Long-term safety and efficacy results from the phase 3b, open-label, multicentre Continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe haemophilia A

Pratima Chowdary | Eric S. Mullins | Barbara A. Konkle | Catherine McGuinn | Young Shil Park | Oleksandra Stasyshyn | Bülent Zulfikar | Werner Engl | Srilatha Tangada

Abstract

Introduction: Previous studies reported the efficacy and safety profile of extended half-life PEGylated recombinant factor VIII (FVIII) rurioctocog alfa pegol (TAK-660, SHP660, BAX 855) in preventing bleeding in haemophilia A patients.

Aim: This study evaluated long-term safety and efficacy of rurioctocog alfa pegol for prophylaxis and treatment of bleeding in previously treated children and adults.

Methods: In this phase 3b, prospective, open-label, multicentre study (NCT01945593), eligible patients ≤ 75 years with severe haemophilia A (FVIII < 1%) received prophylactic rurioctocog alfa pegol in a fixed dose (FD, twice-weekly or less frequent) or pharmacokinetic (PK)-tailored dose regimen. Co-primary endpoints were incidence of confirmed FVIII inhibitory antibody development and spontaneous annualized bleed rate (ABR), analysed using a generalised linear model. Secondary endpoints included overall haemostatic efficacy, occurrence of adverse events and health-related quality of life (HRQoL).

Results: Overall, 216 patients were included; mean (SD) age at enrolment was 22.8 (15.7) years. No patients developed confirmed FVIII inhibitors. The point estimate (95% CI) of mean spontaneous ABR was 1.20 (0.92-1.56) among 186 patients receiving twice-weekly FD prophylaxis and 0.96 (0.54-1.71) among 25 patients receiving PK-tailored prophylaxis. Overall haemostatic efficacy was rated good or excellent in 88.6% of all bleeds. No new safety signals were observed. Patients reported improvements in HRQoL measures of pain, and physical and mental well-being.

Conclusion: These results highlight the long-term safety and efficacy of rurioctocog alfa pegol prophylaxis in previously treated children and adults with severe haemophilia A, with a safety profile similar to previous studies and continuing ABR reduction.
1 | INTRODUCTION

Patients with severe haemophilia A, a rare inherited deficiency of coagulation factor VIII (FVIII), typically experience high morbidity associated with spontaneous and traumatic bleeding episodes.1,2 Standard of care for severe haemophilia A is intravenous administration of regular prophylactic FVIII replacement therapy.1,3 Timely use of prophylaxis can prevent bleeding episodes, development of target joints and the ensuing arthropathy. Prophylactic FVIII replacement therapy is thus recommended to maintain joint health and health-related quality of life (HRQoL).1,3-7

Standard half-life FVIII products require regular infusions up to every other day, and some patients remain at considerable risk for bleeding events despite this frequency.8,9 Use of extended half-life products and prophylaxis personalized to the individual’s FVIII pharmacokinetic profile may benefit patients by reducing the treatment burden while maintaining or even improving treatment efficacy.9,10

Rurioctocog alfa pegol (TAK-660, SHP660, BAX 855; ADYNOVATE® [US]/ ADYNOVITM [Europe]; Baxalta US Inc, a Takeda company, Lexington, MA, USA) is a recombinant FVIII modified with polyethylene glycol (ie [PEG]ylated) resulting in an extended half-life ~1.5 times greater than standard half-life antihemophilic factor (recombinant).11 The safety and efficacy profile of rurioctocog alfa pegol has been reported previously in several studies in paediatric and/or adult patients with haemophilia A;11-13

The Continuation study was conducted to collect long-term safety and efficacy data of rurioctocog alfa pegol for prophylaxis and treatment of bleeding episodes in previously treated paediatric and adult patients with severe haemophilia A who either transitioned from other rurioctocog alfa pegol studies or were newly recruited patients naïve to rurioctocog alfa pegol.

FIGURE 1 Patient disposition and study design. A total of 218 patients enrolled in the study: 2 patients failed screening and 216 patients received at least 1 dose of rurioctocog alfa pegol in any prophylactic regimen. FD, fixed dose; FVIII, factor VIII; PK, pharmacokinetic; q5d, every 5 d; q7d, every 7 d. aThese patient numbers total > 216 because some patients received multiple regimens, as they were able to switch from twice-weekly FD to q5d FD, q7d FD and/or PK-tailored treatment; 186 patients received only FD prophylaxis. bThis patient death was considered unrelated to treatment with rurioctocog alfa pegol.
2 MATERIALS AND METHODS

2.1 Study design, conduct and patients

This was a phase 3b, prospective, open-label, multicentre Continuation study (NCT01945593) conducted at 86 sites in 23 countries (Table S1) from October 2013 to March 2018. The Continuation study was approved by the independent review board at each participating site and was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. Informed consent was obtained from patients prior to enrolment.

Eligible patients with severe haemophilia A (FVIII level < 1%) were ≤ 75 years of age, had completed a previous rurioctocog alfa pegol study (NCT01599819, NCT01736475, NCT02210091, NCT02615691, NCT01913405, or NCT02585960) and were willing to immediately transition to Continuation, or were naïve to rurioctocog alfa pegol but had received treatment with plasma-derived or recombinant FVIII for ≥50 exposure days (patients aged <6 years) or ≥150 exposure days (patients ≥6 years). In addition, patients had a Lansky (patients <16 years) or Karnofsky (patients ≥16 years) performance score of ≥60.

