Received: 19 April 2018 | Revised: 6 July 2018 | Accepted: 26 August 2018

DOI: 10.1111/hae.13612

ORIGINAL ARTICLE

Clinical haemophilia

WILEY Haemophilia

Bleeding events and safety outcomes in persons with haemophilia A with inhibitors: A prospective, multi-centre, non-interventional study

Johnny Mahlangu[1] | Johannes Oldenburg[2] | Michael U. Callaghan[3] | Midori Shima[4] | Elena Santagostino[5] | Maggie Moore[6] | Michael Recht[7] | Claudia Garcia[8] | Renchi Yang[9] | Michaela Lehle[10] | Harrison Macharia[10] | Elina Asikanius[10] | Gallia G. Levy[11] | Rebecca Kruse-Jarres[6]

[1]Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa

[2]Department of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany

[3]Children's Hospital of Michigan, Detroit, Michigan

[4]Department of Pediatrics, Nara Medical University, Kashihara, Nara, Japan

[5]Fondazione IRCCS Ca' Granda Foundation, Ospedale Maggiore Policlinico, Milan, Italy

[6]Washington Center for Bleeding Disorders at Bloodworks Northwest, Seattle, Washington

[7]Oregon Health & Science University, Portland, Oregon

[8]Haematology Department, Hospital Mexico, San Jose, Costa Rica

[9]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China

[10]F. Hoffmann-La Roche Ltd, Basel, Switzerland

[11]Genentech, Inc., South San Francisco, California

Correspondence
Johnny Mahlangu, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa.
Email: johnny.mahlangu@nhls.ac.za

Funding information
F. Hoffmann-La Roche

Abstract

Introduction: Prospectively collected, real-world data on bleeds, haemophilic treatment and safety outcomes in persons with haemophilia A (PwHA) with factor VIII (FVIII) inhibitors are limited. A prospective, global, multi-centre, non-interventional study (NIS; NCT02476942) collected detailed real-world data in PwHA treated per local routine clinical practice.

Aim: To characterize bleeding rates, haemophilic treatment practices, prophylaxis adherence and adverse events (AEs) in adult/adolescent PwHA with inhibitors in the NIS.

Methods: Participants aged ≥12 years with congenital haemophilia A/documented high-titre FVIII inhibitor history were enrolled. Participants remained on their usual treatment; no interventions were applied.

Results: Overall, 103 PwHA with inhibitors enrolled, (median [range] age 31 [12-75] years) and were monitored for median (range) 26.0 (4.1-69.6) weeks. In the episodic (n = 75) and prophylactic (n = 28) treatment groups, respectively, 1244 and 325 bleeds were reported, and 528 (42.4%) and 104 (32.0%) were not treated; annualized bleeding rates (ABRs; 95% confidence interval) were 18.6 (15.2-22.8) and 14.9 (10.5-21.2) for treated bleeds, and 32.7 (27.3-39.1) and 25.0 (18.4-34.0) for all bleeds. Coagulation products used included activated prothrombin complex concentrate (aPCC) and/or recombinant activated FVII. Among participants prescribed aPCC prophylaxis, 35.0% adhered to both prescribed frequency of aPCC administration and prescribed dose. Serious AEs of haemarthrosis and muscle haemorrhage were reported; most common AEs were arthralgia, viral upper respiratory tract infection and pyrexia.

Conclusions: ABRs (treated bleeds and all bleeds) remain high on standard treatment; this prospective NIS demonstrates the need for more effective treatments for PwHA

with inhibitors to reduce/prevent bleeds, with potential to improve prophylaxis adherence and further improve outcomes.

KEYWORDS
blood coagulation factor inhibitors, factor VIII, haemophilia A, non-interventional study, observational study, prospective study

1 | INTRODUCTION

Haemophilia A is characterized by a coagulation factor VIII (FVIII) deficiency, leaving individuals at high risk of frequent bleeding,[1] especially in the joints, leading to arthropathy and poor quality of life.[2,3] Replacement therapy with FVIII concentrate is the standard of care for persons with haemophilia A (PwHA). Approximately 30% of PwHA develop anti-FVIII alloantibodies (inhibitors)[4,5] that diminish or abolish FVIII replacement therapy efficacy,[6] thereby increasing morbidity and mortality.[7,8]

Current standard therapies for PwHA with inhibitors are limited to immune tolerance induction (ITI) to eliminate inhibitors and bypassing agents (BPAs) to prevent or treat bleeding. ITI is demanding, expensive, requires frequent and prolonged infusions and is not always effective.[8,9] The only broadly available BPAs are activated prothrombin complex concentrate (aPCC; FEIBA VH; Shire, Dublin, Ireland[10]) and recombinant activated FVII (rFVIIa; NovoSeven® RT; Novo Nordisk, Bagsvaerd, Denmark[11]), which both require frequent dosing[12] and have suboptimal efficacy.[8,13-15]

