INTRODUCTION

Hemophilia A is an X-linked bleeding disorder resulting from a deficiency of factor VIII (FVIII), with manifestations including severe and recurrent joint bleeding to life-threatening bleeding episodes. In patients with severe hemophilia A (defined as FVIII levels <1%), prophylactic treatment with FVIII replacement therapy to prevent bleeding is the standard of care and has dramatically increased the quality of life for these patients.\(^1\)\(^-\)\(^3\) Patients typically require frequent intravenous infusions (3-4 times weekly) using standard-acting FVIII.
products that have half-lives of around 12 hours. Despite the long-term benefits of prophylaxis in preventing arthropathy, the burden of treatment is a major barrier to adherence in patients with hemophilia A.

To address the burden of frequent dosing, long-acting recombinant FVIII (rFVIII) products have been developed with improved pharmacokinetic properties with the aim of reducing the dosing frequency while minimizing the risk of bleeding. rVIII-SingleChain (AFSTYLA®, CSL Behring) is a novel rFVIII product engineered with a covalent bond between the heavy and light chains to increase molecular stability and was designed to have high binding affinity for von Willebrand factor (VWF). rVIII-SingleChain has a 35% higher AUC and a 29% lower clearance than octocog alfa (ADVATE®, Takeda). Patients treated with rVIII-SingleChain can be dosed 2-3 times a week, allowing some patients to be dosed less frequently compared with standard-acting products, while also maintaining high FVIII activity levels; this may enhance convenience and adherence to therapy. Clinical trials have demonstrated that rVIII-SingleChain is suitable for the control and prevention of bleeding episodes and has an excellent safety profile in adults/adolescents and children.

The increased number of available FVIII products means that there is an expanding choice of products for patients; it is therefore critical to identify the product(s) that can provide the greatest overall benefit, both clinically and economically. No direct head-to-head studies have been conducted to compare efficacy and safety of rFVIII products in hemophilia A.

Here, we investigated real-world use of rVIII-SingleChain (AFSTYLA®) and four other commonly used rFVIII products: rFVIIIFc (Elocta®, Sobi), octocog alfa (rFVIII, ADVATE®, Takeda), octocog alfa (BAY 81-8973, Kovaltry®, Bayer), and moroctocog alfa (ReFacto®, Pfizer) in hemophilia A patients treated prophylactically in Germany. In these patients, we assessed bleeding rates, dosing frequency, and factor consumption. In addition, clinical outcomes in patients currently receiving prophylaxis with rVIII-SingleChain were compared with their prior FVIII product.

2 | METHODS

2.1 | Cohort analysis

A retrospective review of de-identified patient chart data was obtained from pre-existing medical records from 21 Hemophilia Treatment Centers (HTCs) across Germany. In this cohort study, males diagnosed with hemophilia A currently using one of five commonly prescribed rFVIII products for prophylaxis: rVIII-SingleChain, rFVIIIFc, octocog alfa (rFVIII), octocog alfa (BAY 81-8973), or moroctocog alfa were included; a minimum of 8 weeks of prophylaxis treatment were required for patients to be included in the analysis. The study was submitted to an institutional review board and was determined to be exempt under category 4 "Secondary research for which consent is not required." Data were collected from August to November 2018. Where possible, patient selection took into account age and disease severity in order to balance these characteristics among the patient groups using these products.

Data pertaining to patient demographics and characteristics, treatment, and clinical outcomes were collected, including: age, weight, sex, severity of hemophilia A, duration on FVIII product, dosing (dose and frequency) of FVIII products, and number of spontaneous and traumatic bleeds reported over a period of up to 12 months. Both adult/adolescent and pediatric patients were included; for the purposes of this study, patients ≥12 years were defined as adults/adolescents, and patients <12 years were defined as pediatrics. Furthermore, disease severity in hemophilia patients with <1% of normal FVIII blood levels was defined as severe, 1–≤5% was defined as moderate, and >5% was defined as mild.

