




## ORIGINAL ARTICLE

# Turoctocog alfa pegol (N8-GP) in severe hemophilia A: Long-term safety and efficacy in previously treated patients of all ages in the pathfinder8 study

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## Abstract

**Background:** N8-GP (turoctocog alfa pegol; Esperoct) is a glycoPEGylated human recombinant factor VIII (FVIII).

**Objectives:** Pathfinder8 (NCT01480180) was a phase 3, multinational, open-label, nonrandomized trial to investigate the long-term safety and efficacy of N8-GP in people of all ages with severe hemophilia A previously treated with N8-GP.

**Patients/Method:** Patients were recruited from the completed phase 3 pathfinder2 and pathfinder5 trials to receive intravenous N8-GP prophylaxis for up to 104 weeks, administered every 7 days, twice weekly, or three times weekly. Primary and secondary end points were the number of adverse events (AEs) reported and efficacy of treatment, respectively.

**Results:** Overall, 160 patients were exposed to N8-GP for a mean of 179 exposure days and 681 calendar days ( $\approx 1.9$  years) per patient. In total, 119 patients experienced 510 AEs, corresponding to a rate of 1.71 AEs per patient-year of exposure; 97.5% of AEs were mild or moderate in severity, and no AEs led to withdrawal. No patients developed FVIII inhibitors during the trial. The Poisson estimate of mean annualized bleeding rate for all bleeds (excluding surgery) and across all regimens was 1.10

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(median, 0.00), and for spontaneous bleeds was 0.61 (median, 0.00). Most (55.6%) patients experienced no bleeds that required FVIII treatment (excluding perioperative bleeds). The estimated hemostatic success rate for the treatment of 322 bleeding episodes (excluding surgery) was 95.8%, including missing values as failure.

**Conclusions:** Long-term prophylactic use of N8-GP appeared safe and efficacious across all age groups in people with severe hemophilia A previously treated with N8-GP.

#### KEYWORDS

factor VIII, hemophilia A, prophylaxis, safety, turoctocog alfa pegol

#### Essentials

- A total of 160 people with hemophilia A were recruited from pathfinder2 or pathfinder5 into pathfinder8.
- In pathfinder8, 510 adverse events occurred in 119 patients; no patients developed FVIII inhibitors.
- Most (55.6%) patients had no bleeds; estimated annualized bleeding rate was 1.10 (all bleeds).
- Long-term prophylactic use of N8-GP appeared safe and efficacious across all age groups.

## 1 | INTRODUCTION

People with severe hemophilia A typically experience spontaneous recurrent bleeds that may lead to chronic hemophilic arthropathy, pain, and immobility if not treated adequately.<sup>1</sup> Clotting factor replacement therapy to prevent and treat bleeds remains a mainstay of treatment, and extended half-life (EHL) recombinant factor VIII (rFVIII) concentrates can reduce treatment burden, compared with standard half-life factor VIII (FVIII) molecules.<sup>1,2</sup>

N8-GP (turoctocog alfa pegol) is an EHL human rFVIII produced by glycoPEGylation on the truncated B-domain of turoctocog alfa.<sup>3</sup> Its safety and efficacy have been demonstrated in the pathfinder clinical trial program, which includes >1000 patient-years of exposure (excluding pathfinder8) and a total of 270 patients treated, some for >6 years.<sup>4-6</sup> Pathfinder2 (NCT01480180) was a phase 3, multinational, open-label trial evaluating N8-GP in 186 previously treated adolescents or adults (age  $\geq 12$  years) with severe hemophilia A. During the main phase of pathfinder2, patients received prophylaxis with 50 IU/kg N8-GP administered every 4 days (Q4D;  $n = 175$ ) or only on-demand treatment of bleeds ( $n = 12$ ).<sup>6,7</sup> During the extension phase, most patients continued to receive Q4D prophylaxis, although patients with a low bleeding rate could switch to 75 IU/kg N8-GP once weekly (Q7D). By the trial end, patients had received N8-GP for up to 6.6 years (median, 5.4 years).<sup>6</sup> Pathfinder5 (NCT01731600) was a phase 3, multinational, open-label, single-arm trial of 68 previously treated pediatric patients (age <12 years), comprising a main phase and an extension phase. Patients received 60 IU/kg N8-GP prophylaxis twice weekly (BIW) for up to 5.4 years.<sup>8</sup> Patients previously enrolled in pathfinder2 or pathfinder5 were eligible to enroll in pathfinder8 (NCT03528551), an extension trial evaluating the long-term safety and efficacy of N8-GP in previously N8-GP-treated people (all ages) with severe hemophilia A.

## 2 | METHODS

### 2.1 | Patients and trial design

Pathfinder8 was a phase 3, multicenter, multinational, open-label, nonrandomized, interventional trial. It was conducted between April 30, 2018 (first patient first visit) and December 3, 2020 (last patient last visit) and in accordance with the Declaration of Helsinki<sup>9</sup> and the International Conference on Harmonization Good Clinical Practice,<sup>10</sup> including archiving of essential documents and the US Food and Drug Administration Code of Federal Regulations (21 CFR 312.120).<sup>11</sup>

Males with severe congenital hemophilia A (FVIII activity <1%) and ongoing participation in pathfinder2 or pathfinder5 (at the time of transfer) could enroll in pathfinder8 only if they were willing to follow one of the defined N8-GP prophylaxis regimens and were capable of assessing and treating a bleed at home. People with known hypersensitivity to N8-GP, with any disorder other than hemophilia that might jeopardize safety or compliance, or those participating in a clinical trial other than pathfinder2 or pathfinder5 were excluded.