Exclusion criteria included FVIII inhibitory antibodies ≥0.6 Bethesda units (BU) in the Nijmegen modification of the Bethesda assay before or at screening; any inherited or acquired haemostatic defect other than haemophilia A; severe chronic hepatic dysfunction or severe renal impairment; experience of a life-threatening or gastrointestinal bleeding episode within the previous 3 months; and use of other PEGylated drugs or investigational products during study participation.

Patients who developed a high-titre inhibitor (>5 BU), or a low-titre inhibitor (between 0.6 and 5 BU) that could not be managed with the study’s prophylaxis regimen, were discontinued from the study. Patients who required elective major or minor surgical or dental procedures or minor emergency surgical or dental procedures could enrol in the surgery study (NCT01913405) and could return to the Continuation study after completion of the surgery study.

2.2 Treatment

Patients received prophylactic rurioctocog alfa pegol twice weekly either as a fixed dose (FD; 45 ± 5 IU/kg in patients aged ≥12 years or 50 ± 10 IU/kg in those <12 years; dose adjustment to ≤80 ± 5 IU/kg was allowed), or as a pharmacokinetic (PK)-tailored dose (≤80 ± 5 IU/kg) to maintain FVIII trough levels ≥3% and peak levels ≤200%. Patients aged ≥12 years in the FD twice-weekly group who had no spontaneous bleeds for 6 months could switch to FD regimen every 5 days (q5d) and subsequently every 7 days (q7d) if they continued to have zero spontaneous bleeds for

FIGURE 2 Previous rurioctocog alfa pegol studies from which patients transitioned to Continuation. Values in circle intersections represent numbers of patients. PTP, previously treated patients; PK, pharmacokinetic; PUP, previously untreated patients. *An additional 10 patients had not previously participated in a rurioctocog alfa pegol study.
a further 6 months. Following a protocol amendment in May 2014, patients could choose prophylaxis with either the twice-weekly FD or PK-tailored dose regimen; those already receiving q5d or q7d FD prophylaxis could remain on those regimens or switch to PK-tailored prophylaxis. Details of PK assessment methods are provided in Appendix S1. There was no assignment to the various prophylactic regimens. Rurioctocog alfa pegol was used to treat breakthrough bleeds according to bleed severity and per European Medicines Agency guidelines, with doses generally between 10 and 60 IU/kg ± 5 IU/kg (Table S2). Study participation was to continue until the patient had achieved ≥100 exposure days to rurioctocog alfa pegol across all studies.

### TABLE 1  Baseline characteristics of patients by age group

| Characteristic | Age < 6 y (n = 32) | Age ≥ 6 to < 12 y (n = 33) | Age ≥ 12 to < 18 y (n = 30) | Age ≥ 18 y (n = 121) | Total (N = 216) |
|----------------|--------------------|-----------------------------|-----------------------------|---------------------|----------------|
| Age at informed consent, y, mean (SD) | 3.6 (1.3) | 7.8 (1.7) | 14.2 (1.6) | 34.1 (11.5) | 22.8 (15.7) |
| Median (range) | 4 (1-5) | 7 (6-11) | 14 (12-17) | 32 (18-61) | 20 (1-61) |
| Male, n (%) | 32 (100) | 32 (97.0)a | 30 (100) | 121 (100) | 215 (99.5)a |
| Race, n (%) | | | | | |
| White | 22 (68.8) | 22 (66.7) | 24 (80.0) | 84 (69.4) | 152 (70.4) |
| Asian | 7 (21.9) | 9 (27.3) | 5 (16.7) | 37 (30.6) | 58 (26.9) |
| Black/African American | 1 (3.1) | 2 (6.1) | 1 (3.3) | 0 (0) | 4 (1.9) |
| Other/mixed | 2 (6.2) | 0 (0) | 0 (0) | 0 (0) | 2 (1.0) |
| Patients with target joints at entry into their respective original study before Continuation, n (%) | | | | | |
| No target joints | 30 (93.8) | 24 (72.7) | 18 (60.0) | 34 (28.1) | 106 (49.1) |
| 1 target joint | 2 (6.3) | 3 (9.1) | 6 (20.0) | 26 (21.5) | 37 (17.1) |
| 2 target joints | 0 (0) | 5 (15.2) | 3 (10.0) | 26 (21.5) | 34 (15.7) |
| 3 target joints | 0 (0) | 1 (3.0) | 2 (6.7) | 13 (10.7) | 16 (7.4) |
| ≥4 target joints | 0 (0) | 0 (0) | 1 (3.3) | 22 (18.2) | 23 (10.6) |
| Patients with haemophilic arthropathy, n (%) | 0 (0) | 2 (6.1) | 7 (23.3) | 84 (69.4) | 93 (43.1) |
| Treatment regimen prior to current study, n (%) | | | | | |
| Prophylaxis | 30 (93.8) | 33 (100) | 29 (96.7) | 99 (81.8) | 191 (88.4) |
| On demand | 2 (6.3) | 0 (0) | 1 (3.3) | 22 (18.2) | 25 (11.6) |
| Prophylaxis regimen at screening, n | | | | | |
| FD | 32 | 32 | 27 | 113 | 204 |
| PK tailored | 0 | 1 | 3 | 8 | 12 |
| Average spontaneous ABR based on previous 3-6 mo, mean (SD) | | | | | |
| Received prophylaxis prior to current study | 0.1 (0.5) | 0.2 (1.4) | 2.5 (5.5) | 2.3 (5.7) | 1.6 (4.8) |
| Received on-demand treatment prior to current study | 0.0 (0.0) | NA | 57.0 (NA) | 29.4 (23.7) | 28.1 (24.4) |
| Estimated previous rurioctocog alfa pegol EDs, mean (SD) | 47.4 (26.1) | 47.5 (18.1) | 72.1 (51.6) | 58.5 (42.4) | 57.0 (39.6) |
| Average previousb prophylactic FVIII dose per week, n | 30 | 31 | 27 | 76 | 164 |
| Mean (SD) IU/kg | 102.9 (48.50) | 86.7 (37.31) | 88.9 (39.03) | 92.8 (168.63) | 92.8 (118.45) |

