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HEMATOLOGY: RESEARCH ARTICLE

Outcomes in children with hemophilia A with inhibitors: Results from a noninterventional study

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Abstract

Background: Data regarding management of pediatric persons with hemophilia A (PwHA) with factor VIII (FVIII) inhibitors are limited. This prospective noninterventional study (NCT02476942) evaluated annualized bleeding rates (ABRs), safety, and health-related quality of life (HRQoL) in pediatric PwHA with FVIII inhibitors.

Procedure: PwHA aged <12 years with current FVIII inhibitors and high-titer inhibitor history were enrolled. Participants remained on usual treatment; no interventions were applied. Outcomes included ABR, safety, and HRQoL.

Results: Twenty-four PwHA aged 2-11 years (median 7.5) were enrolled and monitored for 8.7-44.1 weeks (median 23.4). In the episodic (n = 10) and prophylactic (n = 14) groups, respectively, 121 of 185 (65.4%) and 101 of 186 (54.3%) bleeds were treated using activated prothrombin complex concentrate (aPCC) and/or recombinant activated FVII (rFVIIa). ABRs (95% confidence interval) were 19.4 (13.2-28.4) and 18.5 (14.2-24.0) for treated bleeds, and 32.7 (20.5-52.2) and 33.1 (22.4-48.9) for all bleeds, respectively. Most prophylactic group participants (92.9%) were prescribed aPCC; 50% adhered to their prescribed treatment regimen. Adherence to prophylactic rFVIIa was not assessed. Serious adverse events included hemarthrosis (12.5%) and mouth

Abbreviations: ABR, annualized bleed rate; Adapted Inhib-QoL, Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden; AE, adverse event; aPCC, activated prothrombin complex concentrate; BMQ, bleed and medication questionnaire; BPA, bypassing agent; CI, confidence interval; FVIII, factor VIII; HA, hemophilia A; Haemo-QoL SF, Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form; HRQoL, health-related quality of life; IQR, interquartile range; ITI, immune tolerance induction; NIS, noninterventional study; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VII; SAE, serious adverse event

hemorrhage (12.5%); the most common nonserious adverse event was viral upper respiratory tract infection (12.5%). HRQoL showed functional impairment at baseline; scores remained stable throughout, with little intergroup variation.

Conclusions: ABRs remained high in pediatric PwHA with inhibitors receiving standard treatment. This study demonstrates the need for more effective treatments, with reduced treatment burden, to prevent bleeds, increase prophylaxis adherence, and improve patient outcomes.

KEYWORDS
blood coagulation factor inhibitors, emicizumab, FVIII, health-related quality of life, hemophilia A, noninterventional study

1 | INTRODUCTION

Management of pediatric persons with hemophilia and factor VIII (FVIII) inhibitors is challenging; acute bleeding episodes are difficult to treat and prophylaxis has limited efficacy, leaving individuals at higher risk of severe bleed-related complications compared with persons with hemophilia without FVIII inhibitors receiving FVIII prophylaxis.[1] Inadequately managed repeated bleeding episodes result in joint and muscle deterioration, significant physical disability, impaired function, and chronic pain, often within the first one to two decades of life,[2,3] and can affect the perceived health-related quality of life (HRQoL) of pediatric persons with hemophilia and FVIII inhibitors.[4]

Additionally, the burden of caring for a child with hemophilia and FVIII inhibitors dramatically impacts the caregiver, more than caring for a child with hemophilia without FVIII inhibitors.[5,6]

In pediatric persons with hemophilia and FVIII inhibitors, the goal is to prevent joint bleeding, reduce the risk of bleed-related joint damage, and maintain or improve HRQoL.[7] Few therapeutic options are available for persons with hemophilia A (PwHA) and FVIII inhibitors, which typically arise at a median age of ≤3 years in developed countries. Immune tolerance induction (ITI) involves frequent, prolonged infusions of FVIII to eradicate inhibitors.[8,9] Treatment may be required for many years, but is not always effective[10,11] and inhibitors may recur.[12] Bypassing agents (BPAs), used to manage bleeds prophylactically or episodically, have short half-lives, limited effectiveness,[13,14] and burdensome administration.[8,15] In pediatrics, the need for frequent intravenous infusions often necessitates use of central venous access devices, which are associated with increased risk of infections or thrombosis.[16,17]

While data on the challenges of managing pediatric PwHA with inhibitors in a real-world setting are limited, data from the DOSE study indicate high bleeding rates (median 13 bleeding episodes reported in the previous year) in PwHA (median [range] age 16.2 [1.6-60.9] years) that interfere with the daily activities of both patients and their caregivers.[18] Notably, bleed days were associated with significantly worse HRQoL than nonbleed days in this observational study.[18] More information regarding the management of pediatric PwHA with FVIII inhibitors would help guide the development of novel treatments for optimized management.