### 2.2 | Treatment

Patients were recruited from pathfinder2 and pathfinder5 to receive intravenous N8-GP (turoctocog alfa pegol; Esperoct<sup>®</sup>; Novo Nordisk A/S) prophylaxis dosed Q7D, BIW, or three times weekly (TIW). BIW and TIW regimens were introduced to investigate the safety and efficacy of N8-GP using alternative dosing to Q4D prophylaxis. Treatment allocation by the investigator was based on previous regimen and bleeding tendency. The Q7D regimen (75 IU/kg bodyweight [BW]) was available upon entry

into pathfinder8 for patients who received Q7D prophylaxis or on-demand treatment in pathfinder2. BIW prophylaxis (dosing alternately every 3 and 4 days) was administered at 50 IU/kg BW (patients aged  $\geq 12$  years) or 60 IU/kg BW (patients aged  $< 12$  years). Patients receiving TIW prophylaxis (dosing every 2, 2, and 3 days) received N8-GP at 50 IU/kg BW (all ages). All children aged  $< 12$  years received BIW or TIW prophylaxis. Patients could switch to BIW or TIW at the investigator's discretion. For treatment of bleeds, doses of 20 to 75 IU/kg BW were administered at the investigator's discretion, depending on bleed location and severity. Single doses were not to exceed 75 IU/kg BW and the total daily dose was not to exceed 200 IU/kg BW. For major surgery, patients received N8-GP (20-75 IU/kg BW) before, during, and after surgery.

The total treatment duration in pathfinder8 was 104 weeks. A 1-month follow-up period after treatment end was applicable to patients who developed an inhibitor or discontinued N8-GP due to lack of hemostatic effect or anaphylaxis.

A post hoc subgroup analysis was performed to investigate if annualized bleeding rate (ABR) changed in patients who switched from Q4D to BIW prophylaxis when moving from pathfinder2 to pathfinder8. This subgroup was selected for investigation because it contained the greatest number of patients switching regimen in pathfinder8.

### 2.3 | Objectives, end points, and assessments

The primary end point was the number of adverse events (AEs) reported. All AEs were considered treatment emergent because patients had received N8-GP in previous trials. AEs were assessed with regard to seriousness, severity, causality, and final outcome. Serious adverse events (SAEs) and nonserious AEs of special interest (AESIs) were followed up until resolution, stabilization, or if the event was otherwise explained (eg, chronic condition) or the patient was lost to follow-up. Bleeds were not reported as AEs/SAEs, unless they were life threatening and/or evaluated by the investigator as related to N8-GP. Definitions of AEs and SAEs are included in Table S1.

Incidence of FVIII inhibitors was a secondary safety end point. A patient was considered to have developed an inhibitor if two separate samples tested positive (defined as  $\geq 0.6$  Bethesda Units [BU], using the Nijmegen modified FVIII Bethesda assay) at the central laboratory, preferably with  $< 2$  weeks between tests. Any single positive test was reported as an AESI. The patient was considered inhibitor negative if the second (confirmatory) inhibitor test was negative.

Secondary efficacy end points included the number of treated bleeds (including spontaneous bleeds) on prophylaxis, hemostatic effect of N8-GP for treatment of bleeds and during major surgery (assessed on a four-point scale: "excellent," "good," "moderate," and "none"), number of N8-GP injections required per bleed, pre-dose FVIII activity levels on prophylaxis (IU/dL), consumption, and change in joint health status, and treatment satisfaction. Definitions of bleeds and hemostatic effect for treatment of bleeds and during

major surgery are reported in Tables S2 to S4, respectively. FVIII activity was measured with a validated chromogenic assay (Coatest SP FVIII assay [Chromogenix, Florham Park, NJ, USA] on the BCS XP analyzer [Siemens Healthineers AG, Erlangen, Germany]). Joint status was assessed using the Hemophilia Joint Health Score (HJHS; Toolkit 2.1). Target joints were defined as a joint with  $\geq 3$  spontaneous bleeds within a consecutive period of 6 months. Target joints were considered resolved when there had been no spontaneous bleeds in the joint for 12 months. Treatment satisfaction was measured using the Hemo-SAT Adults questionnaire (patients aged  $\geq 17$  years). Hemo-SAT domain scores ranged from 0 to 100, with lower scores indicating greater treatment satisfaction; the Hemo-SAT total score was calculated from changes in the other six domain scores.

Exploratory end points included incidence of anti-N8-GP and anti-polyethylene glycol (PEG) antibodies. A radioimmunoassay using radiolabeled N8-GP was used for measuring antibodies against N8-GP and validated according to guidelines<sup>12-15</sup>; a test was performed on positive samples for anti-N8-GP binding antibodies to identify if the antibodies could cross-react with endogenous FVIII. Measurement of PEG in plasma was performed using an exploratory assay developed in accordance with the European Medicines Agency guideline on bioanalytical method validation.<sup>16</sup> Routine laboratory measures and vital signs were assessed.

For the post hoc subgroup analyses, change in ABR was assessed in patients who had an ABR  $> 1$  while on Q4D prophylaxis in pathfinder2, to indicate treatment response following initiation of BIW prophylaxis in pathfinder8. The threshold of ABR  $> 1$  was chosen to reflect the median ABR of 0.84 observed with Q4D prophylaxis in the pathfinder2 end-of-trial results.<sup>6</sup>

### 2.4 | Statistical analyses

All patients enrolled were included in the safety analysis set (SAS). All patients exposed to  $\geq 1$  N8-GP dose in pathfinder8 were included in the full analysis set. For end points based on bleeding episode data, only bleeds treated with N8-GP were included.

ABR of treatment-requiring bleeds was estimated by a Poisson regression model with logarithmic prophylaxis duration as offset and allowing for overdispersion. Poisson regression models were applied separately for each regimen, and estimated ABR was presented with a two-sided 95% confidence interval (CI). Hemostatic response for treatment of bleeds and during major surgery were assessed on a four-point scale; responses of excellent or good were recorded as success, and those of moderate, none, or missing as failure (Tables S3,S4). Hemostatic success rates were estimated with 95% CI using logistic regression, with age group included as a factor and accounting for repeated measures within each patient assuming compound symmetry working correlation (equal variances and equal covariances). Modeling was performed separately for each treatment regimen. A Wilcoxon signed-rank test was used to evaluate whether changes in Hemo-SAT score were statistically significant ( $P < .05$ ).

Measurements of FVIII predose (trough) activity were excluded if postdose activity was lower (or equal to) predose activity, if plasma samples were defrosted during transit, if the samples were taken <7 days since the last treated bleed, or if the dose was not taken within 2 days of the planned window. FVIII activity data before the fourth prophylaxis dose were excluded for each switch in treatment regimen. A mixed model on logarithmic plasma activity levels was used to estimate mean predose FVIII activity, with age as a factor and patient as a random effect.