Abbreviations: ABR, annualized bleeding rate; ED, exposure day; FD, fixed dose; FVIII, factor VIII; NA, not applicable; PK, pharmacokinetic.
aThere was one female patient in the ≥ 6 to < 12 y age group.
bBefore treatment with rurioctocog alfa pegol.
4-point rating scale (none, fair, good, excellent) as assessed by the patient or caregiver at resolution of bleeding and weight-adjusted consumption of rurioctocog alfa pegol for prophylaxis and bleed treatment.

A target joint was defined as a joint that had ≥3 spontaneous bleeds within a 6-month period and was considered resolved if it had no bleeds during a consecutive 6-month period. The number of target joints was determined at entry into their respective original study before Continuation, and the development of new target joints and resolution of target joints was evaluated during the Continuation study.

Safety was assessed via the reporting of AEs, severe allergic events, thrombotic events, vital signs and clinical laboratory parameters. Immunogenicity of rurioctocog alfa pegol was measured by binding antibodies to FVIII, rurioctocog alfa pegol and PEG. Adverse events (AEs), rurioctocog alfa pegol administration, bleeding episodes, response to bleed treatment and patient-reported outcomes (PROs) were recorded using an electronic patient diary.

PROs were evaluated with the psychometrically validated haemophilia-specific Haemo-SYM questionnaire (for bleed and pain severity),17 36-Item Short Form Health Survey (SF-36) for HRQoL status in patients aged ≥14 years and Pediatric Quality of Life Inventory (PedsQL) for HRQoL status in patients <14 years.18,19

2.4 | Statistical analyses

Approximately 250 patients were to be enrolled, with a goal of including 200 evaluable patients with ≥100 exposure days to study treatment. Safety and ABR were assessed in all patients who received ≥1 dose of rurioctocog alfa pegol. The Clopper-Pearson technique was used to calculate the proportion of patients developing confirmed inhibitory antibodies to FVIII. Mean (95% confidence interval [CI]) ABRs were analysed using a generalised linear model fitting a negative binomial distribution with logarithmic link function, with baseline age and ABR as continuous covariates. Changes from baseline to end of treatment in PRO assessments were estimated using the Wilcoxon test for paired samples. Data were analysed using Base SAS® 9.4 (Procedures Guide: Statistical Procedures, Sixth Edition; 2016, SAS Institute Inc, Cary, NC, USA) and SAS/STAT® 15.1 (User’s Guide; 2018, SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

A total of 216 patients received at least one dose of rurioctocog alfa pegol, and 187 patients completed the study (Figure 1). Most patients

| TABLE 2 | Point estimates of mean spontaneous, joint and total ABRs (using a generalised linear model) |
|---|---|---|---|---|---|
| | Age < 6 y | Age ≥ 6 to < 12 y | Age ≥ 12 to < 18 y | Age ≥ 18 y | Total |
| Patients receiving twice-weekly FD prophylaxis, n | 31 | 31 | 23 | 101 | 186 |
| Spontaneous bleeds, n | 43 | 40 | 81 | 208 | 372 |
| Spontaneous ABR, point estimate (95% CI) | 0.66 (0.39-1.09) | 0.76 (0.44-1.33) | 1.77 (1.09-2.86) | 1.26 (0.88-1.81) | 1.20 (0.92-1.56) |
| Joint bleeds, n | 14 | 46 | 73 | 255 | 388 |
| AJBR, point estimate (95% CI) | 0.18 (0.10-0.33) | 0.91 (0.47-1.74) | 1.80 (1.25-2.58) | 1.47 (1.08-2.01) | 1.23 (0.96-1.58) |
| Total (spontaneous and traumatic) bleeds, n | 88 | 101 | 136 | 361 | 686 |
| Total ABR, point estimate (95% CI) | 1.52 (1.04-2.23) | 2.00 (1.32-3.03) | 3.15 (2.26-4.40) | 2.17 (1.67-2.81) | 2.23 (1.85-2.69) |
| | | | | | |
| Patients receiving PK-tailored prophylaxis, n | 4 | 6 | 6 | 9 | 25 |
| Spontaneous bleeds, n | 4 | 9 | 6 | 16 | 35 |
| Spontaneous ABR, point estimate (95% CI) | 0.92 (0.22-3.79) | 0.87 (0.41-1.88) | 0.84 (0.12-5.82) | 1.01 (0.45-2.25) | 0.96 (0.54-1.71) |
| Joint bleeds, n | 2 | 20 | 15 | 21 | 58 |
| AJBR, point estimate (95% CI) | 0.53 (0.22-1.24) | 1.80 (1.47-2.20) | 1.62 (0.52-5.06) | 1.21 (0.46-3.18) | 1.40 (0.91-2.17) |
| Total (spontaneous and traumatic) bleeds, n | 9 | 49 | 22 | 23 | 103 |
| Total ABR, point estimate (95% CI) | 2.44 (0.71-8.36) | 4.98 (3.15-7.86) | 2.55 (0.65-9.95) | 1.38 (0.58-3.32) | 2.64 (1.70-4.08) |

Abbreviations: ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; FD, fixed dose; PK, pharmacokinetic.