Real-world data on bleeding events, bleeding treatments and safety outcomes with the current standard of care for PwHA are often retrospective and may be based on variable or poorly defined endpoints.[16-19] This non-interventional study (NIS; NCT02476942) prospectively collected high-quality, detailed real-world data in PwHA with and without inhibitors treated according to local routine clinical practice. Eligible NIS participants were subsequently able to enrol into a phase 3 study of emicizumab, a subcutaneously administered recombinant humanized bi-specific monoclonal antibody that restores missing FVIIIa function and effective haemostasis by bridging FIXa and FX.[20] This enabled intra-individual comparisons of outcomes before and during emicizumab prophylaxis. Emicizumab is approved (HEMLIBRA®; F. Hoffmann-La Roche, Basel, Switzerland) in several countries for prophylaxis in PwHA with inhibitors in patients of all ages.[21,22]

The objective of this analysis of the NIS was to characterize bleeding events, coagulation product use, adherence to prophylaxis and safety outcomes in adult and adolescent PwHA with inhibitors (Cohort A); health-related quality of life and health status outcomes for this cohort will be reported separately. Cohorts B and C of the NIS include PwHA with inhibitors aged <12 years and PwHA without inhibitors aged ≥12 years, respectively, also to be reported separately.

2 | MATERIALS AND METHODS

2.1 | Study setting and design

This global, multi-centre, prospective NIS enrolled PwHA from 26 May 2015 to 3 February 2016 in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice, principles of the Declaration of Helsinki[23] and local ethics review groups. Participants from Cohort A were enrolled at 33 sites in 12 countries (Appendix S1). Participants and/or legally authorized representatives gave written informed consent/assent before study enrolment. The last participant completed the study on 17 March 2017.

Participant enrolment in Cohort A was estimated based on the approximate number initially planned for the subsequent phase 3 emicizumab study, HAVEN 1 (NCT02622321).[24] Participants were enrolled in the episodic or prophylactic groups based on their treatment regimen at study enrolment, with no protocol-specified interventions (Appendix S2). Study completion occurred when the last participant was either followed for 24 weeks or switched to HAVEN 1.

2.2 | Study participants

Eligible participants were aged ≥12 years with congenital haemophilia A (any severity), a documented history of high-titre FVIII inhibitors (≥5 Bethesda units/mL), documented episodic or prophylactic BPA use for ≥6 months and ≥6 or ≥2 bleeds in the last 6 months on episodic or prophylactic treatment, respectively. Exclusion criteria are described in Appendix S3. Eligibility criteria, data collection and follow-up in the NIS were similar to those used in the subsequent HAVEN 1 study.[24]

2.3 | Endpoints

The primary endpoint was the number of bleeds over time (bleeding rate) for treated bleeds. Additional bleed-related endpoints included all bleeds (both treated and not treated with coagulation products) and cause, type and location of bleeds. Secondary endpoints included type and purpose of coagulation product used and adverse events (AEs); health-related quality of life data will be reported separately.

2.4 | Data collection

Demographic data and medical history were collected from participants' medical records on an electronic case report form (eCRF). Concomitant medications (other than coagulation products for bleed treatment) were also recorded in the eCRF by investigators.

Participants/caregivers used an electronic handheld device to complete a sponsor-developed bleed/medication questionnaire (BMQ). The BMQ included questions on timing of bleed (day, start time), cause of bleed (trauma or surgery/procedure, and if neither assigned to spontaneous), bleed type (joint bleed, muscle bleed, soft tissue or miscellaneous bleed or bruise/haematoma) and location of each type of bleed (eg, hip, elbow, wrist, shoulder, knee or ankle). Participants administered and reported haemophilic medication use (timing of doses and dose of coagulation product), as per investigator-determined dosing and duration of treatment for bleeds and in accordance with local clinical practice and local labelling. Purpose of coagulation product use was reported according to 4 categories (treatment for bleed, usual prophylaxis, one-time prophylaxis and procedure/surgery). Although asked to complete the BMQ daily, participants also could retrospectively enter data for the 3 preceding days. Investigators were instructed to review the data with participants during every clinic visit or monthly phone call. If a participant was unable to enter data for any reason, the investigator was able to do so, in agreement with the participant.

Throughout the study, all AEs were recorded in the eCRF by investigators. Serious AEs (SAEs) were as defined in the International Conference on Harmonisation Guidelines for Good Clinical Practice. Bleeds fulfilling SAE criteria (ie, needed hospitalization) were to be reported as SAEs in the eCRF, while bleeds not fulfilling SAE criteria were to be reported in the BMQ only.

