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ORIGINAL ARTICLE

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Safety and efficacy of damoctocog alfa pegol prophylaxis in patients with severe haemophilia A: Results of an interventional, post-marketing study

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Abstract

Introduction: Damoctocog alfa pegol (BAY 94-9027, Jivi®) is an approved extended half-life factor VIII (FVIII) for treatment of previously treated patients with haemophilia A aged ≥12 years. We report the final results of an interventional, post-marketing study of damoctocog alfa pegol prophylaxis in patients with severe haemophilia A.

Methods: In this open-label, interventional, post-marketing, phase 4 trial (NCT04085458), previously FVIII-treated patients with severe haemophilia A aged ≥18 years received damoctocog alfa pegol for ≥100 exposure days (EDs). Patients initially received 45 IU/kg every 5 days (recommended) or 40 IU/kg twice-weekly. At Visit 3, patients' doses could be increased, or treatment frequency adapted. The primary endpoint was FVIII inhibitor development (titre ≥.6 Bethesda units). Secondary endpoints included anti-polyethylene glycol (PEG) antibody development, treatment-emergent adverse events (AEs) and annualized bleeding rate (ABR).

Results: Overall, 36 patients were enrolled; 32 patients received treatment, of whom, 27 completed the study. No patients developed FVIII inhibitors; three tested transiently positive for low-titre anti-PEG antibodies without clinical relevance. Three patients reported study-drug-related AEs of mild or moderate intensity. Two patients discontinued the study due to AEs. No deaths occurred. Most patients (70%) were treated with E5D/E7D regimens. The median (Q1;Q3) total ABR (N = 30) was 3.0 (.0;9.0) pre-study and 1.8 (.7;5.9) during the study.

Conclusion: Damoctocog alfa pegol individualized prophylaxis regimens were well-tolerated with no immunogenicity concerns. ABRs improved following the switch from pre-study prophylaxis to damoctocog alfa pegol prophylaxis. These results support the favourable safety and efficacy profile of damoctocog alfa pegol prophylaxis.

KEYWORDS
extended half-life, haemophilia A, prophylaxis, recombinant factor FVIII

1 | INTRODUCTION

The gold-standard management of haemophilia A is prophylaxis, for which factor VIII (FVIII) replacement remains the cornerstone, restoring coagulation with infusions of recombinant FVIII (rFVIII) protein to reduce or prevent bleeding and preserve long-term joint function.[1–3] However, incomplete adherence to prescribed dosing regimens, owing to the time commitment and lifestyle changes required to accommodate frequent infusions, can limit treatment success.[1] Individualized prophylaxis is a strategy of tailored dosing based on a patient's characteristics, bleeding pattern, pharmacokinetic profile and lifestyle.[1,4,5] This strategy may mitigate treatment burden through reduced infusion frequency and factor utilization, thus improving adherence.[1] The development of extended half-life FVIII products may further allow for individualization of prophylaxis by facilitating less frequent infusions compared with standard half-life FVIII.[1,6,7]

Damoctocog alfa pegol (BAY 94-9027, Jivi®) is a B-domain deleted rFVIII product that is site-specifically conjugated with polyethylene glycol to extend its half-life.[1,5] Efficacy and safety of damoctocog alfa pegol for prophylaxis and for treatment of bleeding episodes has been demonstrated in the PROTECT VIII (NCT01580293) trial in previously treated patients with severe haemophilia A aged ≥12 years. These patients received treatment for up to 7 years at dose intervals of up to every 7 days (E7D).[5] At PROTECT VIII extension completion, efficacy and safety of damoctocog alfa pegol were confirmed with median total, joint and spontaneous annualized bleeding rates (ABRs) of <2 for treated prophylaxis patients, with 50% of patients bleed-free and 58% joint bleed–free during their last 6 months of treatment in the extension study.[5]

Post-marketing studies are conducted to confirm the safety and efficacy of approved treatments in a broad population, with the aim of extending the data obtained in pre-marketing studies.[8] Here we will report on a post-marketing interventional study (ClinicalTrials.gov identifier: NCT04085458) that was conducted to explore the safety and efficacy of damoctocog alfa pegol in patients with haemophilia A across 13 sites, over 100 exposure-days (EDs), with a follow-up of approximately 2 years. This study contributes to addressing the European Medicines Agency's requirements for FVIII products, which include the collection of safety data from 200 participants, including participants from pre-authorization studies, treated for at least 100 EDs.[9] Here, we report the final results of this post-marketing, open-label study demonstrating efficacy and safety of damoctocog alfa pegol in previously FVIII-treated patients with haemophilia A aged ≥18 years.