*Co-primary endpoint.
(206/216; 95.4%) had participated in a previous rurioctocog alfa pegol study (Figure 2) with a mean (standard deviation [SD]) of 57.0 (39.6) documented previous rurioctocog alfa pegol exposure days. The mean (SD) observation period per patient was 2.2 (1.1) years for the entire study population. Mean age at enrolment was 22.8 years (Table 1). The historical mean (SD) spontaneous ABR (based on all spontaneous bleeds during the 3-6 months prior to enrolment) was 1.6 (4.8) in patients who had received prophylaxis (n = 191) and 28.1 (24.4) in those who had received on-demand treatment prior to the Continuation study (n = 25).

3.2 | Co-primary outcomes

None of the 204 evaluable patients developed a confirmed FVIII inhibitor in this study. One patient, a 3-year-old boy who was receiving twice-weekly prophylaxis, had a single FVIII inhibitor result of 0.6 BU with the Nijmegen assay at 740 days (211 exposure days) after his first exposure to rurioctocog alfa pegol. Upon retesting to confirm the FVIII inhibitor, the antibody titre was negative (<0.4 BU). During the entire observation period of 2.3 years with 289 exposure days to rurioctocog alfa pegol (paediatric study [NCT02210091]: 53 exposure days; Continuation study: 236 exposure days), he did not experience any clinical symptoms or signs consistent with inhibitor development.

Over the mean observation period of 2.2 years per patient, the point estimate (95% CI) of the mean spontaneous ABR (all spontaneous bleeds) was 1.20 (0.92-1.56) in 186 patients receiving twice-weekly FD prophylaxis and was 0.96 (0.54-1.71) in 25 patients receiving a PK-tailored dose regimen (Table 2).

3.3 | Secondary efficacy outcomes

Total ABR in all patients receiving any prophylaxis regimen with rurioctocog alfa pegol was mean (SD) 2.49 (3.12) and median (Q1, Q3) 1.62 (0.52, 2.83). While receiving twice-weekly FD prophylaxis over the observation period of 2.2 years per patient, 186 patients had 372 spontaneous bleeds, 388 joint bleeds and 686 total bleeds (Table 2), which translated into point estimates (95% CI) of 1.23 (0.96-1.58) for mean total annualized joint bleeding rate and 2.23 (1.85-2.69) for mean total ABR. While on a PK-tailored dose regimen, 25 patients had 35 spontaneous bleeds, 58 joint bleeds and 103 total bleeds (Table 2), the point estimates (95% CI) in this group were 1.40 (0.91-2.17) for total annualized joint bleeding rate and 2.64 (1.70-4.08) for total ABR. ABR values for the q5d and q7d regimens are shown in Table S3.

Most patients (180/216; 83.3%) experienced at least one bleeding episode during this long-term study. The mean interval between bleeding episodes was 6.48 months for patients on a FD regimen and 4.03 months for patients on a PK-tailored dose regimen at the time of bleed. Of the 1064 bleeds that occurred during the study, 910 bleeds in 165 patients were treated with rurioctocog alfa pegol. The vast majority of bleeds (89.3%) were treated with one or two

| TABLE 3 | Bleed occurrence and haemostatic efficacy of rurioctocog alfa pegol |
|-----------------|------------------|------------------|------------------|------------------|------------------|
| Age < 6 y | Age ≥ 6 to < 12 y | Age ≥ 12 to < 18 y | Age ≥ 18 y | Total |
| All patients, n | 32 | 33 | 30 | 121 | 216 |
| Patients who experienced a bleed, n | 24 | 22 | 28 | 91 | 165 |
| Total treated bleeds, n | 72 | 126 | 202 | 510 | 910 |
| Patients receiving any FD prophylaxisa, n | 32 | 32 | 30 | 121 | 215 |
| Patients receiving any FD prophylaxis who experienced a bleed, n | 23 | 18 | 27 | 90 | 158 |
| Total treated bleeds, n | 68 | 81 | 180 | 484 | 813 |
| Patients receiving PK-tailored prophylaxis, n | 4 | 6 | 6 | 9 | 25 |
| Patients receiving PK-tailored prophylaxis who experienced a bleed, n | 2 | 6 | 3 | 4 | 15 |
| Total treated bleeds, n | 4 | 45 | 21 | 21 | 91 |
| Haemostatic efficacy rating, no. (%) of bleedsb | | | | | |
| Excellent | 37 (51.4) | 74 (58.7) | 104 (51.5) | 223 (43.7) | 438 (48.1) |
| Good | 26 (36.1) | 43 (34.1) | 76 (37.6) | 223 (43.7) | 368 (40.4) |
| Fair | 3 (4.2) | 2 (1.6) | 8 (4.0) | 35 (6.9) | 48 (5.3) |
| None | 0 (0) | 0 (0) | 1 (0.5) | 3 (0.6) | 4 (0.4) |
| Not reported | 6 (8.3) | 7 (5.6) | 13 (6.4) | 26 (5.1) | 52 (5.7) |
| Infusions to treat each bleed, median (range) | 1.0 (0-10) | 1.0 (0-5) | 1.0 (0-21) | 1.0 (0-10) | 1.0 (0-21) |

