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# 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

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**Introduction**: Outcome data on treatment of patients with haemophilia A spanning several years of real-world evidence collection are currently very limited.

**Aim and methods**: The global prospective long-term Advate® Haemophilia A Outcome Database (AHEAD) cohort study collects real-world data from patients with severe and moderate haemophilia. We report an interim data read-out after three years of observation.

**Results**: A total of 522 patients were enrolled from 21 countries: 334 completed year 1 follow-up, 238 completed year 2 and 136 completed year 3, with an overall follow-up of 811 patient-years. Median annual bleeding rates (ABR) were 1.7 in the prophylaxis group and 8.9 in the on-demand group at year 1 visit, 1.6 and 13.0, respectively, at year 2 visit and 2.2 and 10.3, respectively, at year 3 visit. Moreover, about 42% of patients on prophylaxis vs 12% of patients on on-demand had zero annual joint bleeding rates (AJBR). Effectiveness of prophylaxis and on-demand treatment was deemed excellent/good in the majority of cases. Octocog alfa (Advate®) was well tolerated. The inhibitors that developed in nine patients all disappeared spontaneously. Three patients had been previously exposed to FVIII for ≤50 exposure days (EDs), 3 for >50 EDs and 3 showed a borderline positive inhibitory activity (≤0.6 BU/mL).

**Conclusions**: These data confirm that the goal of zero bleeds is achievable, although not yet achieved in all patients. Understanding reasons behind the lower response to standard prophylaxis regimens in some patients and personalizing prophylactic treatment may further improve outcome in patients with haemophilia A.

**KEYWORDS**
bleeding, haemophilia A, prophylaxis, real-world evidence

## 1 | INTRODUCTION

Haemophilia A is characterized by recurrent bleeding, in particular into joints.[1] The recurrence of clinical and subclinical bleeding in joints leads almost inevitably to severe arthropathy,[2] with declines in patient autonomy and health-related quality of life. The mainstay of haemophilia A treatment is intravenous FVIII replacement therapy when bleeding occurs to resolve it, or regular and continuous replacement to prevent bleed occurrences.[3,4]

Octocog alfa, antihaemophilic factor, plasma/albumin free method (Advate®, Baxalta Inc., Westlake Village, CA, USA) is a recombinant, human, full-length DNA coagulation factor VIII that does not contain

  

human- or animal-derived plasma proteins. Pooled analyses of clinical trials and routine clinical practice studies showed that octocog alfa administered prophylactically, on-demand or during surgery was effective for the prevention and treatment of bleeding episodes.[5-7] In addition, in a comparative study, routine prophylaxis with octocog alfa administered in a standard regimen or in a pharmacokinetic-tailored regimen was effective for the prevention of bleeding episodes in patients with moderately severe or severe haemophilia A, with no significant difference between the two regimens.[8]

Octocog alfa was generally well tolerated in clinical trials[5-7] and postmarketing studies.[9,10] Serious adverse events with octocog alfa therapy included development of high-titre factor VIII inhibitors (usually in previously untreated patients) and hypersensitivity reactions. As expected, the incidence of factor VIII inhibitors (any titre) appeared to be lower in previously treated patients (≤1.5%)[10] than in previously untreated patients (≤27%).[11]

Long-term, real-world data on the course of haemophilia A patients' safety and treatment outcomes are still insufficient, particularly as far as the impact of bleeding on patient lives is concerned, as most clinical trials are limited in study population size and follow-up time period often not longer than 12 months.

For this purpose, an international, multicentre, prospective, non-interventional, long-term, cohort study (AHEAD – Advate in HaEmophilia A outcome Database – Study) was started in haemophilia A patients with a residual FVIII activity of ≤5% who have been prescribed octocog alfa (ADVATE®) without limitations in terms of patient age, treatment regimen, history or presence of inhibitors. This study is aimed at capturing long-term outcome data on patients with haemophilia A receiving treatment as routine clinical practice followed for up to 8 years.

We present here an interim data read-out analysis of patients enrolled in this cohort study after 3 years of observation.

## 2 | METHODS

### 2.1 | Study design

To document the course of haemophilia A and long-term outcomes in terms of effectiveness, safety and quality of life (QoL) in subjects receiving octocog alfa in routine clinical practice, a postauthorization, prospective, international, multicenter, non-interventional study was designed.

A total of approximately 700 subjects with haemophilia A (FVIII ≤5%) were planned to be enrolled. Subjects of any age, gender and ethnicity could be included. Subjects had to be prescribed octocog alfa by the treating clinician prior to study participation. Data are collected over a period of up to 8 years from the time of study enrolment. The treatment regimen, including on-demand and prophylaxis using standardized regimens or individual pharmacokinetic (PK)-guided dosing regimens, or Immune Tolerance Induction (ITI) therapy, as well as the frequency of laboratory, radiologic and clinical monitoring are decided by the treating clinician. Prophylaxis was defined as regular continuous replacement therapy: frequency, dosing and duration were chosen by the Investigator. Study visits coincide with routinely scheduled and emergency visits. A subject diary was provided to each subject at the screening visit and at annual and interval visit(s), as needed, to help with standardization of data collection. The subject diary allowed for capture of the following information: infusion log, bleed occurrence, number of octocog alfa units and infusions required for bleed cessation, global effectiveness assessment for on-demand treatment, acute pain-associated haemophilia, measured with individual bleeding episodes, using a visual analogue scale (VAS), number of days lost from school or work due to bleeding episodes and adverse events.

### 2.2 | Study objectives

The primary objective of the study is to describe joint health outcomes in subjects receiving octocog alfa in routine clinical practice setting, using any treatment regimen. Secondary objectives are to assess haemostatic effectiveness and safety of octocog alfa in a variety of clinical settings including on-demand therapy, routine standardized prophylaxis, individual PK-guided prophylactic therapy and ITI therapy, haemophilia-related co-morbidity and health-related QoL (HR-QoL) in subjects receiving octocog alfa. Despite long-term safety and immunogenicity of octocog alfa being listed among the secondary objectives, these issues have been carefully assessed.

Haemostatic effectiveness for prophylaxis has been assessed on an annual basis by the investigators in subjects who receive at least 6 months of continuous and regular prophylaxis therapy in the previous 12-month period. The assessment is based upon the following: the investigator's professional opinion; the subject's current health status, including the presence or absence of inhibitor; the response to rAHF-PFM in relation to previous experience with prior FVIII therapies and performance in prophylaxis for the prevention of breakthrough bleeding. The investigators have assigned an overall effectiveness rating, using the following definitions:

- Excellent: Same or lower breakthrough bleed rate within the last 12 months compared with previous prophylaxis therapy; if subject did not receive previous prophylaxis therapy with rAHF-PFM, or another FVIII, same or better than expected outcome according to investigator's expectation.
- Good: Minor increase in breakthrough bleed rate within the last 12 months compared with previous prophylaxis therapy; if subject did not receive prophylaxis therapy with rAHF-PFM, or another FVIII, slightly less than expected outcome according to investigator's expectation.
- Fair: Moderate increase in breakthrough bleed rate in the last 12 months compared with previous prophylaxis therapy; if subject did not receive prophylaxis therapy with rAHF-PFM, or another FVIII, somewhat less than expected outcome according to investigator's expectation.
- Poor: Significant increase in breakthrough bleed rate in the last 12 months compared with previous prophylaxis therapy; if subject did not receive prophylaxis therapy with rAHF-PFM, or another FVIII, little to no benefit according to investigator's expectation.