Data were analyzed for patients with severe disease as well as for all patients using one of the rFVIII products, and comparisons were made between the products. The primary outcome measures were annualized bleed rates (ABR) and FVIII consumption. Bleeding rates were annualized by dividing the number of bleeding events by the number of months in the reported time window (2–12 months) and multiplying by 12. Prescribed dosing and infusion frequencies were taken from the most recent prescription of each product; prophylactic factor consumption was standardized by multiplying the dose per infusion by number of infusions per week and dividing by the patient’s weight (kg), reported as international units (IU) of product per kilogram of body weight per week (IU/kg/week).
2.2 Switch analysis

Further analysis of patients described in the cohort analysis above who were receiving prophylaxis with rVIII-SingleChain was conducted. Data were collected about the products they used before switching to rVIII-SingleChain and ABR, dosing frequency, and factor consumption were then compared between rVIII-SingleChain and prior products.

2.3 Statistical methods

Analysis of covariance (ANCOVA) was used to assess the statistical significance of differences in mean ABR and FVIII consumption between the different cohorts of patients. The ANCOVA model used to assess mean ABR differences included age, weight, severity, and consumption as covariates, whereas the model used to assess FVIII consumption included age, weight, and severity. The statistical significance of the differences in proportion of patients with zero bleeds across products was assessed using Fisher’s exact test.

For the switch analysis, paired t-test were used to evaluate the statistical significance of the differences in mean ABR and FVIII consumption while on rVIII-SingleChain vs prior products. McNemar’s test was used to assess the statistical significance of the difference in proportion of patients with zero bleeds between rVIII-SingleChain and prior products.

3 RESULTS

3.1 Cohort analysis

A total of 21 HTCs across Germany provided data for 225 male patients, with patients using rVIII-SingleChain (n = 40), rFVIIIFc (n = 47), octocog alfa (rFVIII; n = 58), octocog alfa (BAY 81-8973; n = 40), or moroctocog alfa (n = 40); patient characteristics are described (Table 1). The majority of patients in each cohort were adults, and among all patients, 33.8% had severe disease. In patients with severe disease, a high proportion were dosing ≤2×/week with rVIII-SingleChain or rFVIIIFc (66.6% and 70.0%, respectively), whereas the majority of patients using standard-acting products were dosed 3×/week (octocog alfa [rFVIII], 60.0%; octocog alfa [BAY 81-8973], 61.5%; and moroctocog alfa, 63.6%; Figure 1A). In addition, another 20% of rFVIIIFc patients with severe disease were dosed every 3 days. In all patients in the cohort analysis, 82.5% and 76.5% were dosed ≤2×/week with rVIII-SingleChain and rFVIIIFc, respectively (Figure 1B). A further 8.5% of patients treated with rFVIIIFc were dosed every 3 days.

In the subgroup of patients with severe disease, median (mean) ABR values were 0.0 (0.3) for rVIII-SingleChain (n = 12), 0.0 (0.8) for rFVIIIFc (n = 20), 0.5 (1.1) for octocog alfa (rFVIII; n = 20), 1.0 (1.5) for octocog alfa (BAY 81-8973; n = 13), and 1.0 (1.4) for moroctocog alfa (n = 11), Table 2. The differences among the products were not statistically significant (P = .1162) as shown by ANCOVA; however, the small sample size for each product likely played a role in this. When grouping products by type (long-acting products: rVIII-SingleChain and rFVIIIFc, n = 32; standard-acting products: octocog alfa [rFVIII], octocog alfa [BAY 81-8973], and moroctocog alfa, n = 44), an ad hoc ANCOVA showed P = .0262 for the difference between the two product types. Of these patients, the proportion with zero bleeds in numerical order was 75.0% for rVIII-SingleChain and 65.0% for rFVIIIFc, followed by the remaining three products where ≤50% of patients achieved zero bleeds (octocog alfa [rFVIII], 50.0%; octocog alfa [BAY 81-8973], 46.2%; and moroctocog alfa, 36.4%; P = .3089 comparing this proportion among the products, Table 2). When the two product types were compared instead of the products, a trend was seen in statistical significance (P = .0618). In addition, median annualized

