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Postauthorization safety surveillance study of antihaemophilic factor (recombinant) reconstituted in 2 mL sterile water for injection in children with haemophilia A

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Abstract

Introduction: Antihaemophilic factor (recombinant) (rAHF; ADVATE®) is approved for prophylaxis and treatment of bleeding in children and adults with haemophilia A. Reconstitution in 2 mL sterile water for injection instead of 5 mL allows for a 60% reduction in infusion volume and administration time, but could increase the likelihood of hypersensitivity and infusion-related reactions, especially in children.

Aim: To assess local tolerability, safety and effectiveness of rAHF 2 mL during routine clinical practice factor VIII (FVIII) replacement (on-demand and prophylaxis) in children with severe (FVIII < 1%) or moderately severe (FVIII 1%-2%) haemophilia A.

Methods: This was a prospective, non-interventional, postauthorization safety surveillance study (NCT02093741). Eligible patients were previously treated with rAHF and had a negative inhibitor test result during ≤10 exposure days prior to study entry.

Results: Of 65 patients enrolled (0-11 years of age), 54 and 11 had severe and moderately severe haemophilia A, respectively; 56 patients received prophylaxis, and 11 had ≤50 exposure days, of which 4 had ≤4 exposure days. No patients reported local hypersensitivity reactions, treatment-related adverse events or developed inhibitors. Investigators rated overall effectiveness of rAHF 2 mL prophylaxis as excellent or good. Ninety-four bleeding events in 34 patients were treated. Haemostatic effectiveness was rated as excellent or good for 75.8% of bleeds; 86.2% of bleeds required 1 or 2 infusions.

Conclusion: In children with severe/moderately severe haemophilia A, no hypersensitivity reactions were reported with rAHF 2 mL treatment, and the safety and effectiveness are consistent with data previously reported for rAHF 5 mL.

KEYWORDS

antihaemophilic factor (recombinant), haemophilia A, on-demand, paediatric patients, prophylaxis

1 | INTRODUCTION

Recombinant factor VIII (FVIII) concentrates are the standard of care for prophylactic and on-demand treatment of patients with haemophilia A.[1,2] In the United States, Canada and Europe, antihaemophilic factor (recombinant) plasma/albumin-free method (rAHF; ADVATE®; Baxalta US Inc., a member of the Takeda group of companies) is indicated for the control and prevention of bleeding episodes (BEs), perioperative management and routine prophylaxis to prevent or reduce the frequency of BEs in children and adults with haemophilia A.[3,4] rAHF was originally approved and marketed for reconstitution in 5 mL sterile water for injection (rAHF 5 mL). Reconstitution in 2 mL sterile water for injection (rAHF 2 mL) allows for the infusion of a 60% smaller volume and potentially a shorter infusion time. In a previous phase I randomized crossover study in adolescent/adult patients with severe haemophilia A, the PK and safety profiles of rAHF 2 mL were shown to be similar to rAHF 5 mL (NCT00952822; clinicaltrials.gov). Use of rAHF 2 mL may shorten administration time and thereby may increase treatment adherence in the paediatric population.[5-7] However, the increased concentration of rAHF could result in higher instances of hypersensitivity and infusion-related reactions, especially in children, and has the potential to influence the safety profile of rAHF.

In order to determine the suitability of smaller infusion volumes in children, a postauthorization safety surveillance (PASS) study was carried out with rAHF 2 mL.

2 | MATERIALS AND METHODS

2.1 | Study design and conduct

This was a prospective, non-interventional, observational study (NCT02093741) conducted in 28 study centres in 8 countries (Canada, Czech Republic, Estonia, France, Germany, Hungary, Portugal and the United Kingdom). The local tolerability, safety and effectiveness of a 6-month course of rAHF 2 mL during routine clinical practice in a paediatric population with haemophilia A were evaluated. This study was conducted between September 2013 and January 2016. The study was conducted in accordance with local and applicable national regulatory requirements. The protocol was approved by the independent ethics committees of all participating sites. All patients had legally authorized representatives provide written informed consent before enrolment.