Abbreviations: FD, fixed dose; PK, pharmacokinetic.

a All patients receiving any FD prophylaxis (twice-weekly, q5d, or q7d).

b Among all patients.
infusions. Overall, a mean (SD) of 1.4 (1.27) and a median (95% CI) of 1.0 (1.3-1.5) infusions were needed to treat each bleeding episode (Table 3). One bleed required 21 infusions; it was a non-joint major bleed (intramuscular haemorrhage of right iliopsoas) of spontaneous/unknown cause that occurred in a patient in the ≥12 to <18 years age group who was receiving FD prophylaxis. Overall haemostatic efficacy was rated by patients or caregivers as good or excellent in 88.5% of all bleeds (Table 3).

At entry into their respective original study before Continuation, target joints were observed in 110 (50.9%) patients: 37 patients had 1 target joint, 34 patients had 2, 16 had 3, and 23 had ≥4. Among the 110 patients with target joints, most (79.1%) were adults and the median (range) age was 30.0 (4–61) years. None of the 106 patients who entered the study without target joints had any target joints at the end of the study. Of the 110 patients who entered with target joints, only 14 had any target joints at study end (8 patients had 1 target joint, 5 patients had 2, and 1 patient had 3).

### 3.4 Exposure to rurioctocog alfa pegol

Table 4 summarizes rurioctocog alfa pegol exposure for prophylaxis by regimen and age group. The overall mean (SD) number of prophylactic infusions per week was 1.74 (0.31), and the mean (SD) weight-adjusted dose per infusion was 51.36 (8.83) IU/kg. Among the 216 patients in the study, there were a total of 45,310 exposure days (45,423 infusions) over an aggregate observation period of 476 patient-years (mean [SD] observation period per patient, 2.2 [1.1] years).

Mean (SD) prophylaxis exposure days among all patients was 195.4 (101.57) days per patient. Overall (prophylaxis and treatment)
Overall, 838 AEs were reported in 174 (80.6%) patients (Table 5), of which 20 AEs in 11 (5.1%) patients were considered related to treatment (Table 6). All treatment-related AEs were mild or moderate in severity. There were no treatment-related serious AEs (SAEs). Only one treatment-related allergic or hypersensitivity reaction was reported: a non-serious mild AE of drug eruption that developed 1.1 days after exposure to rurioctocog alfa pegol. Subsequent prophylactic infusions of rurioctocog alfa pegol were administered as planned without any further reported drug eruption or hypersensitivity reactions, and this AE subsequently resolved.

Fifty-two SAEs (all considered not related to study drug) occurred in 33 (15.3%) patients (Table S4). One fatal SAE occurred in a 15-year-old patient who had transitioned from the phase 2/3 pivotal study to Continuation. He continued twice-weekly rurioctocog alfa pegol prophylaxis for a total of 271 exposure days. This patient experienced an intracerebral haemorrhage that was attributed to his haemophilia and assessed as unrelated to rurioctocog alfa pegol treatment, as it occurred 3 days after his last prophylactic infusion. The patient was treated with antihemophilic factor (recombinant) (ADVATE®; Baxalta US Inc, a Takeda company, Lexington, MA, USA) in the hospital for emergent extracranial ventricular drainage surgery but died 3 days after the bleeding event. During this patient’s study participation, no other AEs or inhibitory or binding antibodies were reported. Bleeding episodes in this patient treated with rurioctocog alfa pegol included one mild spontaneous joint bleed, one mild injury-related muscle bleed and one moderate injury-related joint bleed; haemostatic efficacy was rated ‘excellent’ for all three bleeding episodes.

There were no major changes in vital signs, haematology or clinical laboratory values during long-term exposure to rurioctocog alfa pegol prophylaxis. No development of confirmed FVIII neutralizing antibodies occurred. Non-neutralizing IgG-binding antibodies to FVIII and rurioctocog alfa pegol were observed during the study in five and eight patients, respectively. These antibodies were transient in all but one patient (aged 38 years), who had IgG-binding antibodies to rurioctocog alfa pegol at screening (titre, 1:160), which persisted to the end of the study (titre, 1:320) without any notable safety or efficacy findings.

### 3.6 Patient-reported outcomes

Most patients aged ≥18 years who completed the Haemo-SYM questionnaire (55/91; 60.4%; Figure 3A) had significant improvement from baseline in the total score (P = .0023). A clinically meaningful change from baseline to end-of-study improvement in SF-36 physical component score (Figure 3B) was achieved by 62 of 103 evaluable patients (60.2%; P = .0014), and 40 of 103 patients (38.8%; P = .1098) had improvement from baseline in the SF-36 mental component score (Figure 3B). Although most children (24/39; 61.5%) had clinically meaningful change from baseline to end-of-study improvement on the PedsQL total score, no statistically significant improvement was observed for mean improvement in PedsQL total score (P = .0829; Figure 3C).