2 | METHODS

2.1 | Patients

Males aged ≥18 years with severe haemophilia A (FVIII:C < 1%) receiving prophylaxis treatment were eligible for inclusion in this study. Patients must have had ≥150 EDs prior to study enrolment. Other inclusion criteria included willingness to complete an electronic patient diary (EPD) and provide signed informed consent. Patients who had participated in the PROTECT VIII or PROTECT VIII Kids studies were excluded from the study. Other key exclusion criteria included the presence or history of a FVIII inhibitor (≥.6 Bethesda units/mL), diagnosis of any bleeding disorder other than haemophilia A and platelet count <100,000/mm^3.

2.2 | Study design

This was an interventional phase 4, multicentre, single group, uncontrolled, open-label, post-marketing trial evaluating safety and efficacy of twice-weekly, every 5 days (E5D) and E7D dosing of damoctocog alfa pegol prophylaxis in previously FVIII-treated patients with severe haemophilia A, aged ≥18 years, for up to 2 years (Figure 1). The recommended starting dose was 45 IU/kg E5D, which patients received until the next planned visit after 10–15 exposure days (8–10 weeks, visit 3). Patients experiencing an increased bleeding frequency could switch to twice-weekly 40 IU/kg during the first 8–10 weeks at the investigator's judgment.

Following Visit 3, patients could continue with E5D treatment or switch to a different dose/regimen. The dosing selection at Visit 3 was based on investigator assessment, patient's preference and number of bleeds in the first 8–10 weeks with the following guidance: E7D 60 IU/kg for patients with no bleeds, E5D 60 IU/kg or twice-weekly 40 IU/kg for patients with 1 clinically relevant bleed, or twice-weekly 40 IU/kg for those with ≥2 clinically relevant bleeds. Adoption of this guidance was discretionary and served as a recommendation only. Patients were allowed to change dosing frequency at any time during the study in case of an increase in bleeding frequency. All treatment decisions for identifying appropriate prophylactic treatment regimens were guided by clinical judgement based on individual patient characteristics and treatment response. The total treatment duration was the time to reach 100 EDs.

The study was approved by each site's Independent Ethics Committee and/or Institutional Review Board and was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided their written informed consent prior to study enrolment.

2.3 | Efficacy and safety assessments

Bleeding events and administered infusions were recorded by patients using an EPD. Patients were monitored and blood samples collected at visits every 6 months and analysed in a central laboratory. The primary endpoint was FVIII inhibitor development (titer ≥.6 Bethesda units) by the Nijmegen Bethesda assay. Any positive inhibitor test was confirmed by testing a second, separately drawn sample within 2–4 weeks. Secondary endpoints included incidence of treatment-emergent adverse events (TEAEs), development of treatment-emergent anti-polyethylene glycol (PEG) antibodies, and

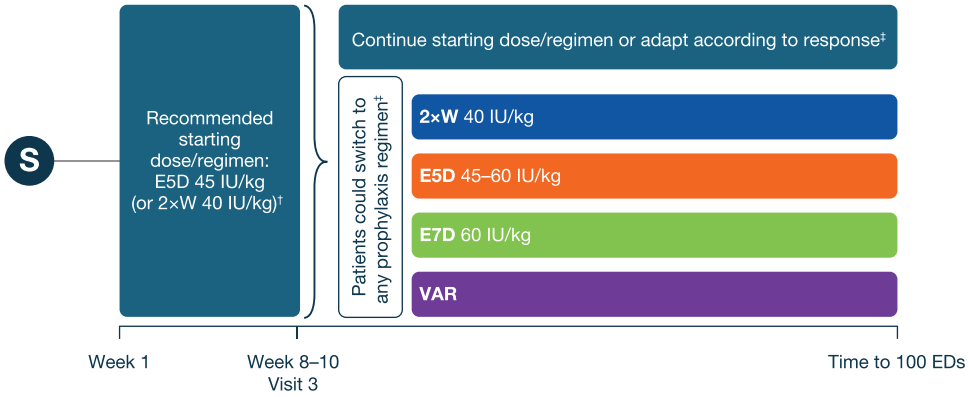

FIGURE 1 Study design[12]. †Patients experiencing an increased bleeding frequency could switch to twice-weekly 40 IU/kg during the first 8–10 weeks at the investigator's judgment. ‡Based on investigator's judgement, patient preference and the number of bleeds in the first 8–10 weeks; dosing recommendations were provided as guidance but were not mandatory. 2 × W, twice weekly; E5D, every 5 days; E7D, every 7 days; ED, exposure day; S, screening; VAR, variable frequency.

