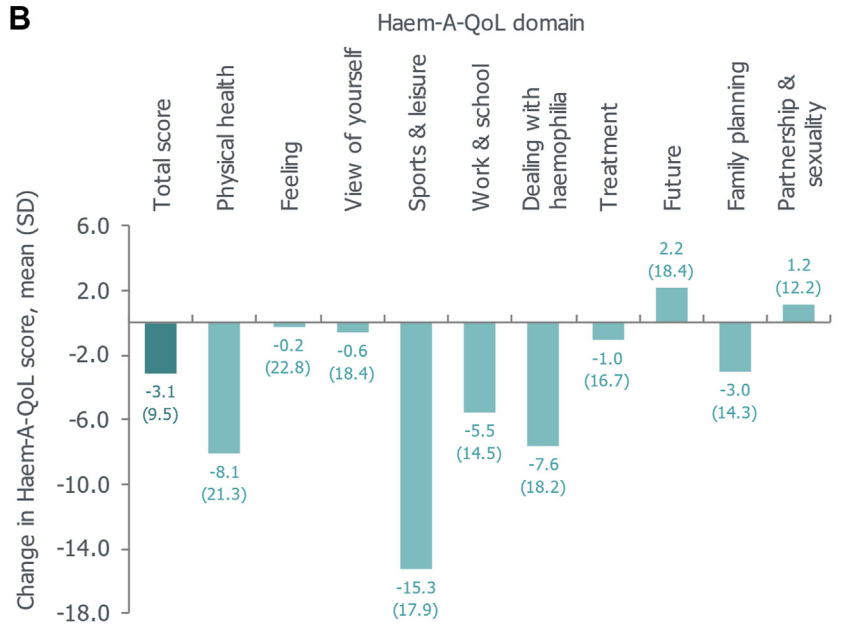
4 | DISCUSSION

The results of this post hoc analysis of long-term data from A-LONG/ASPIRE and B-LONG/B-YOND studies further demonstrate that switching patients with severe HA and HB, across age groups, from on-demand FVIII/FIX therapy to prophylaxis with rFVIIIFc/rFIXFc provides benefit in clinical outcomes and HRQoL. Findings from A-LONG/ASPIRE also suggest improvements in joint health with rFVIIIFc prophylaxis. Following the switch to rFVIIIFc/rFIXFc prophylaxis, median ABRs were reduced and sustained at low levels for up to 5 years with stable factor usage. Although comparisons should be met with caution due to differences in patient characteristics (including disease severity and age), study population sizes, and duration of outcome assessment periods, these findings are consistent with the currently available real-world data reporting the switch experience of patients from on-demand therapy to rFVIIIFc/rFIXFc prophylaxis [31–38].

International real-world studies have demonstrated improved bleeding outcomes in patients with moderate to severe HA after switch from on-demand treatment with SHL FVIII to rFVIIIFc prophylaxis [31,32]. Similarly, several real-world studies of patients with HB who switched from SHL FIX on-demand treatment to rFIXFc prophylaxis demonstrated improved bleeding control with reduced injection frequency and lower factor consumption [33–37]. Furthermore, a multicenter longitudinal Canadian observational study found that switching from SHL products (with >80% of patients on



	Total score	Physical health	Feeling	View of yourself	Sports & leisure	Work & school	Dealing with haemophilia	Treatment	Future	Family planning	Partnership & sexuality
n	50	53	53	53	41	47	53	52	53	34	50
On-demand, mean (SD)	30.7 (14.7)	39.9 (19.2)	21.1 (21.8)	32.5 (17.4)	59.6 (25.3)	21.3 (18.5)	18.7 (15.0)	27.0 (17.5)	36.3 (17.7)	23.4 (29.2)	16.2 (23.7)
Prophylaxis, mean (SD)	26.3 (15.2)	31.1 (26.1)	15.8 (20.0)	30.8 (20.3)	48.0 (24.4)	16.9 (20.9)	15.3 (21.5)	24.6 (12.4)	34.5 (22.2)	17.9 (24.7)	18.2 (30.3)



	Total score	Physical health	Feeling	View of yourself	Sports & leisure	Work & school	Dealing with haemophilia	Treatment	Future	Family planning	Partnership & sexuality
n	29	34	34	35	25	28	34	35	34	20	34
On-demand, mean (SD)	34.2 (15.2)	44.3 (20.0)	28.1 (19.1)	41.7 (18.8)	61.1 (21.0)	23.4 (22.3)	24.5 (16.9)	33.6 (17.9)	42.6 21.6)	20.5 (24.6)	16.7 (25.2)
Prophylaxis, mean (SD)	31.1 (17.8)	36.2 (25.1)	27.9 (25.8)	41.1 (22.4)	45.9 (25.5)	17.9 (21.6)	16.9 (18.9)	32.6 (15.5)	44.9 (27.7)	17.5 (25.5)	17.9 (25.4)

