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RECOMBINANT SINGLECHAIN FACTOR VIII IN SEVERE HEMOPHILIALONGTERM SAFETY AND EFFICACY IN PREVIOUSLY TREATED PATIENTS IN THE AFFINITY EXTENSION STUDY

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ORIGINAL ARTICLE

Recombinant single-chain factor VIII in severe hemophilia: Long-term safety and efficacy in previously treated patients in the AFFINITY extension study

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Abstract

Background: rVIII-SingleChain is a recombinant single-chain factor VIII used to treat people with hemophilia A.

Objectives: The aim of this extension study was to investigate the long-term safety and efficacy of rVIII-SingleChain prophylaxis in ≥200 previously treated patients (PTPs) with hemophilia A with ≥100 exposure days (EDs).

Methods: In total, 222 patients were enrolled, of which 204 rolled over from prior rVIII-SingleChain studies. The median age was 21 years (range, 2–65 years), including 155 patients ≥12 years and 67 patients <12 years. Patients continued with their previously assigned dose and regimen, or switched at the investigator's discretion. Patients were treated for a mean duration of 31 months (range, 1–47 months), the mean ED was 342 (standard deviation, 135.5), and 212 (95.5%) patients achieved >100 EDs. When the study ended, most patients were on either a prophylaxis regimen of 34.9 (17–62) IU/kg, 3×/week (N = 88; 39.6%), or 37.2 (13–65) IU/kg, 2×/week regimen (N = 72; 32.4%).

Results: Hemostatic efficacy was rated excellent or good in 87.1% of assessed bleeds. The median (range) annualized bleeding rate was 1.21 (0.0–42.6), and the annualized spontaneous bleeding rate (AsBR) was 0.32 (0.0–33.0) for prophylaxis regimens. Median AsBR was similar for patients treated 3×/week and 2×/week (0.31 and 0.30, respectively). Surgical hemostatic efficacy was rated excellent or good in 100% of surgeries. No inhibitors, anaphylactic reactions, or thromboembolic events were reported in PTPs.

Conclusion: These results confirm the safety and efficacy of rVIII-SingleChain as a long-term prophylaxis treatment modality for PTPs with severe hemophilia A.

KEYWORDS
clinical efficacy, clinical trial, hemophilia A, prophylaxis, rVIII-SingleChain, safety

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Essentials

- The long-term safety and efficacy of rVIII-SingleChain was assessed in people with hemophilia A.
- Most patients maintained or reduced the frequency of prophylaxis regimens with rVIII-SingleChain.
- rVIII-SingleChain showed a favorable safety profile with no associated inhibitor development.
- Routine prophylaxis was effective in maintaining long-term low annualized bleeding rates.

1 | INTRODUCTION

Hemophilia A is an X-linked bleeding disorder resulting from a deficiency of factor VIII (FVIII), with manifestations of the severe form of recurrent joint bleeding and bleeding in soft tissue to life-threatening bleeding episodes.[1] Prophylaxis with FVIII replacement therapy is a mainstay of standard of care for people with severe hemophilia A (defined as FVIII levels <1%).[1,2] The use of prophylaxis to maintain FVIII levels above 1% to decrease the risk of both bleeding and consequent complications is well established.[3] However, some patients still experience breakthrough bleeds on prophylaxis, and targeting higher troughs may be more appropriate to reduce the risk of arthropathy development.[4] Furthermore, as bleeding phenotype is affected by a variety of patient characteristics, individualizing prophylactic regimens is essential to decrease the likelihood of spontaneous bleeds.

rVIII-SingleChain (AFSTYLA; CSL Behring, King of Prussia, PA, USA), a recombinant single-chain FVIII, is a B-domain truncated construct with a covalent bond between the heavy and light chains, which results in increased molecular stability and a higher binding affinity to von Willebrand factor than octocog alfa.[5] The AFFINITY clinical trial program (phase I/III: NCT01486927; phase III: NCT02093897; phase III extension: NCT02172950) was designed to evaluate the efficacy, safety, and pharmacokinetics of rVIII-SingleChain in people with severe hemophilia A. These studies have shown that the majority of people treated using rVIII-SingleChain have excellent hemostatic efficacy for both the prevention and treatment of bleeds and a favorable safety profile, with no previously treated patient (PTP) developing an inhibitor to FVIII.[6,7] Annualized bleeding rates (ABRs) were low, and annualized spontaneous bleeding rates (AsBRs) were zero across all prophylaxis regimens in both adult/adolescent and pediatric patient populations. A substudy of patients undergoing major surgery also demonstrated the efficacy of rVIII-SingleChain in the perioperative hemostatic management of patients.[6]

Adult and adolescent PTPs from the phase I/III study,[6] and pediatrics from the phase III[7] studies could enroll in the phase III extension study. Here, we describe the long-term safety and efficacy of rVIII-SingleChain in adults, adolescents, and children with severe hemophilia A reporting the final PTP results from this extension study.