| TABLE 1 Baseline patient characteristics for patients included in the cohort analysis |
|------------------------------------------|--------------------------------|--------------------------------|
| **Long-acting**                          | **Standard-acting**           |                                |
| rVIII-SingleChain (n = 40)               | Octocog alfa (rFVIII) (n = 58) | Octocog alfa (BAY 81-8973) (n = 40) |
| rFVIIIFc (n = 47)                        | Octocog alfa (n = 40)         | Moroctocog alfa (n = 40)       |
| Age, y                                   |                                |                                |
| 29.9 (12.4)                              | 31.7 (13.2)                   | 31.4 (9.4)                     |
| 32.0 (15.4)                              | 34.2 (14.3)                   |                                |
| Age group, n (%)                         |                                |                                |
| Adult/Adolescents (≥12 y)               | 45 (95.7)                     | 40 (100)                       |
| 39 (97.5)                                | 54 (93.1)                     |                                |
| Pediatrics (<12 y)                       | 2 (4.3)                       | 0 (0)                          |
| 1 (2.5)                                  | 4 (6.9)                       |                                |
| Weight, kg                               | 69.5 (16.2)                   | 69.6 (17.1)                    |
| 75.6 (13.2)                              | 72.5 (16.3)                   | 75.1 (9.7)                     |
| Severity                                 |                                |                                |
| Severe, n (%)                            | 20 (42.6)                     | 11 (27.5)                      |
| 12 (30.0)                                | 20 (34.5)                     |                                |
| Moderate/mild, n (%)                     | 27 (57.4)                     | 29 (72.5)                      |
| 28 (70.0)                                | 38 (65.5)                     |                                |
| Duration of observation, wk, mean (range)| 47 (8-78)                     | 52 (52-52)                     |
|                                          | 52 (52-52)                    | 52 (52-52)                     |

Note: Data presented are mean (SD), unless otherwise stated.
Abbreviations: SD, standard deviation.
spontaneous bleed rate (AsBR) values were 0.0 across all products, and mean values ranged from 0.1 with rVIII-SingleChain to 0.8 with octocog alfa (BAY 81-8973; \( P = .3088 \), Table 2). The percentage of patients reporting zero spontaneous bleeds were: rVIII-SingleChain, 91.7%; rFVIIIFc, 85.0%; octocog alfa (rFVIII), 70.0%; octocog alfa (BAY 81-8973), 69.2%; and moroctocog alfa, 54.5% \( (P = .2250, \text{Table 2}) \). Again, ad hoc analyses comparing the two product types instead of the products showed some trending toward statistical significance \( (P = .0975 \) for AsBR and \( P = .0360 \) for the percentage of patients with zero spontaneous bleeds).

When considering all patients, irrespective of disease severity, median ABR values were comparable between all products, with patients in each cohort having a median ABR of 0.0 (Table 2). Mean ABR values ranged from 0.4 with rVIII-SingleChain to 1.2 with octocog alfa (BAY 81-8973; \( P = .0158 \), Table 2). During the reporting period, numerically, a higher proportion of patients experienced zero bleeds using rVIII-SingleChain (75.0%) or rFVIIIFc (78.7%), compared with those using other products, octocog alfa (rFVIII; 58.6%), octocog alfa (BAY 81-8973; 55.0%), or moroctocog alfa (57.5%; \( P = .0482 \), Table 2). In addition, median AsBR values were 0.0 across all products (means as shown in Table 2, \( P = .0649 \)), and the percentage of patients reporting zero spontaneous bleeds were rVIII-SingleChain, 92.5%; rFVIIIFc, 89.4%; octocog alfa (rFVIII), 82.8%; octocog alfa (BAY 81-8973), 77.5%; and moroctocog alfa, 70.0% \( (P = .0555 \), Table 2).