ABRs for total, spontaneous, trauma and joint bleeds. Additional efficacy assessments included the proportion of patients with zero bleeds, and resolution of target joints. Active target joints were reported by the investigator using the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee's definition of ≥3 spontaneous bleeds into the same joint within a 6-month period during the study.[10] A target joint was considered resolved if ≤2 spontaneous bleeds occurred into the same previous target joint during the last 12 months of the study. FVIII utilization was also assessed.

2.4 | Statistical analyses

Patients were analysed by regimen, as assigned at Visit 3. Patients who switched prophylaxis regimen after Visit 3 were assigned to a variable frequency (VAR) group. Patients who received ≥1 infusion of damoctocog alfa pegol were included in the safety analysis set. All patients who received ≥1 infusion of damoctocog alfa pegol and had EPD data for ≥3 months were included in the modified intent-to-treat (mITT) population. Safety was assessed for the safety analysis set and assessment of efficacy was performed for the mITT population. All ABRs were calculated based on total time on prophylaxis. All analyses were descriptive and non-confirmatory. Statistical analysis was performed using SAS software 9.4. Summary statistics were calculated for continuous data, and frequencies were calculated for categorical data.

3 | RESULTS

3.1 | Patients

Overall, 36 patients were enrolled. Of these, 32 patients received treatment with damoctocog alfa pegol and were included in the safety analysis set. A total of 30 patients received ≥1 infusion of damoctocog alfa pegol and had EPD data for ≥3 months. These patients were included in the mITT population. The median (range) total time in the study for the mITT population was 1.3 (.31–2.00) years with a median (range) of 105.0 (30–119) EDs. For the 32 patients included in the safety analysis set, median (range) total time in the study was 1.3 (.03–2.00) years with a median (range) of 104.5 (5–119) EDs.

Demographics and baseline disease characteristics are presented for the mITT population. The mean (standard deviation [SD]) age of patients was 43.3 (15.2) years and mean (SD) body mass index was 25.6 (4.4) kg/m^2 (Table 1). All patients were Caucasian (n = 30 [100.0%]), and the majority were of non-Hispanic or Latino origin (n = 28 [93.3%]); 2 (6.7%) patients identified as Hispanic or Latino. At baseline, 10 (33.3%) patients presented with an active target joint (Table 1). The mean (SD) age at first treatment was 1.9 (2.8) years, and 30.5 (19.1) years at prophylaxis start (Table 1). Most patients (n = 24 [80.0%]) received on-demand treatment as their first treatment regimen, and three (10.0%) patients received regular prophylaxis. Prior to start of the study, patients were receiving regular prophylaxis at a dosing frequency of every other day (n = 8 [26.7%]), three times per week (n = 10 [33.3%]), two times per week (n = 9 [30.0%]) or every 3 days (n = 3 [10.0%]). Of the 29 patients with available data, the median (quartile [Q]1; Q3) pre-study ABR was 3.0 (.0; 9.0) (Table 1).

At baseline, three (10.0%) patients were assigned to a twice-weekly damoctocog alfa pegol prophylaxis regimen and 27 (90.0%) patients were assigned to E5D prophylaxis. At Visit 3, a total of nine (30.0%) patients were assigned to receive twice-weekly prophylaxis, 10 (33.3%) patients were assigned to E5D prophylaxis, and 11 (36.7%) patients were assigned to E7D prophylaxis. Most patients remained on the regimen assigned to them at Visit 3 until the end of the study: seven (77.8%) patients continued to receive twice-weekly prophylaxis, eight (80.0%) patients continued with E5D prophylaxis, and nine (81.8%) patients continued with E7D prophylaxis. Six patients had switched regimen between Visit 3 and end of the study and were analysed in the VAR treatment group. Three patients in the VAR group decreased their dose frequency—two from twice-weekly to E5D, and one from E5D to E7D. Three patients increased their dose

TABLE 1 Demographics and baseline disease characteristics (mITT population[a]).