### 2.3 | Enrolment criteria

Subjects with all of the following criteria were eligible for this study: haemophilia A (FVIII ≤5%), octocog alfa already prescribed by the treating physician, informed consent provided by the subject or subject's legally authorized representative.

Subjects with any of the following criteria were not eligible for this study: known hypersensitivity to the active substance or any of the excipients, known allergic reaction to mouse or hamster proteins, participation in another clinical study involving an investigational product or device within 30 days prior to study enrolment or another FVIII concentrate or device during the course of this study.

### 2.4 | Statistics

No hypothesis testing or interval estimation was applied; the sample size for the study was based on statistical considerations. The sample size of approximately 700 subjects was selected as a reasonable number for a non-interventional study that can feasibly be expected to recruit in the five years planned for the study.

Continuous variables are expressed as means ± standard deviations and median and min/max range. Categorical variables are expressed as frequencies and percentages. Fisher's exact tests and/or Chi-Square tests have been used to compare qualitative variables, and Student's *t*-test for quantitative unpaired data. A *P*-value <0.05 is considered statistically significant in an exploratory sense.

In addition to descriptive statistics (location parameters), Kaplan-Meier analyses (time-to-event) and multivariate analyses to identify prognostic factors are planned at the end of the study. Analyses were performed using available data, due to the non-interventional nature of the study, missing values are expected.

The incremental cost-effectiveness ratio (ICER) was calculated considering costs associated with prophylaxis regimen (including cost of breakthrough bleed treatment) and cost of on-demand regimen and the clinical outcome in term of number of bleeds occurred in patients on the two different regimens.

This study reports preliminary analysis after up to 3-year observation period of enrolled patients, which was carried out in May-July 2016. Safety data are reported for all patients reported until this date.

## 3 | RESULTS

### 3.1 | Population

This prospective study commenced in June 2011. As of August 2016, 590 patients have been enrolled in this study from 91 study sites initiated globally in 21 countries: Australia, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, France, Greece, Hungary, Italy, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

This report summarizes an interim data read-out carried out in May 2016. The analysis includes 522 patients from 21 countries, 334 of whom completed the year 1 follow-up, 238 completed year 2 and 136 completed year 3, with an overall follow-up of 811 patient years. Patient distribution at screening is shown in Figure 1.

Median age at enrolment was 17 years (min-max: 0-78). Of these 522 patients, 57.3% of patients had severe haemophilia A (FVIII:C < 1%) (Table 1). In total, 406 patients (77.8%) were on prophylaxis, 109 (20.9%) were treated on-demand (OD) and 7 (1.3%) were on ITI treatment at enrolment. Patients on prophylaxis were mainly treated every 2 or 3 days or two or three times a week (88%); the remaining patients were treated once per week (10%), or daily (2%).

The majority of patients (77.0%) were Caucasian (16.3% missing data). Other characteristics of patients according to their treatment regimens at enrolment are summarized in Table 1.

### 3.2 | Effectiveness

A median annualized bleeding rate (ABR) of 1.7 in the prophylaxis group and 8.9 in the on-demand group at year 1 visit, 1.6 and 13.0, respectively, at the year 2 visit and 2.2 and 10.3, respectively, at the year 3 visit (Figure 2, Table 2) were reported. Of these, median annualized joint bleeding rate (AJBR) was 0.9 in the prophylaxis group after the first year of follow-up and 1.0 after the second and third year, while it was 6.5, 5.9 and 8.8 in those treated OD at year-1, -2 and -3 visits respectively (Figure 2). Similar numbers were reported for the subgroup of severe haemophilia patients, representing the majority of subjects (Table 2).

More than one-third of subjects on prophylaxis had an ABR of less than 1 (42.3% in year 1, 41.7% in year 2 and 34.7% in year 3). Overall, 30.2%, 31.8% and 32.7% had an ABR of zero in year 1, 2 and 3 respectively. The AJBR was less than 1 at year-1 visit for 54% of patients in the prophylaxis group, 52% at year-2 visit and 49% at the year-3 visit. Of these patients, zero joint bleeds have been reported in 43%, 43% and 38% at year-1, -2 and -3 visits respectively. In the OD group, 59%, 48% and 61% of patients had an AJBR ≥ 6 after the first, second and third year, respectively, compared to only 11%, 11% and 12% in the prophylaxis group (Figures 2 and 3). About one-fourth of patients treated on-demand showed an AJBR less than 1 at year 1 and 2 (27% and 22%, respectively), but none at year 3 (Figure 3). As expected, the great majority had moderate haemophilia A (only 4 patients had severe haemophilia A).

Table 3 shows the overall number of bleeding episodes according to haemophilia severity and treatment after 1, 2 and 3 years follow-up. Only 49% of major bleeding episodes in patients on prophylaxis were spontaneous, compared to 78% in patients on on-demand treatment, this difference being statistically significant (Chi-square 17.74, $P < 0.01$).

Figure 4 shows the number of bleeding episodes by location: as expected, the majority is reported in joints, followed by muscles and subcutaneous tissues. Among joints, greatest prevalence was ankles, followed by knees and elbows (Figure 5). Shoulder, hip and wrist bleeds were reported less frequently.

The median annualized total factor consumption per patient was 241 494 IU (5625 IU/kg), 242 057 IU (5534 IU/kg) and 244 510 IU (5472 IU/kg) in the prophylaxis group and 32 601 IU (467 IU/kg),

