Received: 7 May 2020 | Accepted: 20 July 2020

DOI: 10.1111/jth.15036

ORIGINAL ARTICLE

Long-term safety and efficacy of N8-GP in previously treated pediatric patients with hemophilia A: Final results from pathfinder5

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Funding information
Novo Nordisk A/S

Abstract

Background: N8-GP (turoctocog alfa pegol; Esperoct®, Novo Nordisk A/S, Bagsvaerd, Denmark) is a glycoPEGylated, extended half-life human recombinant factor VIII (FVIII).

Objective: Here, we report end-of-trial safety and efficacy results from the completed N8-GP pathfinder5 trial.

Methods: pathfinder5 (NCT01731600) was a multi-national, open-label, single-arm, non-randomized, non-controlled trial in previously treated male patients aged <12 years old with severe hemophilia A that comprised a main and an extension phase. During the main phase, patients received twice-weekly N8-GP 60 IU/kg for 50 exposure days (~26 weeks). During the extension phase, patients received the same regimen until the end of trial (first patient in main phase, 20 February 2013; trial end, 28 September 2018).

Results: Sixty-eight patients were exposed to N8-GP for a median time of ~4.9 years on regimen. Of the 63 patients who started in the extension phase, 62 completed the trial. No FVIII inhibitors (≥0.6 BU) or other safety concerns were detected. The overall estimated annualized bleeding rate was 1.08 (median 0.81), and nearly 20% of patients had no bleeds during the entire trial. The proportion of patients with no annual bleeds increased with time, with 56% of patients experiencing no bleeds and 86% experiencing no spontaneous bleeds during the fourth year of exposure. All baseline target joints of patients who participated in both phases of this trial were resolved in slightly over 2 years.

Conclusion: Overall, data from the completed pathfinder5 trial show that long-term (median 4.9 years) N8-GP treatment was efficacious and well tolerated in previously treated pediatric patients with severe hemophilia A.

KEYWORDS

child, clinical trial, factor VIII, hemophilia A, turoctocog alfa pegol

Trial Registration – NCT01731600

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 20 July 2020

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1 | INTRODUCTION

Prophylactic factor VIII (FVIII) replacement therapy has been shown to reduce the incidence of bleeding episodes, and resultant complications such as hemophilic arthropathy. Prophylaxis with FVIII concentrate is thus the current standard of care for the treatment of hemophilia A in both adults and children.[1,2]. Compared with standard plasma-derived or recombinant FVIII products, extended half-life (EHL) FVIII products offer the opportunity to reduce the injection frequency and may result in better compliance as well as improve quality of life.

N8-GP (turoctocog alfa pegol; Esperoct®, Novo Nordisk A/S) is a glycoPEGylated human recombinant (r)FVIII with an extended half-life (~1.6-fold in adults and ~1.9-fold in children[3,4]) compared with standard rFVIII products. N8-GP is licensed for prophylaxis and the on-demand treatment of bleeding episodes, as well as the perioperative management of people with hemophilia A. The pathfinder5 trial was a key component of the N8-GP clinical trial program and assessed the efficacy, tolerability, and pharmacokinetics (PK) of N8-GP in previously treated pediatric patients aged <12 years old. The pathfinder5 trial comprised a main phase and an extension phase. Results from the main phase, which encompassed 50 exposure days (EDs) of twice-weekly 60 IU/kg N8-GP treatment, showed a median annualized bleeding rate (ABR) of 1.95, with 42.6% of patients experiencing no bleeding episodes,[4] maintenance or improvement in health-related quality of life (QoL) measure,[5] and good tolerability.[4] Following completion of the main phase, patients could continue prophylactic treatment with N8-GP in an extension phase, totaling up to 5.5 years of treatment.

Here, we report the end-of-trial safety and efficacy results of the combined main and extension phases from the completed pathfinder5 trial.

Essentials

- Pediatric patients with hemophilia A received N8-GP prophylaxis in the pathfinder5 trial.
- Of 68 patients, 62 completed the trial. Median exposure was ~4.9 years. No inhibitors developed.
- Approximately 19% of patients experienced no bleeds during the trial; ~47% experienced no spontaneous bleeds.
- All baseline target joints of patients who participated in the trial resolved.

2 | MATERIALS AND METHODS

2.1 | Trial design

pathfinder5 (ClinicalTrials.gov identifier: NCT01731600) was a multinational, open-label, single-arm, non-randomized, non-controlled trial in previously treated male patients aged <12 years old with severe congenital hemophilia A, comprising a main phase and an extension phase.

Methods and results from the main phase, which began on 20 February 2013, have been previously described.[4] Briefly, each patient participated in the main phase until 50 EDs to N8-GP had been achieved. When the main phase was completed, patients were offered the option to continue treatment in the extension phase, which lasted from the end of the main phase for each patient until trial completion on 28 September 2018 (Figure 1).