A multicenter noninterventional study (NIS; NCT02476942) was designed to prospectively collect data on bleeding events, treatment, safety, and HRQoL in PwHA with or without FVIII inhibitors treated per local clinical practice. Data from adolescent/adult PwHA with (Cohort A) and without inhibitors (Cohort C) in this NIS have been previously reported.[19,20] Here, we report data from pediatric PwHA with inhibitors (Cohort B).

Eligible participants were subsequently enrolled in HAVEN 2 (NCT02795767), a Phase III trial of emicizumab (HEMLIBRA®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), allowing intraindividual comparisons of bleed-related endpoints before and during emicizumab prophylaxis.[21] Emicizumab, a recombinant, humanized, bispecific, monoclonal antibody, improves hemostasis by bridging activated factor IX and factor X to replace the function of missing activated FVIII.[22] Emicizumab is approved in many countries for routine prophylaxis in PwHA with or without FVIII inhibitors of all ages.[23,24]

2 | METHODS

2.1 | Study setting and design

The setting and design of this global, multicenter, prospective NIS have been described previously[19] (Figure S1). Pediatric participants (Cohort B) were enrolled from February 2016 to July 2016 in China, Costa Rica, Germany, Spain, Italy, Japan, USA, and South Africa. The NIS was approved by local ethics review groups; legal guardians of pediatric participants signed informed consent, and participants signed informed assent where applicable.

Based on the minimum number of participants initially planned for HAVEN 2, the enrollment target for the NIS Cohort B was 30 participants. Participants were enrolled in the episodic or prophylactic group based on their current regimen. Treatments and assessments were conducted per routine clinical practice; no additional clinical or laboratory assessments were required. Study completion occurred when the

last participant was followed for 24 weeks, discontinued treatment, or switched to HAVEN 2.

2.2 | Study participants

Eligible participants were aged <12 years with congenital hemophilia A (HA) with high-titer FVIII inhibitor history (≥5 Bethesda units/mL) and current FVIII inhibitors, receiving either episodic or prophylactic BPAs, and had experienced ≥4 bleeds in the last 6 months (participants aged ≥2-11 years) or ≥2 bleeds in the previous 3 months (participants aged <2 years). Exclusion criteria were as follows: abnormal hematologic, hepatic or renal function; known thromboembolic disease; bleeding disorder other than hemophilia A; ongoing ITI with FVIII or FVIII prophylaxis; active significant infection; or known hypersensitivity against globulin preparations.[19] Participants who had previously undergone ITI that was not successful could participate in this study. Eligibility criteria and methods of data collection and follow up were similar to those in HAVEN 2.[21]

2.3 | Endpoints

The primary endpoint was the number of treated bleeds over time (bleeding rate). Other bleed-related endpoints included bleeding rates for all bleeds (treated and untreated) as well as the cause (traumatic, spontaneous, surgery/procedure), type (joint, muscle, other), and location (eg, elbow, ankle, knee, calf, buttock, other). Secondary endpoints were type of coagulation product, reason for treatment, adverse events (AEs), and HRQoL.

2.4 | Data collection

Demographic data and medical history from participants' medical records, AEs, and bleeds that qualified as serious AEs (SAEs; eg, life threatening or required hospitalization), and use of concomitant medications (other than coagulation products before/during the study) were recorded in the electronic case report form.

Bleeding events and hemostatic treatments were recorded daily by the participants' legally authorized representative through a bleed and medication questionnaire (BMQ) provided by the sponsor in an electronic handheld device. Details of the BMQ have been previously described.[19] Briefly, the BMQ included questions on bleed type, location, cause, and timing. No additional procedures to ascertain the validity of bleeding events as reported by participants or their caregivers were implemented. Participants reported use of hemophilia medication (timing and dose) and reason for treatment (bleed, usual prophylaxis, preventative dose before activity, or preventative dose for procedure/surgery). If participants missed an entry for a particular day, they could retrospectively enter data for up to 7 succeeding days.

Children aged 8-11 years self-reported HRQoL using the Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form (Haemo-QoL SF)[25] monthly via the electronic handheld device; caregivers of children aged 0-11 years completed the Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden (Adapted Inhib-QoL)[26] to obtain proxy HRQoL and aspects of the burden of hemophilia on the caregiver (Supporting Information Methods). Both HRQoL measures are scored from 0 to 100, with higher scores being reflective of greater impairments in HRQoL.[25,26]

2.5 | Data sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

2.6 | Analyses

There was no predefined hypothesis testing; all analyses were descriptive. Results are presented for all participants and separately by treatment regimen (episodic or prophylactic). Efficacy period (for bleed-related endpoints) and observation time (for safety reporting) were defined as the time between the day of handheld device activation and the date of study withdrawal or completion, whichever occurred first. Bleed definitions (adapted from standard criteria)[27] are consistent with HAVEN 2 (Supporting Information Methods).

Annualized bleeding rate (ABR) was derived using two methods. Model-based ABR was estimated via a negative binomial regression model, which accounted for different follow-up times (efficacy periods) as an offset in the model, and is reported with 95% confidence intervals (CIs). Median ABR was also calculated using the following equation: ABR = [(number of bleeds)/(number of days during efficacy period)] × 365.25, and is reported with interquartile ranges (IQRs). A summary of the incidence, cause, type, and location of bleeds was provided.