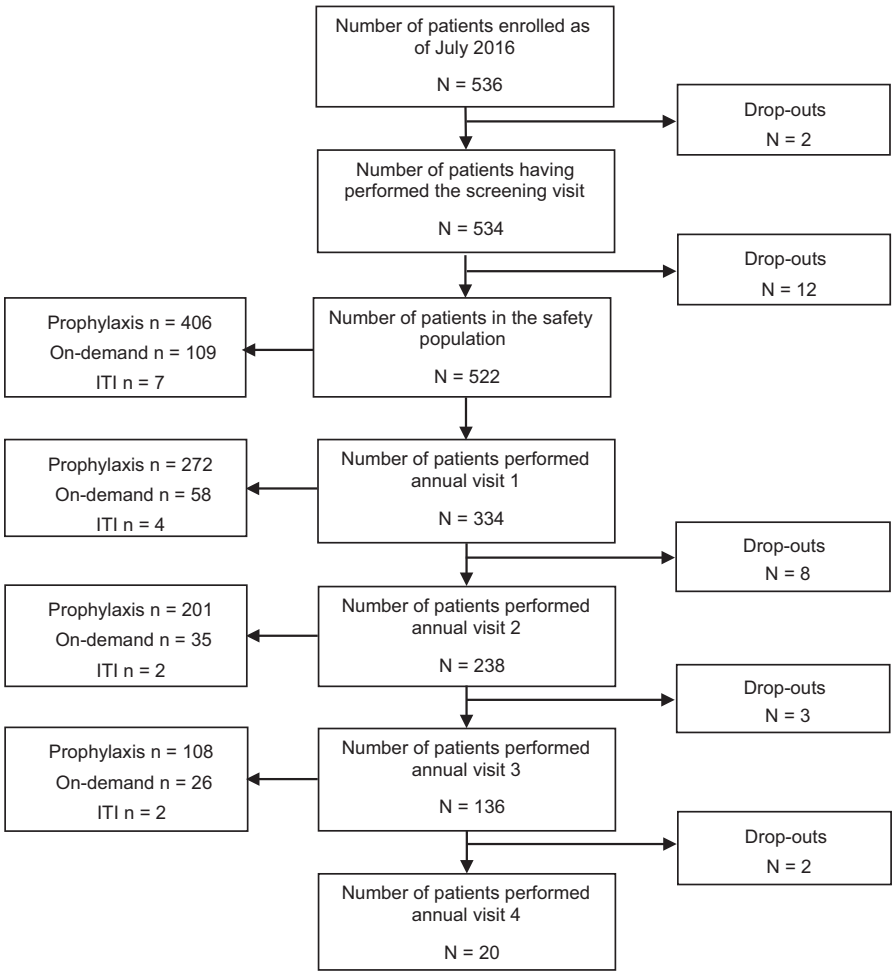


**FIGURE 1** Subject disposition. Of the overall 27 subjects withdrawn or dropped out, 9 switched to another FVIII product, 3 withdrew consent, 8 did not meet the enrolment criteria, 1 adverse event, 1 unsatisfactory therapeutic response (ITI); 2 for non-compliance with the study protocol and 3 for non-specified other reasons

26 164 IU (410 IU/kg) and 46 793 IU (629 IU/kg) in the OD group during year 1, 2, and 3 respectively (Table 4).

The incremental cost-effectiveness ratio (ICER) per bleeding episode avoided due to prophylaxis treatment (i.e. the difference in cost between prophylaxis and on-demand treatment, divided by the difference in bleeding rate) in the first year is 20 192 US$ (376 US$/kg), assuming a unit price of 0.8 US$.

Effectiveness of prophylaxis assessed by investigators was excellent/good in 95% of cases during the first, 96% the second and 93% the third year of observation (Figure 6). Effectiveness for treating an acute bleeding event assessed by patient/caregiver was excellent/good in 88% of bleeding in prophylaxis patients and 80% in OD patients during year 1, 92% and 93% during year 2 and 92% and 90% during year 3, respectively.

Bleeding episodes were resolved by a median number of 1 infusion in patients treated either prophylactically or on-demand (Table 5).

### 3.3 | Safety

As of May, 2016, a total of 522 subjects have been enrolled in the study. A total of 868 adverse events (AEs) were reported in 203 patients. Of these, 78 events were serious adverse events (SAEs), which occurred in 63 patients. Six of these SAEs, occurred in 6 patients and were deemed by the investigators to be possibly or probably related to the study product: these 6 patients developed inhibitors, all of which were transient (spontaneously disappeared without any treatment change and/or intervention). Three of these patients developed a transient inhibitor at the age of 1 year and within 50 exposure days (EDs) reached peak levels of 1.9, 2.8 and 11 BU/mL respectively. The remaining 3 patients developed a transient inhibitor after more than 50 EDs at the ages of 2, 4 and 41 years with peak titres of 1.1 BU/mL or below. There were three additional patients who showed transient borderline positive inhibitory activity (0.5-0.6 BU/mL), deemed as a non-SAEs, as they were deemed non-clinically relevant and did not impact the continuation of treatment.

Of the remaining 72 SAEs unrelated or unlikely related to study product, 25 were deemed severe, of which 2 were intracranial bleeds, 5 musculoskeletal bleeds, 5 infections in the lower respiratory tract, 1 central venous access infection, 1 surgical bleed, 3 hospitalizations for orthopaedic surgery and 8 others.

Of the remaining 790 non-SAEs, only one was deemed probably related to study product: a mild allergic reaction with rhinitis (recovered). The remaining 789 were deemed non-related or unlikely related to study product: 10 were deemed severe (plantar fasciitis, arthrodesis in right foot joint, head trauma, rhinitis with otitis, 3 ankle arthropathies, knee arthropathy, coxarthrosis and osteopenia).

**TABLE 1** Patient characteristics according to treatment regimen at screening

| | Prophylaxis (N = 406) | On-demand (N = 109) | ITI (N = 7) | Total (N = 522) |
|---|---|---|---|---|
| Age | | | | |
| Mean (SD) | 18.3 (15.87) | 30.6 (21.37) | 5.9 (4.22) | 20.7 (17.85) |
| Median (min-max) | 14.0 (0-78) | 33.0 (0-74) | 4.0 (2-13) | 17.0 (0-78) |
| Age Groups [number of patients (%)] | | | | |
| Infants (<2 years) | 25 (6.2%) | 15 (13.8%) | 0 (0%) | 40 (7.7%) |
| Children (2 to <12 years) | 159 (39.2%) | 18 (16.5%) | 6 (85.7%) | 183 (35.1%) |
| Adolescents (12 to <18 years) | 42 (10.3%) | 3 (2.8%) | 1 (14.3%) | 46 (8.8%) |
| Adults (≥18 years) | 179 (44.1%) | 73 (67.0%) | 0 (0%) | 252 (48.3%) |
| Missing | 1 (0.2%) | 0 (0%) | 0 (0%) | 1 (0.2%) |
| Haemophilia severity [number of patients (%)] | | | | |
| Severe (FVIII <1%) | 246 (60.6%) | 47 (43.1%) | 6 (85.7%) | 299 (57.3%) |
| Moderately severe (FVIII 1% to ≤2%) | 126 (31.0%) | 40 (36.7%) | 1 (14.3%) | 167 (32.0%) |
| Moderate (FVIII 2% to ≤5%) | 32 (7.9%) | 22 (20.2%) | 0 (0%) | 54 (10.3%) |
| No grading available | 2 (0.5%) | 0 (0%) | 0 (0%) | 2 (0.4%) |
| History of inhibitors | | | | |
| Patients with inhibitor history (%) | 93 (23.0%) | 8 (7.5%) | 7 (100%) | 108 (20.8%) |
| Ongoing at screening | 9 | 2 | 5 | 16 |
| Target Joints at screening | | | | |
| Patients with target joints (%) | 120 (30.5%) | 44 (41.9%) | 2 (28.6%) | 166 (32.9%) |
| Missing | 13 | 4 | 0 | 17 |
| # target joints per patient: Mean (SD) | 2.4 (1.64) | 4.3 (2.97) | 3.5 (3.54) | 2.9 (2.23) |
| # target joints per patient: Median (min-max) | 2.0 (0-7) | 3.5 (1-12) | 3.5 (1-6) | 2.0 (0-12) |