### 3 | RESULTS

#### 3.1 | Patients

In total, 160 patients from 25 countries were enrolled and exposed to N8-GP during pathfinder8 (102 patients from pathfinder2; 58 from pathfinder5). Of these, 25 started the trial with Q7D prophylaxis, 133 with BIW, and 2 with TIW (Figure 1). Six patients switched regimen during the trial, 16 withdrew, and 144 (90.0%) completed the trial. Baseline characteristics are presented in Table 1.

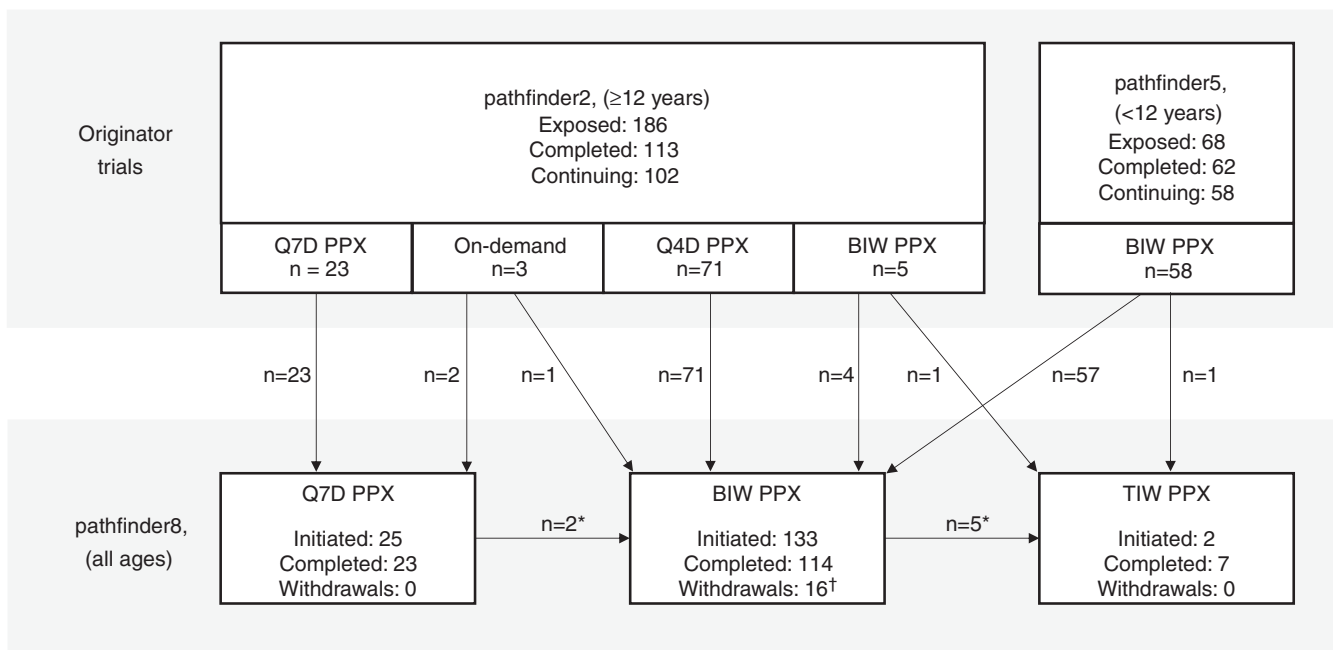
Patients were exposed to N8-GP for a mean of 179 (range, 30-312) exposure days (EDs) and 681 (range, 137-862) calendar days per patient across all regimens, corresponding to a cumulative total of 28 698 EDs and time in trial of 298 years. The longest duration of exposure to N8-GP observed in the pathfinder program was ≈8.4 years, comprising 6.3 years in pathfinder2 and 2.1 years in pathfinder8.

#### 3.2 | Safety

From the SAS (n = 160), 119 patients experienced 510 AEs (Table 2), corresponding to a rate of 1.71 AEs per patient-year of exposure. Most (97.5%) AEs were mild or moderate in severity. Thirteen AEs in 13 patients were reported as severe. The most common AEs were upper respiratory tract infection (n = 33 events), epistaxis (n = 30), nasopharyngitis (n = 26), and arthralgia (n = 15). Eight (1.6%) of 510 AEs were evaluated as probably or possibly related to N8-GP. No AEs led to withdrawal.

Nineteen (11.9%) patients had 22 SAEs; 3 SAEs of seizures occurred in 3 patients, two of which were evaluated as probably/possibly related to N8-GP. A 12-year-old patient with a history of cognitive disorder and prior intracranial hemorrhage was diagnosed with seizure, hospitalized, and treated. A 16-year-old patient with no history of seizure or cognitive disorders experienced a seizure; the brain computed tomography (CT) scan, neurologic examination, magnetic resonance imaging, cardiac evaluation, and electroencephalogram results were without any abnormal findings. A 9-year-old patient with no history of seizure or cognitive disorders experienced a seizure after an unwitnessed fall; the head CT scan showed no evidence of bleeding; the event was assessed as unlikely related to N8-GP. Following the seizure events, all three patients continued N8-GP treatment, with no reoccurrences of seizure reported. One fatal event of malignant melanoma occurred, which was assessed as unlikely related to N8-GP.