Participants were considered compliant with completing the BMQ if the questionnaire was completed at least every 8 days; reminders to enter data were sent daily via the electronic handheld device. The total number of days that participants were expected to complete the questionnaire was used to determine BMQ compliance rate.

Adherence with prophylaxis was evaluated in terms of dose administered and frequency of administration, and included participants in the prophylactic group with activated prothrombin complex concentrate (aPCC) prescription for >3 months during the study. Adherence with recombinant activated FVII (rFVIIa) was not assessed because only two participants were prescribed rFVIIa prophylaxis. Adherence with prescribed frequency of drug administration was categorized by

TABLE 1 Demographics and clinical characteristics

	Episodic n = 10	Prophylactic n = 14	All N = 24
Age			
Median (range) age, years	6.5 (2-11)	8.0 (3-11)	7.5 (2-11)
0 to <2, n (%)	0	0	0
2 to <6, n (%)	4 (40)	2 (14)	6 (25)
6 to <12, n (%)	6 (60)	12 (86)	18 (75)
Race, n (%)			
Caucasian	3 (30)	8 (57)	11 (46)
Asian	5 (50)	3 (21)	8 (33)
Black/African American	1 (10)	1 (7.1)	2 (8.3)
Multiple	0	1 (7.1)	1 (4.2)
Unknown	1 (10)	1 (7.1)	2 (8.3)
Bleeds in previous 6 months			
Participants, n	9[a]	14	23[a]
Mean (SD)	9.9 (4.6)	6.0 (2.9)	7.5 (4.1)
Median (range)	8.0 (4-17)	5.0 (4-15)	6.0 (4-17)
Previously treated with immune tolerance induction, n (%)	1 (10)	11 (79)	12 (50)

[a]Excludes one patient due to corresponding bleeds occurring in the previous 4 months, not 6 months, as reported by investigators based on medical records.

the proportion of weeks participants administered the required number of injections (high, >80%; moderate, 60-80%; low, <60%).[28,29] Adherence with prescribed dose was categorized by the proportion of administered doses versus prescribed dose (high, ≥80%; low, <80%).

3 | RESULTS

3.1 | Study population

Twenty-four male PwHA with FVIII inhibitors aged 2-11 (median 7.5) years were enrolled: 10 receiving episodic treatment and 14 receiving prophylaxis with BPAs (Table 1). Both the median (range) efficacy period and median (range) observation time in the episodic and prophylactic groups, respectively, were 31.2 (21.3-44.1) and 17.9 (8.7-36.4) weeks. All participants completed the study; six (60%) in the episodic group and 13 (92.9%) in the prophylactic group were eligible to subsequently enter HAVEN 2 (Figure S2).

Medical conditions were reported in three (30%) participants in the episodic group and seven (50%) in the prophylactic group (Table S1); conditions reported in more than one participant were seasonal allergy, attention-deficit hyperactivity disorder, and dermatitis. Proportions of participants receiving concomitant medications other than hemophilia medications were similar in the episodic (70%) and prophylaxis (71.4%) groups (Table S2); the most common medications were analgesics, nonsteroidal antiinflammatory drugs, and iron formulations. Compliance with BMQ reporting was high and stable during the study; 89.6 and 95.3% of the patient-reported outcome questionnaires were completed in the episodic and prophylactic groups, respectively.

3.2 | Bleed outcomes

Overall, 371 bleeds were experienced by 24 participants; 222 were treated (53.6% spontaneous; 46.4% traumatic; Figure S3). For all bleeds, the proportion of traumatic bleeds was 55.7% in the episodic group and 44.1% in the prophylactic group (Figure S3).

For treated bleeds, model-based ABR (95% CI) was 19.4 (13.2-28.4) and 18.5 (14.2-24.0) in the episodic and prophylactic groups, respectively; median ABR (IQR) was 18.1 (14.2-24.8) and 16.1 (11.0-25.8) (Figure 1; Table S3). For all bleeds in the episodic and prophylactic groups, respectively, model-based ABR (95% CI) was 32.7 (20.5-52.2) and 33.1 (22.4-48.9); median ABR (IQR) was 26.2 (14.5-31.9) and 17.2 (12.4-44.5). Most participants (80%, episodic; 85.7%, prophylaxis) had an ABR >10 for treated bleeds. In both treatment groups, ~40% of all bleeds were untreated, the majority (85.3%) of which were reported as "other" bleeds (bleeds by location presented in Table S4).

The most frequent types of treated bleeds were joint bleeds, primarily in the elbow and ankle (Table S4; Figure S4). In the episodic and prophylactic groups, treated joint bleed model-based ABR (95% CI) was 10.4 (5.2-20.9) and 8.3 (5.7-12.0), and median ABR (IQR) was 5.4 (4.3-14.8) and 6.2 (3.1-11.5), respectively (Table S3).