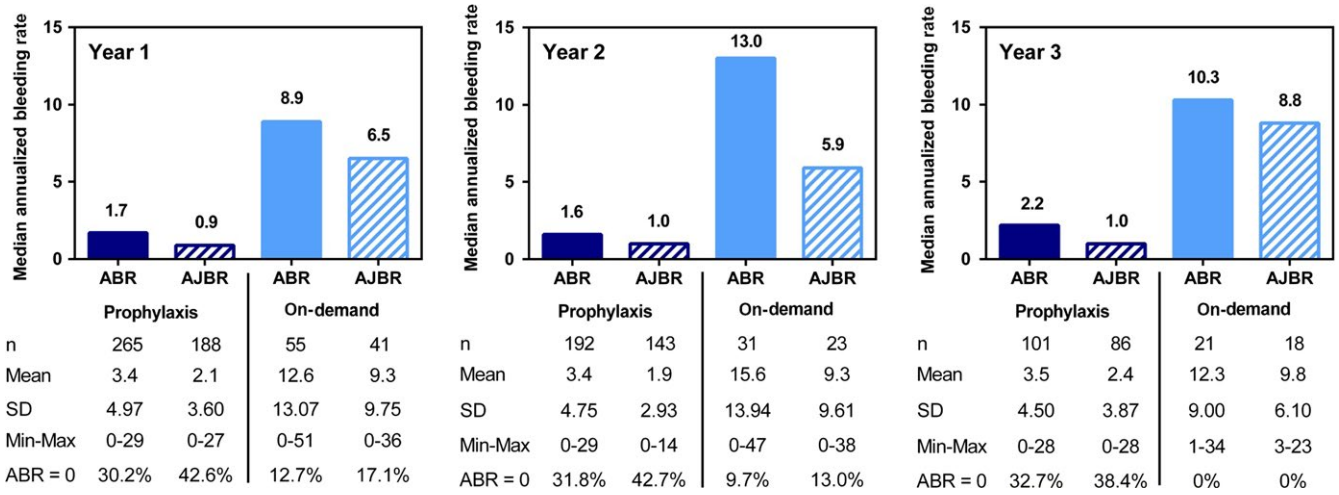


**FIGURE 2** Annualized bleeding rate and joint bleeding rates in patient treated prophylactically or on-demand at year-1, year-2 and year-3 visits. n = Patients with non-missing data on number of bleeding episodes [Colour figure can be viewed at wileyonlinelibrary.com]

Ten patients had an inhibitor at screening: in four of these patients, inhibitors spontaneously disappeared during the study; an additional two patients continued to show a low anamnestic response (<5 BU/mL) continuing exposure to FVIII; in the remaining four patients no follow-up is available yet.

## 4 | DISCUSSION

Real-world, long-term data in a large cohort of patients on treatment outcomes are very limited. For this reason we started a non-interventional prospective cohort study in June 2011 with the aim of

**TABLE 2** Annualized number of bleeding episodes for year 1, 2 and 3 according to haemophilia severity

| Annualized bleeding rate | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | Prophylaxis | On-demand | Prophylaxis | On-demand | Prophylaxis | On-demand |
| All bleeds | | | | | | |
| Overall | | | | | | |
| n (missing) | 265 (7) | 55 (3) | 192 (9) | 31 (4) | 101 (7) | 21 (5) |
| Mean (SD) | 3.4 (4.97) | 12.6 (13.07) | 3.4 (4.75) | 15.6 (13.94) | 3.5 (4.50) | 12.3 (9.00) |
| Median (min-max) | 1.7 (0-29) | 8.9 (0-51) | 1.6 (0-29) | 13.0 (0-47) | 2.2 (0-28) | 10.3 (1-34) |
| <1% FVIII | | | | | | |
| n (missing) | 152* (6) | 22 (2) | 107 (6) | 8 (3) | 55 (5) | 6 (2) |
| Mean (SD) | 3.5 (4.30) | 14.0 (12.30) | 3.3 (4.13) | 18.4 (14.33) | 3.7 (3.93) | 15.8 (8.13) |
| Median (min-max) | 2.0 (0-21) | 12.1 (0-41) | 1.9 (0-22) | 15.6 (3-46) | 2.9 (0-16) | 17.9 (6-27) |
| 1% to <2% FVIII | | | | | | |
| n (missing) | 95 (1) | 26 (1) | 72 (3) | 21 (1) | 44 (2) | 14 (2) |
| Mean (SD) | 3.3 (5.64) | 14.3 (14.29) | 3.8 (5.76) | 15.5 (14.26) | 3.5 (5.22) | 11.4 (9.33) |
| Median (min-max) | 1.0 (0-29) | 9.8 (0-51) | 1.0 (0-29) | 13.0 (0-47) | 1.4 (0-28) | 9.4 (1-34) |
| 2% to 5% FVIII | | | | | | |
| n (missing) | 17 (0) | 7 (0) | 13 (0) | 2 (0) | 2 (0) | 1 (1) |
| Mean (SD) | 3.5 (6.75) | 2.2 (3.57) | 2.2 (3.19) | 5.4 (7.70) | 1.5 (2.08) | 3.9 |
| Median (min-max) | 0.9 (0-27) | 1.2 (0-10) | 1.7 (0-11) | 5.4 (0-11) | 1.5 (0-3) | 3.9 (4-4) |
| Joint bleeds | | | | | | |
| Overall | | | | | | |
| n (missing) | 188 (84) | 41 (17) | 143 (58) | 23 (12) | 86 (22) | 18 (8) |
| Mean (SD) | 2.1 (3.60) | 9.3 (9.75) | 1.9 (2.93) | 9.3 (9.61) | 2.4 (3.87) | 9.8 (6.10) |
| Median (min-max) | 0.9 (0-27) | 6.5 (0-36) | 1.0 (0-14) | 5.9 (0-38) | 1.0 (0-28) | 8.8 (3-23) |
| <1% FVIII | | | | | | |
| n (missing) | 111 (47*) | 17 (7) | 85 (28) | 6 (5) | 43 (17) | 6 (2) |
| Mean (SD) | 2.3 (3.04) | 12.1 (9.97) | 1.9 (2.61) | 12.7 (9.21) | 2.7 (3.06) | 12.8 (6.78) |
| Median (min-max) | 1.0 (0-12) | 9.4 (0-32) | 1.0 (0-12) | 11.8 (1-26) | 1.9 (0-12) | 13.6 (5-23) |
| 1% to <2% FVIII | | | | | | |
| n (missing) | 64 (32) | 21 (6) | 47 (28) | 15 (7) | 41 (5) | 11 (5) |
| Mean (SD) | 1.8 (3.38) | 8.0 (9.65) | 2.2 (3.59) | 8.8 (10.13) | 2.1 (4.65) | 8.8 (5.51) |
| Median (min-max) | 0.8 (0-19) | 5.1 (0-36) | 0.6 (0-14) | 5.7 (0-38) | 0.9 (0-28) | 7.3 (3-18) |
| 2% to 5% FVIII | | | | | | |
| n (missing) | 13 (4) | 3 (4) | 11 (2) | 2 (0) | 2 (0) | 1 (1) |
| Mean (SD) | 2.8 (7.49) | 2.1 (3.61) | 1.4 (2.15) | 3.0 (4.20) | 1.0 (1.39) | 3.9 |
| Median (min-max) | 0.0 (0-27) | 0.0 (0-6) | 0.0 (0-6) | 3.0 (0-6) | 1.0 (0-2) | 3.9 (4-4) |

*1 missing, with no grading available.

enrolling at least 500 patients with a follow-up period of up to 8 years. The study involved a diverse population, with patients ranging from 0 to 78 years of age, and about two-third of patients had severe haemophilia A (FVIII < 1%).