2.2 | Study participants

Eligible participants were previously treated patients aged ≤12 years with severe (baseline FVIII activity <1%) or moderately severe (baseline FVIII activity 1%–2%) haemophilia A. Patients were required to have a documented history of prior exposure to rAHF. For inclusion in the study, patients ≤2 years of age were required to have had ≥3 exposure days (EDs) to rAHF. For patients with ≤50 EDs, all prior EDs must have been to rAHF. For patients with >50 EDs, the most recent 20 EDs prior to study entry must have been to rAHF. In addition, patients were required to have documented evidence of a negative inhibitor titre (<0.6 Bethesda units [BU] by the Nijmegen modification Bethesda assay) during the most recent 10 EDs prior to study entry. Patients were excluded if they had known hypersensitivity to any product component, required a major surgical procedure at the time of enrolment, had no prior exposure to a FVIII concentrate, were currently being treated with an immune tolerance induction regimen, were diagnosed with an inherited or acquired haemostatic defect other than haemophilia A or had participated in another clinical study involving an investigational product or device within 30 days prior to enrolment.

2.3 | Study treatment

Study treatment was administered as routine clinical practice by caregivers at home and by investigators in the hospital/clinic. Approximately 80% of patients with administration information available had a central venous access catheter/port. All patients received rAHF 2 mL for all on-demand and prophylactic FVIII replacement therapy during the 6-month observation period. rAHF 2 mL was infused at a rate determined by the patient's comfort level and at not more than 10 mL/min. The treating physician determined the treatment regimen according to product labelling information and standard practice.[3,4] Guidelines for on-demand rAHF dosing for BEs and surgery are summarized in Table S1. For prophylaxis, the recommended rAHF treatment regimen was 20-40 IU/kg body weight at intervals of 2-3 days (for patients aged <6 years, 20-50 IU/kg, 3-4 times per week).

2.4 | Study objectives

2.4.1 | Primary objective and outcome measures

The primary objective of the PASS study was to assess the incidence of local and general hypersensitivity and infusion-related reactions, irrespective of product-related causality for AEs, such as dyspnoea, wheezing/bronchospasm, chest tightness, rash, hives, pruritus, angioedema, flushing, cyanosis, dizziness/light-headedness, weak pulse and loss of consciousness, or infusion-related reactions such as pyrexia, hypotension, cardiac arrest, nausea, headache and fatigue, or local infusion-related reactions such as erythema, pain, tenderness, swelling and induration.

2.4.2 | Secondary safety-related objectives and outcome measures

Secondary safety-related objectives were to assess AEs possibly or probably related to rAHF. AEs were monitored, and relatedness to

study drug was assessed by the treating physician at interval and termination visits. Any AEs that resulted in hospitalization of the patient were considered serious AEs (SAEs). Immunogenicity was assessed in all patients, and frequency of testing was determined by the investigator on the basis of routine screening schedule, as appropriate within respective countries and subject to clinical guidelines or clinical signs. Inhibitor testing was recommended if clinical signs suggested inhibitor development (increased bleeding tendency, high consumption, lack of response or effectiveness, decreased incremental recovery, shortened half-life). If an inhibitor was suspected, it was recommended that FVIII incremental recovery should be measured. Negative inhibitor titre was defined as that below the limit of inhibitor detection of the local laboratory or, if the local laboratory reference value was not available, <0.6 BU by the Nijmegen modification Bethesda assay,[8] or <1 BU by a non–Nijmegen modification Bethesda assay.[9]

2.4.3 | Secondary effectiveness-related objectives and outcome measures

Secondary effectiveness-related objectives were subjective assessments of haemostatic effectiveness for prophylactic and on-demand treatment with rAHF 2 mL. For each infusion used to treat a BE, caregivers or investigators (for treatments given at home or in the hospital/clinic, respectively) rated the effectiveness of treatment with rAHF 2 mL as excellent, good, fair or none (Table S2); the number of rAHF 2 mL infusions and units used was collected at interval and termination visits.