Bleed definitions were adapted from standard criteria defined by the Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis.[25] Treated bleeds were defined as events requiring administration of coagulation factors for signs of bleeding (eg, pain and swelling). Joint bleeds were defined as bleeds producing an unusual joint sensation, and increasing swelling or warmth of the skin over the joint, increasing pain or progressive loss of range of motion or use of the limb. Spontaneous bleeds were those with no known contributing factor. Traumatic bleeds had a known or suspected cause. Bleeds and haematomas related to procedure/surgery or invasive diagnostic procedures were not counted as bleeds. Additional bleed definitions were previously published.[24]

2.5 | Analyses

The NIS was not designed as a confirmatory study; thus, all analyses were descriptive. Results are presented for all participants and by episodic or prophylactic treatment based on participants' initial group assignments by the investigator. The efficacy period (for bleed-related endpoints) and observation time (for safety reporting) began on the first day each individual had the opportunity to report bleed or coagulation product data, and ended on the date of withdrawal from the NIS or study completion, whichever occurred earlier.

2.6 | Primary analysis

Annualized bleeding rate (ABR) was derived using 2 methods. Model-based ABR was estimated using a negative binomial regression model, including an offset variable to account for individual follow-up times (efficacy periods), and was reported with 95% confidence intervals (CIs). Calculated ABR was derived using the following equation: ABR = [(number of bleeds)/(number of days during efficacy period)] × 365.25 and was reported as median and interquartile range (IQR). A summary of the number, type, location and cause was provided for all bleeds.

2.7 | Secondary analysis

Coagulation product use (number of doses and cumulative dose) was characterized by frequency tables and summary statistics. The purpose of haemophilic treatment use was summarized as the proportion of participants reporting each possible category for all treatments over the course of the study. The number of participants with an AE or SAE and numbers of AEs and SAEs were summarized.

2.8 | Other analyses

A participant was considered compliant with reporting BMQ data if bleeding events and bleed medications were entered at least every 4 days (reminders to enter data were sent daily via the electronic device). BMQ compliance rate was based on the total number of participants expected to complete the questionnaire during the study.

Participants in the prophylactic group with an aPCC prescription for ≥3 months during the study were included in the analysis of adherence to aPCC prophylaxis during the efficacy period. Adherence to the prescribed frequency of drug administration was categorized by the proportion of fully compliant weeks (ie, participant administered the required number of injections for >80%, 60%-80% or <60% of study weeks). Adherence to prescribed dose was categorized by the proportion of administered dose compared with the prescribed dose (≥80% or <80%). Adherence to the prescribed frequency of administration as per adherence to prescribed doses was also described. Adherence to rFVIIa prophylaxis was not assessed because prophylaxis is not defined in the drug label,[11] and only 4 of 11 participants in the prophylactic group treated with rFVIIa had a prescription exclusively for rFVIIa prophylaxis.

3 | RESULTS

3.1 | Study population

All but 1 of the 103 participants were male (episodic, n = 75; prophylaxis, n = 28; Table 1). One participant withdrew due to unknown

TABLE 1 Participant demographics and characteristics

Characteristic	Episodic (n = 75)	Prophylaxis (n = 28)	All (N = 103)
Sex, n (%)			
Male	74 (98.7)	28 (100.0)	102 (99.0)
Female	1 (1.3)	0	1 (1.0)
Age, years			
Median (range)	33 (13-75)	23 (12-75)	31 (12-75)
≥12 and <18, n (%)	8 (10.7)	9 (32.1)	17 (16.5)
≥18, n (%)	67 (89.3)	19 (67.9)	86 (83.5)
Race, n (%)			
White	41 (54.7)	18 (64.3)	59 (57.3)
Asian	25 (33.3)	8 (28.6)	33 (32.0)
Black/African American	9 (12.0)	1 (3.6)	10 (9.7)
Multiple	0	1 (3.6)	1 (1.0)
Median (range) bleeding events in 6 months before entry to NIS, n[a]	8.0 (6-48)	4.5 (2-48)	7.0 (2-48)
Previously treated with immune tolerance induction, n (%)	6 (21.3)	16 (57.1)	32 (31.1)

NIS, non-interventional study.
[a]Collected from participant medical records and documented in the electronic case report form.

reasons before reporting any bleed or treatment data. Overall, the median (range) age was 31 (12-75) years. Participants in the episodic group were older than those in the prophylactic group. More than half of the participants were white (57.3%), and approximately one-third were Asian (32.0%). The highest number of participants was enrolled in the United States (14 episodic and 8 prophylaxis), followed by China (13 episodic and 1 prophylaxis; Appendix S1). Both the median (range) efficacy period and observation time were 25.4 (4.1-69.6) weeks in the episodic group and 26.9 (8.1-49.3) weeks in the prophylactic group. A total of 91 (88.3%) participants completed the study (reasons for discontinuation in Appendix S2); 68 subsequently entered HAVEN 1. Twelve participants discontinued before completing the study, 1 of which entered HAVEN 1.