During the main phase of the trial, patients received N8-GP ~60 IU/kg (range 50-75 IU/kg) administered by intravenous injection twice weekly for prophylaxis. An increase in dosing frequency to every third day (Q3D) was permitted based on the patient's bleeding pattern. Extra doses of N8-GP were administered if the patient experienced a bleeding episode or for minor surgery. Bleeding episodes were treated with N8-GP 20-75 IU/kg, depending on the severity and location.

Patients continued with the same twice-weekly or Q3D prophylactic regimen during the extension phase. After 12 months' treatment with N8-GP (main and extension phases combined), the investigator was permitted to prescribe extra coverage prior to physical activities. Patients could undergo minor surgical procedures while participating in the trial; patients requiring major surgery were withdrawn. The maximum total daily dose of N8-GP permitted was 200 IU/kg.

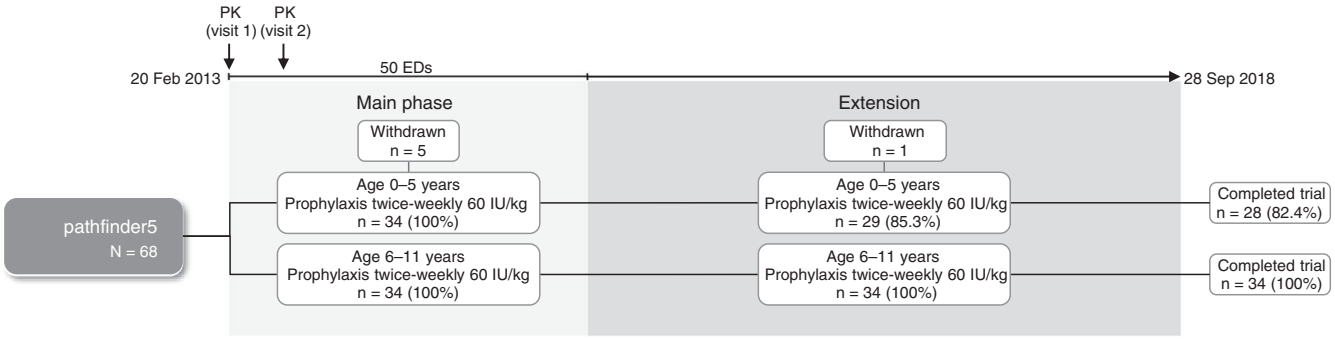


FIGURE 1 Patient disposition in the main and extension phases of the pathfinder5 trial. EDs, exposure days; PK, single-dose pharmacokinetic assessment

The trial was approved according to local regulations by the appropriate ethics committees or institutional review boards and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from each child's legal guardian prior to enrollment. In cases in which a child was able to give their assent to participate, an appropriate assent form was completed.

2.2 | Patients

Full inclusion/exclusion criteria have been published previously.[4] Briefly, this trial included male patients aged <12 years with severe congenital hemophilia A (FVIII activity <1%) previously treated with FVIII products (>150 EDs for patients aged 6-11 years and >50 EDs for those aged 0-5 years). Patients with a history of, or that had any history of FVIII inhibitors, human immunodeficiency virus (HIV), any thromboembolic event, or a platelet count <50 000 platelets/μL were excluded.

2.3 | Objectives, endpoints, and assessments

Detailed methodology for efficacy and safety assessments and clinical visit schedule have been previously described in the main phase publication.[4] Briefly, all patients were required to participate in regular clinic visits throughout both the main phase (~every 5 weeks) and extension phase (~every 3 months) of the trial.

The primary objective was to evaluate the immunogenicity of N8-GP in previously treated pediatric patients with hemophilia A. The incidence of inhibitory antibodies against N8-GP was analyzed using a Nijmegen-modified Bethesda assay[6] capable of identifying antibodies toward N8-GP, as well as rFVIII cross-reactivity (see Meunier et al[4] for details). Analyses of anti-N8-GP binding and anti-polyethylene glycol (PEG) antibodies have been previously described[4].

Safety was assessed as a key secondary endpoint through frequency of adverse events (AEs), serious AEs (SAEs), and medical events of special interests (MESI; defined as inhibitor formation, allergic reactions, thromboembolic events, medication errors, and suspected transmission of an infectious agent via a trial product).

Secondary efficacy endpoints included ABR, the hemostatic effect of N8-GP when used for treatment of bleeds (assessed by the patient or caregiver on a 4-point scale), the consumption of N8-GP during prophylaxis (IU/kg per year and number of injections) and per bleeding episode (IU/kg and number of injections), and the effect of treatment on patient-reported outcomes (PROs). N8-GP efficacy in the treatment of bleeding episodes (hemostatic effect) was assessed using a 4-point scale: excellent, good, moderate, none.[4] "Excellent" and "good" responses were considered as success, while "moderate," "none," and "missing" were considered failure.