Patient bleed characteristics during treatment with rAHF 2 mL were summarized by severity and anatomical location (joint and non-joint).

At the termination visit, the overall effectiveness of prophylaxis with rAHF 2 mL was assessed by the treating physician using a 4-point ordinal scale (Table S3).

2.4.4 | Secondary non-clinical objectives and outcome measures

Secondary non-clinical objectives were to assess caregivers' satisfaction with and preference for rAHF 2 mL treatment. Caregivers of patients who received treatment with rAHF 5 mL prior to enrolment had the option to complete a short survey at the beginning and end of the 6-month study period to capture data on their prior infusion experience with rAHF 5 mL (baseline survey) and satisfaction with rAHF 2 mL (follow-up survey). The baseline and follow-up surveys included the same treatment-related questions concerning practical factors (eg time to mix, time to infuse and ease of infusing) and emotional factors (eg the patient's and caregiver's levels of anxiety). The follow-up survey also included questions that asked caregivers if they had a preference for rAHF 5 mL or rAHF 2 mL.

Another secondary objective was to assess the infusion volume of rAHF 2 mL and the duration of time needed to mix and infuse FVIII treatment.

2.5 | Data collection (patient diary)

Patients/caregivers were provided with a diary to capture the following information related to study treatment administered at home as applicable: rAHF 2 mL prophylactic infusion log, AEs, BEs, subjective haemostatic effectiveness for each BE treated, units of rAHF and number of infusions of rAHF to treat each BE and the number of days the patient and caregiver missed normal daily activities. Diary entries were assessed by the investigator and transcribed to the Case Report Form during scheduled hospital/clinic visits.

2.6 | Statistical analysis

No formal sample size calculation was performed. The enrolment of 73 patients was targeted to offset an estimated dropout rate of 17% (which was experienced in a previous phase 3b study of rAHF in paediatric patients) and subsequently provide approximately 60 evaluable patients. The safety analysis set consisted of data for all patients who received ≥1 dose of rAHF 2 mL. The effectiveness analysis set for BEs consisted of all data for all patients who reported ≥1 new BE treated with rAHF 2 mL. Differences in infusion volume, time to mix and infuse FVIII and satisfaction with rAHF 5 mL prior to study entry vs rAHF 2 mL during the study were assessed by the Wilcoxon signed-rank test at the 5% level of significance against a 2-sided alternative.

3 | RESULTS

3.1 | Patient population

A total of 65 patients with severe (n = 54) or moderately severe (n = 11) haemophilia A were enrolled at 28 sites, and 64 patients completed the study. All patients were male, with the exception of 1 female patient. One patient who received prophylaxis withdrew because they switched to another FVIII product. Sixteen patients were ≤2 years of age, 27 patients were >2 and ≤6 years of age and 22 patients were >6 and ≤12 years of age. Nine patients received on-demand treatment and 56 received prophylaxis with rAHF 2 mL. Prior to study entry, 11 of the 65 (17%) patients had ≤50 EDs, including 8 patients who had ≤20 EDs, of which 4 patients had ≤4 EDs. For 2 patients, the data for EDs were unknown. The median duration of study participation was 189 days (range, 128-295). During the study, median EDs were lower in patients ≤2 years of age (26 EDs; range, 0-87) than in the other 2 age groups: >2 and ≤6 years of age (79 EDs; range, 25-163) and >6 and ≤12 years of age (80 EDs; range,

0-164). Patient demographics and medical history are summarized in Table 1.

3.2 | Hypersensitivity and infusion-related reactions

For the primary outcome measure, no infusion-related hypersensitivity reactions occurred during the study (Table 2).

3.3 | Adverse events and immunogenicity

There were 61 AEs reported in 26 (40%) patients, including 13 SAEs in 9 (13.8%) patients (Table 2). No AEs were deemed by the investigator as related to treatment with rAHF 2 mL treatment. The most frequently reported AEs were influenza-like illness, pyrexia and cough, each reported by 4.6% of patients. The SAEs included infections (n = 4), dental caries (n = 2), extravasation, peripheral oedema, arthralgia, joint swelling, muscle haemorrhage and haematoma. During the 6-month observation period, none of the 65 patients had a positive inhibitor titre.