No FVIII inhibitors ( $\geq 0.6$  BU) were reported. One patient (BIW prophylaxis) tested positive for cross-reacting anti-N8-GP



**FIGURE 1** Participant flow. \*Two patients switched from Q7D to BIW regimen and five patients switched from BIW to TIW, including one patient who switched regimen twice (ie, from Q7D to BIW, and then from BIW to TIW). <sup>†</sup>16 patients withdrew from the trial due to withdrawal by patient (n = 7), withdrawal by parent/guardian (n = 5), protocol deviation (n = 3), lost to follow-up (n = 1); no patient withdrew from the trial due to AEs. AE, adverse event; BIW, twice weekly; PPX, prophylaxis; Q4D, every 4 days; Q7D, once weekly; TIW, three times weekly

**TABLE 1** Demographics and baseline characteristics

	Prophylaxis dose frequency			
	Q7D	BIW	TIW	Total
Number of patients	25	135	7	160
Mean (SD) age at baseline, y	35.1 (12.7)	27.3 (16.8)	25.3 (17.8)	28.4 (16.4)
Age groups, n (%)				
0-11 y	0 (0)	29 (21.5)	1 (14.3)	29 (18.1)
12-17 y	0 (0)	28 (20.7)	3 (42.9)	29 (18.1)
≥18 y	25 (100)	78 (57.8)	3 (42.9)	102 (63.8)
Race, n (%)				
Asian	3 (12)	17 (12.6)	1 (14.3)	21 (13.1)
Black or African American	1 (4)	4 (3)	...	5 (3.1)
White	21 (84)	110 (81.5)	6 (85.7)	130 (81.3)
Other	...	1 (0.7)	...	1 (0.6)
NA	...	3 (2.2)	...	3 (1.9)
Number of patients with baseline target joints	2	3	...	5
Number of target joints	4	3	...	7

Abbreviations: BIW, twice weekly; NA, not available; Q7D, once weekly; SD, standard deviation; TIW, three times weekly.

**TABLE 2** Adverse events

	Prophylaxis dose frequency			
	Q7D	BIW	TIW	Total
Number of patients	25	135	7	160
Total risk time, y <sup>a</sup>	46.20	241.37	8.30	298.37
All adverse events, n (%) E [R]	17 (68.0) 58 [1.26]	101 (74.8) 444 [1.84]	4 (57.1) 8 [0.96]	119 (74.4) 510 [1.71]
Serious adverse events, n (%) E [R]	4 (16.0) 7 [0.15]	15 (11.1) 15 [0.06]	...	19 (11.9) 22 [0.08]
Adverse events by severity, n (%) E [R]				
Mild	13 (52.0) 39 [0.84]	88 (65.2) 358 [1.48]	3 (42.9) 5 [0.60]	101 (63.1) 402 [1.35]
Moderate	9 (36.0) 18 [0.39]	44 (32.6) 74 [0.31]	2 (28.6) 3 [0.36]	55 (34.4) 95 [0.32]
Severe	1 (4.0) 1 [0.02]	12 (8.9) 12 [0.05]	...	13 (8.1) 13 [0.04]
Adverse event by outcome, n (%) E [R]				
Fatal	...	1 (0.7) 1 [0]	...	1 (0.6) 1 [0]
Adverse event by relationship, n (%) E [R]				
Related adverse events	1 (4.0) 1 [0.02]	4 (3.0) 7 [0.03]	...	5 (3.1) 8 [0.03]
AEs leading to withdrawal, n (%) E [R]	...	...	...	...

Abbreviations: %, percentage of patients with AE; AE, adverse event; BIW, twice weekly; E, number of adverse events; N, number of patients with adverse event; Q7D, once weekly; R, number of adverse events per patient-years of risk time (E/total risk time); TIW, three times weekly.

<sup>a</sup>Total risk time: the cumulative sum of time spent in the trial (from the time of informed consent at trial entry to the end of the trial) for all patients. All AEs are considered treatment emergent. Patients may be summarized under more than one treatment category if they switched regimen during the trial; however, AEs are only represented under the treatment where they occurred.

antibodies (visits 1, 3, 5 and 7); the patient's antibody test at the end-of-treatment visit was negative. Nine patients had anti-PEG antibodies during the trial (five were positive at baseline; four developed antibodies during the trial); these patients continued to receive N8-GP prophylaxis; none experienced AEs or decreased FVIII activity related to anti-PEG antibodies. There was no consistent pattern to the incidence of PEG antibodies and, in general, no increase in

PEG plasma concentration in relation to EDs during the trial across all regimens (Figure S1).

No significant medical or safety concerns were identified, and no safety issues observed with laboratory or vital signs parameters. Overall, there were no apparent differences in the AE and SAE rates among the three prophylaxis regimens, nor in the safety profiles between pediatric and adult patients (data not shown).

### 3.3 | Prevention of bleeding episodes

All 160 patients received prophylaxis; 89 (55.6%) had no treatment-requiring bleeds during the trial (excluding perioperative bleeds). Poisson estimates of mean ABRs for patients on Q7D, BIW, or TIW prophylaxis were 2.65, 0.78, and 1.69, respectively. The Poisson estimate of mean ABR for all bleeds (excluding surgery) and across all regimens was 1.10 (95% CI, 0.62-1.95), with a median ABR of 0.0 (interquartile range [IQR]: 0.0-1.0) (Table 3). Of all 160 patients, 120 (75.0%) had no spontaneous bleeds that required treatment during the trial. The Poisson estimate of mean and median ABR for spontaneous bleeds across all regimens was 0.61 (95% CI, 0.24-1.53) and 0.0 (IQR, 0.0-0.2), respectively.

A subgroup analysis was performed in 71 patients who transitioned from Q4D prophylaxis in pathfinder2 (mean [standard deviation (SD)] treatment duration, 5.3 [0.8] years) to BIW in pathfinder8 (mean [SD] treatment duration, 1.8 [0.5] years). In this subgroup, patients who had higher ABRs on Q4D prophylaxis in pathfinder2 demonstrated a more marked reduction in ABR following transition to BIW prophylaxis compared with patients who had lower ABRs in pathfinder2 (Figure 2). Of these 71 patients, 30 (42.3%) had a mean ABR >1 while on Q4D treatment (mean [SD] ABR for these 30 patients in pathfinder2, 3.78 [3.38]). Most (27/30; 90.0%) patients with

an ABR >1 in pathfinder2 demonstrated an improvement in ABR following transition to BIW prophylaxis in pathfinder8, with a mean (SD) change in ABR of -2.72 (2.9); 3 of the 30 patients demonstrated an increase in ABR, with a mean (SD) change in ABR of 2.67 (2.4). Of the 71 patients in this subgroup, 41 (57.7%) had a mean ABR ≤1 while on Q4D treatment (mean [SD] ABR for these patients in pathfinder2, 0.34 [0.33]). Following transition to BIW prophylaxis in pathfinder8, the mean (SD) change in ABR was -0.11 (0.61).