FIGURE 3 **Mean change in Haem-A-QoL score between on-demand treatment and prophylaxis with (A) rFVIIIFc in A-LONG/ASPIRE and (B) rFIXFc in B-LONG/B-YOND.** The total Haem-A-QoL score was estimated provided at least 38 questions were answered by the subject at a particular visit; sub-scores if at least 75% of questions were answered. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for adults; rFVIIIFc, recombinant factor VIII Fc fusion protein; rFIXFc, recombinant factor IX Fc fusion protein; SD, standard deviation.

prophylaxis preswitch) to rFVIIIFc/rFIXFc led to a reduction in factor utilization while preserving low ABR [38]. In particular, there was a statistically significant decrease in ABR in pediatric patients with HA who switched to rFVIIIFc [38]. Some studies have reported that the most common patient- and clinician-reported reason for switching from SHL to rFIXFc/rFVIIIFc prophylaxis was to reduce treatment burden; however, it should be noted that the reasons for switching were only available for a few subjects and were not stratified by previous regimen (eg, some patients received prophylaxis prior to rFIXFc/rFVIIIFc) [33,38].

In the analysis reported here, most subjects (in both the HA and HB populations) were from regions other than Europe and North America, particularly those aged 12 to 25 years and those who switched to prophylaxis at entry to or during ASPIRE/B-YOND (and therefore received on-demand treatment for the longest duration). Across the total population of the pivotal studies, including subjects who received prestudy prophylaxis, a more even distribution between Europe, North America, and other regions was observed than in the present analysis [20,22]. This could be attributed to prophylaxis being the standard of care in well-resourced countries, particularly for children with severe hemophilia, whereas this is infrequently undertaken in resource-constrained countries due to limited availability and affordability [1].

Potential challenges of prophylaxis include frequent injections with SHL products, which may give rise to difficulty with venous access, poor adherence to prescribed therapy, and high treatment costs [39]. IP with EHL products, such as rFVIIIFc/rFIXFc, has the potential to overcome these limitations [40]. In a survey of practicing physicians across Europe, most participants reported that switching to rFVIIIFc/rFIXFc improved quality of life, treatment adherence and disease control, and reduced treatment burden [40]. The possibility to individualize treatment regimens with rFVIIIFc/rFIXFc may serve to bridge the global disparity in prophylaxis that is currently observed among patients with hemophilia [1,41].

This analysis also demonstrated that switching to rFVIIIFc and rFIXFc prophylaxis provided clinical benefits beyond ABR, including improvements in joint health and HRQoL. In the HB study population, the median number of target joints at B-LONG entry and the proportion of ≥1 target joints at baseline increased with age. Similarly, for HA, subjects aged ≥41 years had the greatest median number of target joints at A-LONG entry. These findings reflect previous suboptimal treatment with greater exposure to clinical (and subclinical) bleeds in this generation of patients. Indeed, the clinical manifestation of joint disease progresses over time and increases with delayed prophylaxis [42]. Therefore, early prophylaxis is considered critical for long-term joint health [1].

After switching to prophylaxis with rFVIIIFc, subjects aged 12 to 25 years had the greatest improvement in mHJHS. Subjects aged 26 to 40 years in the HA population experienced the least improvement but had the greatest reduction in mean total Haem-A-QoL score (HRQoL improvement), indicating that rFVIIIFc clinical outcomes may not reflect patient-reported outcomes. Of note, the slightly higher ABRs of subjects aged 26 to 40 years may have been skewed by the inclusion of the 3 subjects with MP. This is in contrast with the HB population, where subjects aged 26 to 40 years had the most improved patient-reported and clinical outcomes with the greatest percentage of subjects with a meaningful change in Haem-A-QoL as well as a reduced first to last median weekly prophylactic dose. Subjects with HB aged between 26 and 40 years also had the lowest median ABRs after switching to prophylaxis, which could be explained by this group having the highest percentage of subjects on WP in the first 6 months of prophylaxis. The 12 to 25 years group in the HB population had the lowest ABRs during on-demand treatment, which could be due to them receiving on-demand treatment for a shorter duration than that received by the other age groups.