3.3 | Management with hemophilia treatments

Most participants (83.3%) received aPCC and 50% received rFVIIa (Table 2); ~33% in each group used both treatments. In the episodic and prophylactic groups, respectively, participants used a median (range) of 28 (3-124) and 134 (11-321) doses of aPCC and 25 (1-93) and 21 (3-193) doses of rFVIIa (Table 2).

In the episodic group, most participants used aPCC or rFVIIa for treatment of bleeding (70 and 60%, respectively); fewer used aPCC or rFVIIa prior to activity (30 and 10%, respectively), and 10% used rFVIIa prior to a procedure/surgery (Table 2). One participant switched from episodic to prophylactic treatment halfway through his efficacy period, but was included in the episodic group for data analysis.

In the prophylactic group, most participants (92.9%) used aPCC for treatment of bleeding, whereas only 28.6% used rFVIIa. Few patients used aPCC or rFVIIa prior to activity (14.3 and 7.1%, respectively); 14.3% used rFVIIa prior to a procedure/surgery (Table 2).

3.4 | Adherence with prophylaxis

Adherence with prophylaxis was evaluated in participants in the prophylactic group who received aPCC (12/14); participants who received

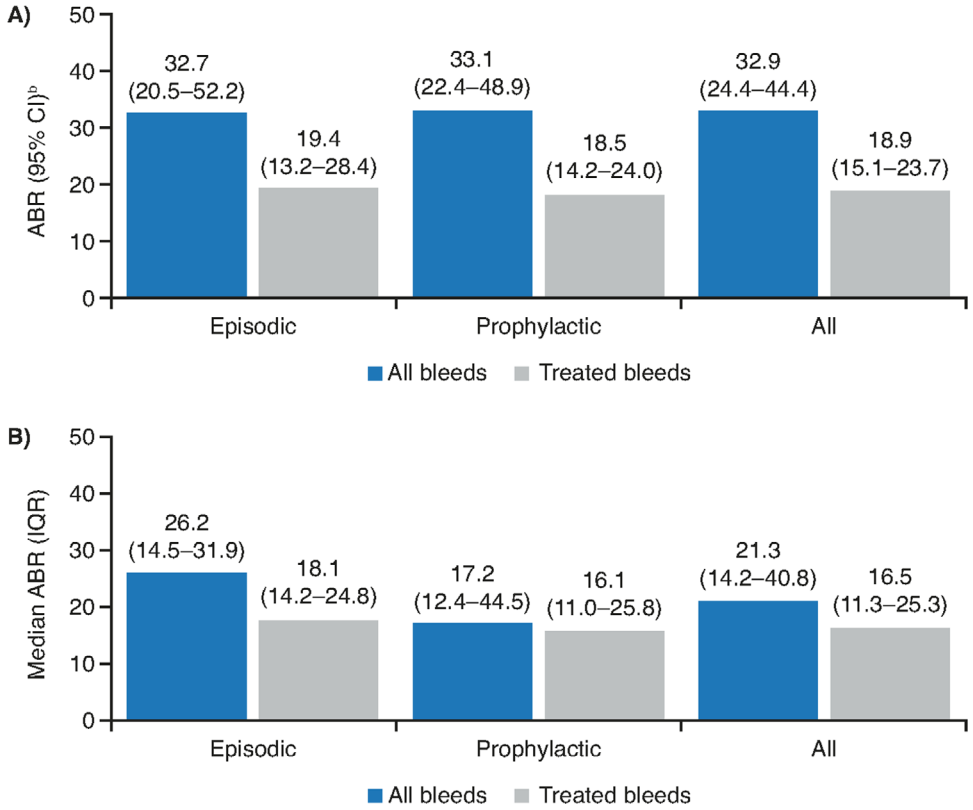

FIGURE 1 Annualized bleed rates.[a] A, Model-based ABR (95% CI). B, Calculated median ABR (IQR). [a]All bleeds comprised both treated and untreated bleeds. All bleeds were included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure were excluded. An event was considered a treated bleed if coagulation factors were administered to treat signs of bleeding (pain, swelling, etc), irrespective of the time between the bleed and the treatment. [b]Negative binomial regression model. ABR, annualized bleeding rate; CI, confidence interval; IQR, interquartile range

rFVIIa (2/14) were excluded due to the small patient number. Participants received a median (range) of 7.45 (0.4-14.0) aPCC doses/week, including those administered for treatment of breakthrough bleeds. The median (range) administered dose of aPCC prescribed for prophylaxis was 69.30 (44.0-90.6) units/kg. The median proportion of weeks that participants were adherent to their prescribed frequency of aPCC administration was 91% (range 20-100%). Overall, 58.3% of participants adhered to their prescribed frequency of aPCC administration for >80% of study weeks, 8.3% for 60-80% of study weeks, and 33.3% for <60% of study weeks. All participants except one (91.7%) adhered to their prescribed dose of aPCC, of whom 50% also adhered to the frequency of dosing (Table 3).