3.4 | Effectiveness

The characteristics of reported bleed events are summarized by age group and treatment regimen in Table 3. Overall, 30 of 65 (46.2%) patients had zero bleeds, including half of the patients who received prophylaxis (28/56 patients).

For the 55 patients with available data, the overall haemostatic effectiveness of prophylaxis with rAHF 2 mL was rated by the treating physician as 'excellent' in 45 of 55 (81.8%) patients and 'good' in 10 of 55 (18.2%); all 10 patients with 'good' ratings had severe haemophilia A (Figure 1A). For 1 patient, no information was available.

By study completion, 34 of 65 (52.3%) patients had experienced BEs, with relatively more patients affected when receiving on-demand treatment (7/9, 77.8%) than patients receiving prophylaxis (27/56, 48.2%). The majority of treated BEs (76/94, 80.9%) were of minor severity, and 51 of 94 (54.3%) BEs occurred at sites other than joints. There were only 2 bleeds of major severity (Table 3), both of which were muscle bleeds that occurred secondarily to an injury in a boy aged 4 years during prophylaxis. For 77 of 94 (81.9%) BEs treated with rAHF 2 mL, patients reported that their normal activities/days at school were not disrupted.

Across all age groups, most (86.2%) BEs were treated with 1 infusion (62/94, 66.0%) or 2 infusions (19/94, 20.2%) of rAHF 2 mL (Figure 1B). The effectiveness of treatment was assessed as excellent or good for 75.8% of infusions. Per infusion, a mean (SD) dose of 43.4 (45.0) IU/kg rAHF 2 mL was administered in a mean (SD) volume of 3.3 (3.6) mL. Mean (SD) infusion duration was 3.5 (2.3) minutes (Table 4).

Five patients received rAHF 2 mL perioperatively for 6 invasive procedures (3 tooth extractions, 1 tonsillectomy, 1 change of port catheter, 1 surgical resection of a chalazion). Postoperative global effectiveness was assessed as excellent in all 6 (100%) procedures.

3.5 | Patient/caregiver treatment satisfaction and preference

Of the patients who had received prior treatment with rAHF 5 mL and completed the baseline survey (n = 45), 93.3% of caregivers were either very satisfied or satisfied with rAHF 5 mL. At the completion of treatment with rAHF 2 mL, 95.6% of caregivers (n = 45) were very satisfied or satisfied with rAHF 2 mL treatment. Caregivers' preferences for rAHF 2 mL vs rAHF 5 mL are shown in Figure 2. Of the 29 caregivers who completed the survey at the end of the rAHF 2 mL

TABLE 1 Patient demographics

	Age group			
	≤2 y (n = 16)	>2 to ≤6 y (n = 27)	>6 to ≤12 y (n = 22)	Total (N = 65)
Age, y				
Mean ± SD	1.1 ± 0.68	4.6 ± 1.15	8.4 ± 1.50	5.0 ± 3.05
Median (range)	1.0 (0-2)	5.0 (3-6)	8.0 (7-11)	5.0 (0-11)
Male, n (%)	16 (100)	27 (100)	21 (95.5)	64 (98.5)
Race, n (%)				
White	8 (50.0)	17 (63.0)	4 (18.2)	29 (44.6)
Asian	0	0	0	0
Black	0	0	0	0
Other	0	0	1 (20.0)	1 (3.3)
Missing	8 (50.0)	10 (37.0)	17 (77.3)	35 (53.8)
Haemophilia A severity, n (%)				
Moderately severe	3 (18.8)	4 (14.8)	4 (18.2)	11 (16.9)
Severe	13 (81.3)	23 (85.2)	18 (81.8)	54 (83.1)