Target joint status was also evaluated. A target joint was defined as a single joint with ≥3 bleeding episodes in six consecutive months. Per protocol, a target joint was no longer considered a target joint if there were no bleeding episodes for a consecutive 12 months. The International Society on Thrombosis and Haemostasis (ISTH) definition of target joint resolution, published after this trial was initiated, was used in a post-hoc analysis: "Where there have been ≤2 bleeds into the joint within a consecutive 12-month period, the joint is no longer considered a target joint."[7]

Patient-reported outcome questionnaires were collected prior to N8-GP dosing and at the end of the main phase (~26 weeks). During the extension phase, PRO questionnaires were collected annually. Detailed methods of the questionnaires used and main phase results have been previously published.[5] In short, aged-based versions of the Haemo-QoL questionnaires were distributed to patients in the age groups 4-7 years (Haemo-QoL I) and 8-12 years (Haemo-QoL II) and their parents. The Haemo-QoL questionnaire was collected prior to N8-GP dosing and at the end of the main phase (~26 weeks). During the extension phase, Haemo-QoL was collected annually and at the end of trial. For the assessment of PROs, changes in patient scores using the Haemo-QoL questionnaires over time from baseline to trial end were investigated.

Pharmacokinetic assessments were performed during the main phase of the trial.[4,8]

In addition, pre-dose blood samples (taken at 72 or 96 hours since the last dose) for the determination of FVIII trough level were collected during clinical visits throughout the main and extension phases of the trial. FVIII activity was measured using a chromogenic substrate assay kit (Chromogenix Coamatic Factor VIII [diaPharma, West Chester, PA, USA]), calibrated using a product-specific standard.

2.4 | Statistical analyses

The safety analysis set and the full analysis set were identical and included all patients exposed to N8-GP.

The FVIII inhibitor rate was calculated by dividing the number of patients with positive inhibitors by the number of patients with at least 50 EDs. The one-sided 97.5% upper confidence limit was based on exact calculations in the binomial distribution.

Annualized bleeding rate was estimated using a Poisson regression model with log (prophylaxis duration) as offset and estimating over-dispersion by Pearson's scale. The estimated ABR was presented together with a two-sided 95% confidence interval (CI). The hemostatic effect was analyzed as success rate using logistic regression, accounting for repeated measures for each patient and assuming a compound symmetry working correlation.

Trough levels were calculated by mixed-model analysis on the log-transformed plasma activities with age group as fixed effect and patient as a random effect.

Results are presented by age as follows: 0-5 years old, 6-11 years old, and total.

3 | RESULTS

3.1 | Patients

Overall, of the 68 patients enrolled in pathfinder5, 63 patients completed the main phase and enrolled in the extension phase. Sixty-two patients completed the entire trial (Figure 1). Six patients were withdrawn from the trial, five during the main phase (for full details see Meunier et al[4]). A single patient was withdrawn during the extension phase at parental request after 453 EDs to a prophylaxis regimen due to a perceived lack of efficacy. A total of 23 patients underwent 45 minor surgical procedures during the trial period.

Patient demographics and baseline characteristics (described in Meunier et al[4]) were representative of a pediatric population with severe hemophilia A. Mean baseline age (standard deviation [SD]) was 6.0 years (3.0 [1.3] years in the 0-5 years age group and 8.9 [1.7] years in the 6-11 years age group). For patients previously receiving prophylactic treatment, the mean dose of the previous FVIII product was 33.7 IU/kg and the median ABR was 4.0, while for those previously receiving on-demand treatment the mean dose was 23.3 IU/kg and the median ABR was 12. Six patients (three patients in the 0-5 years age group and three patients in the 6-11 years age group) had clinically significant abnormal findings in the musculoskeletal system at baseline. Thirteen patients (five patients in the 0-5 years age group and eight patients in the 6-11 years age group) had target joints (≥3 bleeds in the joint within 6 months) at baseline, of which one did not continue to the extension phase.

3.2 | N8-GP exposure

Across the entire trial, 68 patients were exposed to N8-GP for a total of 305.72 years on regimen (median 4.9 years per patient). Patients aged 0-5 years were on trial for a median 4.6 years (max, 5.4; median 482.5 EDs per patient), while patients aged 6-11 years were on trial for a median 4.9 years (max, 5.4; median 517.0 EDs per patient). A single patient switched from twice-weekly to Q3D regimen at 80 EDs (no reason for the switch given, and no bleeds at the time of switch).

3.3 | Safety

No FVIII inhibitors (≥0.6 BU) were detected during this trial. The one-sided 97.5% upper confidence limit for the inhibitor incidence was 0.067.

Low-titer N8-GP binding (non-neutralizing) antibodies were reported for two patients during the main phase of the trial. Neither case was associated with AEs (see Meunier et al[4] for full details). As reported for main phase, 21 patients tested positive for anti-PEG antibodies prior to N8-GP exposure.[4] Anti-PEG antibodies had no effect on FVIII activity. Only one patient became positive for anti-PEG antibodies during the trial. All patients who participated in extension phase were negative for anti-PEG antibodies at the end of trial.