Among the 71 patients in this subgroup, 45 (63.4%) had no bleeds on Q4D prophylaxis during the last year of pathfinder2. Due to withdrawal, completion of the study, or switching to a different dosing regimen, 61 patients remained in this subgroup in the second year of pathfinder8, of whom 47 (77.0%) had no bleeds while on BIW prophylaxis.

### 3.4 | Treatment of bleeding episodes

In total, 72 patients (45.0%) experienced 327 bleeds during the trial. The estimated success rate for the treatment of 322 bleeding episodes (excluding 5 bleeds during surgery) was 95.8%, including missing values recorded as failure (Table 4). Most (54.7%) of the 327 bleeds were spontaneous; the most frequent location of bleeds was the joint

**TABLE 3** Annualized bleeding rate

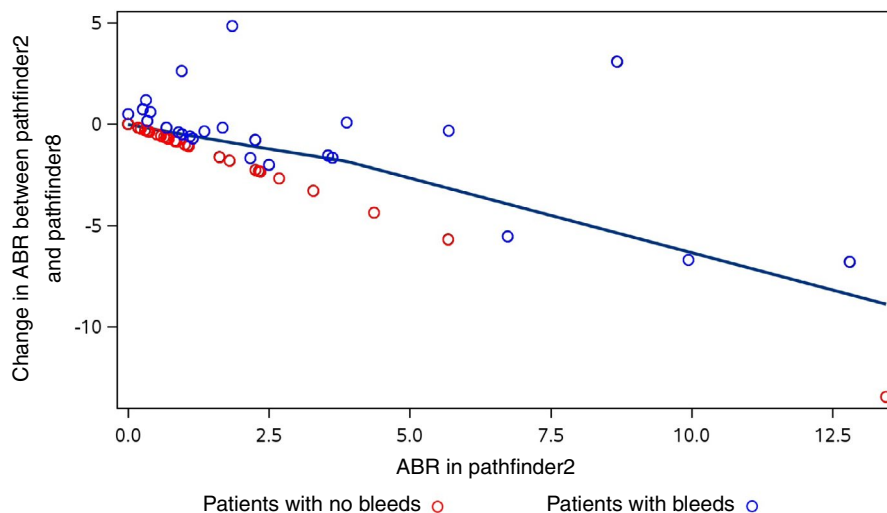
	Prophylaxis dose frequency			
	Q7D	BIW	TIW	Total
Number of patients	25	135	7	160
Mean treatment period, y	1.84	1.77	1.19	1.83
Annualized bleeding rate, all bleeds <sup>a</sup>				
Patients with bleeds, <sup>b</sup> n (%)	9 (36.0)	61 (45.2)	3 (42.9)	71 (44.4)
Patients without treatment-requiring bleeds, <sup>b</sup> n (%)	16 (64.0)	74 (54.8)	4 (57.1)	89 (55.6)
Number of bleeds <sup>b</sup>	122 <sup>c</sup>	186	14	322 <sup>c</sup>
Median ABR (IQR)	0.00 (0.00-1.47)	0.00 (0.00-1.00)	0.00 (0.00-1.56)	0.00 (0.00-1.00)
Poisson estimate of mean ABR (95% CI)	2.65 <sup>c</sup> (0.64-10.98)	0.78 (0.55-1.10)	1.69 (0.64-4.44)	1.10 (0.62-1.95)
ABR, spontaneous bleeds <sup>a</sup>				
Patients with bleeds <sup>b</sup> , n (%)	9 (36.0)	29 (21.5)	3 (42.9)	40 (25.0)
Patients without treatment-requiring bleeds <sup>b</sup> , n (%)	16 (64.0)	106 (78.5)	4 (57.1)	120 (75.0)
Number of bleeds <sup>b</sup>	98	73	8	179
Median ABR (IQR)	0.00 (0.00-0.94)	0.00 (0.00-0.00)	0.00 (0.00-1.56)	0.00 (0.00-0.23)
Poisson estimate of ABR (95% CI)	2.13 (0.41-10.95)	0.31 (0.18-0.52)	0.96 (0.48-1.94)	0.61 (0.24-1.53)

Abbreviations: ABR, annualized bleeding rate; BIW, twice weekly; CI, confidence interval; IQR, interquartile range; Q7D, once weekly; TIW, three times weekly.

<sup>a</sup>For patients withdrawing prematurely, the planned treatment duration was used; for completers, the actual treatment duration was used. Missing diary period and surgery period was excluded when relevant.

<sup>b</sup>Excluding five bleeds during surgery.

<sup>c</sup>One patient in the Q7D regimen experienced 92 bleeds (in part possibly due to difficulty in distinguishing between bleed-related pain and joint pain); the Q7D prophylaxis regimen was retained at the request of the patient.



**FIGURE 2** Change in ABR in subgroup of patients who transitioned from Q4D prophylaxis (pathfinder2) to BIW treatment (pathfinder8). Scatterplot including LOWESS curve (fitted in SAS with proc sgplot) to examine possible trends present in the change in ABR in the subgroup of patients who transitioned from Q4D prophylaxis in pathfinder2 to BIW prophylaxis in pathfinder8 ( $n = 71$ ), in relation to ABR outcomes in pathfinder2. A negative trend was observed, whereby patients with a higher ABR on Q4D prophylaxis in pathfinder2 demonstrated larger reductions in the ABR on BIW prophylaxis during pathfinder8. (Note: no randomized control group was available for statistical comparison in the subgroup analyses to evaluate causality of the observed reductions in ABR. Furthermore, allowance should be made for regression to the mean when interpreting results.) Coloring denotes bleed outcomes for this subgroup in pathfinder8 (ie, blue dot indicates patients who experienced a bleed in pathfinder8; red dot indicates patients who did not experience a bleed in pathfinder8). ABR, annualized bleeding rate; BIW, twice weekly; LOWESS, locally weighted scatterplot smoothing; Q4D, every 4 days

(66.7%); the location of bleeds did not appear to differ among prophylaxis regimens. Of 327 bleeds, 325 (99.4%) were classified as mild or moderate, and 2 joint bleeds were classified as severe. A total of 309 (94.5%) bleeds were resolved with 1 to 2 N8-GP infusions. The mean (SD) number of injections to treat a bleed was 1.4 (1.1). The estimated hemostatic success rate appeared similar across three prophylaxis regimens, ranging from 95.3% (95% CI, 88.9-98.1) for BIW prophylaxis to 100% for Q7D and TIW prophylaxis. One patient on Q7D prophylaxis experienced 92 treated bleeds: Despite this high number, the Q7D regimen was continued at the patient's request.