Characteristic	Twice-weekly ($n = 7$)	Every 5 days ($n = 8$)	Every 7 days ($n = 9$)	Variable frequency ($n = 6$)	Total ($N = 30$)
Age at enrolment, years, mean (SD)	50.4 (12.3)	42.1 (12.9)	37.4 (17.9)	45.5 (16.6)	43.3 (15.2)
Baseline BMI, kg/m^2, mean (SD)	28.0 (5.3)	24.4 (5.3)	24.7 (2.9)	25.8 (3.6)	25.6 (4.4)
Age at first treatment, years, mean (SD)	2.2 (2.3)	1.2 (.8)	1.1 (.7)	3.3 (5.8)	1.9 (2.8)
Type of first treatment regimen, n (%)					
Missing	0	1 (12.5)	2 (22.2)	0	3 (10.0)
On demand	6 (85.7)	7 (87.5)	5 (55.6)	6 (100.0)	24 (80.0)
Regular prophylaxis	1 (14.3)	0	2 (22.2)	0	3 (10.0)
Age at prophylaxis start, years, mean (SD)	37.7 (13.8)	29.3 (15.3)	28.4 (28.1)	26.8 (17.3)	30.5 (19.1)
Dosing frequency prior to study, *n* (%)					
Two times per week	1 (14.3)	2 (25.0)	2 (22.2)	4 (66.7)	9 (30.0)
Three times per week	3 (42.9)	4 (50.0)	2 (22.2)	1 (16.7)	10 (33.3)
Every 3rd day	0	0	3 (33.3)	0	3 (10.0)
Every other day	3 (42.9)	2 (25.0)	2 (22.2)	1 (16.7)	8 (26.7)
Pre-study ABR, *n*	7	8	8	6	29
Median (Q1; Q3)	3.0 (.0; 9.0)	2.0 (.0; 4.5)	5.5 (.0; 14.0)	4.5 (.0; 9.0)	3.0 (.0; 9.0)
Number of patients with active target joint, *n* (%)	2 (28.6)	2 (25.0)	3 (33.3)	3 (50.0)	10 (33.3)
Type of target joint, *n* (%)					
Ankle	1 (50.0)	1 (50.0)	2 (66.7)	3 (100.0)	7 (70.0)
Elbow	1 (50.0)	1 (50.0)	1 (33.3)	3 (100.0)	6 (60.0)
Knee	0	1 (50.0)	2 (66.7)	0	3 (30.0)
Shoulder	1 (50.0)	0	0	0	1 (10.0)

[a]Patients who received ≥1 infusion of damoctocog alfa pegol and had bleeding data for ≥3 months were included in the mITT population.
Abbreviations: ABR, annualized bleeding rate; BMI, body mass index; mITT, modified intent-to-treat; Q, quartile; SD, standard deviation.

frequency—one from E7D to E5D, one from E7D to twice-weekly and one from E5D to twice-weekly. By the end of the study, 21/30 (70.0%) patients received E5D or E7D prophylaxis.

3.2 | Safety

Safety data are presented for the safety analysis set ($N = 32$). Adverse events reported during the study are presented in Table 2. Study-drug-related AEs of injection site erythema, skin wound, hypersensitivity, dysgeusia, cough, pruritus and rash maculo-papular, classed as either mild or moderate, were observed in three (9.4%) patients. Two (6.3%) patients reported serious AEs (fall [$n = 1$], osteoarthritis [$n = 1$]); neither were study drug related. Two (6.3%) patients discontinued due to study-drug-related AEs (skin wound in the left arm and hypersensitivity reaction); no other discontinuations or deaths occurred. No patients developed FVIII inhibitors during the study. Anti-drug antibodies were identified at the penultimate visit in three (9.4%) patients. All three of these patients tested transiently positive for very-low-titre anti-PEG antibodies, of whom, one patient also tested transiently positive for low-titre anti-damoctocog alfa pegol antibodies. Anti-PEG antibodies had no neutralizing activity, none were IgM in class and no antibodies had clinical impact. No patients tested positive for anti-drug antibodies at the end of study.