### 3.5 Safety

Overall, 838 AEs were reported in 174 (80.6%) patients (Table 5), of which 20 AEs in 11 (5.1%) patients were considered related to treatment (Table 6). All treatment-related AEs were mild or moderate in severity. There were no treatment-related serious AEs (SAEs). Only one treatment-related allergic or hypersensitivity reaction was reported: a non-serious mild AE of drug eruption that developed 1.1 days after exposure to rurioctocog alfa pegol. Subsequent prophylactic infusions of rurioctocog alfa pegol were administered as planned without any further reported drug eruption or hypersensitivity reactions, and this AE subsequently resolved.

Fifty-two SAEs (all considered not related to study drug) occurred in 33 (15.3%) patients (Table S4). One fatal SAE occurred in a 15-year-old patient who had transitioned from the phase 2/3 pivotal study to Continuation. He continued twice-weekly rurioctocog alfa pegol prophylaxis for a total of 271 exposure days. This patient experienced an intracerebral haemorrhage that was attributed to his haemophilia and assessed as unrelated to rurioctocog alfa pegol treatment, as it occurred 3 days after his last prophylactic infusion. The patient was treated with antihemophilic factor (recombinant) (ADVATE®; Baxalta US Inc, a Takeda company, Lexington, MA, USA) in the hospital for emergent extracranial ventricular drainage surgery but died 3 days after the bleeding event. During this patient’s study participation, no other AEs or inhibitory or binding antibodies were reported. Bleeding episodes in this patient treated with rurioctocog alfa pegol included one mild spontaneous joint bleed, one mild injury-related muscle bleed and one moderate injury-related joint bleed; haemostatic efficacy was rated ‘excellent’ for all three bleeding episodes.

There were no major changes in vital signs, haematology or clinical laboratory values during long-term exposure to rurioctocog alfa pegol prophylaxis. No development of confirmed FVIII neutralizing antibodies occurred. Non-neutralizing IgG-binding antibodies to FVIII and rurioctocog alfa pegol were observed during the study in five and eight patients, respectively. These antibodies were transient in all but one patient (aged 38 years), who had IgG-binding antibodies to rurioctocog alfa pegol at screening (titre, 1:160), which persisted to the end of the study (titre, 1:320) without any notable safety or efficacy findings.

### 3.6 Patient-reported outcomes

Most patients aged ≥18 years who completed the Haemo-SYM questionnaire (55/91; 60.4%; Figure 3A) had significant improvement from baseline in the total score (P = .0023). A clinically meaningful change from baseline to end-of-study improvement in SF-36 physical component score (Figure 3B) was achieved by 62 of 103 evaluable patients (60.2%; P = .0014), and 40 of 103 patients (38.8%; P = .1098) had improvement from baseline in the SF-36 mental component score (Figure 3B). Although most children (24/39; 61.5%) had clinically meaningful change from baseline to end-of-study improvement on the PedsQL total score, no statistically significant improvement was observed for mean improvement in PedsQL total score (P = .0829; Figure 3C).

### 3.5 Safety

Overall, 838 AEs were reported in 174 (80.6%) patients (Table 5), of which 20 AEs in 11 (5.1%) patients were considered related to treatment (Table 6). All treatment-related AEs were mild or moderate in severity. There were no treatment-related serious AEs (SAEs). Only one treatment-related allergic or hypersensitivity reaction was reported: a non-serious mild AE of drug eruption that developed 1.1 days after exposure to rurioctocog alfa pegol. Subsequent prophylactic infusions of rurioctocog alfa pegol were administered as planned without any further reported drug eruption or hypersensitivity reactions, and this AE subsequently resolved.

Fifty-two SAEs (all considered not related to study drug) occurred in 33 (15.3%) patients (Table S4). One fatal SAE occurred in a 15-year-old patient who had transitioned from the phase 2/3 pivotal study to Continuation. He continued twice-weekly rurioctocog alfa pegol prophylaxis for a total of 271 exposure days. This patient experienced an intracerebral haemorrhage that was attributed to his haemophilia and assessed as unrelated to rurioctocog alfa pegol treatment, as it occurred 3 days after his last prophylactic infusion. The patient was treated with antihemophilic factor (recombinant) (ADVATE®; Baxalta US Inc, a Takeda company, Lexington, MA, USA) in the hospital for emergent extracranial ventricular drainage surgery but died 3 days after the bleeding event. During this patient’s study participation, no other AEs or inhibitory or binding antibodies were reported. Bleeding episodes in this patient treated with rurioctocog alfa pegol included one mild spontaneous joint bleed, one mild injury-related muscle bleed and one moderate injury-related joint bleed; haemostatic efficacy was rated ‘excellent’ for all three bleeding episodes.