### 3.5 | Surgery

Of 160 patients, 12 (7.5%) underwent 17 major surgeries, which included the following procedures: knee prosthesis ( $n = 2$ ), right ankle replacement ( $n = 1$ ), cholecystectomy ( $n = 2$ ), arthrotomy and total knee insert replacement ( $n = 1$ ), hip replacement ( $n = 1$ ), right ankle arthrodesis ( $n = 1$ ), tonsillectomy/adenoidectomy ( $n = 1$ ), laparoscopy/laparotomy ( $n = 1$ ), tonsillectomy ( $n = 1$ ), arthrotomy ( $n = 1$ ), ulnar nerve decompression ( $n = 1$ ), intraoral lesion excision ( $n = 2$ ), circumcision ( $n = 1$ ), and laparoscopic hernia repair ( $n = 1$ ). Of the 17 surgeries, hemostatic response was rated as excellent for 11 and good for 5; for the remaining surgery, the response was missing. The estimated hemostatic success rate of N8-GP during all major surgeries was 93.6% (95% CI, 64.7-99.2), including the missing value recorded as failure.

### 3.6 | Joint health

There were five patients with a total of seven target joints at pathfinder8 baseline. By the trial end, three of them had  $\geq 1$  baseline target joint resolved, and two of these three patients had all baseline target joints resolved. During the trial, two patients on BIW prophylaxis and one patient on TIW prophylaxis who did not have target joints at baseline developed new target joints; target joints did not resolve for the two patients on BIW prophylaxis, but were resolved in the patient on TIW prophylaxis. One patient with baseline target joints who received Q7D prophylaxis developed one new target joint.

The mean (SD) changes in total score from the HJHS from visit 1 to end of treatment in patients on Q7D ( $n = 21$ ), BIW ( $n = 112$ ), and TIW prophylaxis ( $n = 2$ ) were, respectively, 0.238 (7.75), -0.116 (7.40) and -10.0 (14.1). Mean (SD) change in total score from the HJHS for all patients ( $n = 139$ , including four patients who switched regimen) was -0.173 (7.47), with the decrease in score denoting a reduction in symptom severity.

### 3.7 | Consumption

The mean annual consumption rate of N8-GP for prophylaxis per patient per year for the respective Q7D, BIW, and TIW regimen were 3878 IU/kg, 5320 IU/kg, and 7646 IU/kg (Table 5). The mean doses for prophylaxis and treatment of bleeds are reported in Table 5.

**TABLE 4** Details of bleeding episodes and hemostatic response to N8-GP

	Prophylaxis dose frequency			Total
	Q7D	BIW	TIW	
Number of patients	25	135	7	160
Patient with bleeds, n (%)	10 (40)	61 (45.2)	3 (42.9)	72 (45)
Bleeding episodes, n (%)	123 (100) <sup>a</sup>	190 (100)	14 (100)	327 (100) <sup>a</sup>
Cause of bleed, n (%)				
Spontaneous	98 (79.7)	73 (38.4)	8 (57.1)	179 (54.7)
Traumatic	24 (19.5)	113 (59.5)	6 (42.9)	143 (43.7)
Surgical	1 (0.8)	4 (2.1)	...	5 (1.5)
Location of bleed, n (%)				
Joint	88 (71.5)	120 (63.2)	10 (71.4)	218 (66.7)
Muscular	10 (8.1)	24 (12.6)	2 (14.3)	36 (11)
Skin	22 (17.9)	31 (16.3)	2 (14.3)	55 (16.8)
Mouth, gums or nose	2 (1.6)	10 (5.3)	...	12 (3.7)
Other	1 (0.8)	5 (2.6)	...	6 (1.8)
Classification of bleed, n (%)				
Mild or moderate	123 (100)	188 (98.9)	14 (100)	325 (99.4)
Severe	...	2 (1.1)	...	2 (0.6)
Haemostatic response for treatment of bleeds (excluding surgery)				
Patients with bleeds, n (%)	9 (36)	61 (45.2)	3 (42.9)	71 (44.4)
Number of bleeds, n (%)	122 (100)	186 (100)	14 (100)	322 (100)
Excellent	114 (93.4)	94 (50.5)	8 (57.1)	216 (67.1)
Good	8 (6.6)	80 (43)	6 (42.9)	94 (29.2)
Moderate	0 (0)	4 (2.2)	0 (0)	4 (1.2)
None	0 (0)	0 (0)	0 (0)	0 (0)
Missing	0 (0)	8 (4.3)	0 (0)	8 (2.5)
Success, n (%) (including missing as failure)	122 (100)	174 (93.5)	14 (100)	310 (96.3)
Success rate <sup>b</sup> (95% CI), (including missing as failure)	100	95.3 (88.9-98.1)	100	95.8 (89.8-98.4)

Abbreviations: BIW, twice weekly; CI, confidence interval; Q7D, once weekly; TIW, three times weekly.

<sup>a</sup>One patient in the Q7D regimen experienced 92 bleeds (in part possibly due to difficulty in distinguishing between bleed-related pain and joint pain); the Q7D prophylaxis regimen was retained at the request of the patient.

<sup>b</sup>Analyzed using logistic regression accounting for repeated measures within patient.

### 3.8 | FVIII activity

The mean (95% CI) predose (trough) FVIII activity was 0.016 (0.011-0.023) IU/mL, 0.042 (0.035-0.049) IU/mL, and 0.049 (0.018-0.133) IU/mL for patients on Q7D, BIW, or TIW prophylaxis, respectively. The predose (trough) FVIII activity levels differed as expected in response to increasing dosing frequency.