Overall mean consumption in patients with severe disease using rVIII-SingleChain \( (n = 12) \) was 83.2 IU/kg/week, 97.2 IU/kg/week with rFVIIIFc \( (n = 20) \), 92.5 IU/kg/week with octocog alfa (rFVIII; \( n = 20 \)), 104.0 IU/kg/week with octocog alfa (BAY 81-8973), and 102.1 IU/kg/week with moroctocog alfa \( (P = .1766 \), Figure 2A); as discussed above, the small sample size of patients with severe disease on each product is likely an important factor for such \( P \) values. An ad hoc ANCOVA comparing consumption for rVIII-SingleChain (not combined with rFVIIIFc due to the numerical difference as observed) and the three short-acting products combined indicated trending toward statistical significance \( (P = .0831 \) ). When including all patients, the mean FVIII consumption across all dosing frequencies for the rVIII-SingleChain cohort was 59.2 IU/kg/week with rVIII-SingleChain, compared with 81.1 IU/kg/week with rFVIIIFc, 82.7 IU/kg/week with octocog alfa (rFVIII), 91.4 IU/kg/week with octocog alfa (BAY 81-8973), and 81.4 IU/kg with moroctocog alfa \( (P = .0001 \), Figure 2B).
3.2 Switch analysis

In patients treated with rVIII-SingleChain prophylaxis, 37 had data available for prior FVIII therapy and were included in the switch analysis. Overall, 97.3% (36/37) of patients were ≥12 years and 32.4% (12/37) of patients had severe disease. The average length of treatment on rVIII-SingleChain was 44 (range 8-78) weeks.

Of the 37 patients who had received prior treatment with FVIII products, the majority (75.7%) were treated with standard-acting rFVIII; 21.6% were treated with plasma-derived FVIII, and one patient (2.7%) was using a long-acting rFVIII product. Twenty-one (56.8%) patients were on prophylaxis with their prior drug, and all of them infused factor at least 3×/week before switching to rVIII-SingleChain. After switching to prophylaxis with rVIII-SingleChain, 71.4% of these 21 patients were dosed ≤2×/week.

Prior to the switch, 16 (43.2%) patients were treating on-demand; after switching to prophylaxis with rVIII-SingleChain, the majority (78.4%) of the 37 patients were on a 2×/week dosing regimen (Figure 3). After patients had switched from prophylaxis with their prior FVIII product to prophylaxis with rVIII-SingleChain, mean ABRs were also somewhat reduced (0.7 vs 0.2) compared with the prior FVIII product ($P = .0469$, Table 3). In addition, the mean AsBR reduced from 0.3 with the prior therapy to 0.0 with rVIII-SingleChain ($P = .0691$, Table 3). Furthermore, the proportion of patients with zero bleeds (spontaneous or trauma-related) increased from 57.1% to 81.0% after switching to rVIII-SingleChain ($P = .1167$, Table 3), and the proportion of patients with zero spontaneous bleeds increased from 76.2% to 95.2% ($P = .0027$, Table 3).

For patients switching to rVIII-SingleChain, prophylactic consumption decreased in 18/21 patients, with a mean reduction of 32% (from 109.4 to 74.5 IU/kg) compared with prior FVIII products ($P < .0001$, Figure S1). Of the patients on a 2×/week regimen with rVIII-SingleChain (n = 15), mean weekly consumption reduced from 115.1 to 66.0 IU/kg/week when switching from prior FVIII to rVIII-SingleChain ($P < .0001$). Furthermore, mean factor consumption reduced by 41.6% (112.5 to 65.7 IU/kg, $P < .0001$) in patients (n = 13) who switched from a dosing frequency of 3×/week with prior FVIII to 2×/week with rVIII-SingleChain.