The most common comorbidities at the initial visit were hepatitis C (including chronic hepatitis C) and hypertension (Appendix S4). The proportions of participants receiving concomitant medications were comparable for the episodic and prophylactic regimens (72.0% and 75.0%, respectively). Most commonly administered medication classes included analgesics, non-steroidal anti-inflammatory agents and opioid analgesics. Prior ITI use (episodic, 21.3%; prophylaxis, 57.1%) was consistent with rates reported by Carcao et al.[26]

Compliance with BMQ reporting was high and stable over the duration of the study; 94.6% and 84.2% of questionnaires were completed in the episodic and prophylactic groups, respectively.

3.2 | Bleed outcomes

In total, 1244 and 325 bleeds were reported by participants on episodic and prophylactic regimens, respectively (Table 2). A substantial proportion of bleeds were not treated in either the episodic or prophylactic groups (528 [42.4%] and 104 [32.0%], respectively); overall, 64% were spontaneous bleeds and 36% were traumatic.

Of treated bleeds, 57.6% were spontaneous and 42.4% were due to trauma; 42.7% of spontaneous bleeds and 36.7% of traumatic bleeds were not treated (Table 2). Overall, 71.2% of treated bleeds occurred in the joints. In the episodic and prophylactic groups, respectively, the most frequent locations for treated joint bleeds were the knees (29.8% and 32.7%), elbows (24.6% and 21.1%) and ankles (19.6% and 27.2%).

For all bleeds, most participants had an ABR >10 in the episodic (67 [89.3%]) and prophylactic (21 [75.0%]) groups. ABR (95% CI) for treated and all bleeds, respectively, was 18.6 (15.2-22.8) and 32.7 (27.3-39.1) with episodic treatment and 14.9 (10.5-21.2) and 25.0 (18.4-34.0) with prophylaxis (Figure 1A). Median (IQR) calculated ABR for treated and all bleeds, respectively, was 14.1 (6.5-25.9) and 21.7 (14.1-40.4) with episodic treatment, and 8.8 (5.3-17.2) and 16.8 (10.1-36.2) with prophylaxis (Figure 1B).

3.3 | Haemophilia A treatments

Among all 103 participants, the most commonly used haemophilia A treatment was aPCC (75.7%), while 44.7% used rFVIIa (Table 3). In addition, 13 (12.6%) participants received standard half-life FVIII, 1-deamino-8-D-arginine vasopressin (DDAVP), cryoprecipitate and/or fresh frozen plasma/whole blood. In all but 2 cases, participants treated with standard half-life FVIII also received aPCC. In the episodic and prophylactic groups, respectively, participants received a

TABLE 2 Bleeds by cause and type during the NIS

	Episodic (n = 75)	Prophylaxis (n = 28)	All (N = 103)
All bleeds, n[a,b]	1244	325	1569
Cause, n (%)			
Spontaneous	698 (56.1)	244 (75.1)	942 (60.0)
Traumatic	546 (43.9)	81 (24.9)	627 (40.0)
Type, n (%)			
Joint	819 (65.8)	197 (61.6)	1016 (64.8)
Muscle	178 (14.3)	51 (15.7)	229 (14.6)
Soft tissue	96 (7.7)	26 (8.0)	122 (7.8)
Bruise/haematoma	106 (8.5)	36 (11.1)	142 (9.1)
Miscellaneous	45 (3.6)	15 (4.6)	60 (3.8)
Treated bleeds, n[a,b]	716	221	937
Cause, n (%)			
Spontaneous	376 (52.5)	164 (74.2)	540 (57.6)
Traumatic	340 (47.5)	57 (25.8)	397 (42.4)
Type, n (%)			
Joint	520 (72.6)	147 (66.5)	667 (71.2)
Muscle	104 (14.5)	40 (18.1)	144 (15.4)
Soft tissue	41 (5.7)	16 (7.2)	57 (6.1)
Bruise/haematoma	28 (3.9)	10 (4.5)	38 (4.1)
Miscellaneous	23 (3.2)	8 (3.6)	31 (3.3)

NIS, non-interventional study.
[a]72-hour rule applied (Appendix S3).
[b]Bleeds due to procedure/surgery in the episodic (n = 9) and prophylactic (n = 1) groups were not included.