3.5 | Safety outcomes

The only AE reported in ≥3 participants in either treatment arm was upper respiratory tract infection (3/14 prophylactic group). Approximately 30% of participants in each group experienced SAEs (Table 4). The most common SAEs were hemarthrosis (1/10 episodic group; 2/14 prophylactic group) and mouth hemorrhage (2/10 episodic therapy; 1/14 prophylaxis).

Six traumatic bleeds that qualified as SAEs were reported in four participants: one event in one participant in the episodic group and five events in three participants in the prophylactic group. The most frequent cause of trauma was strenuous activity. There were no fatal AEs and no participant was withdrawn from the study due to AEs.

3.6 | HRQoL

The Haemo-QoL SF was completed by three of four eligible participants (aged 8-11 years) in the episodic group, and eight of eight participants in the prophylactic group. The Adapted Inhib-QoL was completed by all caregivers (n = 24).

Mean scores at baseline across the majority of HRQoL domains on both measures indicated functional impairments. The greatest impairments were seen in the "Sports & School" and "Family" domains for the Haemo-QoL SF (Table S5), and the "Dealing with Inhibitor" domain for the Adapted Inhib-QoL (Table S6).

Mean scores did not change substantially over the study period for "Physical Health" (Figure 2) or other domains (Figure S5), whether reported by children (Haemo-QoL SF) or caregivers (Adapted Inhib-QoL).

TABLE 2 Hemophilia treatments

	Episodic n = 10	Prophylactic[a] n = 14	All[a] N = 24
Total participants with ≥1 treatment, n (%)	10 (100)	14 (100)	24 (100)
Reason for treatment			
Treatment for bleed	10 (100)	13 (93)	23 (96)
Usual prophylaxis dose	1 (10)[b]	14 (100)	15 (63)
Preventive dose before activity	4 (40)	2 (14)	6 (25)
Preventative dose for procedure/surgery	1 (10)	2 (14)	3 (13)
Participants treated with aPCC, n (%)	7 (70)	13 (93)	20 (83)
Number of doses, median (range)[c]	28 (3-124)	134 (12-321)	103 (3-321)
aPCC cumulative dose, median (range), U/kg[c]	2344.4 (96-11 395)	8920.7 (638-15 757)	6656.1 (96-15 757)
Number of bleeds treated with aPCC only, n	72	68	140
aPCC dose administered per bleed, median (range), U/kg	140.9 (15.3-1581.4)	360.8 (33.3-2378.4)	216.1 (15.3-2378.4)
Number of aPCC doses per bleed, median (range)	2.0 (1-17)	4.0 (1-26)	3.0 (1-26)
Reason for treatment			
Treatment for bleed	7 (70)	13 (93)	20 (83)
Usual prophylaxis dose	1 (10)[b]	13 (93)	14 (58)
Preventive dose before activity	3 (30)	2 (14)	5 (21)
Preventative dose for procedure/surgery	0	0	0
Participants treated with rFVIIa, n (%)[d]	6 (60)	6 (43)	12 (50)
Number of doses, median (range)[c]	25 (1-93)	21 (3-197)	21 (1-197)
rFVIIa cumulative dose, median (range), μg/kg[c]	7453.7 (71-26 390)	2928.1 (632-24 035)	5313.1 (71-26 390)
Number of bleeds treated with rFVIIa only, n	45	15	60
rFVIIa dose administered per bleed, median (range), μg/kg	603.5 (156.3-4400.0)	533.3 (174.4-5945.9)	591.7 (156.3-5945.9)
Number of rFVIIa doses per bleed, median (range)	2.0 (1-42)	2.0 (1-52)	2.0 (1-52)
Reason for treatment			
Treatment for bleed	6 (60)	4 (29)	10 (42)
Usual prophylaxis dose	1 (10)[b]	2 (14)	3 (13)
Preventive dose before activity	1 (10)	1 (7.1)	2 (8.3)
Preventative dose for procedure/surgery	1 (10)	2 (14)	3 (13)
Participants treated with both aPCC and rFVIIa, n (%)	3 (30)	5 (36)	8 (33)
Number of bleeds treated with aPCC and rFVIIa, n	4	18	22
aPCC dose administered per bleed, median (range), U/kg	245.8 (66.7-1357.1)	66.7 (58.0-1648.4)	66.7 (58.0-1648.4)
Number of aPCC doses per bleed, median (range)	4.0 (1-16)	1.0 (1-20)	1.0 (1-20)
rFVIIa dose administered per bleed, median (range), μg/kg	2301.9 (71.4-3703.7)	1171.1 (110.0-2600.0)	1171.1 (71.4-3703.7)
Number of rFVIIa doses per bleed, median (range)	1.0 (1-9)	6.0 (1-12)	5.5 (1-12)

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; ITI, immune tolerance induction; NIS, noninterventional study; rFVIIa, recombinant activated factor VII.

[a]One participant in the prophylactic group initiated ITI during the NIS and received standard half-life FVIII.