4 DISCUSSION

This study assessed real-world experience of rFVIII products in Germany through a retrospective review of patient chart data. In this cohort study, bleed rates were low and comparable between products; however, rVIII-SingleChain demonstrated lower mean consumption than the other commonly used products assessed, as well as similar dosing frequency to rFVIIIFc as the two long-acting products included in this analysis.
This study confirms the efficacy of rVIII-SingleChain as previously observed in the pivotal trial; the improved pharmacokinetic profile of rVIII-SingleChain compared with conventional products may lead to higher FVIII trough levels or allow some patients to reduce their infusion frequency which may in turn reduce the burden of treatment. However, it is important to note that all patients in the pivotal trial had severe disease, whereas in this analysis, the majority of patients (66%) had mild/moderate disease. Prior to switching to rVIII-SingleChain, 43.2% of patients were treated on-demand. Of the patients who switched from prophylaxis with their prior product to prophylaxis with rVIII-SingleChain, all were dosed at least 3×/week, while the majority (71.4%) were dosed 2×/week after the switch, including eight out of the 12 patients (66.6%) with severe disease. This suggests that the 2×/weekly regimen is an acceptable prophylactic regimen for many patients including those previously treated on-demand. Treatment burden is a major challenge when patients consider switching from on-demand to prophylaxis; however, switching to prophylaxis may be beneficial, as it may prevent morbidity associated with long-term joint damage resulting from recurrent bleeding. In addition, in those patients already receiving prophylaxis prior to switching to rVIII-SingleChain, the reduction in infusion frequency may reduce overall treatment burden, and the reduced consumption indicates potential economic benefit may ensue.

Similar bleeding rates were observed among FVIII products in this analysis, and the low ABRs overall suggests bleeding risk was generally well managed. The cohort analysis shows that long-acting
As a result, in the patients who switched from prior product to rVIII-SingleChain, the expected annual consumption may reduce from 398,216 to 271,180 IU for a 70-kg patient. A previous study in the US found that patients using rVIII-SingleChain in all patients as well as in those specifically with severe disease did not reach statistical significance likely due to the small sample sizes as a major factor. This may influence therapy preference when considering treatment cost. While statistical significance may be important in assessing the differences in consumption, the net numerical differences also can be very meaningful when it comes to economic implications. For example, using the mean consumption from all patients and applying the list prices per IU in Germany (€1.08 rVIII-SingleChain, €1.06 rFVIIIFc, €0.93 octocog alfa [rFVIII], €0.91 octocog alfa [BAY 81-8973], and €1.03 moroctocog alfa), obtained from Pricentric ONE by EVERSANA (Accessed November 14, 2019), the total annual costs are expected to be €232,207, €313,380, €278,730, €303,112, and €305,460, respectively, for a patient with a body weight of 70 kg. In addition, the switch analysis of the prophylaxis-to-prophylaxis treatment group demonstrated a 32% reduction in mean weekly factor consumption across all treatment regimens after patients switched to rVIII-SingleChain. As a result, in the patients who switched from prior product to rVIII-SingleChain, the expected annual consumption may reduce from 398,216 to 271,180 IU for a 70-kg patient. A previous study in the US found that patients switching from standard-acting products to long-acting products resulted in higher expenditure over 2 years; however, that analysis did not include rVIII-SingleChain.11

Overall, in this analysis, rVIII-SingleChain was demonstrated to be effective, suggesting that this long-acting product provides a reliable option for patients with hemophilia A. Individualized prophylaxis regimens that reduce infusion frequency and FVIII consumption can minimize the burden and cost of treatment while maintaining excellent bleeding protection.