3.3 | Bleeding outcomes

3.3.1 | Annualized bleeding rates

Bleeding outcomes are presented for the mITT population ($N = 30$). Total, spontaneous and joint ABRs from Visit 3 to end of study are presented in Figure 2. Median (Q1; Q3) total, joint and spontaneous ABRs ($N = 30$) were 1.8 (.7; 5.9), .3 (.0; 2.7) and 1.4 (.0; 3.0), respectively, from baseline to end of study.

3.3.2 | Zero bleeds

The proportion of patients achieving zero bleeds during the last 24 weeks of treatment and during the last year of treatment are shown in Figure 3. In the last 24 weeks of treatment ($n = 28$), 53.6% ($n = 15$) of patients had zero total bleeds and 71.4% ($n = 20$) of patients had zero joint bleeds. Of the 26 patients who had available data on bleeds

TABLE 2 Adverse events during the post-marketing interventional study (safety analysis set).

Patients, *n* (%)	Prophylaxis (*N* = 32)
Any AE	21 (65.6)
Mild	14 (43.8)
Moderate	5 (15.6)
Severe	2 (6.3)
Any study drug-related AE	3 (9.4)[a]
Mild	2 (6.3)
Moderate	1 (3.1)
Severe	0
Any SAE	2 (6.3)
Any study-drug-related SAE	0
Discontinuation of study drug due to AE	2 (6.3)
Discontinuation of study drug due to SAE	0
Presence of FVIII inhibitor (titre ≥.6 Bethesda units)	0
Presence of PEG antibody in plasma	3 (9.4)

[a]Study drug-related AEs were observed in three patients: injection site erythema, skin wound (leading to discontinuation), hypersensitivity (leading to discontinuation), dysgeusia, cough, pruritus and rash maculo-papular.
Abbreviations: AE, adverse event; FVIII, factor VIII; PEG, polyethylene glycol; SAE, serious adverse event.

during their last year of treatment, 30.8% (*n* = 8) had zero total bleeds and 61.5% (*n* = 16) had zero joint bleeds. Of the 17 patients receiving extended dosing intervals (E5D or E7D) who had available data on bleeds during their last year of treatment, 35.3% (*n* = 6) had zero total bleeds and 58.8% (*n* = 10) had zero joint bleeds. In the E7D group (*n* = 9), 77.8% of patients experienced zero joint bleeds during their last year of treatment.

3.3.3 | Target joints

At baseline, 22 active target joints were observed in 10 patients, as reported by the investigator. During the study, four target joints developed (one each in four patients), and 19 target joints resolved in eight patients. At the end of the study, seven active target joints were observed in five patients.

3.4 | FVIII utilization

In the mITT population (*N* = 30), the median (range) total FVIII dose per kg per prophylaxis infusion was 50.6 (40–63) IU/kg with a median (range) of 73.6 (54–99) prophylaxis infusions per year. The median (range) annual FVIII utilization for prophylaxis was 3603 (3160–4460) IU/kg/year. Compliance with prophylaxis treatment (actual/planned prophylaxis infusions) was approximately 100% for all regimens. Data on FVIII utilization at baseline are unavailable.

4 | DISCUSSION

These data from patients with haemophilia A show that individualized prophylaxis regimens of damoctocog alfa pegol were efficacious and well tolerated, with no immunogenicity concerns. Most patients started on an E5D regimen. The majority of patients (70%) had ≤1 bleed during the first 8–10 weeks of prophylaxis and thus received extended-interval prophylaxis (E5D or E7D) following Visit 3. Three patients reported study-drug-related AEs, which were all mild or moderate in severity. Two patients discontinued treatment due to a skin wound and a hypersensitivity reaction, respectively. There were isolated instances of low-titre positive anti-PEG and/or anti-damoctocog alfa pegol antibody results followed by negative results, these findings are consistent with results from the PROTECT VIII studies and are likely false positive findings associated with assay variability and are not an indicator of treatment-emergent antibodies. These transient antibody findings were of no clinical relevance, suggesting that periodic screening for anti-PEG antibodies in the absence of clinical suspicion is not necessary. No patients developed FVIII inhibitors, although it should be noted that all patients were PTPs and had already had >150 EDs to FVIII prior to enrolment, while inhibitors usually develop, if they are going to, within the first 50 EDs.[11] As observed in PROTECT VIII,[5] the individualized prophylaxis regimens as per approved label used in the present post-marketing study of damoctocog alfa pegol were shown to be efficacious and well-tolerated in patients with haemophilia A. These data demonstrate the favourable safety and efficacy profile of damoctocog alfa pegol.