2 | METHODS

2.1 | Study design and dosing regimens

A multicenter, nonrandomized, open-label phase III extension study (NCT02172950) in males both with and without previous exposure to FVIII replacement therapy was conducted. Written informed consent was obtained from all patients or their legal guardians, and consent could be withdrawn at any time. Patients were enrolled in one of three arms of the extension study: arm 1 included PTPs of all ages who had participated in the AFFINITY clinical trial program with rVIII-SingleChain; arm 2 included previously untreated patients, aged 0 to <18 years who had not been exposed to any FVIII product (these data will be presented separately); and arm 3 included PTPs aged <65 years with at least 50 exposure days (EDs) to any FVIII product, who had not previously been enrolled in any rVIII-SingleChain study. This article reports the results of the PTPs and arm 1 and arm 3 of the extension study.

Patients could be treated on demand with rVIII-SingleChain, or assigned to routine prophylaxis with rVIII-SingleChain two to three times per week (20–50 IU/kg in adults and adolescents; 15–50 IU/kg in pediatrics), or other doses or dosing frequencies at the investigator's discretion based on the patient's weight, pharmacokinetic (PK) profile, previous FVIII regimen, and bleeding phenotype. Doses of rVIII-SingleChain are provided per infusion, unless otherwise stated. In the event of a bleeding episode, all patients were treated with rVIII-SingleChain at a dose determined by the investigator based on the severity of the bleeding episode. The desired FVIII level for the treatment of a bleeding episode was based on World Federation of Haemophilia (WFH) recommendations,[1] and dose escalation to higher-intensity regimens was permitted as determined by the investigator. PTPs were followed for up to 60 months, allowing for patients to achieve 100 EDs as required by the 2019 European Medicines Agency guidelines.[8]

2.2 | End points

2.2.1 | Safety assessments

The primary safety end point was the incidence of inhibitor development, determined as the total number of patients developing inhibitors against FVIII, after at least 100 EDs to rVIII-SingleChain during their participation in the study. Secondary safety end points included the incidence of antibodies against rVIII-SingleChain and Chinese hamster ovary (CHO) cell–derived protein, and the frequency, severity, and relatedness of adverse events (AEs) and serious adverse events (SAEs) to rVIII-SingleChain. The rate of inhibitor formation to FVIII was evaluated from the time of the first dose through to the end-of-study visit. The incidence of inhibitor formation was tested at the closest visit after 10, 50, and 100 EDs in PTPs. Inhibitors were titrated by the Bethesda assay according to the Nijmegen modification and inhibitor antibodies were categorized as low (≥0.6–5 Bethesda units [BU]/mL) or high (>5 BU/mL) titer. In addition, the number of AEs, SAEs, and treatmentemergent AEs and SAEs (TEAE/

TESAEs) and whether they were related or unrelated to treatment with rVIII-SingleChain were reported by the investigator.

2.2.2 | Efficacy assessments

The efficacy end points were ABR and AsBR during prophylaxis and on-demand treatment, treatment success for bleeding episodes, defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale (excellent, good, moderate, poor/none), percentage of bleeding episodes requiring 1, 2, 3, or >3 injections of rVIII-SingleChain to achieve hemostasis (1, 2, 3, or >3), consumption of rVIII-SingleChain, and treatment success for surgery, using the 4-point efficacy evaluation of surgical treatment scale (Appendix S1).

2.3 | Statistical analyses

Safety was assessed in all participants exposed to rVIII-SingleChain. An exact two-sided 95% Clopper-Pearson confidence interval (CI) was used for estimating the incidence of inhibitor formation. Efficacy analyses were conducted in participants who received at least one dose of rVIII-SingleChain as part of either on-demand treatment or routine prophylaxis. Prophylaxis consumption of rVIII-SingleChain was also determined and expressed as number of injections and IU/kg per month and per year; per month was calculated as sum of prophylaxis doses (IU/kg) per subject × (365.25/12) / (efficacy evaluation period); per year was calculated as sum of prophylaxis doses (IU/kg) per subject * 365.25 / (efficacy evaluation period). Each dose (IU/kg) was calculated using the total IU recorded and the most recent recorded value of weight (kg).