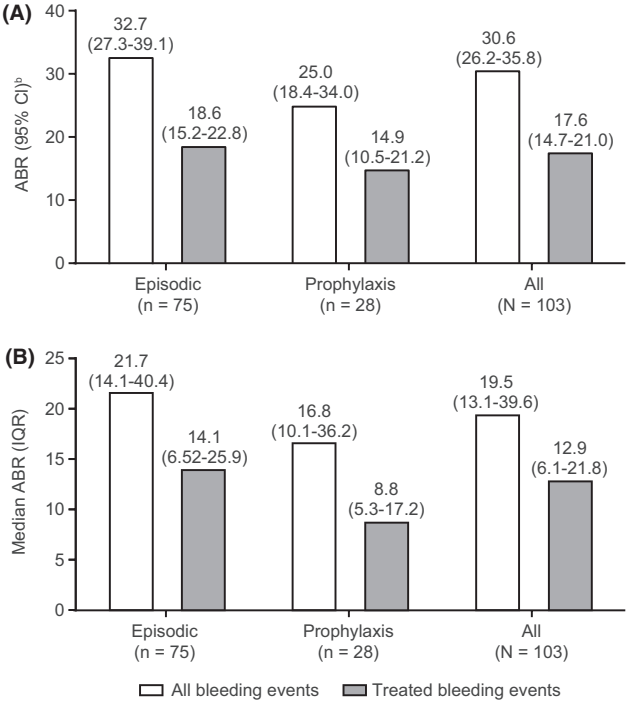

FIGURE 1 Participants' ABRs[a] for all and treated bleeds. [a]Bleeding events due to procedure/surgery were excluded. Bleeding events began at the first sign of bleed and ended 72 hours after the last treatment for the bleed; any symptoms of bleeding at the same location of injections ≤72 hours apart were considered the same bleed. [b]ABR (95% CI) was determined using the negative binomial regression model. ABR, annualized bleeding rate; CI, confidence interval; IQR, interquartile range

median (range) of 11 (1-232) and 70 (1-460) doses of aPCC or 16 (1-674) and 14 (1-92) doses of rFVIIa during the efficacy period.

In the episodic group, 93.3% reported treatment for bleeds, 46.7% for one-time prophylaxis and 13.3% for procedure/surgery (Appendix S5). Six (8.0%) participants in the episodic group reported usual prophylaxis (3 switched from episodic to usual prophylaxis during the study; 3 each reported 1 or multiple doses of usual prophylaxis). In the prophylactic group, 100% of participants reported usual prophylaxis, 89.3% for treatment for bleeds, 46.4% for one-time prophylaxis and 3.6% for procedure/surgery.

3.4 | Adherence to prophylaxis

Adherence to prophylaxis was analyzed in 20 of 22 participants in the prophylactic group prescribed and treated with aPCC; 2 were excluded because they were prescribed aPCC for <3 months during the study (due to study withdrawal).

Adherence to the prescribed frequency of aPCC prophylactic administration for >80% of study weeks was observed in 40.0% of participants, for 60%-80% of study weeks in 20.0% and for <60% of study weeks in 40.0% of participants. Overall, participants adhered to the prescribed frequency of aPCC administration for a median 70.0% of weeks on study. Participants received a median (IQR) 3.0 (2.7-4.6) doses of aPCC per week. Adherence to ≥80% of prescribed aPCC doses was observed in 55.0% of participants and <80% of doses in 45.0% of participants. Overall, adherence to both prescribed frequency of aPCC administration and prescribed aPCC dose was high among 35.0% of participants and low in 35.0% (Appendix S6).

3.5 | Safety outcomes

In the episodic and prophylactic groups, respectively, 67 and 38 AEs were reported in 27 (36.0%) and 19 (67.9%) participants (Table 4). Most common AEs included arthralgia, viral upper respiratory tract infection and pyrexia. Twenty-five and 20 SAEs were reported in 10 (13.3%) and 8 (28.6%) participants, respectively. Haemarthrosis was the most common serious bleed type, followed by muscle haemorrhage. No fatal outcomes were reported, and no participants withdrew due to an AE.

One thromboembolic event (TE) was reported during the NIS. A 16-year-old male receiving episodic haemophilic treatment was hospitalized for a joint bleed and later experienced a myocardial infarction. The participant was initially treated with multiple doses

TABLE 3 Haemophilic treatments

	Episodic (n = 75)	Prophylaxis (n = 28)	All[a] (N = 103)
aPCC			
Participants exposed, n (%)	53 (70.7)	25 (89.3)	78 (75.7)
Median (range) doses, n[b]	11 (1-232)	70 (1-460)	20 (1-460)
Median (range) cumulative dose, units[c]	34 000.0 (6000-1 157 411)	332 278.0 (900-1 321 000)	94 028.5 (600-1 321 000)
rFVIIa			
Participants exposed, n (%)	35 (46.7)	11 (39.3)	46 (44.7)
Median (range) doses, n[b]	16 (1-674)	14 (1-92)	15 (1-674)
Median (range) cumulative dose, µg[c]	115 000.0 (120 000-4 672 000)	84 000.0 (2000-822 000)	112 515.0 (2000-4 672 000)
Other[d]			
Exposures, n (%)	8 (10.7)[d]	5 (17.9)	13 (12.6)