There were no major changes in vital signs, haematology or clinical laboratory values during long-term exposure to rurioctocog alfa pegol prophylaxis. No development of confirmed FVIII neutralizing antibodies occurred. Non-neutralizing IgG-binding antibodies to FVIII and rurioctocog alfa pegol were observed during the study in five and eight patients, respectively. These antibodies were transient in all but one patient (aged 38 years), who had IgG-binding antibodies to rurioctocog alfa pegol at screening (titre, 1:160), which persisted to the end of the study (titre, 1:320) without any notable safety or efficacy findings.
This phase 3b Continuation study in 216 children and adults with severe haemophilia A revealed long-term safety and efficacy consistent with previous rurioctocog alfa pegol studies and previous studies with the parent molecule, antihemophilic factor (recombinant). It is noteworthy that no patients developed confirmed inhibitory antibodies to PEGylated FVIII during the study, given a mean observation period per patient of 2.2 years. The proportion of patients (13.4%) who discontinued prematurely from this long-term study is within the range reported for other FVIII replacement therapy studies (4.7% to 20%) and may be higher than some studies owing to the long-term nature of this study.

The point estimates of mean spontaneous ABRs reported for rurioctocog alfa pegol prophylaxis in the Continuation study (FD twice-weekly regimen, 1.20; PK-tailored dose regimen, 0.96) were similar to or slightly lower than the mean spontaneous ABRs of 2.11 and 1.16 observed in previous PROLONG-ATE and paediatric phase 2/3 rurioctocog alfa pegol studies. Similar observations can be made regarding total and joint ABRs. Most patients experienced resolution of their target joints during the Continuation study. Overall, protective efficacy of and control of bleeding episodes were generally consistent across patients who received prophylaxis with rurioctocog alfa pegol using FD or PK-tailored dosing. Observed HRQoL benefits included improvements from baseline in pain, physical health and mental well-being.

Limitations associated with extension studies should be taken into consideration when interpreting the final results of this study. Importantly, as this study was designed in accordance with regulatory guidance on the evaluation of FVIII in children aged <12 years, comparison with a control group receiving prophylaxis with a conventional FVIII product was not possible. As patients were not assigned randomly to the different prophylaxis regimens, but instead allowed to switch from twice-weekly FD rurioctocog alfa pegol to less frequent FD or PK-tailored dosing, and because patient numbers varied across treatment and age groups, robust comparisons between the prophylaxis regimens were not possible. These limitations were offset in part by the long follow-up period and representativeness of the haemophilia A population across a wide age range.
5 | CONCLUSIONS

In previously treated children and adults with severe haemophilia A in the Continuation study, long-term prophylaxis with rurioctocog alfa pegol was efficacious. The safety and immunogenicity profile was similar to that observed in previous studies\(^{11,12,20}\) and consistent with that reported for the non-PEGylated parent molecule, antihemophilic factor (recombinant),\(^ {32}\) indicating that PEGylation did not have an effect on product safety. No patients developed FVIII inhibitory antibodies, and the observed spontaneous and total ABRs were lower at the end of study than at baseline.

ACKNOWLEDGEMENTS

The authors would like to thank all patients and their caregivers who took part in the Continuation study, as well as the Continuation study investigators and sites (NCT01945593; see https://clinicaltrials.gov/ct2/show/NCT01945593). This study was funded by Baxalta US Inc, a Takeda company, Lexington, MA, USA, and Baxalta Innovations GmbH, a Takeda company, Vienna, Austria. Medical writing and editorial support was provided by Margit Rezabek, DVM, PhD, employee of Excel Medical Affairs (Fairfield, CT, USA) and was funded by Baxalta US Inc, a Takeda company, Lexington, MA, USA.

DISCLOSURES

PC has served in speaker bureaus for Baxalta/Shire,* Biogen, CSL Behring, Novo Nordisk, Pfizer, Roche and Sobi; and has received consultancy fees from Baxalta/Shire,* Bayer, Biogen, BioMarin, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Sobi and Spark; and research support from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer and Sobi. EM has received consultancy fees and honoraria from Shire,* and has served on an advisory board for Octapharma. BAK has received consultancy fees from BioMarin, Genentech, Pfizer, Sanofi and Spark; and research funding from Bioverativ/Sanofi, Pfizer, Sangamo, Shire* and Spark. CM has received consultancy fees and has served on advisory boards for Baxalta/Shire,* BioMarin, BPL, Genentech/Roche, Kedron and Octapharma; and has received research support from Baxalta/Shire,* Genentech/Roche, Pfizer and Spark Therapeutics. YSP has received research funding from Bayer, Greencross and Pfizer. OS has received consultancy fees from Novo Nordisk, Pfizer and Roche; and has served in speaker bureaus for Baxalta/Shire,* Novo Nordisk, Pfizer and Roche. BZ has served on advisory boards for Novo Nordisk, Pfizer, Shire* and Sobi; and has received research funding from Pfizer; and consultancy fees from Roche. 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 Takeda company.

AUTHOR CONTRIBUTIONS

PC, EM, BAK, CM, YSP, OS and BZ were principal investigators of the study, and recruited and treated patients. WE and ST designed the study and analysed the data. All authors participated in reviewing and interpreting the data and contributed to the development of the manuscript. All authors have read and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within 3 months from initial 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.