The ABR and the AsBR were calculated according to the following formula: number of treated events × 365.25 / (efficacy evaluation period), excluding data from the PK and surgical parts of the study. Statistical comparisons were based on estimates from a Poisson model, and descriptive statistics included the median and interquartile range. All tests were performed at the two-sided .05 level of significance.

3 | RESULTS

3.1 | Study population

A total of 222 PTPs with a median age of 21 years (range, 2–65 years) were enrolled in the extension study from October 2014 to March 2016, with the last patient visit in December 2018; including 204 PTPs from the lead-in studies; patient characteristics are described in Table 1, with a total of 11 patients treated on demand and 211 treated with a prophylaxis regimen. Overall, 88.7% (197/222) of PTPs completed the study; 4 patients discontinued due to AEs (hypersensitivity, periprosthetic fracture, nephritis, and bleed assessed as unrelated to rVIII-SingleChain), 10 patients elected to withdraw from the study for unspecified reasons, and 10 patients discontinued at the physician's discretion and due to reasons beyond the control of the study. One patient was withdrawn due to lack of efficacy. There was one unrelated patient death associated with a TESAE of generalized tonic-clonic seizure (see Safety section). The mean time in the extension study for all patients was 31 (standard deviation [SD], 39.91) months; the mean number of EDs for all patients was 341.9 (SD, 135.48), and the target of ≥100 EDs was achieved by 212 (95.5%) patients.

TABLE 1 Baseline demographics and patient characteristics

Age, y, median, n (%)	
Total population	222 (21.0)
<6 years	25 (3.0)
≥6-<12 years	42 (9.0)
≥12-18 years	23 (13.0)
≥18-65 years	132 (30.0)
Race, n (%)	
White	158 (71.2)
Asian	50 (22.5)
Black	12 (5.4)
Other	2 (0.9)
Ethnicity, n (%)	
Hispanic	10 (4.5)
Not Hispanic	212 (95.5)
Dosing regimen, n (%)	
Every second day	14 (6.3)
3×/week	97 (43.7)
2×/week	85 (38.3)
Other	15 (6.8)
On demand	11 (4.9)

3.2 | Prophylaxis dosing regimens

The majority of patients maintained or reduced the frequency of prophylaxis regimens during treatment with rVIII-SingleChain. Of the 211 (95%) patients assigned to prophylaxis at the start of the study, 97 (43.7%) were infusing 3×/week and 85 (38.3%) were infusing 2×/week (Tables 1 and 2). Fifteen patients were treated on other initial regimens, which included 1×/week or every 3 days, and other final regimens included 1×/week, every 3 days, every 5 days, or every 4 days. Overall, 90 of 222 (40.5%) PTPs required dose adjustments during the study; only 22 patients (9.9%) required >2 dose adjustments. At the end of the study, 88 patients (39.6%) continued dosing 3×/week and 72 (32.4%) patients maintained a dosing regimen of 2×/week (Table 2). The mean final assigned dose for patients treated on the 3×/week regimen (n = 97) was 34.9 (SD, 9.11) IU/kg and for the 2×/week regimen (n = 85) was 37.2 (SD, 10.13) IU/kg

(Table 3). The median prophylaxis dose was 33.0 IU/kg and 38.0 IU/kg for the 3×/week and 2×/week regimen, respectively. In addition, the overall median consumption for patients on prophylaxis with rVIII-SingleChain dosing 3×/week (n = 97) was 4885.88 IU/kg per year, and dosing 2×/week (n = 85) was 3529.44 IU/kg per year.

3.3 | Safety of rVIII-SingleChain

During the extension study, no inhibitors or antibodies to CHO proteins were detected, and no anaphylactic reactions or thromboembolic events were reported in PTPs. A total of 20 (9.0%) patients were positive for noninhibitory antibodies against rVIII-SingleChain at baseline (prior to their first exposure to rVIII-SingleChain in the AFFINITY program). Overall, 34 (15.3%) patients were positive at any time during the study, of which 16 (7.2%) were negative at baseline. There was no loss of clinical efficacy associated with noninhibitory antibodies against rVIII-SingleChain.