A total of 838 AEs were reported in 66 patients over 305.72 patient years of exposure, a rate of 2.74 AEs per patient-year of exposure (Table 1). The most common AEs were upper respiratory tract infection (51 events), nasopharyngitis (37 events), cough (32 events), epistaxis (31 events), pyrexia (26 events), and gastroenteritis (23 events). Overall, there were only 27 AEs classified as nervous system disorders in the entire trial, 22 of which were classified as headache, with the remaining 5 being dizziness, dizziness postural, dyslexia, post-traumatic headache, and tongue biting. A single AE was classified as a renal and urinary disorder (pollakiuria), and a single AE was classified as a hepatobiliary disorder (hepatomegaly).

Patients in the 0-5 years age group experienced a slightly higher rate of AEs than those aged 6-11 years. This was largely due to a higher frequency of AEs reflecting common diseases in small children, such as nasopharyngitis, epistaxis, and cough.

TABLE 1 Summary of AEs during the pathfinder5 trial

	Younger children (0-5 years) (N = 34)	Older children (6-11 years) (N = 34)	Total (N = 68)
Exposure days	14 596	17 542	32 138
All AEs, N (%) [E]	33 (97.1) [429]	33 (97.1) [409]	66 (97.1) [838]
Probably or possibly related	7 (20.6) [12]	4 (11.8) [4]	11 (16.2) [16]
SAEs, N (%) [E]	11 (32.4) [13]	5 (14.7) [5]	16 (23.5) [18]
Probably or possibly related	2 (5.9) [2]	–	2 (2.9) [2]
AEs by severity, N (%) [E]			
Mild	28 (82.4) [345]	32 (94.1) [369]	60 (88.2) [714]
Moderate	26 (76.5) [74]	17 (50.0) [38]	43 (63.2) [112]
Severe	8 (23.5) [10]	2 (5.9) [2]	10 (14.7) [12]
MESI, N (%) [E]	5 (14.7) [10]	5 (14.7) [6]	10 (14.7) [16]

Abbreviations: AE, adverse event; E, number of events; MESI, medical event of special interest; N, Number of patients with adverse event; SAE, serious AE.

Most AEs were of mild or moderate severity, with only 12 events rated as severe AEs (Table 1). Overall, 16 AEs were considered possibly or probably related to treatment, 13 of which occurred during the main phase of the trial.[4]

A total of 18 SAEs were reported in 16 patients (23.5%). Two of these events in two patients were evaluated by the investigator as possibly related to trial product (one patient was withdrawn after severe allergic reaction after his fourth exposure and one patient was withdrawn after bruising associated with minimal trauma) and were reported in the main phase of the trial.[4]

Sixteen MESIs were reported in 10 (14.7%) patients, 9 of which were considered to be possibly or probably related to trial product. Most MESIs occurred during the main phase (see Meunier et al[4] for full details), with three MESIs occurring during the extension phase (two events of allergic edema, both moderate, and one event of mild urticarial; all patients recovered and continued on the trial product).

No thromboembolic events or deaths occurred during the trial. No patients were withdrawn due to AEs during the extension phase (two patients in the 0-5 years age group were withdrawn due to AEs in the main phase; for full details see Meunier et al[4]). Results of laboratory parameters, vital signs, and other safety-related examinations revealed no clinically relevant changes as a result of N8-GP treatment.

3.4 | Bleeding episodes

3.4.1 | Patients with zero bleeds

Overall, 13 (19.1%) patients experienced no bleeding episodes throughout the entire duration of this trial (both main and extension phases; Table 2). A greater proportion of patients aged 0-5 years (23.5%) did not bleed during the trial compared with patients aged 6-11 years (14.7%). With regards to bleeding cause, 47.1% of the total patient population experienced no spontaneous bleeds throughout the trial duration; 26.5% of the total patient population experienced no traumatic bleeds.

The proportion of patients who experienced no bleeding episodes increased with each year of treatment with N8-GP (Figure 2A-C). While approximately 32% of the 63 patients that participated in both the main and extension phases experienced no bleeding episodes during the first year of treatment, approximately 56% during year 4 and approximately 70% during year 5 had no bleeding episodes. This trend was also observed regardless of bleeding cause, with approximately 86% and 89% of patients overall experiencing no spontaneous bleeding episodes in their fourth and fifth years of treatment, respectively (Figure 2C).