[b]One participant in the episodic group reported usual prophylaxis doses for both aPCC and rFVIIa due to switching to prophylactic treatment during the NIS.

[c]All hemophilia-related treatments, including treatment for bleeds, usual prophylaxis, and preventative doses.

[d]Prophylactic treatment with rFVIIa is not defined in the drug label.

4 | DISCUSSION

This study prospectively collected data from a pediatric cohort of PwHA with FVIII inhibitors treated episodically or prophylactically with BPAs per local clinical practice.

The current standard-of-care treatment for pediatric PwHA who have developed inhibitors to FVIII includes a trial of ITI, where available.[30] Half of the participants in this NIS had previously undergone ITI (Table 1).

Bleeding rates in the NIS were high, with no notable difference between the episodic and prophylaxis groups for treated and all bleeds.

TABLE 3 Adherence with aPCC prophylaxis by frequency of prescribed dose

	Participants prescribed aPCC n = 12	
Adherence with prescribed frequency of aPCC administration	≥80% Adherent doses	<80% Adherent doses
>80% Adherent weeks, participants, n (%)	6 (50)	1 (8.3)
60-80% Adherent weeks, participants, n (%)	1 (8.3)	0
<60% Adherent weeks, participants, n (%)	4 (33)	0

Abbreviation: aPCC, activated prothrombin complex concentrate.

TABLE 4 Safety summary

Adverse event	Episodic n = 10	Prophylaxis n = 14	All N = 24
Total number of AEs	12	28	40
Total participants experiencing ≥1 AE, n (%)	6 (60)	9 (64)	15 (63)
Fatal AE	0	0	0
Serious AE	3 (30)	4 (29)	7 (29)
Grade ≥3 AE	3 (30)	4 (29)	7 (29)
Participants with HA-associated events reported as SAEs,[a] n (%)			
Hemarthrosis	1 (10)	2 (14)[b]	3 (13)
Mouth hemorrhage	2 (20)	1 (7.1)	3 (13)
Muscle hemorrhage	0	2 (14)	2 (8.3)
Upper gastrointestinal hemorrhage	0	1 (7.1)	1 (4.2)
Puncture site hemorrhage	0	1 (7.1)	1 (4.2)
Hematuria	0	1 (7.1)	1 (4.2)
Hematoma	0	1 (7.1)	1 (4.2)

Abbreviations: AE, adverse event; HA, hemophilia A; SAE, serious adverse event.

[a]Some participants reported more than one SAE; bleeds were not reported as AEs unless they qualified as serious AEs.

[b]In the prophylaxis group, two participants experienced nine serious AEs of hemarthrosis; two events (22%) were caused by trauma and seven (78%) were spontaneous bleeds.

The similar bleeding rates may have been confounded by several factors; in particular, the requirement for patients to have experienced a minimum number of bleeds to participate in the study, regardless of prior treatment regimen, and the tendency to prescribe prophylactic therapy to patients with a higher frequency of bleeding. While this NIS contributes additional bleed data in line with previous studies,[14,31-33] direct comparisons with the literature are not straightforward due to the lack of standardized bleed definitions and methodologies for data collection.

There was a high incidence of treated joint bleeds in both the episodic and prophylactic groups. Of all bleeds, most were reported as "other" possibly due to the high incidence of bruises or hematomas resulting from high physical activity in children. Similar proportions of participants used aPCC and rFVIIa in the episodic group; in the prophylactic group, however, aPCC was the most commonly used agent, consistent with the fact that aPCC is the only product with a label for prophylaxis in most countries.

Half of the participants had high adherence with prescribed aPCC prophylaxis in terms of frequency of administration and prescribed dose. The number of weekly administered prophylactic doses of aPCC was high (median 7.45 doses/week), revealing a substantial burden of treatment for these children and their caregivers. This burden was further highlighted by the impairments in HRQoL reported by patients and their caregivers in both treatment groups. Impairments were maintained throughout the study, with little variation in scores between the two groups. Despite adherence with aPCC prophylaxis, bleeding rates were high and similar to those seen in the episodic group, highlighting a need for more effective treatment in this population. The NIS provides data that differentiates between treated and all bleeds, thus revealing that a substantial proportion of bleeds were untreated in pediatric PwHA with inhibitors regardless of treatment regimen, which may reflect the high treatment burden and limited efficacy of BPAs.[8,13-15]

Bleed-related outcomes in adolescent/adult PwHA and FVIII inhibitors in this NIS were previously reported.[19] Differences between the adolescent/adult and the pediatric populations were observed. For treated bleeds, ABRs (model-based and median) were higher in children versus adolescents/adults, with a greater difference between the prophylactic groups than the episodic groups (Table S3). For treated joint bleeds, the higher ABR observed in children versus adolescents/adults may be explained by the different methods of data collection for joint bleeds in these cohorts. For adolescents/adults, reports of aura in combination with at least one other joint bleed symptom (eg, increased swelling/warmth of the skin over the joint, increased pain, progressive loss of range of motion, or difficulty using the limb as compared with baseline) were required for a joint bleed to be recorded. For children, suspected joint bleeds were recorded as such regardless of the number of symptoms because it was not considered reliable to collect information from the caregiver on the joint bleed symptoms in children. In addition, children may be more likely to experience bleeds due to greater activity and a higher incidence of trauma.