A total of 170 (76.6%) PTPs experienced 870 TEAEs; 611 (70.2%) were mild, 238 (27.4%) were moderate, and 21 (2.4%) were severe. Two patients experienced 10 nonserious TEAEs (7 related to dizziness in one patient and 3 related to drug hypersensitivity in the other patient) that were considered related to rVIII-SingleChain by the investigator. The TEAE of dizziness occurred in one (52-year-old) patient and was mild in intensity; the patient continued treatment with rVIII-SingleChain. The three TEAEs of hypersensitivity occurred in one (55-year-old) patient and were mild/moderate in intensity; although the patient recovered, the decision was made to discontinue rVIII-SingleChain.

In addition, 22 patients (9.9%) experienced a total of 31 TESAEs, 3 of which led to withdrawal from the study (muscle hemorrhage, periprosthetic fracture, and nephritis). One patient (44 years old, treated 3×/week at 30 IU/kg) experienced a TESAE (generalized tonic-clonic seizure convulsions) and subsequently died. The patient was compliant with his prophylaxis regimen of 30 IU/kg 3×/week throughout his participation in the study; however, he stopped taking rVIII-SingleChain 9 days before the event onset, and his death was assessed as not related to rVIII-SingleChain treatment. No autopsy was performed; therefore, cause of death cannot be ascertained. None of the TESAEs leading to study withdrawal were considered related to rVIII-SingleChain, and all were resolved with the exception of the fatality described above.

3.4 | Efficacy of rVIII-SingleChain

The prophylactic efficacy of rVIII-SingleChain was maintained during long-term treatment, with low ABRs, AsBRs, and annualized joint bleeding rates across regimens and similar efficacy in both adult/adolescent and pediatric patients. In all patients treated with prophylaxis, median ABR was 1.21 and median AsBR was 0.32 (Table 3); the median AsBR for patients treated 3×/week was 0.31 and for 2×/week was 0.30. The percentage of patients reporting zero treated bleeding events on prophylaxis was 12.0% (3/25) for patients aged <6 years, 9.8% (4/40) for patients aged ≥6–<12 years, 4.5% (1/22) for patients aged ≥12–<18 years and 27.6% (34/122) for patients aged ≥18 years. ABR was substantially lower in patients treated with prophylaxis compared with on-demand treatment. In patients aged <12 years, median ABR in those treated with rVIII-SingleChain prophylaxis (n = 65) was 1.96, compared with 51.44 in the patient treated on demand (n = 1). Similarly, for patients aged ≥12 years, median ABR for those treated with prophylaxis (n = 144) was 0.98 compared with 13.26 for those treated on demand (n = 10).

A total of 2521 bleeding events were reported during the study; of these, rVIII-SingleChain was used to treat 2413 bleeds. Hemostatic efficacy was rated for each of these bleeding events with 1715 (71%) of all bleeds rated as excellent by the investigator, and 386 (16%) rated as good, giving an overall treatment success rate of 87.1% (95% CI, 75.3%%-93.7%). Overall, 86.3% of bleeds were successfully treated with one or two injections.

Additionally, the development of noninhibitory antidrug antibodies (ADAs) did not impact the ABR, which remained similar in patients with and without noninhibitory ADAs. Furthermore, the type of prophylaxis treatment regimen (ie, rVIII-SingleChain every second day, 2×/week or 3×/week) did not appear to impact the efficacy of treatment as assessed by the ABR.

TABLE 2 Comparison of treatment prophylaxis regimens at the start and end of the extension study (n = 211)

		Final regimen (*n* = 211)			
		Every second day	3×/week	2×/week	Other
Initial regimen (n = 211)	Every second day	13	–	1	…
	3×/wk	2	88	7	…
	2×/wk	…	10	72	3
	Other	…	2	3	10

Note: Other initial regimens included: 1×/week or every 3 days; Other final regimens included: 1×/week, every 3 days, every 5 days, or every 4 days. Dark gray shading indicates regimens were maintained in the extension study; light gray shading indicates a decrease in injection frequency during the extension study; no shading indicates an increase in injection frequency during the extension study.