TABLE 2 Details of bleeding episodes for pediatric patients with severe hemophilia A receiving prophylactic treatment with N8-GP in the pathfinder5 trial

	Younger children (0-5 years) (N = 34)	Older children (6-11 years) (N = 34)	Total (N = 68)
Patients with bleeds, N (%)	26 (76.5)	29 (85.3)	55 (80.9)
Bleeding episodes, N	108	222	330
Cause of bleed, N (%)			
Spontaneous	30 (27.8)	75 (33.8)	105 (31.8)
Traumatic	75 (69.4)	147 (66.2)	222 (67.3)
After minor surgery[a]	1 (0.9)	–	1 (0.3)
Not known	2 (1.9)	–	2 (0.6)
Site of bleed, n (%)			
Joint	42 (38.9)	122 (55.0)	164 (49.7)
Muscular	17 (15.7)	47 (21.2)	64 (19.4)
Skin	24 (22.2)	32 (14.4)	56 (17.0)
Mouth, gums, nose	9 (8.3)	9 (4.1)	18 (5.5)
Stomach	–	1 (0.5)	1 (0.3)
Other	16 (14.8)	11 (5.0)	27 (8.2)
Classification of bleed, n (%)			
Mild/moderate	106 (98.1)	221 (99.5)	327 (99.1)
Severe	2 (1.9)	1 (0.5)	3 (0.9)
Duration of bleed[b]			
N	85	158	243
Mean hours (SD)	35.6 (41.7)	34.1 (49.7)	34.6 (47.0)

Abbreviation: SD, standard deviation.

[a]Bleed incorrectly categorized as "After minor surgery" for 1 subject; correct category not known.

[b]Duration was only calculated if both the start and stop time of a bleed was reported.