Limitations of this retrospective analysis include the small sample size which lacks a specific random selection scheme and the potential under-estimation of the proportion of patients with severe disease compared with the general patient population in Germany12; therefore, the sample used in this analysis may not reflect the overall German hemophilia A population. The interpretation of the results for all patients should consider the possible impact of differing numbers of patients with severe disease in patients using each product, as well as adjusting for additional patient characteristics such as joint status, target joints, VWF levels, and pharmacokinetic parameters. Additional research may be needed in larger sample sizes conducted over a longer period of time to further evaluate real-world experience and identify treatment patterns in patients with hemophilia A.13 Nevertheless, our study included patients with mild/moderate disease as well as those with severe disease and findings were consistent between the entire patient sample and when restricting the analysis to those with severe disease (approximately one-third of patients). Additional limitations include the lack of information about the location, severity, treatment, and outcomes of bleeding events. In addition, the reasons for switching to rVIII-SingleChain were not reported and potential selection bias from the centers contributing data may limit generalizing to the patient population as a whole. Lastly, as the mean duration of observation for rVIII-SingleChain was shorter than the other two products (47 vs 52 weeks), the percentage of patients with no bleeds may be slightly higher than observed if the duration of observation was the same. While acknowledging the limitations in this study, the results presented here are consistent with the experience of rVIII-SingleChain clinical trials, demonstrating reduced consumption with less frequent dosing while maintaining bleed control.

5 | CONCLUSION

In conclusion, this is the first study evaluating the clinical benefits of a range of FVIII products using real-world data in Germany. This analysis suggests that patients, including those with severe disease, can be dosed less frequently using rVIII-SingleChain compared with standard-acting products, which may reduce the burden of treatment. In this

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### Table 3: Bleeding rates in patients who have switched from prophylaxis with their prior FVIII product to prophylaxis with rVIII-SingleChain

|                     | Prior FVIII | rVIII-SingleChain | P-value |
|---------------------|------------|------------------|---------|
| **ABR**             |            |                  |         |
| Median (min, max)   | 0.0 (0.0, 3.0) | 0.0 (0.0, 2.0) |         |
| Mean (SD)           | 0.7 (1.0)  | 0.2 (0.5)        | 0.0469  |
| Patients with zero bleeds, n (%) | 12 (57.1)  | 17 (81.0)        | 0.1167  |
| **AsBR**            |            |                  |         |
| Median (min, max)   | 0.0 (0.0, 2.0) | 0.0 (0.0, 1.0) |         |
| Mean (SD)           | 0.3 (0.6)  | 0.0 (0.2)        | 0.0691  |
| Patients with zero spontaneous bleeds, n (%) | 16 (76.2)  | 20 (95.2)        | 0.0027  |

Abbreviations: ABR, annualized bleed rate; AsBR, annualized spontaneous bleed rate; SD, standard deviation.
analysis, patients treated with rVIII-SingleChain had the lowest factor consumption compared with other FVIII products. rVIII-SingleChain provides excellent bleeding protection with bleed rates comparable to those observed with other FVIII products. This analysis also demonstrates that rVIII-SingleChain provides effective bleed prevention in patients who switched to rVIII-SingleChain prophylaxis, allowing the majority of patients to be treated on a 2-week regimen, and patients were able to reduce their factor consumption without compromising clinical outcome. Given the limitations of this study, further research with a larger sample, longer duration, and potentially more robust design is needed to confirm these results.

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CONFLICT OF INTEREST
SY and PS are employees of CSL Behring; GM is an employee of Adivo Associates; MO received grants/research support from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Shire/Takeda, and Swedish Orphan Biovitrum, consultancy and speaker fees from Bayer, Biotest, Novo Nordisk, CSL Behring, Pfizer, and Swedish Orphan Biovitrum.

AUTHOR CONTRIBUTIONS
SY contributed to the conception, design, and analysis of the study, as well as drafting of the manuscript. GM contributed to the conception, design, data collection, and analysis as well as manuscript development. MO and PS provided intellectual discussion and were integral to reviewing the manuscript.

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

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