TABLE 3 Factor consumption and efficacy of rVIII-SingleChain prophylaxis in PTPs

	All patients	3×/wk	2×/wk	Every second day	Other
Final assigned dose, IU/kg	(n = 222)	(n = 97)	(n = 85)	(n = 14)	(n = 15)
Median (min-max)	35.0 (13-68)	33.0 (17-62)	38.0 (13-65)	36.0 (21-64)	40.0 (20-68)
Mean (SD)	36.3 (10.21)	34.9 (9.11)	37.2 (10.13)	36.9 (12.49)	42.6 (12.26)
ABR	(n = 209)	(n = 96)	(n = 84)	(n = 14)	(n = 15)
Median (Q1, Q3)	1.21 (0.33, 3.03)	0.99 (0.33, 2.76)	1.23 (0.30, 3.14)	1.25 (0.67, 3.40)	2.45 (1.66, 8.75)
Mean (SD)	2.84 (4.98)	2.39 (4.70)	2.70 (3.70)	2.55 (3.09)	6.85 (10.59)
AsBR					
Median (Q1, Q3)	0.32 (0.00, 1.19)	0.31 (0.00, 0.95)	0.30 (0.0, 1.59)	0.00 (0.00, 1.70)	0.99 (0.39, 1.53)
Mean (SD)	1.20 (3.00)	1.19 (3.70)	1.32 (2.54)	0.66 (0.98)	1.15 (1.25)
AjBR					
Median (Q1, Q3)	0.64 (0.00, 1.98)	0.46 (0.00, 1.58)	0.78 (0.00, 2.48)	0.68 (0.00, 1.68)	1.97 (0.66, 3.19)
Mean (SD)	1.89 (3.85)	1.66 (4.25)	2.02 (3.11)	1.34 (2.23)	3.23 (5.72)
Patients with zero treated bleeding events					
Number of patients, n (%)	42 (19.9)	17 (17.5)	21 (24.7)	3 (21.4)	1 (6.7)

Note: Other initial regimens included: 1×/week or every 3 days; Other final regimens included: 1×/week, every 3 days, every 5 days, or every 4 days.
Abbreviations: ABR, annualized bleed rate; AjBR, annualized joint bleed rate; AsBR, annualized spontaneous bleed rate; PTP, previously treated patient; SD, standard deviation.

TABLE 4 Consumption of rVIII-SingleChain for surgical prophylaxis and intraoperative blood loss

	Day of surgery		Postsurgical period			
	Presurgery	Intraoperative	>0 to ≤72 h	>0 to ≤168 h	>0 to ≤336 h	Total
Dose, IU/kg	(n = 21)	(n = 0)	(n = 19)	(n = 19)	(n = 19)	(n = 24)
Median (min-max)	71.5 (49-161)		233.5 (36-448)	338.0 (36-774)	407.4 (36-1344)	495.8 (50-3381)
Mean (SD)	76.9 (33.16)		226.1 (112.63)	344.1 (193.05)	434.2 (313.30)	683.8 (762.22)
Observed blood loss (ml)	…	(n = 30)	…	…	…	…
Median (min-max)	…	5.0 (0-400)	…	…	…	…
Mean (SD)	…	56.7 (94.22)	…	…	…	…

Abbreviation: SD, standard deviation

3.5 | rVIII-SingleChain in surgical prophylaxis

Twenty-four patients underwent a total of 32 surgical procedures that required general, spinal, or regional anesthesia (circumcision [7], dental extraction [4], knee arthroplasty [2]; lengthening of Achilles tendon [2]; port placement/removal [2]; appendectomy [1]; arthrodose of ankle joint [1]; arthroscopic synovectomy [1]; closed exposure and placement of gold chain [1]; debridement and application of hemovac [1]; excision, curettage, and bone [1]; hip replacement [1]; ilizarov of right distal femur [1]; knee manipulation [1]; knee replacement [1]; knee space and immobilization [1]; open reduction [1]; osteotomy [1]; saucerization and debridement [1]; wound drain and skin grafting [1]). Overall, investigators assessed hemostatic efficacy of rVIII-SingleChain in surgical prophylaxis as excellent in 28 of 32 surgeries and as good in 4 of 32 surgeries. A summary of the consumption of rVIII-SingleChain for surgery and intraoperative blood loss is presented in Table 4. Trough FVIII levels were not monitored during the surgical procedure.