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.
[a]Some participants received >1 coagulation product.
[b]A dose is equivalent to 1 infusion.
[c]Represents total amount reported during the NIS.
[d]Includes factor VIII (standard half-life), 1-deamino-8-D-arginine vasopressin (DDAVP; intravenous), cryoprecipitate and/or fresh frozen plasma/whole blood; 1 participant received DDAVP and cryoprecipitate.

of rFVIIa during the first 2 days of hospitalization then switched to multiple doses of aPCC over 4 consecutive days (cumulative aPCC dose exceeded 200 U/kg per day during 2 of the 4 days).

4 | DISCUSSION

To our knowledge, this NIS is the first such report of a large global cohort of adult and adolescent PwHA with inhibitors and the first instance of prospective real-world data used as a control for a phase 3 study. Participant compliance with BMQ reporting was high and consistent during the NIS, justifying the feasibility of using an electronic device to record participant-reported medication and outcomes. The NIS provided high-quality documentation of bleeds, coagulation product use and safety outcomes from PwHA with inhibitors treated according to local routine clinical practice. These results contributed to an intra-individual analysis (n = 24) within the emicizumab HAVEN 1 study, which found that bleeding rate in PwHA with inhibitors treated with once-weekly subcutaneous emicizumab prophylaxis was reduced by 79% ($P < 0.0001$) vs BPA prophylaxis in the NIS (ABR [95% CI], 3.3 [1.3-8.1] vs 15.7 [11.1-22.3], respectively).[24]

Similar proportions of spontaneous and traumatic treated bleeds were observed, most occurring in the joints. Bleeding rates with prophylaxis were high and in line with those reported in the literature for PwHA with inhibitors,[14,27] suggesting that participants were not sufficiently protected from bleeding with their current regimen. However, comparison of bleeding rates across studies is challenging due to limited publications, lack of alignment and transparency on the definition of bleeds and lack of published comparisons between all and treated bleeds, both of which were evaluated here. This NIS is the first real-world study to differentiate between treated bleeds and all bleeds, demonstrating a substantial proportion (40.0%) of untreated bleeds in PwHA with inhibitors, most of which occurred spontaneously. This observation may not have been previously reported because most other studies appear to focus on bleeds requiring treatment.

The most frequently used BPA for prevention and treatment of bleeding was aPCC; rFVIIa was used by fewer participants, likely reflecting its lack of approval worldwide for prophylactic use.[11] In the prophylactic group, high adherence to the prescribed frequency of aPCC administration (>80% of study weeks) and prescribed aPCC doses (≥80% of doses) was each low, perhaps reflecting the burden of multiple intravenous infusions required per week. Only 35% of participants showed high adherence to both prescribed frequency of administration and prescribed dose with aPCC. The reasons for non-adherence to aPCC prophylaxis remain undefined and represent an area for future research.

Frequently occurring AEs included arthralgia, viral upper respiratory infection and pyrexia. A high proportion of participants in the prophylactic group reported haemarthrosis (17.9%) and muscle haemorrhage (3.6%), further indicating that even high use of currently available treatments does not provide sufficient bleed prevention/

TABLE 4 Adverse events

Adverse event (MedDRA)[a]	Episodic (n = 75)	Prophylaxis (n = 28)	All (N = 103)
Adverse events, n	67	38	105
Participants with ≥1 adverse event, n (%)	27 (36.0)	19 (67.9)	46 (44.7)
Serious adverse events, n	25	20	45
Participants with ≥1 serious adverse event, n (%)	10 (13.3)	8 (28.6)	18 (17.5)
Common adverse events (occurring in ≥5% of participants overall), n (%)			
Arthralgia	3 (4.0)	2 (7.1)	5 (4.9)
Viral upper respiratory tract infection	1 (1.3)	4 (14.3)	5 (4.9)
Pyrexia	6 (8.0)	0	6 (5.8)
Haemorrhage-associated events reported as serious adverse events, n (%)			
Serious adverse events, n	17	13	30
Participants with ≥1 serious adverse event, n (%)	7 (9.3)	6 (21.4)	13 (12.6)
Haemarthrosis	4 (5.3)	5 (17.9)	9 (8.7)
Muscle haemorrhage	3 (4.0)	1 (3.6)	4 (3.9)
Haemorrhage	0	1 (3.6)	1 (1.0)
Haematuria/haemorrhage urinary tract	1 (1.3)	1 (3.6)	2 (1.9)
Pharyngeal haematoma	1 (1.3)	0	1 (1.0)
Gingival bleeding	1 (1.3)	0	1 (1.0)

MedDRA, Medical Dictionary for Regulatory Activities version 20.0.
[a]MedDRA System Organ Class (McLean, VA, USA) was used for the preferred terms used to classify adverse events. Serious adverse events were as defined in the International Conference on Harmonisation Guidelines for Good Clinical Practice.

control. The higher rate of haemarthrosis in the prophylactic group may be explained by the possible development of haemophilic arthropathy due to significant bleeding before approval of aPCC for prophylaxis.[10] One TE of myocardial infarction occurred in a participant after receiving multiple days of treatment with rFVIIa followed by aPCC.