4.1 | Strengths and limitations

Notably, the ASPIRE and B-YOND extension studies approximated real-world clinical practice with individualized dosing regimens administered over long periods and dosing flexibility with the option to switch treatment regimens at any time [24,25]. This is in line with the World Federation of Hemophilia guidelines, which recommend that prophylaxis should be individualized to consider a patient's bleeding phenotype, joint status, pharmacokinetics, self-assessment, and preference [1]. However, the limitations of a clinical trial under controlled settings apply [25]. Given that treatments were allocated in a nonrandomized manner and patients could elect to switch to a prophylaxis regimen, there is a potential of selection bias [20,22]. However, as reported previously, the design did not appear to affect the study results as multiple subgroup analyses supported the primary analysis of bleeding rates [20,22]. Furthermore, an important consideration when interpreting pooled data is that subjects received different prophylactic regimens with varying adequacy.

Despite the attempt to evaluate joint health outcomes with rFIXFc prophylaxis, only a small number of subjects with HB had sufficient baseline joint data available for comparison with the on-study period. It should be noted that the discrepancies in the number of subjects with target joints between the HA and HB populations may be attributed to the difference in target joint definitions between the pivotal rFVIIIFc and rFIXFc studies as the inclusion period of bleeds was extended from 3 months in the earlier rFIXFc studies to 6 months in the rFVIIIFc studies. Additionally, the rFVIIIFc studies included patients considered to have severe HA (<1 IU/dL [<1%] endogenous FVIII activity), whereas the rFIXFc studies also included patients considered to have moderate disease severity, as less stringent criteria were used to define severe HB at the time (≤2 IU/dL [≤2%] endogenous FIX activity), which may be due to lower availability of patients with HB than of those with HA [1,20,22,24,25]. Although consensus has not yet been reached, some studies suggest that patients with HB may have a less severe bleeding tendency compared with patients with HA [43]. However, patients with HB still experience musculoskeletal bleeding and resultant joint disease [1,43].

The use of Haem-A-QoL to measure HRQoL has been validated in previous studies and allowed the evaluation of the most notable HRQoL improvements in the physical health and sports & leisure domains across rFVIIIFc and rFIXFc [27]. However, the number of subjects who provided Haem-A-QoL responses varied between the different domains (n = 34-53/67 subjects with HA who switched to rFVIIIFc prophylaxis; n = 20-35/50 subjects with HB who switched to rFIXFc prophylaxis). Additionally, only a subgroup of the full population who provided responses could be followed for the entire follow-up period, which may limit generalizability. Potential for response bias should also be considered in the interpretation of the results.

4.2 | Conclusions

This longitudinal subgroup analysis of combined data from the pivotal (A-LONG/B-LONG) and extension (ASPIRE/B-YOND) studies for HA and HB provides important insight into how switching patients from on-demand treatment to prophylaxis with rFVIIIFc/rFIXFc benefits their clinical and HRQoL outcomes. Furthermore, these data provide helpful longitudinal information on the treatment experience of patients with hemophilia across various ages and regions.

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AUTHOR CONTRIBUTIONS

M-T.Á-R., A.D.S., M.V.R., H.P., L.B., J.S., S.C., and H.C. made substantial contributions to study conception or design. M-T.Á-R., A.D.S., M.V.R., H.P., L.B., J.S., S.C., and H.C. made substantial contributions to the acquisition, analysis and interpretation of the data. M-T.Á-R., A.D.S., M.V.R., H.P., L.B., J.S., S.C., and H.C. drafted the article or revised it critically for important intellectual content. All authors read and approved the final version of the article.

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RELATIONSHIP DISCLOSURE

M-T.Á-R. served on advisory boards and speakers bureau for Amgen, Bayer, BioMarin, Bioverativ, CSL Behring, Grifols, LFB, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, and Takeda; and received research funding from Takeda. A.D.S. received research funding from Novo Nordisk, Freeline Therapeutics Ltd., and Pfizer; served on advisory boards for Sanofi; is a foundation council member of the Novo Nordisk Hemophilia Foundation; and is a board member of the Indiana Hemophilia and Thrombosis Center. M.V.R. received research funding to the University from Alnylam, BioMarin, Bioverativ, CSL Behring, Novo Nordisk, OPKO Biologics, Sangamo, Spark, and Takeda; served on advisory boards for Alnylam, Bayer, BioMarin, Bioverativ, MOGAM, Spark, and Takeda; and received nonfinancial support (study drug) from Shire. H.P. is an employee of Sobi. L.B. is an employee of Sobi. J.S. is an employee and shareholder of Sobi. S.C. is an employee and shareholder of Sanofi. H.C. received consulting fees from BioMarin, CSL Behring, Roche Chugai, and Sobi; received payment/honoraria for lectures/speakers bureau from BioMarin, CSL, Roche Chugai, and Sobi; received payment for expert testimony from BioMarin; and received support for attending meetings from Novo Nordisk and Roche.

DATA AVAILABILITY

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by EMA and/or FDA, 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 at 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.

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SUPPLEMENTARY MATERIAL

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