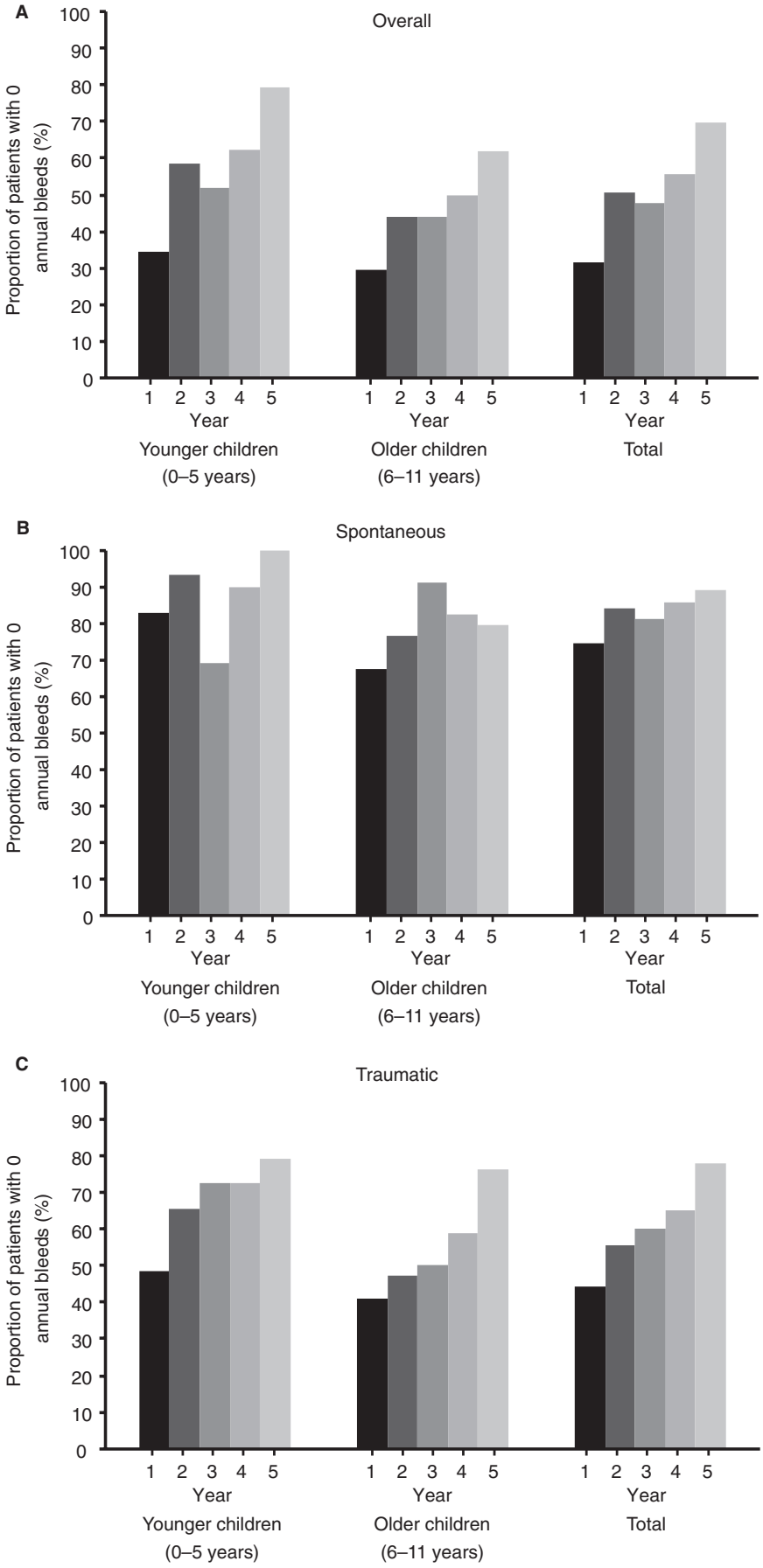


FIGURE 2 Patients with zero annual bleeds during the pathfinder5 trial (n = 63). Proportions of patients with zero (A) overall bleeds, (B) spontaneous bleeds, and (C) traumatic bleeds in a given year of treatment. Only patients who participated in both the main and extension phases of the trial were included in this analysis. Patients were analyzed through the fifth year of treatment or until trial end, whichever came first

3.4.2 | Overall bleeds

Fifty-five patients (80.9%) were treated for 330 bleeds during the trial (Table 2). Only three bleeds (0.9%) were classified as severe (two in patients in the 0-5-year age group and one in the 6-11-year age group). All severe bleeds (one muscle bleed, one joint bleed, and one bleed of the mouth) were traumatic. Hemostatic response was rated as "good" for two patients and "moderate" for one patient. All other bleeds were of mild/moderate severity. Most (67.3%) bleeds were traumatic, with 31.8% spontaneous. The mean duration of bleeds was 35.6 hours (range 0.2-209.6) in children aged 0-5 years and 34.1 hours (0.2-376.0) in those aged 6-11 years.

3.4.3 | Target joint bleeds

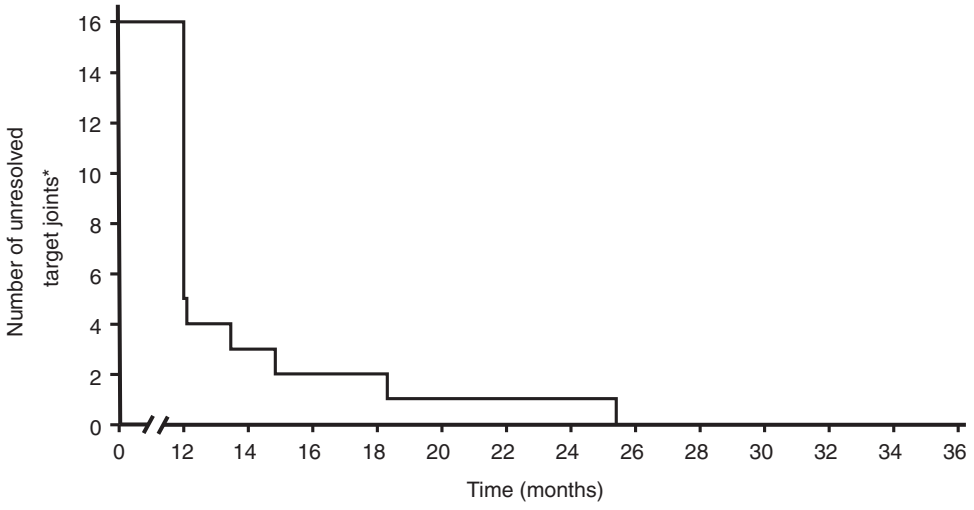
Of the 13 patients who reported a target joint at baseline during main phase, 6 (46.2%) reported no further bleeding episodes in the target joint during the trial. The other 7 patients (53.8%; 1 patient in the 0-5 years age group and 6 patients aged 6-11 years) reported 29 bleeds affecting the target joint. A single patient with no baseline target joints developed new target joints during the ongoing study. His right ankle met criteria for a target joint at 26.3 months and was resolved at 38.3 months. His right elbow met criteria for a target joint at 5.9 months, was resolved as 20.1 months, met criteria again at 28.4 months, and was resolved again at 44.3 months.

3.4.4 | Resolution of baseline target joints using protocol criteria

One patient with a target joint only participated in main phase, which lasted fewer than 12 months and thus was not included in resolution analysis. Thus, a total of 12 patients with 16 total target joints met the baseline target joint criteria. After the first 12 months of treatment, 11 of 16 (68.8%) target joints were considered resolved according to the per-protocol definition (no bleeding episodes for a consecutive 12 months; Figure 3). Fifteen of 16 baseline target joints were resolved within <2 years of treatment, and all baseline target joints reached the per-protocol definition of resolution by 25.4 months of N8-GP treatment (Figure 3).