This study has some limitations. Higher bleeding rates may have been reported in the episodic group due to the requirement for ≥6 bleeds in the last 6 months while on episodic treatment. In addition, investigators may have selected participants with significant bleeding on current standard therapy who they deemed would benefit the most from emicizumab in the subsequent HAVEN 1 study. The observation time for some participants was <24 weeks; however, >60% had an observation time >24 weeks and none had an observation time <4 weeks.

In conclusion, data from the NIS demonstrate the need for more efficient and effective therapies for adolescent and adult PwHA with inhibitors, with the potential to improve adherence to prophylactic regimens and thus improve bleed outcomes. Additionally, novel, long half-life therapies such as emicizumab, which require less frequent dosing and can be administered subcutaneously, may contribute to improved adherence by reducing the burden associated with prophylaxis.

ACKNOWLEDGEMENTS

This study was sponsored by F. Hoffmann-La Roche Ltd. Medical writing assistance for this manuscript was provided by Daniella Babu, PhD, of Envision Pharma Group, and funded by F. Hoffmann-La Roche Ltd.

CONFLICT OF INTEREST

JM has received research grants from Bayer, Biogen, Biomarin, CSL, Novo Nordisk, Sobi, Roche and Unique; member of scientific advisory committee of Amgen, Bayer, Biotest, Biogen, Baxalta, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche and Spark; member of speaker bureau of Alnylam, Bayer, Biotest, Biogen, Novo Nordisk, Pfizer, Sobi, Shire, Roche, ISTH and WFH. JO received reimbursement for attending symposia/congresses and/or honoraria for consulting, and/or funds for research from Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Swedish Orphan Biovitrum. MC reports consultancy and advisory boards with honoraria from Shire, Octapharma, Grifols, Pfizer, Bayer, Roche/Genentech, Bioverativ and Hema; speakers bureaus for Shire,

Roche/Genentech, Bayer and Novo Nordisk; research support for Shire and Pfizer; principal investigator or subinvestigator for clinical trials for Pfizer, Roche/Genentech, Novo Nordisk, Global Blood Therapeutics, Sancilio and Amgen; owns stock in Alnylam. MS is a board member of the FEIBA and Advate Safety Board in Japan organized by Baxalta; has received honoraria for consultancy meetings from Baxalta, Pfizer, Biogen, Bayer, CSL Behring, Kaketsuken, Chugai Therapeutic Company and Novo Nordisk and received unrestricted grants supporting research from Baxalta, Pfizer, Bayer, Kaketsuken, Novo Nordisk, Chugai Pharmaceutical Company and CSL Behring. ES has been a member of advisory committees and/or speaker bureaus for Bayer, Shire, CSL Behring, Pfizer, Novo Nordisk, Sobi, Bioverativ, Roche, Grifols, Kedrion and Octapharma. MM and RY have nothing to disclose. MR has received research funding to his institution from Bioverativ, Genentech, Novo Nordisk and Shire and has been a paid consultant for Bioverativ, CSL Behring, Genentech, Inc, Kedrion, Novo Nordisk, Pfizer, Shire and uniQure. CG has received honoraria from Novo Nordisk, Jansen and Roche. ML, HM and EA are employees of Roche. GGL is an employee of Genentech. RK-J has acted as a paid consultant to Grifols, Genentech/Roche, Novo Nordisk, Pfizer and Shire and received research funding from CSL Behring, Pfizer and Roche.

AUTHOR CONTRIBUTIONS

HM and EA conducted the data analysis, and vouch for the completeness and accuracy of the data and analyses. JM, JO, MC, MS, ES, MM, MR, CG, RY, ML, HM, EA, GGL, RK-J directed the development of the first draft of the manuscript by Envision Pharma Group (funded by F. Hoffmann-La Roche Ltd) and the authors subsequently critically reviewed the draft. All the authors had access to the data and confirmed adherence to the protocol and statistical analysis plan during the study conduct.