The data read-out analysis carried out in July 2016 confirmed, after an overall follow-up of 811 patient-years, that octocog alfa was well tolerated with an excellent safety profile. Effectiveness of bleeding treatment was excellent/good in the majority of cases. Importantly, a high effectiveness of octocog alfa prophylaxis, in comparison to on-demand treatment, was observed among about one-third of patients with zero bleeds and overall median ABRs in the first 3 years ranging from 1.6 to 2.2. Interestingly, this study showed that prophylaxis has not modified the pattern of most affected bleeding sites in comparison with on-demand treatment.

These real-world findings demonstrate that, at least in one-third of patients, the goal of zero bleeds can be achieved and is also potentially achievable in another third of patients (Figure 3), who experienced less than 3 bleeds a year. Still, a clinically relevant percentage of patients to bleed

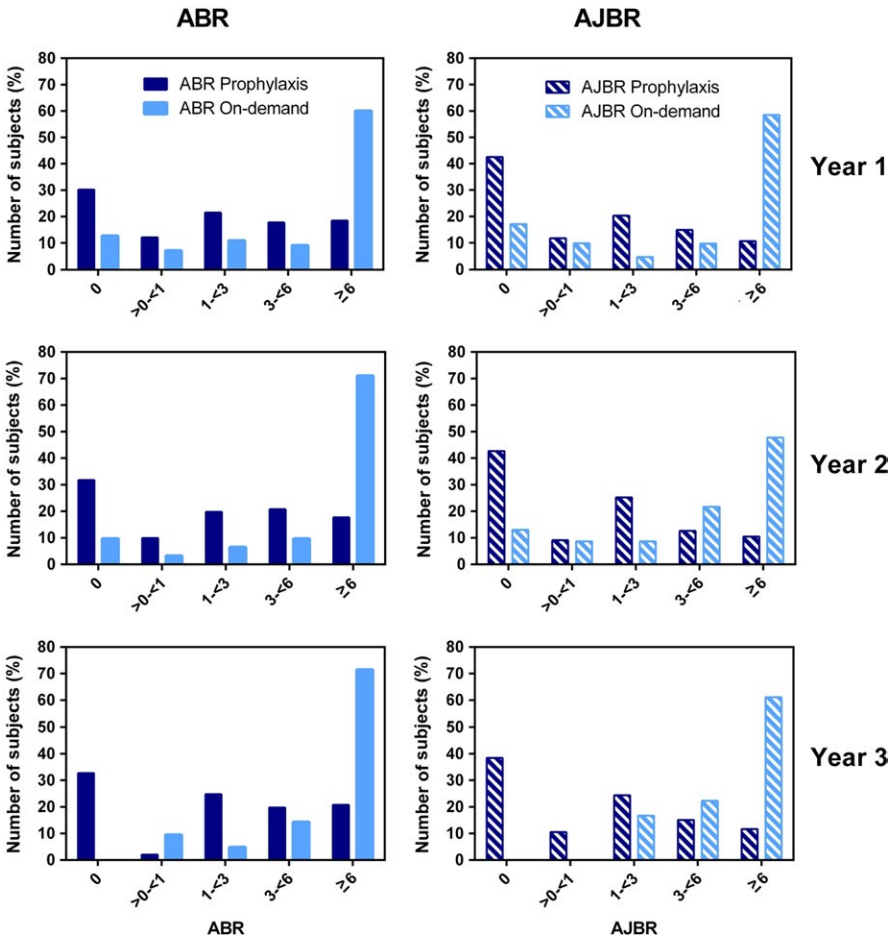


**FIGURE 3** Categorized ABR and AJBR for annual visit 1, 2 and 3 [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Overall number of bleeding episodes for year 1, 2 and 3

| | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | Prophylaxis (N = 272) | On-demand (N = 58) | Prophylaxis (N = 201) | On-demand (N = 35) | Prophylaxis (N = 108) | On-demand (N = 26) |
| Descriptive overall statistics | | | | | | |
| n* | 265 | 55 | 192 | 31 | 101 | 21 |
| Patient with bleeding episodes (%) | 185 (69.8%) | 48 (87.3%) | 131 (68.2%) | 28 (90.3%) | 68 (67.3%) | 21 (100.0%) |
| Total number of bleeds | 945 | 613 | 616 | 413 | 403 | 256 |
| Severity of bleeding episodes | | | | | | |
| # of minor bleeding episodes (%) | 624 (88.0%) | 478 (81.3%) | 424 (86.7%) | 226 (83.4%) | 282 (83.4%) | 168 (92.8%) |
| # of major bleeding episodes (%) | 75 (10.6%) | 63 (10.7%) | 56 (11.5%) | 18 (6.6%) | 40 (11.8%) | 11 (6.1%) |
| Unknown | 10 (1.4%) | 47 (8.0%) | 9 (1.8%) | 27 (10.0%) | 16 (4.7%) | 2 (1.1%) |
| Missing | 236 | 25 | 127 | 142 | 65 | 75 |
| Cause of bleeding episodes | | | | | | |
| # of spontaneous bleeding episodes (%) | 251 (34.7%) | 358 (60.2%) | 162 (32.9%) | 187 (49.0%) | 128 (36.5%) | 137 (55.2%) |
| # of traumatic bleeding episodes (%) | 335 (46.3%) | 136 (22.9%) | 214 (43.5%) | 113 (29.6%) | 150 (42.7%) | 57 (23.0%) |
| Unknown | 138 (19.1%) | 101 (17.0%) | 116 (23.6%) | 82 (21.5%) | 73 (20.8%) | 54 (21.8%) |
| Missing | 221 | 18 | 124 | 31 | 52 | 8 |

*Patients with non-missing data on number of bleeding episodes.