TABLE 2 Safety summary

Parameter	Age group ≤2 y (n = 16)	>2 to ≤6 y (n = 27)	>6 to ≤12 y (n = 22)	Total (N = 65)
Exposure days at screening and during the trial, n	16	25	21	62
Mean ± SD	35.3 ± 34.0	79.5 ± 27.9	68.3 ± 36.5	64.3 ± 36.7
Median (range)	26.0 (0-87)	79.0 (25-163)	80.0 (0-164)	72.0 (0-164)
All AEs				
Patients, n (%)	8 (50.0)	14 (51.9)	4 (18.2)	26 (40.0)
AEs, n	24	33	4	61
Study drug–related AEs, n	0	0	0	0
Hypersensitivity reactions, n	0	0	0	0
SAEs				
Patients, n (%)	2 (12.5)	6 (22.2)	1 (4.5)	9 (13.8)
SAEs, n	2	10	1	13
Study drug–related SAEs, n	0	0	0	0
Deaths, n	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

TABLE 3 Bleed characteristics of patients

	Age group ≤2 y (n = 16)	>2 to ≤6 y (n = 27)[a]	>6 to ≤12 ys (n = 22)	Total (N = 65)
Patients with bleeds, n (%)	11 (68.8)	11 (40.7)	12 (54.5)	34 (52.3)
Number of bleeds	32	28	48	108
	Treatment regimen			
	Prophylaxis (n = 56)[a]	**On-demand (n = 9)**		**Total (N = 65)**
Patients with bleeds, n (%)	27 (48.2)	7 (77.8)		34 (52.3)
Number of bleeds	83	25		108
	Prophylaxis (n = 73)	**On-demand (n = 25)**		**Total (N = 98)**
Treated episodes, n (%)	69 (94.5)	25 (100)		94 (95.9)
Number of infusions	128	33		161
	Age group			
Treated bleeds	**≤2 y (n = 25)**	**>2 to ≤6 y (n = 25)**	**>6 to ≤12 y (n = 44)**	**Total (N = 94)**
Severity/intensity, n (%)				
Major	0 (0)	2 (8.0)	0 (0)	2 (2.1)
Minor	14 (56.0)	18 (72.0)	44 (100)	76 (80.9)
Unknown	11 (44.0)	4 (16.0)	0 (0)	15 (16.0)
Missing	0 (0)	1 (4.0)	0 (0)	1 (1.1)
Anatomical site, n (%)				
Joint	6 (24.0)	6 (24.0)	27 (61.4)	39 (41.5)
Non-joint	17 (68.0)	18 (72.0)	16 (36.4)	51 (54.3)
Missing	2 (8.0)	1 (4.0)	1 (2.3)	4 (4.3)

[a]Data on bleeding episodes not available for 1 patient who received prophylaxis (age group, >2 to ≤6 years).

treatment period, 23 (79.3%) preferred the decreased infusion volume owing to the overall convenience of treatment. In addition, most caregivers (n = 22, 75.9%) preferred the reduced infusion time of treatment with rAHF 2 mL compared with that of rAHF 5 mL (n = 1, 3.4%). Overall (n = 28), the majority of caregivers (n = 19, 67.9%) preferred rAHF 2 mL, 8 (28.6%) caregivers had no preference and