ORCID

Pratima Chowdary https://orcid.org/0000-0002-6690-8586
Eric S. Mullins https://orcid.org/0000-0002-1544-9068
Barbara A. Konkle https://orcid.org/0000-0002-3959-8797
Catherine McGuinn https://orcid.org/0000-0002-3421-0925
Bülent Zulfikar https://orcid.org/0000-0002-7586-6939

REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1-e47.
2. Mannucci PM, Tuddenham EG. The hemophilias—from royal genes to gene therapy. N Engl J Med. 2001;344(23):1773-1779.
3. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. J Blood Med. 2014;5:207-218.
4. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535-544.
5. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood. 2015;125(13):2038-2044.
6. O’Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes. 2018;16(1):84.
7. Klamroth R, Pollmann H, Hermans C, et al. The relative burden of haemophilia A and the impact of target joint development on health-related quality of life: results from the ADVATE Post- Authorization Safety Surveillance (PASS) study. Haemophilia. 2011;17(3):412-421.
8. Lieuw K. Many factor VIII products available in the treatment of haemophilia A: an embarrassment of riches? J Blood Med. 2017;8:67-73.
9. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of haemophilia. Ther Adv Hematol. 2018;9(9):295-308.
10. Morfini M, Gherardini S. Pharmacokinetic-based prediction of real-life dosing of extended half-life clotting factor concentrates on hemophilia. Ther Adv Hematol. 2018;9(6):149-162.
11. Konkle BA, Stasyslyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015;126(9):1078-1085.
12. Mullins ES, Stasyslyn O, Alvarez-Román MT, et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. Haemophilia. 2017;23(2):238-246.
13. Gruppo R, Lopez-Fernandez MF, Wynn TT, Engl W, Shankhawaty M, Tangada S. Perioperative haemostasis with full-length,
PEGylated, recombinant factor VIII with extended half-life (rurioctocog alfa pegol) in patients with haemophilia A: Final results of a multicentre, single-arm phase III trial. *Haemophilia.* 2019;25(5):773-781.

14. Mullins E, Kefurt C, Engl W, Tangada S. Design of a phase 3, prospective, multicenter, open-label study of safety and hematostatic efficacy of rurioctocog alfa pegol in previously untreated patients <6 years of age with severe hemophilia A. *Haemophilia.* 2019;25(Suppl 1):83.

15. Klamroth R, Windyga J, Radulescu V, et al. PK-guided rurioctocog alfa pegol prophylaxis in patients with severe Hemophilia A targeting two FVIII trough levels: results from the phase 3 PROPEL study. *Res Pract Thromb Haemost.* 2019;3(51):106-107.

16. 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(2):247-251.

17. Rentz A, Flood E, Butler R, et al. Psychometric evaluation of a patient-reported symptom assessment tool for adults with haemophilia (the HAEMO–SYM). *Haemophilia.* 2009;15(5):1039-1047.

18. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr.* 2003;3(6):329-341.

19. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800-812.

20. Brand B, Gruppo R, Wynn TT, et al. Efficacy and safety of pegylated full-length recombinant factor VIII with extended half-life for perioperative haemostasis in haemophilia A patients. *Haemophilia.* 2016;22(4):e251-e258.

21. Auerswald G, Thompson AA, Recht M, et al. Experience of Advate rAHF-PFM in previously untreated patients and minimally treated patients with haemophilia A. *Thromb Haemost.* 2012;107(6):1072-1082.

22. Blanchette VS, Shapiro AD, Liesner RJ, et al. Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients. *J Thromb Haemost.* 2008;6(8):1319-1326.

23. Khair K, Mazzucconi MG, Parra R, et al. Pattern of bleeding in a large prospective cohort of haemophilia A patients: a three-year follow-up of the AHEAD (Advate in HaEmophilia A outcome Database) study. *Haemophilia.* 2018;24(1):85-96.

24. Négrier C, Shapiro A, Berntorp E, et al. Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of Advate in previously treated patients. *Thromb Haemost.* 2008;100(2):217-223.

25. Shapiro AD, Schoenig-Diesing C, Silvati-Fidell L, Wong WY, Romanov V. Integrated analysis of safety data from 12 clinical interventional studies of plasma- and albumin-free recombinant factor VIII (rAHF-PFM) in haemophilia A. *Haemophilia.* 2015;21(6):791-798.

26. Tarantino MD, Collins PW, Hay CR, et al. RAHF-PFM Clinical Study Group. Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia.* 2004;10(5):428-437.

27. Klukowska A, Szczepanski T, Vlodov V, et al. Long-term tolerability, immunogenicity and efficacy of Nuwiq(R) (human-cl rhFVIII) in children with severe haemophilia A. *Haemophilia.* 2018;24(4):595-603.

28. Kulkarni R, Karim FA, Glamocanin S, et al. Results from a large multinational clinical trial (guardian3) using prophylactic treatment with turoctocog alfa in paediatric patients with severe haemophilia A: safety, efficacy and pharmacokinetics. *Haemophilia.* 2013;19(5):698-705.

29. 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(3):317-325.

30. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIII:Fc) in subjects with haemophilia A. *Haemophilia.* 2016;22(1):72-80.

31. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products; 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf. Accessed January 29, 2019.

32. ADVATE [antihemophilic factor (recombinant)] full prescribing information; 2018. Available from: https://www.shirecontent.com/PI/PDFs/ADVATE_USA_ENG.pdf. Accessed September 19, 2018

**SUPPORTING INFORMATION**

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

**How to cite this article:** Chowdary P, Mullins ES, Konkle BA, et al. Long-term safety and efficacy results from a phase 3b, open-label, multicentre Continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe haemophilia A. *Haemophilia.* 2020;26:e168–e178. [https://doi.org/10.1111/hae.14052](https://doi.org/10.1111/hae.14052)