Overall, for the mITT population, ABR was numerically lower during the study compared with pre-study ABR. However, this study may be limited by its relatively low sample size. When the data are stratified by prophylaxis regimen, patients with anomalous high ABRs could have had a pronounced effect on the median values for each regimen group. For example, higher total ABRs were observed for patients receiving twice-weekly prophylaxis (*n* = 7), compared with the total mITT population (*N* = 30) and those receiving less frequent dosing regimens. It is of note, however, that the patients receiving twice-weekly prophylaxis were characterized by a high treatment frequency pre-study, with three patients having had received every-other-day prophylaxis and three patients receiving prophylaxis three times per week. These patients were also the oldest subpopulation (mean [SD] age = 50.4 [12.3] years), and a later start of first prophylaxis versus those in the other treatment regimens (mean [SD] age at start of first prophylaxis = 37.7 [13.8] years). Thus, the patients receiving twice-weekly prophylaxis had a poor treatment history and are therefore likely to have poorer joint status and a higher tendency to bleed compared with patients in the other treatment regimens, although other explanatory factors could be considered.

Patients who experienced zero bleeds whilst receiving prophylaxis during the first 8–10 weeks were recommended to switch to E7D

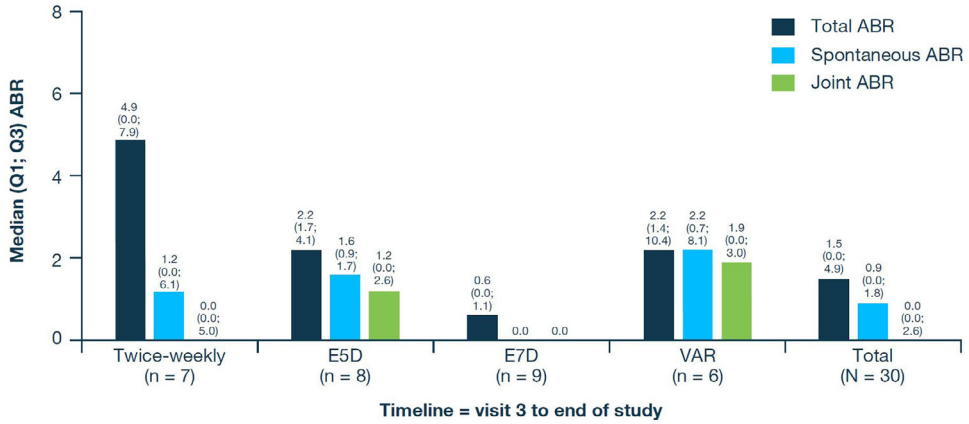

FIGURE 2 Median total, spontaneous and joint ABR† (mITT population‡). †Evaluation period covers time from Visit 3 to end of study. These data consider all bleeds, including untreated bleeds. ‡Patients who received ≥1 infusion of damoctocog alfa pegol and had bleeding data for ≥3 months were included in the mITT population. ABR, annualized bleeding rate; E5D, every 5 days; E7D, every 7 days; mITT, modified intent-to-treat; Q, quartile; VAR, variable frequency.