A greater proportion of pediatric participants adhered to aPCC prophylaxis versus adolescents/adults (50% vs 35%),[19] possibly due to caregiver involvement in the pediatric cohort and recognition of the importance of early prophylaxis to prevent joint damage.[34-38] A difference in treatment burden was observed in children versus adolescents/adults; median administered aPCC dose was 7.45 versus 3.0 doses/week, respectively. It should be noted, however, that these results include aPCC doses used to treat bleeding events as well as

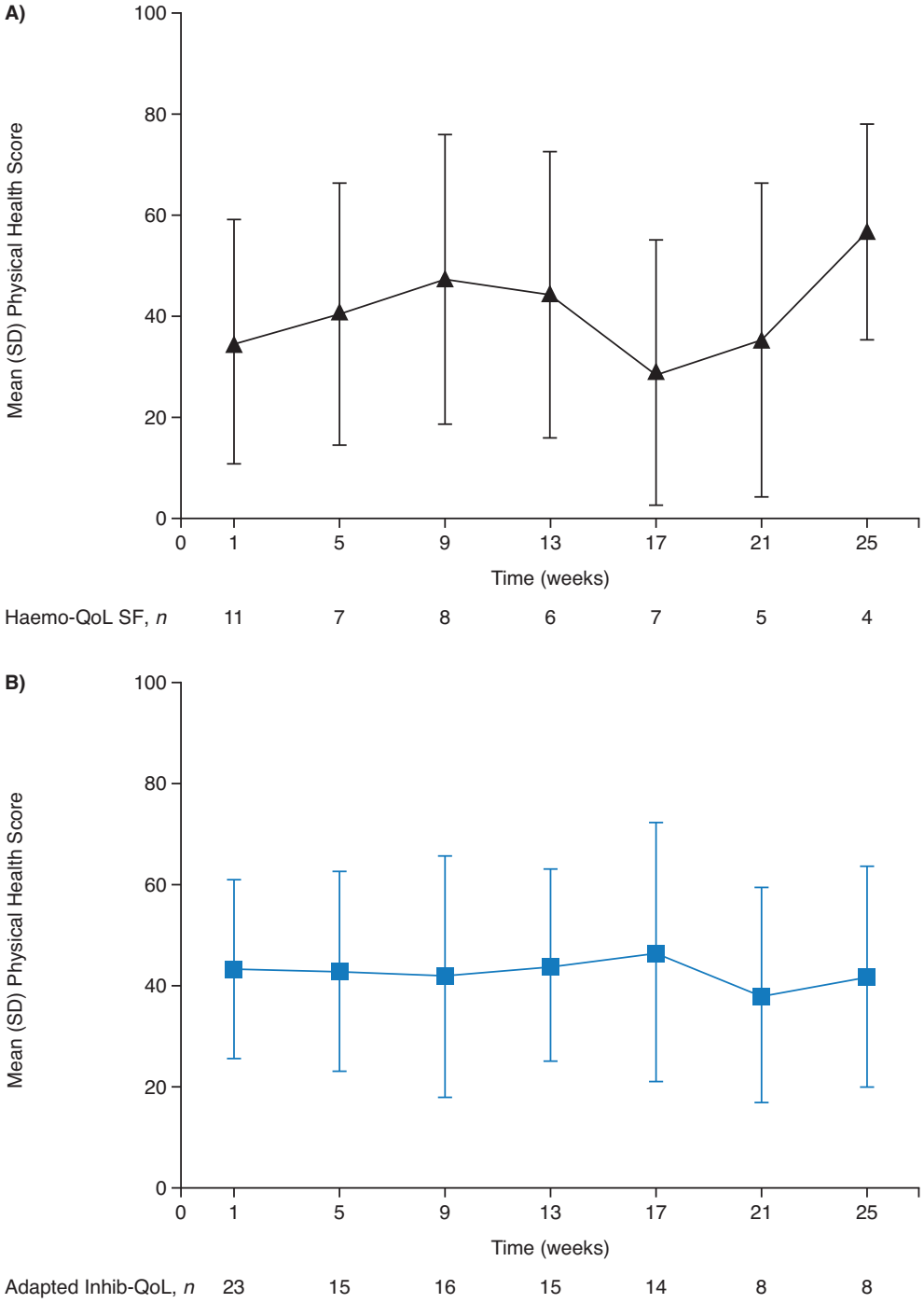

FIGURE 2 Physical health domain scores over time for (A) Haemo-QoL SF and (B) Adapted Inhib-QoL. Baseline measurements were taken at Week 1. High values in Haemo-QoL SF and Adapted Inhib-QoL imply high impairments in HRQoL. Adapted Inhib-QoL, Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden; Haemo-QoL SF, Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form; HRQoL, health-related quality of life; SD, standard deviation

for usual prophylaxis, and the higher treatment burden in children may also be due to the higher treated bleed ABR in children (16.1) versus adolescents/adults (8.8).[19]