4 | DISCUSSION

The AFFINITY clinical trial program was a large international study, enrolling patients of all ages, assessing the long-term use of rVIII-SingleChain. PTPs achieved 92 462 EDs (702.3 subject-years and 76 584 infusions) across the AFFINITY program with 75 906 EDs (572.6 subject-years and 74 201 infusions) completed in arms 1 and 3 of the extension study (mean, 341.9 days) with rVIII-SingleChain; a longer duration of assessment compared with clinical trials for other recombinant FVIII (rFVIII) products.[9,10] Data from this long-term extension study are consistent with previously reported data,[6,7] confirming the well-characterized safety and efficacy of rVIII-SingleChain in PTPs with severe hemophilia A. rVIII-SingleChain was well tolerated across all age groups and did not lead to development of FVIII inhibitors, anaphylactic reactions, or anti-CHO antibodies.

These data also confirm that rVIII-SingleChain can be used safely and effectively using dosing intervals that are less frequent than

standard-acting products.[11] This extension study allowed for dosing flexibility across all treatment groups, and the individualization of dosing reflects routine clinical practice. Dosing regimens can be tailored to the individual needs of the patient by increasing/decreasing the infusion frequency and/or dose to maintain FVIII activity levels >1 IU/dL, as recommended by the WFH.[1] Of 97 (43.7%) patients initially assigned to 3×/week regimens, 88 (39.6%) remained on 3×/week at the end of the study. Eighty-five (38.2%) patients were initially assigned to 2×/week regimens and 72 (32.4%) patients remained on 2×/week at the end of the study. Overall, 17 patients had a regimen of greater dosing frequency at the end of the study compared to their initial assignment, and 11 patients shifted to a regimen of lower frequency at the end of the study compared to their initial assignment. A total of 238 dose adjustments were made over the course of the study, and only four dose adjustments were due to lack of efficacy. Most dose adjustments were due to patient weight changes, treatment optimization, bleeds, and clinical practice. The mean dose per infusion for patients treated on a 3×/week regimen was similar to that for those treated on a 2×/week regimen (34.9 IU/kg vs 37.2 IU/kg, respectively), suggesting that patients treated less frequently did not require higher doses to maintain bleed protection.

Data in this extension study have shown that the number of bleeding events in pediatric patients on prophylaxis was substantially lower compared with on-demand treatment. The number of bleeding events per year is low across the pediatric population, and the highest proportion corresponds to the traumatic bleeding events due to higher physical activity and naturally accelerated clearance of FVIII.

Furthermore, long-term safety and efficacy using rVIII-SingleChain prophylaxis has been confirmed, with low ABRs and AsBRs when using 3×/weekly and 2×/weekly dosing regimens, and importantly, the median doses for these regimens are comparable to the lead-in study (3×/weekly, 30.0 IU/kg and 2×/weekly, 35.0 IU/kg[6]), confirming the predictability of factor consumption.

Other commercially available recombinant products, including BAX 855 (ADYNOVATE; Takeda, Tokyo, Japan), BAY94-9027 (JIVI; Bayer, Whippany, NJ, USA), and rFVIIIFc (ELOCTATE; Bioverativ, Waltham, MA, USA) have reported similar dosing regimens using 2 to 3× weekly infusions.[12-14] Dosing intervals and factor consumption for adult/adolescent patients treated with other rFVIII products were: BAX 855, 40 to 50 IU/kg 2×/week (median prophylaxis infusion, 44.6 IU/kg)[12]; BAY 94-9027, 30 to 40 IU/kg 2×/week (median prophylaxis infusion, 37.5 IU/kg), 45 to 60 IU/kg every 5 days (median prophylaxis infusion, 46.2 IU/kg), or 60 IU/kg 1×/week (median prophylaxis infusion, 58.9 IU/kg)[10]; rFVIIIFc, 25–65 IU/kg every 3 to 5 days (median prophylaxis infusion, 77.9 IU/kg), or 65 IU/kg 1×/week (median prophylaxis infusion, 65.6 IU/kg).[15] Furthermore, the ASPIRE extension study with patients (n = 110) treated with an individualized rFVIIIFc prophylaxis regimen (median, 3.5 days intervals), reported median weekly doses of 79.5 IU/kg (range, 73.7-100.9 IU/kg).[9] When considering these data reported in the literature, patients treated on a 2×/week regimen with rVIII-SingleChain demonstrated a comparable median prophylaxis dose with BAX 855 and BAY 94-2027 (38.0, 44.6, and 37.5 IU/kg, respectively).