ORCID

Johnny Mahlangu http://orcid.org/0000-0001-5781-7669
Johannes Oldenburg http://orcid.org/0000-0003-3038-2145
Michael U. Callaghan http://orcid.org/0000-0001-8742-0275
Rebecca Kruse-Jarres http://orcid.org/0000-0001-6547-5240

REFERENCES

1. Mannucci PM, Tuddenham EG. The hemophilias–from royal genes to gene therapy. *N Engl J Med*. 2001;344:1773-1779.
2. Ferreira AA, Leite IC, Bustamante-Teixeira MT, et al. Health-related quality of life in hemophilia: results of the Hemophilia-Specific Quality of Life Index (Haem-a-Qol) at a Brazilian blood center. *Rev Bras Hematol Hemoter*. 2013;35:314-318.
3. Poon JL, Doctor JN, Nichol MB. Longitudinal changes in health-related quality of life for chronic diseases: an example in hemophilia A. *J Gen Intern Med*. 2014;29(suppl 3):S760-S766.
4. Powell JS. Recombinant factor VIII in the management of hemophilia A: current use and future promise. *Ther Clin Risk Manag*. 2009;5:391-402.
5. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia*. 2003;9:418-435.
6. World Federation of Hemophilia. About bleeding disorders. How are inhibitors diagnosed? https://www.wfh.org/en/page.aspx?pxml:id=648. Accessed October 4, 2017.
7. Coppola A, Di Capua M, Di Minno MN, et al. Treatment of hemophilia: a review of current advances and ongoing issues. *J Blood Med*. 2010;1:183-195.
8. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. *Blood*. 2014;124:3365-3372.
9. Rocino A, Cortesi PA, Scalone L, et al; European Haemophilia Therapy Strategy Board (EHTSB); European Haemophilia Therapy Strategy Board EHTSB. Immune tolerance induction in patients with haemophilia A and inhibitors: effectiveness and cost analysis in an European cohort (the ITER study). *Haemophilia*. 2016;22:96-102.
10. *FEIBA [prescribing information]*. Westlake Village, CA: Baxalta US Inc.; 2017.
11. *NovoSeven [prescribing information]*. Bagsvaerd, Denmark: Novo Nordisk A/S, 2016.
12. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven®) in children vs. adults with haemophilia A. *Haemophilia*. 2004;10:352-359.
13. Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost*. 2007;5:1904-1913.
14. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. 2011;365:1684-1692.
15. Berntorp E. Differential response to bypassing agents complicates treatment in patients with haemophilia and inhibitors. *Haemophilia*. 2009;15:3-10.
16. Chai-Adisaksopha C, Hillis C, Thabane L, Iorio A. A systematic review of definitions and reporting of bleeding outcome measures in haemophilia. *Haemophilia*. 2015;21:731-735.
17. Negrier C, Voisin S, Baghaei F, et al; FEIBA PASS Study group. Global Post-Authorization Safety Surveillance study: real-world data on prophylaxis and on-demand treatment using FEIBA (an activated prothrombin complex concentrate). *Blood Coagul Fibrinolysis*. 2016;27:551-556.
18. Young G, Cooper DL, Gut RZ; HTRS Investigators. Dosing and effectiveness of recombinant activated factor VII (rFVIIA) in congenital haemophilia with inhibitors by bleed type and location: the experience of the Haemophilia and Thrombosis Research Society (HTRS) Registry (2004–2008). *Haemophilia*. 2012;18:990-996.
19. Chambost H, Santagostino E, Laffan M, Kavakli K; ONE Registry Steering Committee on behalf of the investigators. Real-world outcomes with recombinant factor VIIa treatment of acute bleeds in haemophilia patients with inhibitors: results from the international ONE registry. *Haemophilia*. 2013;19:571-577.
20. Sampei Z, Igawa T, Soeda T, et al. Identification and multidimensional optimization of an asymmetric bispecific IgG antibody mimicking the function of factor VIII cofactor activity. *PLoS One*. 2013;8:e57479.
21. *HEMLIBRA [prescribing information]*. South San Francisco, CA: Genentech Inc., 2017.
22. European Medicines Agency. *Hemlibra [summary of product characteristics]*. Welwyn Garden City, UK: Roche; 2018.
23. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.

24. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377:808-818.
25. Blanchette VS, Key NS, Ljung LR, et al; Subcommittee on Factor VIII Factor IX and Rare Coagulation Disorders of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935-1939.
26. Carcao M, Avilla ML, Aledort L, Leissinger C; Factor Utilization Expert Working Group of the International Prophylaxis Study Group (IPSG) and other Survey Investigators. Prophylaxis practices in children and adults with severe hemophilia A or B and inhibitors. *J Thromb Haemost*. 2015;13(Suppl. 2):360.
27. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20:65-72.

SUPPORTING INFORMATION

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

How to cite this article: Mahlangu J, Oldenburg J, Callaghan MU, et al. Bleeding events and safety outcomes in persons with haemophilia A with inhibitors: A prospective, multicentre, non-interventional study. *Haemophilia*. 2018;24:921–929. https://doi.org/10.1111/hae.13612