Despite the prospective nature of this NIS and its granular data collection methods, the interpretation of these results may potentially be limited by study eligibility criteria. Participants were required to have had a minimum number of bleeds during the 6 months prior to the study; thus, investigators may have selected participants with significant bleeding on current standard therapy who they deemed would benefit the most from emicizumab therapy in the subsequent Phase III trial. Therefore, the study population was likely to include individuals with a severe bleeding phenotype, and bleeding rates observed in this

study may be an overestimate for the general population of pediatric PwHA and inhibitors.

This NIS provides data on the current standard-of-care treatment with episodic or prophylactic hemophilia regimens in pediatric PwHA and inhibitors. Although the study inclusion criteria required participants to have experienced a minimum number of bleeds in the previous 6 months, reported outcomes showed high bleeding rates despite high adherence to prophylaxis. These children experienced a high treatment burden with numerous weekly infusions and notable incidence of hemarthrosis, as well as concomitant impairments in HRQoL, suggesting that there remains a substantial unmet need for improved treatment options in this patient population.

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CONFLICT OF INTEREST

Johannes Oldenburg has received consultancy from Baxter, Bayer, Biotest, Biogen, CSL, Grifols, Novo Nordisk, Octapharma, Chugai, Pfizer, Roche, Baxalta, and Sobi; honoraria from Baxter, Bayer, Biotest, Biogen, CSL, Grifols, Novo Nordisk, Octapharma, Chugai, Pfizer, Roche, Baxalta, and Sobi; research funding from Baxalta (investigator clinical studies), Baxter, Bayer, Biotest, CSL, Grifols, Novo Nordisk, and Octapharma; and has membership on an entity's board of directors or advisory committees for Baxter, Bayer, Biotest, Biogen, CSL, Grifols, Novo Nordisk, Octapharma, Chugai, Pfizer, Roche, Baxalta, and Sobi. Midori Shima has received consultancy from Biogen, Baxalta, and Chugai; research funding from Bayer, Novo Nordisk, Pfizer, Baxalta, Chugai, and CSL; honoraria from Bayer, Novo Nordisk, Pfizer, Biogen, Baxalta, Chugai, Kaketsuken, and CSL; and has membership on an entity's board of directors or advisory committees for Baxalta and Chugai. Rebecca Kruse-Jarres has received honoraria from Baxalta, Bayer, CSL Behring, Grifols, Pfizer, and Roche; and research funding from Pfizer and Roche. Elena Santagostino has received honoraria from Bayer, Pfizer, CSL Behring, Novo Nordisk, Grifols, Sobi, Octapharma, Kedrion, Roche, Shire/Takeda, Bioverativ, Spark, and Uniqure. Johnny Mahlangu has received research grants from Bayer, Biogen, CLS, Novo Nordisk, and Roche; and is a member of advisory committees for Baxalta, Biogen, CLS, Novo Nordisk, and Roche; received speaker's bureau fees from Amgen, Bayer, Biogen, Biotest, and CLS. Maria Elisa Mancuso has received personal fees from Bayer, CSL Behring, Novo Nordisk, Roche, Octapharma, Pfizer, Sobi/Biogen, Bioverativ, Baxalta/Shire, Biotest, Kedrion, and Grifols. Victor Jiménez-Yuste has received grants from Novo Nordisk, Shire/Takeda, Bayer, Pfizer, Grifols, Sobi, and Octapharma; and personal fees from Novo Nordisk, Shire/Takeda, Bayer, Pfizer, Grifols, Sobi, Octapharma, CSL Behring, and Roche. Sylvia von Mackensen is a consultant for Roche. Nives Selak Bienz is an employee of F. Hoffmann-La Roche Ltd. Sammy Chebon, Michaela Lehle, and Elina Asikanius are employees of and hold stocks/shares in F. Hoffmann-La Roche Ltd. Peter Trask and Gallia G. Levy are employees of Genentech Inc. and hold stocks/shares in F. Hoffmann-La Roche Ltd.

AUTHOR CONTRIBUTIONS

Johannes Oldenburg, Midori Shima, Rebecca Kruse-Jarres, Johnny Mahlangu, and Victor Jiménez-Yuste contributed to the study design, collected data for this study, and contributed to the interpretation of the data. Elena Santagostino and Maria Elisa Mancuso collected data for this study and contributed to the interpretation of the data. Michaela Lehle, Elina Asikanius, Peter Trask, and Gallia G. Levy contributed to the study design and participated in both the analysis and interpretation of the data. Nives Selak Bienz and Sammy Chebon participated in both the analysis and interpretation of the data. Sylvia von Mackensen contributed to the interpretation of the data. All authors were involved with drafting of this article and revising it critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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