3.4.5 | Resolution of baseline target joints using ISTH criteria

Using the ISTH definition of target joint resolution (≤2 bleeds within a consecutive 12 months), 14 of 16 (87.5%) target joints were



	Unresolved target joints*			
Age group	Baseline	12 months	24 months	36 months
Total, N** (joints)	12 (16)	4 (5)	1 (1)	0 (0)
0–5 years	4 (6)	1 (1)	0 (0)	0 (0)
6–11 years	8 (10)	3 (4)	1 (1)	0 (0)

FIGURE 3 Baseline target joints over time in pathfinder5. Only patients that participated in main and extension phase are included in the analysis (n = 12 patients with 16 target joints). *A single joint with ≥3 bleeding episodes in 6 consecutive months was defined as a target joint. Per protocol, a target joint was no longer considered a target joint if there were no bleeding episodes within 12 consecutive months. **Only patients who participated in the main phase and extension phase of the trial were included in this analysis

resolved after the first 12 months, which was the earliest possible time point. The remaining two target joints were resolved within 2 years (13.3 months and 22.2 months). Bleeds in baseline target joints of patients who participated in both the main and extension phase are listed in Table S1 in supporting information.

3.5 | Annualized bleeding rate

The overall estimated ABR was 1.08 (0.78 versus 1.33 in patients aged 0-5 and 6-11 years, respectively). The median ABR was 0.81 (0.61 versus 0.93 in the 0-5 and 6-11 years age groups, respectively; Table 3). Overall estimated ABR by cause of bleed was 0.73 for traumatic bleeds and 0.34 for spontaneous bleeds.

3.6 | Hemostatic response

The estimated success rate for the treatment of all bleeding episodes (with missing responses counted as failures) was 81.6% (95% CI: 75.2; 86.7; Table 4). Excluding missing values, the success rate was 83.7% (95% CI: 77.0; 88.8). The estimated success rate for spontaneous bleeds (79.6%) was lower than that for traumatic bleeds (82.7%). Comparable success rates were observed between age groups for both spontaneous and traumatic bleeds.

The hemostatic success rate for the 65 patients who had previously been on prophylactic treatment was 79.9%. Among the three patients who received on-demand treatment prior to trial entry, one patient experienced no bleeds and two (both aged 0-5 years) experienced seven bleeding episodes, which were all treated successfully.

The success rate for bleeding episodes treated within the first 2 hours was 81.5% versus 78.8% for those treated at later time points. Taking into consideration bleed location, treatment success rates ranged from 73.8%-100%.

In total, 291/330 (88.2%) bleeding episodes were treated with ≤2 injections of N8-GP. The mean (range) total dose used for the treatment of bleeds using one or two injections was 78.4 (44.9; 145.5) IU/kg in the 0-5 years age group and 73.6 (29.7; 146.8) IU/kg in the 6-11 years age group. The mean (range) dose used from start to stop of a bleed was 102.8 (44.9; 564.9) IU/kg in the 0-5 years age group and 91.0 (29.7; 344.8) IU/kg in the 6-11 years age group.

There were no apparent differences in N8-GP consumption between age groups. The mean consumption of N8-GP per patient, including prophylaxis (total of 31 685 injections), treatment of bleeding episodes, minor surgeries, and PK doses was comparable between the two age groups: 6779 IU/kg/year in the 0-5 years age group and 6760 IU/kg/year in the 6-11 years age group. The overall mean (median) prophylaxis dose was 64.7 (65.1) IU/kg; 65.4 (66.5) IU/kg in the 0-5 years age group and 64.1 (64.0) IU/kg in the 6-11 years age group.

3.7 | Pharmacokinetics

Results of the two PK assessments (one with previous FVIII product and one with N8-GP) during the main phase of the trial have been published.[4,8] In short, geometric mean half-lives were 13.6 hours for patients aged 0-5 years and 14.2 hours for patients aged 6-11 years; areas under the curve$_{0-inf}$ were 2147 IU/h/dL and 2503 IU/h/dL, respectively.[8] The mean FVIII trough levels (pre-dose FVIII activity) were 1.6 IU/dL (95% CI, 1.2; 2.1 IU/dL) for patients aged 0-5 years

TABLE 3 Annualized bleeding rates in pathfinder5

	Younger children (0-5 years) (N = 34)	Older children (6-11 years) (N = 34)	Total (N = 68)
Bleeds per patient, min; max	0; 11	0; 29	0; 29
Mean treatment period, years	4.088	4.904	4.496
Annualized bleeding rate (ABR)			
ABR, Poisson estimate (95% CI)	0.78 (0.46; 1.30)	1.33 (0.93; 1.91)	1.08 (0.81; 1.44)
Median (IQR)	0.61 (0.20; 1.19)	0.93 (0.20; 2.11)	0.81 (0.20; 1.62)
Spontaneous bleeds	30	75	105
ABR, Poisson estimate (95% CI)	0.22 (0.06; 0.82)	0.45 (0.19; 1.05)	0.34 (0.17; 0.68)
Median (IQR)	0.09 (0.00; 0.22)	0.20 (0.00; 0.41)	0.19 (0.00; 0.31)
Traumatic bleeds	75	147	222
ABR, Poisson estimate (95% CI)	0.54 (0.36; 0.82)	0.88 (0.66; 1.19)	0.73 (0.57; 0.93)
Median (IQR)	0.31 (0.00; 0.87)	0.79 (0.20; 1.44)	0.45 (0.00; 1.11)

Abbreviations: CI, confidence interval; IQR, interquartile range.