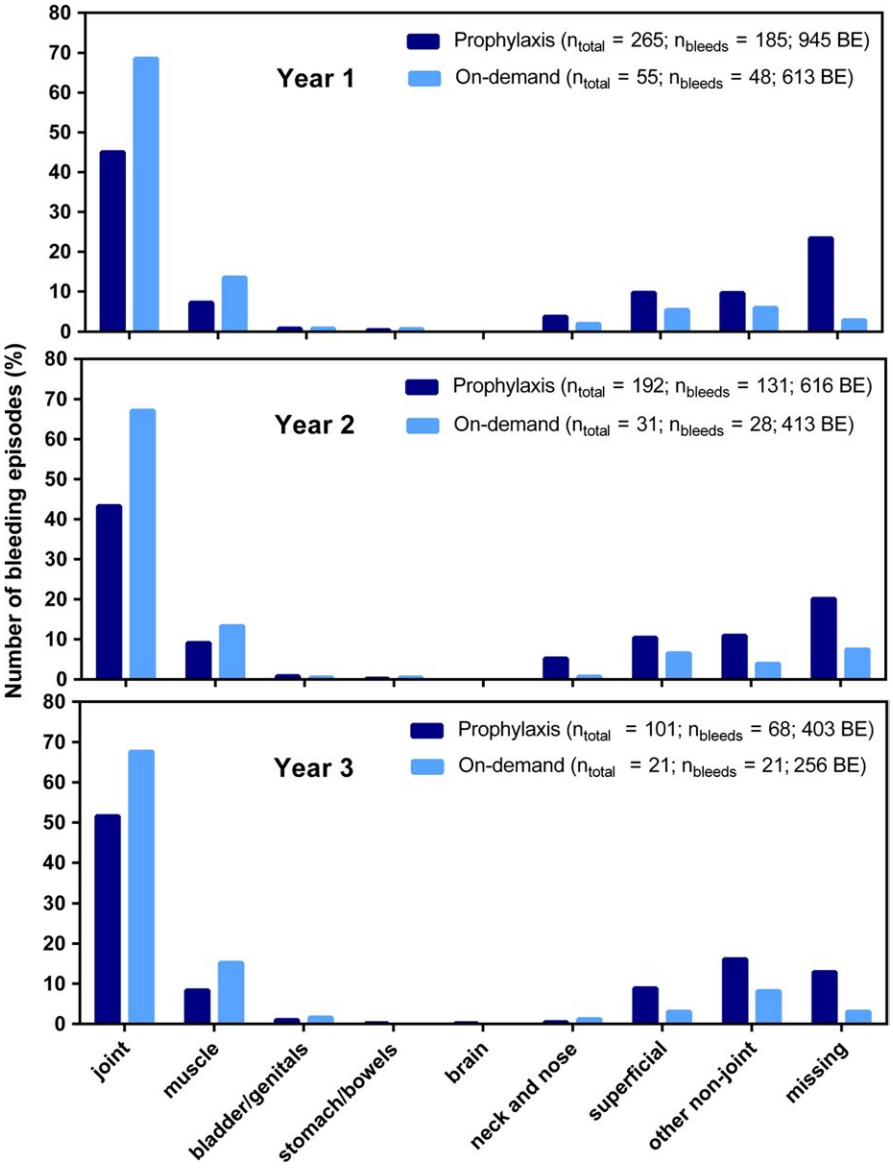


**FIGURE 4** Number of bleeding episodes by bleed location. $n_{total}$ = Patients with non-missing data on number of bleeding episodes; $n_{bleeds}$ = Patients with bleeding episodes; BE = total number of bleeding episodes [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** ADVATE Consumption (including on-demand treatment)

| | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | **Prophylaxis (n = 272)** | **On-demand (n = 58)** | **Prophylaxis (n = 201)** | **On-demand (n = 35)** | **Prophylaxis (n = 108)** | **On-demand (n = 26)** |
| Annualized total dose (IU) | | | | | | |
| n* | 268 | 38 | 193 | 20 | 105 | 19 |
| Mean (SD) | 272 428 (187 179) | 52 844 (63 331) | 274 039 (173 724) | 43 637 (51 750) | 266 792 (155 142) | 44 508 (39 400) |
| Median (min-max) | 241 494 (1990-1 095 728) | 32 601 (525-313 065) | 242 057 (607-1 205 801) | 26 164 (1675-199 841) | 244 510 (17 121-695 850) | 46 793 (91.3-139 140) |
| Annualized number of infusions | | | | | | |
| n* | 268 | 38 | 193 | 20 | 105 | 19 |
| Mean (SD) | 176.5 (46.5) | 26.1 (23.7) | 183.9 (44.7) | 23.3 (22.0) | 181.3 (53.4) | 28.5 (25.7) |
| Median (min-max) | 182.6 (1.0-365.2) | 18.0 (1.2-104.4) | 182.6 (0.4-470.3) | 19.3 (3.0-87.0) | 182.6 (8.6-364.7) | 23.4 (0.8-93.1) |

*Patients with non-missing data on dose and infusions.

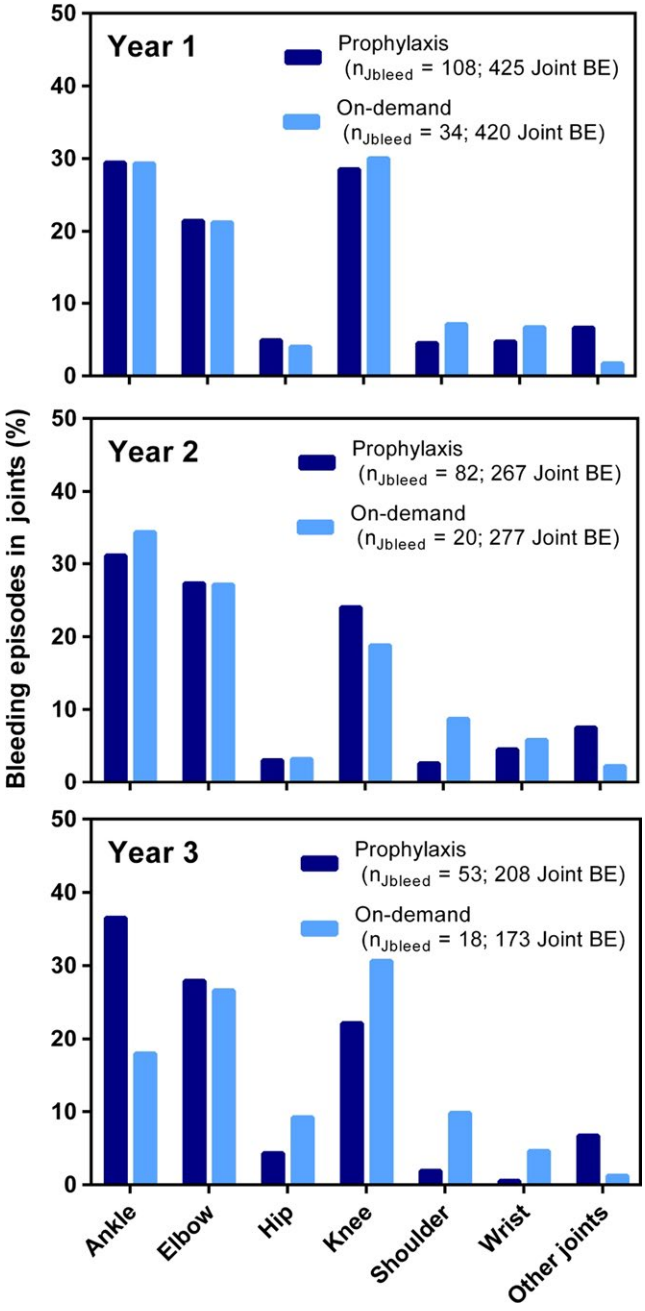


**FIGURE 5** Joint bleeding episodes by bleeding sites. $n_{Jbleed}$ = Number of patients with joint bleeding episodes; Joint BE = total number of joint bleeding episodes [Colour figure can be viewed at wileyonlinelibrary.com]

frequently. Research will hopefully provide more insights that can explain at least partially these differences in bleeding phenotype. Perhaps biomarkers can identify patients who might deserve a more aggressive treatment regimen.