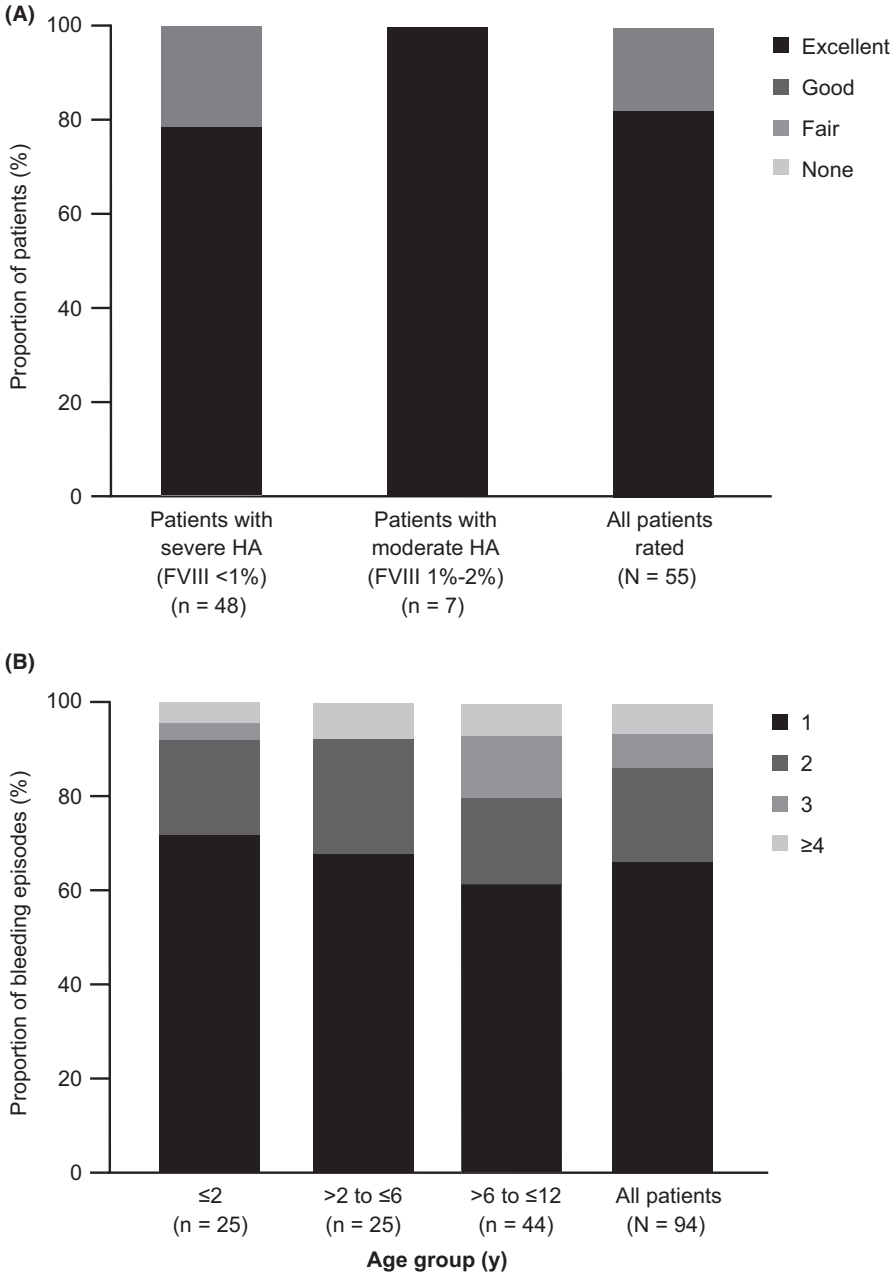

FIGURE 1 A, Haemostatic effectiveness of prophylaxis with rAHF 2 mL by haemophilia A severity. Results are displayed by disease severity based on baseline FVIII activity levels. For 1 patient, no overall judgement of the effectiveness of prophylaxis was provided. N values indicate number of patients. B, The proportion of bleeding episodes treated with 1, 2, 3 or ≥4 infusions of rAHF 2 mL, categorized by age group. N values indicate number of bleeding episodes. FVIII, factor VIII; HA, haemophilia A; rAHF, antihaemophilic factor (recombinant)

a single (3.6%) caregiver, although 'very satisfied' with rAHF 2 mL treatment in general, preferred rAHF 5 mL.

4 | DISCUSSION

Decreasing the volume of sterile water for injection used for the reconstitution of rAHF from 5 to 2 mL allows for a shorter infusion time, although the excipient concentration increases by approximately 2.5-fold. Despite this increase, no hypersensitivity reactions were observed, and the safety profile of rAHF 2 mL in this study was consistent with that reported previously for rAHF 5 mL in children and adolescents/adults.[10-12] Overall safety outcomes with rAHF 2 mL were comparable between patients aged ≤2 years and >2 to ≤12 years, and similar to those reported previously for rAHF 5 mL in patients aged <6 years.[13] Thus, the increased excipient concentration did not impact the tolerability of rAHF infusion across age groups. Furthermore, this is supported by a meta-analysis of the overall rAHF clinical trial population of 1188 patients (median age, 21.6 years).[10]