### 3.9 | Treatment satisfaction

For the subgroup of patients who transitioned from Q4D prophylaxis in pathfinder2 to BIW prophylaxis in pathfinder8, a significant reduction in total Hemo-SAT Score ( $P < .05$ ) was observed from the start of pathfinder2 to the end of pathfinder8, which was contributed to by all domains. A significant reduction in total Hemo-SAT

Score ( $P < .05$ ) was also demonstrated between the start and end of pathfinder8 for this subgroup of patients on BIW prophylaxis (Figure 3).

## 4 | DISCUSSION

Pathfinder8 was a phase 3 trial investigating the safety and efficacy of N8-GP for prophylaxis and treatment of bleeds in people of all ages with severe hemophilia A who were previously treated with N8-GP. Patients were enrolled from pathfinder2 and pathfinder5 to receive up to 104 weeks of treatment in pathfinder8. Long-term N8-GP prophylaxis demonstrated a good safety profile across all ages, with an average of 1.71 AEs per patient-year of exposure and no patients developing FVIII inhibitors. N8-GP demonstrated high rates of hemostatic success for treatment of bleeds and major surgery,

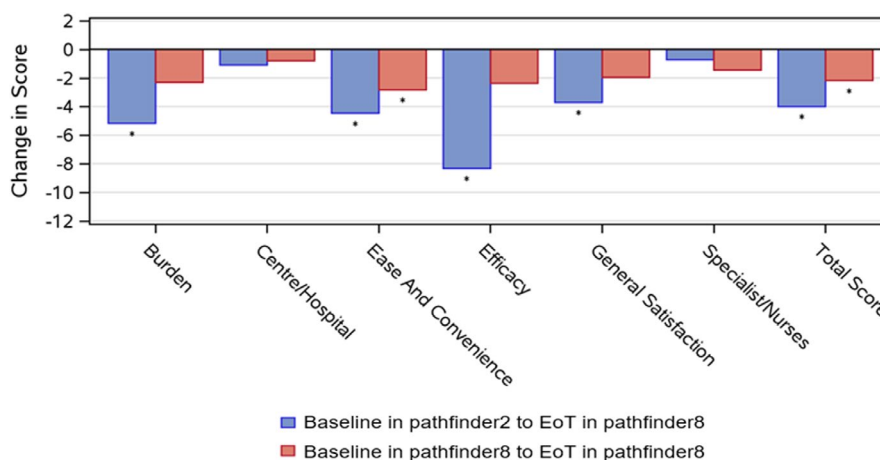


**TABLE 5** Consumption of N8-GP

	Prophylaxis dose frequency			Total
	Q7D	BIW	TIW	
Number of patients	25	135	7	160
Mean (SD) consumption for treatment <sup>a</sup> per patient, IU/kg/y	4050 (468.5)	5424 (559.1)	7740 (710.9)	5220 (828.1)
Mean (SD) consumption for prophylaxis per patient, IU/kg/y	337.5 (39.0)	452.0 (46.6)	645.0 (59.2)	435.0 (69.0)
Average prophylaxis dose				
Number of prophylaxis doses	2381	24434	1195	28013
Mean (range) prophylaxis dose, IU/kg	75.2 (53.9-84.3)	52.7 (43.8-75.5)	52.1 (51.2-54.0)	55.9 (43.8-84.3)
Average dose for treatment of bleed				
Number of patients	10	61	3	72
Number of bleeds	123	190	14	327
Mean (range) dose for treatment of bleed, IU/kg/bleed	91.3 (25.9-325.0)	81.9 (29.7-375.0)	61.1 (52.0-74.6)	83.0 (25.9-375.0)

Abbreviations: BIW, twice weekly; Q7D, once weekly; SD, standard deviation; TIW, three times weekly.

<sup>a</sup>Consumption used for treatment includes all doses given.



**FIGURE 3** Mean change from baseline to end of treatment in total Hemo-SAT Adult Scores for the subgroup of patients who transitioned from Q4D prophylaxis in pathfinder2 to BIW prophylaxis in pathfinder8. \* $P < .05$  for change in score using Wilcoxon signed-rank test. Change in total Hemo-SAT Adult Scores are reported from pathfinder2 trial baseline to end of treatment in pathfinder8 (blue bars;  $n = 64$ ), and from pathfinder8 trial baseline to end of treatment in pathfinder8 (red bars;  $n = 65$ ). Two patients who ended pathfinder2 on Q4D prophylaxis received on-demand treatment at the beginning of pathfinder2. BIW, twice weekly; EoT, end of trial

and was effective for bleed prevention across different regimens. Overall, 55.6% of patients had no treatment-requiring bleeds, and 75.0% had no spontaneous bleeds during the trial (excluding bleeds during surgery).

In pathfinder8, there were no apparent differences in the incidence of AEs or SAEs between each prophylaxis regimens, indicating that long-term N8-GP prophylaxis was well tolerated. No patients developed FVIII inhibitors, which is consistent with the low rate of inhibitor development in pathfinder2 and pathfinder5,<sup>6,8</sup> and similar to findings reported in previously treated patients following long-term treatment with other EHL molecules, including efmoctocog alfa (Eloctate),<sup>17</sup> ruriococog alfa pegol (Adynovate),<sup>18</sup> or

damococog alfa pegol (Jivi).<sup>19,20</sup> In pathfinder8, anti-PEG antibodies were not associated with AEs, and in general the plasma concentration of PEG did not increase over time, which is consistent with results for other PEGylated FVIII molecules.<sup>19,21,22</sup> The AEs of infections and neurological events have been observed in previous studies of people with hemophilia.<sup>23-25</sup>

The hemostatic success rates observed for treatment of bleeds (95.8%) and major surgery (93.5%) were similar to those observed for bleeds in pathfinder2 (83.2%)<sup>6</sup> and pathfinder5 (81.6%).<sup>8</sup> These results compare with hemostatic responses for treatment of bleeds with other EHL FVIII molecules, including efmoctocog alfa ( $\geq 73\%$  of first infusions for the treatment of acute bleeds rated as excellent/

good),<sup>17</sup> rurioctocog alfa pegol (88.6% excellent/good response for hemostatic efficacy),<sup>18</sup> and damoctocog alfa pegol (87.4% hemostatic response in pediatric patients).<sup>20</sup>