These data mirror what has been observed in a parallel ongoing study with similar aims and evaluation criteria in 402 German patients currently being treated with octocog alfa. That study showed that 39% of 226 patients had an ABR of 0 and 53% had 0 AJBR in the first year of follow-up.[12] The data from these two studies will later be merged and will then provide information on more than 1000 patients prospectively followed.

Of note, the great majority of patients were on standard prophylaxis. Patients still experiencing bleeding episodes might require a more personalized approach to treatment. In fact, a better individualization of prophylaxis regimens based on patients' characteristics and individual PK response may provide better outcomes and would be a more efficient use of such expensive treatment.[11] This study will also collect PK parameters aiming to evaluate their association with bleeding rate in the final data analysis, to improve outcome with a further individualized treatment.

Data from this study provide an important prospective validation of what was previously reported by other retrospective and prospective studies.[13-15] It is particularly interesting to compare our data with the data of the Orthopedic Outcome Study (OOS).[13] In this study, Aledort et al showed an average number of bleeds of 9.5 in patients with severe haemophilia A on prophylaxis and 25.5 in patients on OD treatment, compared to 3.4 and 12.8, respectively, in our study. This discrepancy might be attributed to the different attitude in prescribing and starting prophylaxis more than 20 years ago, and the difference between the two cohort sizes (66 severe haemophilia A patients on prophylaxis and 411 patients on OD treatment in the OOS cohort vs 246 and 47, respectively, in the AHEAD study cohort). Dosing regimens have probably changed over time with a better availability of factor concentrates. The ESCHQoL study,[16] which compared bleeding frequencies among regions with different levels of factor consumption (>5 IU per capita, 2-5 IU per capita and <2 IU per capita), showed a statistically lower incidence of bleeding episodes in regions with higher factor use per capita.

Very recently Klamroth et al[17] reported the outcome of a German cohort of 215 patients with haemophilia A, all severities. A median of 3.7 bleeding events (min-max: 0-26) was reported in 54 patients on prophylaxis, as compared to 1.7 median bleeds (min-max: 0-29) in 272 patients in the AHEAD study. A direct comparison cannot be made because of probable differences between the two cohorts.

The annual cost of prophylaxis (including cost of breakthrough bleeds) in the current AHEAD study cohort was about 200 000 US$ (4400 US$/kg). This cost is comparable to what was reported by other prospective studies[14,18] and much higher than on-demand treatment. Some clinicians may have chosen to treat patients on-demand, particularly adults, based on their low bleeding frequency and/or joint status.

The AHEAD study is the first, long-term, prospective study carried out in a large cohort of haemophilia A patients aiming to evaluate long-term treatment outcome for up to 8 years. The large body of data provided by this study provides the opportunity to explore important treatment-related issues. Nevertheless, there are limitations inherent to the study design. The major limitations are those typical of a non-interventional study: lack of a standardized treatment protocol and a control arm, with most safety and effectiveness parameters based on participant recall or self-reported information. However, this level of information is generally available to clinicians for evaluating treatment outcomes at single patient/centre level. Data on adherence/concordance with the prescribed regimen, which may have an impact on treatment outcomes, were

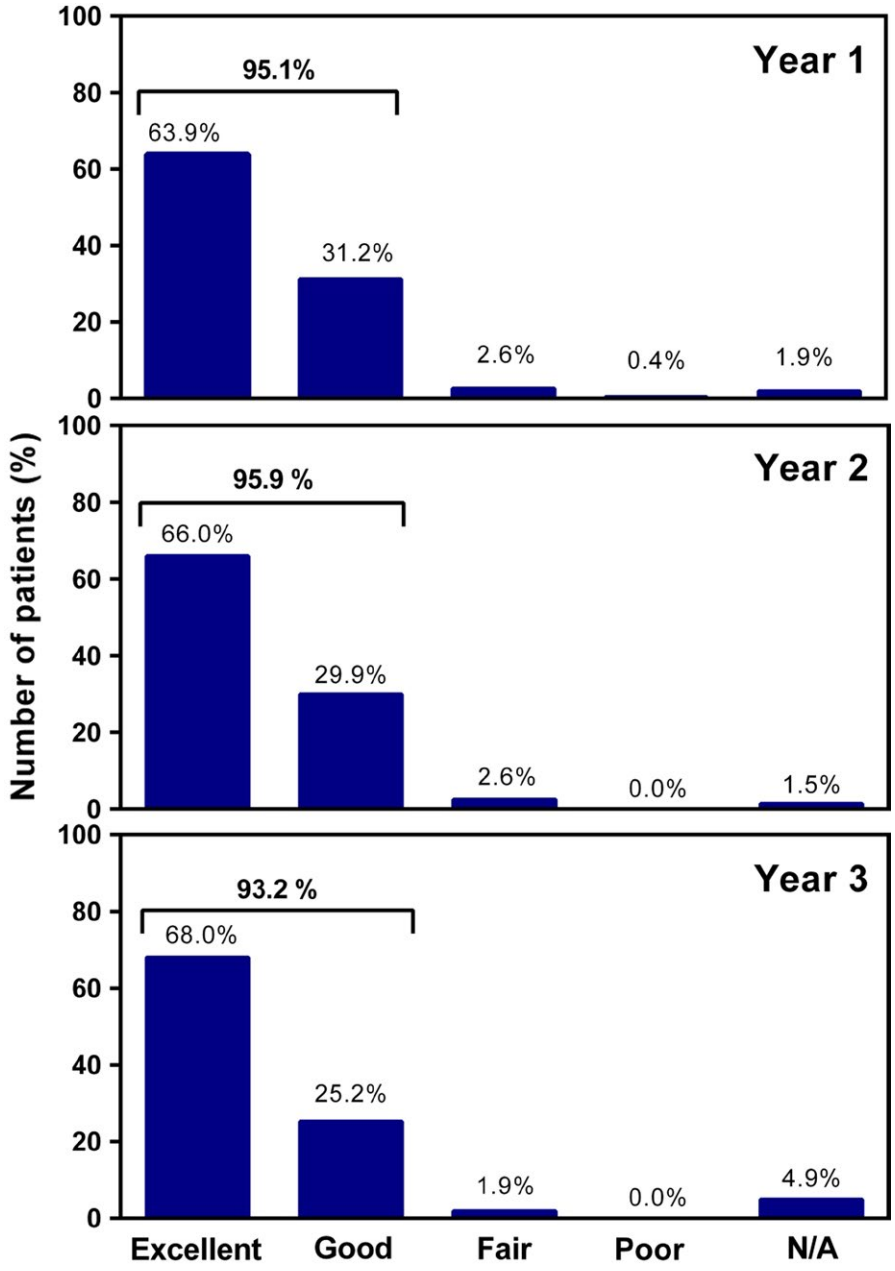


**FIGURE 6** Overall effectiveness of prophylaxis year 1: n = 266 patients (6 with missing entries); year 2: n = 194 patients (3 with missing entries); year 3: 103 patients (4 with missing entries) [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 5** Treatment of bleeding episodes

| | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | Prophylaxis (N = 185; 945 BE) | On-demand (N = 48; 613 BE) | Prophylaxis (N = 131; 616 BE) | On-demand (N = 28; 413 BE) | Prophylaxis (N = 68; 403 BE) | On-demand (N = 21; 256 BE) |
| No. of infusions for bleed cessation | | | | | | |
| BE n* | 724 | 595 | 492 | 369 | 352 | 250 |
| Mean (SD) | 2.0 (4.3) | 1.6 (1.1) | 2.0 (2.2) | 1.6 (1.5) | 2.2 (2.4) | 1.9 (1.8) |
| Median (min-max) | 1 (0-98) | 1 (0-9) | 1 (0-22) | 1 (1-17) | 1 (0-19) | 1 (0-18) |
| No. of units for bleed cessation (IU) | | | | | | |
| BE n* | 724 | 595 | 492 | 369 | 352 | 250 |
| Mean (SD) | 2899 (5941) | 3161 (2794) | 2762 (4551) | 2854 (3878) | 3497 (4562) | 3550 (3506) |
| Median (min-max) | 2000 (0-81 000) | 3000 (0-29 000) | 2000 (0-60 000) | 1500 (500-39 500) | 2000 (0-42 000) | 3000 (0-37 000) |

*Information on additional bleeding events (BE) is missing.
IU: international units.

not collected in this study. Patient compliance represents one of the major obstacles to an efficacious personalized prophylaxis and it can introduce an underestimation of prophylaxis effectiveness in bleeding prevention. Compliance evaluation has not been included in the original protocol, but it has been recently added with an amendment. Another limitation of this report is that this is a preliminary analysis after a 3-year period rather than a final study analysis after complete follow up and data cleaning. Despite this, we felt compelled to update the treating haemophilia clinical community on the preliminary outcomes of this study.

## 5 | CONCLUSIONS

Despite the typical limitations of a non-interventional study, this preliminary analysis confirms that octocog alfa is effective and well tolerated. The goal of zero bleeds with prophylactic treatment is achievable for many patients, although not yet achieved in the majority of patients. Understanding the reasons behind the lower response to standard regimens will further improve personalization of dosing and possibly outcomes.

Moreover, these findings represent a reliable benchmark for current and new products and treatment approaches. Longer follow-up will provide further valuable information on long-term outcomes including joint health in this large cohort of patients.

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## DISCLOSURES

GS, KS and AG are employed at Baxalta Innovations GmbH, now part of Shire. KK has received advisory board or speaker fees and research funding from Baxalta, Pfizer, Octapharma, NovoNordisk, Bayer and SOBI. MGM has received speaker's bureau fees from Amgen, Novartis, Shire, Baxalta, Novonordisk, Bayer, Pfizer and Kedrion; honoraria for advisory board participation from Baxalta and Novonordisk. RP has received advisory board or speaker fees and research funding from Baxalta, Pfizer and SOBI. DAT has received advisory board or speaker fees and research funding from Baxalta, Pfizer, Octapharma, NovoNordisk, Bayer and SOBI. CH has received advisory board or speaker fees or research funding from Shire, Pfizer, Octapharma, NovoNordisk, Bayer, SOBI, LFB, NovoNordisk, Kedrion and CSL Behring. ES has received speaker's bureau fees from Shire, Baxalta, Bayer, NovoNordisk, CSL Behring, Kedrion and Grifols; honoraria for advisory board participation from Shire, Baxalta, Bayer, NovoNordisk, Pfizer, CSL Behring, Kedrion, Grifols, Octapharma, Uniqure, BioMarin and Roche; unrestricted research grant from Pfizer. JO has received grants/research support from Shire, Bayer, Biogen Idec, Biotest, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum; honoraria or consultation fees: Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum; and participated in speaker's bureau for Shire, Bayer, Biogen Idec, Biotest, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum.

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## REFERENCES

1. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet*. 2003;361:1801-1809.
2. Roosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. *Haemophilia*. 2006;12(Suppl 3):117-121.
3. Mannucci PM. Hemophilia: treatment options in the twenty-first centruy. *J Thromb Haemost*. 2003;1:1349-1355.
4. Report of a joint WHO/WFH/ISTH meeting. Delivery of treatment for haemophilia. http://www1.wfh.org/publication/files/pdf-1451.pdf. Accessed September 5, 2016.
5. Tarantino MD, Collins PW, Hay PW, et al. 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;10:428-437.
6. Blanchette VS, Shapiro AD, Liesner RJ, et al. Plasma and albumin free recombinant factor VIII (rAHF-PFM): pharmacokinetics, efficacy and safety in previously treated pediatric patients. *J Thromb Haemost*. 2008;6:1319-1326.
7. Shapiro A, Berntorp E, Pabinger I, 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;100:217-223.
8. Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost*. 2012;10:359-367.
9. Oldenburg J, Goudemand J, Valentino L, et al. Postauthorization safety surveillance of ADVATE [antihaemophilic factor (recombinant), plasma/albumin-free method] demonstrates efficacy, safety and low-risk for immunogenicity in routine clinical practice. *Haemophilia*. 2010;16:866-877.
10. Iorio A, Marcucci M, Cheng J, et al. Patient data meta-analysis of Post-Authorization Safety Surveillance (PASS) studies of haemophilia A patients treated with rAHF-PFM. *Haemophilia*. 2014;20:777-783.
11. Mantovani LG, Rota M, Cortesi P, Steinitz K, Reininger A, Gringeri A. Meta-analysis on incidence of inhibitors in 1,945 previously untreated patients treated with recombinant factor VIII products: Is there a difference? *Blood*. 2015;126:289.
12. Huth-Kuehne A, Klamroth R, Khair K, et al. Striving for a bleed free world - an interim analysis from the AHEAD study. Poster presented at EAHAD Congress 2016. P067.
13. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med*. 1994;236:391-399.

14. 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;357:535-544.
15. Tagliaferri A, Franchini M, Coppola A, et al. Effects of secondary prophylaxis started in adolescent and adult haemophiliacs. *Haemophilia*. 2008;14:945-951.
16. Schramm W, Gringeri A, Ljung R, et al. Haemophilia care in Europe: the ESCHQoL study. *Haemophilia*. 2012;18:729-737.
17. Klamroth R, Miesbach W, Staritz P. Prospective evaluation of treatment regimens, efficacy and safety of a recombinant factor VIII concentrate in haemophilia A: the German EffeKt study. *Haemophilia*. 2016;22:684-691.
18. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011;9:700-710.

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