In this PASS study involving 65 previously treated patients, none developed anti-FVIII inhibitors during the study. These data are consistent with those from the rAHF clinical development programme[12-14] and routine clinical practice.[10] Even though patient numbers are small in this study population, 17% (n = 11) of patients had ≤50 EDs at study entry (12% [n = 8] had ≤20 EDs); patients are at highest risk for developing inhibitors to FVIII replacement therapy during the first 50 EDs.[15]

Effectiveness of prophylaxis and haemostatic management observed with rAHF 2 mL were comparable with that reported in

clinical development and postauthorization programmes for rAHF 5 mL,[11-14] with 50% of patients receiving prophylaxis in this study experiencing no bleeds during observation. In studies involving rAHF and other standard half-life FVIII products, the percentage of paediatric/adolescent patients with zero bleeds ranged from 26.3% to 50.0%, of which the majority were less than 50%.[3,16-19] This suggests that a diluent volume of 2 mL results in similar circulating FVIII levels as with 5 mL and therefore does not affect product effectiveness.

The majority of caregivers in this study preferred the smaller infusion volume of rAHF 2 mL, particularly regarding the burden of treatment parameters, which included overall convenience, time needed to mix and infuse FVIII and ease of infusion. This may be especially beneficial for young children who can have difficult venous access and may be uncomfortable with infusions. These findings align with results from a survey of nurses from haemophilia treatment centres who recorded observations during infusion of 2.5 mL or 10 mL of a recombinant FVIII product in 47 children under the age of 3 years.[20] The smaller infusion volume was associated with greater nurse satisfaction as a result of the 49% reduction in loss of venous access and less frequent need for repeat venipuncture compared with the 10 mL infusions.[20] Children/caregivers and adults with haemophilia have rated treatment burden (eg lengthy infusion times, multiple vials needed per infusion) as an important factor in determining their preference for prophylactic regimens as well as their willingness to pay for therapy.[21,22] Decreasing patient/caregiver treatment burden has the potential to improve adherence to prophylactic therapy and thereby optimize outcomes in paediatric patients.

TABLE 4 Treatment of bleeding episodes

Parameter	Number of infusions for bleeds (N = 161)
Infusion duration, min	
Mean ± SD	3.5 ± 2.3
Median (range)	2.0 (1-20)
Number of infusions[a]	111
Dose, IU/kg	
Mean ± SD	43.4 ± 45.0
Median (range)	35.59 (6.41-494.01[b])
Number of infusions	161
Volume administered per infusion, mL	
Mean ± SD	3.3 ± 3.6
Median (range)	2.0 (2-36)
Number of infusions[c]	160

[a]Data not available for 50 patients.

[b]Data point 494.01 results from 1 patient who received 18 vials of 2 mL antihaemophilic factor (recombinant) for a mild joint bleed (knee).

[c]Data not available for 1 patient.

The limitations of this study are those known to be associated with observational PASS studies and include the small number of patients, especially when limited further by age (≤12 years of age), the voluntary nature of keeping diaries, the potential to treat bleeds when there may not be a true bleed, the possibility to underreport bleeds toward the end of a prophylaxis period and the lack of a direct comparator. However, taking the general limitations related to non-interventional studies into consideration, these results are likely to be representative of the population of previously treated paediatric patients with severe or moderately severe haemophilia A.