In total, five patients had target joints at baseline; for three patients  $\geq 1$  target joints resolved; of these, two patients had all target joints resolved. The mean change in HJHS for all patients was  $-0.17$ , indicating that N8-GP maintained and marginally improved joint health. Maintenance of joint health over time with long-term prophylaxis is consistent with findings observed with other EHL molecules.<sup>17,18,26</sup>

Poisson estimate of mean ABR for overall bleeds with N8-GP was 1.10, which was comparable to pathfinder5 (ABR, 1.08),<sup>8</sup> but slightly lower than pathfinder2 (ABR for Q4D prophylaxis, 2.14; ABR for Q7D prophylaxis, 1.31).<sup>6</sup> The trend for reduction in ABR over time between pathfinder2 and pathfinder8 may in part be attributed to the more frequent prophylaxis regimen administered to most patients during pathfinder8, effectively converting patients to a milder bleeding phenotype. The reduction may also be due to patients receiving long-term regular prophylaxis, as observed with other EHL FVIII molecules whereby ABR decreased over time between the trial's main and extension phases.<sup>17-19,27</sup> Median ABR in pathfinder8 (0.0) was consistent with long-term studies of efmoctocog alfa (median ABR,  $<1.0$ ),<sup>17</sup> rurioctocog alfa pegol (1.62),<sup>18</sup> and damoctocog alfa pegol (1.49).<sup>19</sup>

The post hoc subgroup analysis exploring the effect of transitioning from Q4D prophylaxis in pathfinder2 to BIW prophylaxis in pathfinder8 indicated that patients with an ABR  $>1$  with Q4D prophylaxis had a more marked reduction in ABR following transition to BIW prophylaxis compared with patients who had lower ABRs in pathfinder2. Most patients with an ABR  $>1$  with Q4D prophylaxis demonstrated a reduction in ABR following transition to BIW prophylaxis. These results suggest that although treatment with Q4D prophylaxis is effective for most patients, there might be a small proportion of patients for whom transitioning to BIW prophylaxis could improve efficacy outcomes. These findings support World Federation of Haemophilia recommendations for individualization of prophylaxis based on bleeding phenotype.<sup>1</sup> However, because of the lack of a control group and the nonrandomized trial design, the cause of ABR reduction is undefined, and could be attributed to the change in prophylaxis regimen, the longer duration of prophylaxis, or regression toward the mean, among other factors. Most patients in this subgroup responded well to Q4D prophylaxis, and 63% were without bleeds during the last year of pathfinder2. Most patients with no bleeds on Q4D prophylaxis in pathfinder2 continued to have no bleeds on BIW prophylaxis in pathfinder8, while a few patients experiencing bleeds in pathfinder2 were without bleeds in pathfinder8. An improvement in treatment satisfaction was observed in this subgroup, despite a small increase in infusion frequency.

One limitation of the trial is the lack of baseline joint status data from pathfinder2. This parameter is crucial for assessing joint health before treatment initiation; the lack of data may limit the ability to draw conclusions about change in joint health over time. Another

limitation is the potential for sampling bias because patients enrolled in the trial were those who had received N8-GP treatment previously and were likely already responding well to treatment. Additionally, the relatively low number of patients who received Q7D and TIW prophylaxis may limit the ability to draw definitive conclusions regarding the long-term safety and efficacy of these regimens with N8-GP. Finally, in the post hoc analysis, no control group was available because all patients on Q4D prophylaxis in pathfinder2 had transitioned to other dosing regimens (primary BIW prophylaxis) in pathfinder8, as per the study design.

## 5 | CONCLUSION

Previously N8-GP-treated people of all ages with severe hemophilia A from pathfinder2 and pathfinder5 were enrolled to receive up to 104 weeks of N8-GP prophylaxis in pathfinder8, with the longest observed duration of exposure across pathfinder2 and pathfinder8 of  $\approx 8.4$  years. Long-term prophylactic use of N8-GP appeared to be safe across all age groups in people with severe hemophilia A, with none developing inhibitors against FVIII. N8-GP demonstrated high rates of successful hemostatic response for treatment of bleeding episodes and major surgery. It was effective for bleed prevention across different prophylaxis regimens, with the majority of people experiencing no spontaneous bleeds that required treatment over the entire duration of the trial. Data from the pathfinder8 trial demonstrated that long-term N8-GP appeared to be safe and was efficacious for previously treated people of all ages with severe hemophilia A.

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## RELATIONSHIP DISCLOSURE

SL has received grants, consulting fees, and support for the present manuscript from Novo Nordisk. KK has received payment of honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, and Takeda; and has received support for attending meetings from Novo Nordisk, Pfizer, and Roche. RK has received grants from Bayer, CSL Behring, and Leo Pharma; consulting fees from Bayer, BioMarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, and Takeda; and payment of honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Bayer, BioMarin, Biotest, CSL Behring, Daiichi Sankyo, Grifols, Leo Pharma, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Shire/Takeda, and uniQure. MM has received consultancy fees and support for attending meetings from Novo Nordisk; and payment of honoraria

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#### AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

#### DATA AVAILABILITY STATEMENT

Data sets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union and the United States will be shared with bona fide researchers submitting a research proposal requesting access to data. The access request proposal form and the access criteria can be found at [novonordisk-trials.com](http://novonordisk-trials.com). Data will be available permanently after research completion and approval of product and product use in both the European Union and the United States on a specialized Statistical Analysis System data platform. The analyses available for use will be those as approved by the Independent Review Board (IRB) according to the IRB Charter (see [novonordisk-trials.com](http://novonordisk-trials.com)). Individual participant data will be shared in data sets in a deidentified/anonymized format. In addition, the study protocol and redacted Clinical Study Report will be available according to Novo Nordisk data-sharing commitments.

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## SUPPORTING INFORMATION

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

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