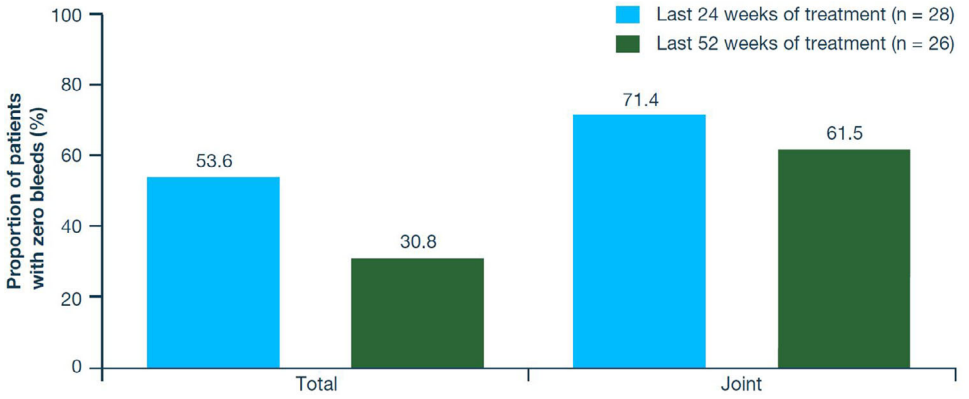

FIGURE 3 Proportions of patients with zero bleeds during treatment (mITT population†)[12]. †Patients who received ≥1 infusion of damoctocog alfa pegol and had EPD data for ≥3 months were included in the mITT population. EPD, electronic patient diary; mITT, modified-intent to-treat.

prophylaxis at Visit 3. Of those who were assigned E7D prophylaxis at Visit 3, all but two patients (9/11; 81.8%) remained on the regimen until the end of the study. This group of patients had the lowest median ABR of all prophylaxis regimens. These data suggest that bleed incidence is an effective selection criterion for individualizing prophylaxis, and that in those patients with lower bleeding tendencies, E7D is an effective prophylaxis regimen for damoctocog alfa pegol.

While the mean age of patients first receiving FVIII treatment was 1.9 years, for most patients (80.0%), this first treatment was on demand, with the mean age for starting prophylaxis being 30.5 years. These data suggest that many patients included in the mITT population started prophylaxis late; such a late start to prophylaxis (tertiary prophylaxis) may be due to a more moderate bleeding phenotype early in life in many of these patients. However, the pre-study median (Q1; Q3) ABR of 3.0 (.0—9.0) despite prophylaxis suggests that the moderate bleeding phenotype deteriorated, leading to the need for tertiary prophylaxis. It should be noted that the pre-study ABR was collected retrospectively from medical records, which may have resulted in an underestimation of the pre-study bleed rate, whereas the bleeds during the study were collected prospectively via EPD. Prophylaxis with damoctocog alfa pegol was effective despite this poor treatment history, as ABRs remained low, and a large proportion of patients achieved zero bleeds while receiving damoctocog alfa pegol prophylaxis. That some patients were not able to achieve zero bleeds does emphasise the need for ongoing work in the field. It is likely that these patients were older and already had damaged joints, whereas we might expect patients receiving primary prophylaxis to enjoy the benefits of better joint protection and so it is possible that further improvements will be seen over time. These results, consistent with those of PROTECT VIII[5] provide further evidence that prophylaxis offers benefit to a wide range of patients and that they can continue to improve the longer they receive it.

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data. All authors contributed to the development of the manuscript, reviewed and commented on each draft, and approved the final draft. The authors acknowledge Sharon Eastwood for her contribution to the development of this manuscript and thank Graeme Baldwin and Lianne Holloway, of Darwin Healthcare Communications (Oxford, England) for providing medical writing support, which was fully funded by Bayer, in accordance with Good Publication Practice guidelines.

CONFLICT OF INTEREST STATEMENT

P.A. Holme has received grant/research support to institution from Bayer, Octapharma, Pfizer, Shire, Sobi and has given lectures/consulted for Bayer, Biomarin, CSL, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, Sobi. **L.H. Poulsen** has received grant/research support from Pfizer and congress support from Bayer, Novo Nordisk, Octapharma, Pfizer and Sobi. **C. Tueckmantel** is an employee of Bayer. **M. Maas Enriquez** is a former employee of Bayer. **M.T. Alvarez Román** has received grant/research support from Shire/Takeda, speaker bureau fees from Amgen, Bayer, CSL Behring, Novartis, Novo Nordisk, Roche, Shire/Takeda and Sobi. **R. De Cristofaro** has received grant/research support from Sobi and Takeda, is a consultant for Bayer and Takeda, has received congress support from Bayer and honoraria for participation as a speaker to scientific congresses and boards from Bayer, Sobi, Pfizer, Roche, CSL-Behring, and Takeda.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 01 January 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ETHICS STATEMENT

Prior to study start, all investigators were sufficiently trained on their ethical and regulatory obligations, all study sites obtained independent ethics committee/institutional review board approval and all participants or their guardians provided written informed consent as required according to local regulations.

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