In conclusion, the observed safety profile of rAHF 2 mL was consistent with previous reports of rAHF 5 mL, and there was no evidence of increased risk of hypersensitivity infusion-related or infusion site reactions with rAHF 2 mL. Similarly, effectiveness was comparable with that previously reported for the 5 mL preparation of rAHF. Therefore, the more concentrated preparation of rAHF 2 mL provides an alternative to rAHF 5 mL for paediatric patients with haemophilia A across all age groups, from safety and effectiveness perspectives. In addition, patients and caregivers

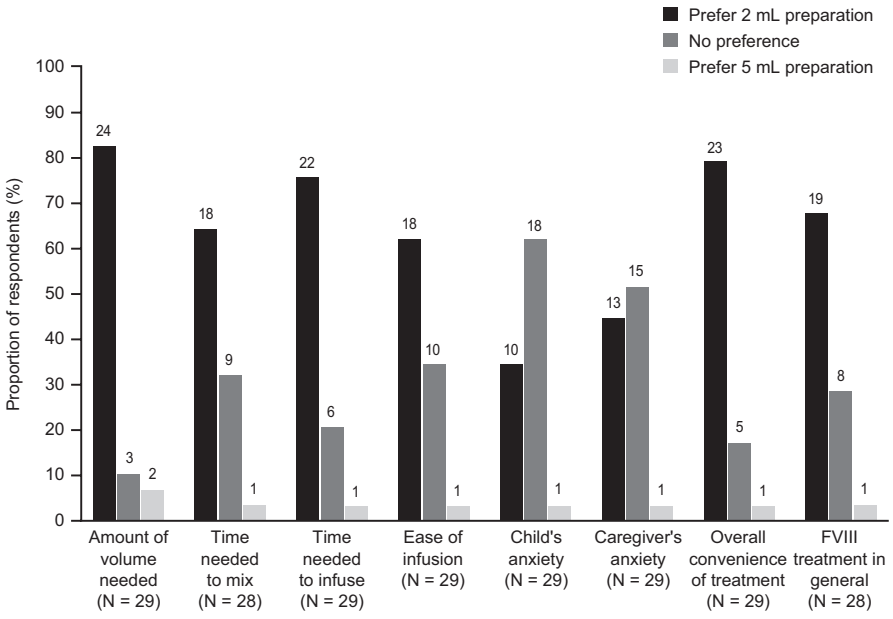

FIGURE 2 Caregiver preferences for rAHF 2 mL vs rAHF 5 mL. The data illustrate the preferences of caregivers who responded to the survey. The number of respondents to each question (N) out of 65 patients is indicated on the x-axis, with the number of respondents per preference included on the appropriate column. FVIII, factor VIII; rAHF, antihaemophilic factor (recombinant)

preferred the ease of preparation, smaller infusion volume and shorter infusion time of rAHF 2 mL. Combined with reports of reduced anxiety for both patients and caregivers, the less time-consuming treatment using rAHF 2 mL has clear potential to improve treatment adherence.

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DISCLOSURES

JM has received support to attend meetings from CSL Behring, participated in advisory board meetings for Chugai-Roche and CSL Behring, and participated as a speaker for Chugai-Roche and Novartis. BG has been a consultant for Shire/Takeda. JB has received honoraria as a consultant for Novo Nordisk, Roche and Shire,* and a member of a speakers bureau for CSL Behring, Novo Nordisk, Pfizer, Roche, Shire and Sobi.* FHS has received honoraria as a consultant for and received travel grants from Baxter/Baxalta/Shire,* Bayer, CSL Behring, Novo Nordisk, Pfizer and Sobi, and as member of a speakers bureau for CSL Behring and Pfizer. BW has received consulting and travel fees from CSL Behring, Chugai, Novo Nordisk, Roche, Shire/Takeda and Sobi. JG and GS were employees of Baxalta US Inc.* at the time of the study. AN and JD are employees of Baxalta Innovations GmbH.* WE is an employee of Baxalta Innovations GmbH* and a Takeda stock owner. ST is an employee of Baxalta US Inc.* and a Takeda stock owner. *A member of the Takeda group of companies.

AUTHOR CONTRIBUTIONS

JM, BG, JB, FHS and BW were principal investigators of this study. JG, AN, JD, WE, ST and GS designed the study, and WE analysed the data. All authors were involved in drafting, reading and approving the manuscript.

DATA AVAILABILITY STATEMENT

The data sets, including the redacted study protocol, redacted statistical analysis plan and individual participants' data supporting the results reported in this article, will be available three months after the submission of a request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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