These data demonstrate that some patients can be switched to less frequent dosing regimens while maintaining low bleed rates.[16,17] Patients treated with rVIII-SingleChain may be able to substantially reduce their number of infusions per year (eg, switching from a 3×/week to 2×/week regimen can result in up to 52 fewer infusions per year), which could be critical for patients who struggle with venous access and also help improve treatment compliance.

5 | CONCLUSION

The results of the AFFINITY extension study confirm the findings of the previous studies and demonstrate that rVIII-SingleChain has a favorable safety profile and is not associated with inhibitor development in PTPs with severe hemophilia A. rVIII-SingleChain is also highly efficacious and these data have demonstrated the value of routine prophylaxis as patients are able to maintain low bleed rates during long-term use.

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AUTHOR CONTRIBUTIONS

JM enrolled participants; collected data; was involved in the planning, data analysis, and content analysis of the manuscript; and approved the final version. FK enrolled patients, collected data, made significant contributions to the writing of the manuscript, revised the manuscript critically, and approved the final version. OS enrolled patients, collected data, and approved the final version. BK collected data, revised the manuscript critically, and approved the final version. BS was involved in protocol study design, amendments, data collection, data cleaning, efficacy and safety data analysis, drafting, and reviewing and editing the manuscript; and approved the final version. SL was involved in protocol study design, amendments, data collection, data cleaning, efficacy and safety data analysis, drafting, and reviewing and editing the

manuscript; and approved the final version. AS was involved in amendments, drafting, and reviewing and editing the manuscript; and approved the final version. BG was involved in protocol study design, amendments, efficacy and safety data analysis, reviewing and editing the manuscript, and report approval; and approved the final version. TC was involved in data collection, statistical analysis, data cleaning, drafting, and reviewing and editing the statistical methods in the manuscript, and approved the final version. IP participated in planning the study design, included patients, reviewed and interpreted study results, made significant contributions to the writing of the manuscript, and approved the final version.

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REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-47.
2. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125:2038-2044.
3. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost*. 2009;7:413-420.
4. Valentino LA, Pipe SW, Collins PW, et al. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. *Haemophilia*. 2016;22:514-520.
5. Zollner S, Raquet E, Claar P, et al. Non-clinical pharmacokinetics and pharmacodynamics of rVIII-SingleChain, a novel recombinant single-chain factor VIII. *Thromb Res*. 2014;134:125-131.
6. Mahlangu J, Kuliczkowski K, Karim FA, et al. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. *Blood*. 2016;128:630-637.
7. Stasyshyn O, Djambas Khayat C, Iosava G, et al. Safety, efficacy and pharmacokinetics of rVIII-SingleChain in children with severe hemophilia A: results of a multicenter clinical trial. *J Thromb Haemost*. 2017;15:636-644.
8. Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII: C inhibitors: improved specificity and reliability. *Thromb Haemost*. 1995;73:247-251.
9. Nolan B, Mahlangu J, Pabinger I, et al. Recombinant factor VIII Fc fusion protein for the treatment of severe haemophilia A: final results from the ASPIRE extension study. *Haemophilia*. 2020;26:494-502.
10. Lalezari S, Reding MT, Pabinger I, et al. BAY 94–9027 prophylaxis is efficacious and well tolerated for up to >5 years with extended dosing intervals: PROTECT VIII extension interim results. *Haemophilia*. 2019;25:1011-1019.
11. Highlights of prescribing information: ADVATE 2003. Available at: https://www.fda.gov/downloads/BloodBloodProducts/ucm059095.pdf Accessed December 1, 2020.
12. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood*. 2015;126:1078-1085.
13. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. *Haemophilia*. 2016;22:72-80.
14. Shah A, Coyle T, Lalezari S, et al. BAY 94–9027, a PEGylated recombinant factor VIII, exhibits a prolonged half-life and higher area under the curve in patients with severe haemophilia A: comprehensive pharmacokinetic assessment from clinical studies. *Haemophilia*. 2018;24:733-740.
15. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123:317-325.
16. Simpson ML, Desai V, Maro GS, Yan S. Comparing factor use and bleed rates in U.S. hemophilia A patients receiving prophylaxis with 3 different long-acting recombinant factor VIII products. *J Manag Care Spec Pharm*. 2020;26(4):504-512.
17. Olivieri M, Sommerer P, Maro G, Yan S. Assessing prophylactic use and clinical outcomes in hemophilia A patients treated with rVIII-SingleChain and other common rFVIII products in Germany. *Eur J Haematol*. 2020;104:310-317.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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