TABLE 4 Hemostatic response in pathfinder5

	Younger children (0-5 years)	Older children (6-11 years)	Total
Bleeding episodes, N	108	222	330
Hemostatic response, N (%)			
Excellent	47 (43.5)	96 (43.2)	143 (43.3)
Good	48 (44.4)	74 (33.3)	122 (37.0)
Moderate	9 (8.3)	44 (19.8)	53 (16.1)
None	2 (1.9)	2 (0.9)	4 (1.2)
Missing	2 (1.9)	6 (2.7)	8 (2.4)
Success rate[a]			
Rate (%)	87.1	77.7	81.6
95% CI	76.4; 93.4	69.5; 84.2	75.2; 86.7
Traumatic bleeds, N (%)			
Success	68 (90.7)	113 (79)	181 (81.5)
Failure[a]	7 (9.3)	34 (23.1)	41 (18.5)
Spontaneous bleeds, N (%)			
Success	24 (80.0)	57 (76.0)	81 (77.1)
Failure[a]	6 (20.0)	18 (24.0)	24 (22.9)
Number of injections to treat bleed, N (%)			
≤2	95 (88.0)	196 (88.3)	291 (88.2)
>2	13 (12.0)	26 (11.7)	39 (11.8)

Abbreviation: CI, confidence interval.

[a]"Missing" included as failure. Success rate analyzed using logistic regression accounting for repeated measures within subject and assuming compound symmetry working correlation. Only bleeds treated with N8-GP are included.

and 2.4 IU/dL (95% CI, 1.8; 3.1 IU/dL) for patients aged 6-11 years. Mean trough levels increased slightly over the duration of this study to approximately 3 IU/dL by the study end.

3.8 | Patient-reported outcomes

The change in total scores for Haemo-QoL at the end of trial indicated an improvement in patient QoL as rated by patients aged 4-7 years (change −18.7; SD 17.7) and their parents (−9.7; SD 24.2), and for those rated by patients aged 8-11 years (change −7.6; SD 9.1) and their parents (−10.0; SD 9.7).

4 | DISCUSSION

The analysis of pathfinder5 end-of-trial data assessed the long-term safety and efficacy of N8-GP in previously treated pediatric patients with severe hemophilia A during the course of both the main phase and extension phase of the study, following patients for more than 5 years of treatment with a median of approximately 4.9 years on trial. Overall, in the completed trial, patients were exposed to the trial product for nearly ten times the duration of the main phase[4] and other published pediatric EHL FVIII replacement product trials.[9,10] During this time, no patients developed FVIII inhibitors, resulting in an incident rate of 0.0. Furthermore, no other safety concerns were identified, and no thromboembolic events occurred during the trial. Similarly, the results for laboratory parameters and other safety-related examinations indicated no clinically relevant changes as a result of N8-GP treatment.

In total, 838 AEs were reported in 97.1% of patients in this trial. Patients were on regimen for an approximate median of 4.9 years, resulting in a rate of 2.74 AEs per patient-year of exposure. Furthermore, only 18 SAEs occurred during this trial, 5 in the main phase,[4] meaning that only 13 SAEs—none related to trial product—occurred in 63 patients over an approximate 4.3 years of exposure after the main phase. The two SAEs (cases of hypersensitivity and hemorrhage) that were considered to be possibly or probably related to N8-GP treatment occurred in the main phase.[4] Furthermore, there was only a single withdrawal during the extension phase of this trial.

The end-of-trial safety profile appeared similar for the two age groups assessed. While the incidence of AEs was higher in the 0-5 years age group compared with those aged 6-11 years, this difference was mainly driven by AEs frequently seen in younger children. Thus, we can conclude that N8-GP treatment was well tolerated in this pediatric population during long-term use.

During the main phase of the trial, the median ABR was 1.95[4]a rate comparable to median ABRs observed in pediatric trials of other

EHL FVIII replacement products.[9,10] Analysis of end-of-trial results, however, showed that long-term N8-GP treatment was associated with a lower ABR (median 0.81) than in the main phase, with only one patient withdrawal during the entire extension phase, as mentioned above. This change was driven by a decrease in annual ABR after the first year of N8-GP treatment, possibly indicating a greater level of patient confidence in the trial product in terms of treatment of minor traumas and corroborating the long-term beneficial effects of sustained high FVIII trough levels supported by the twice-weekly N8-GP regimen.

As has been observed with other EHL factor products,[9] the median ABR was slightly lower in the younger children aged 0-5 years (0.61) compared with patients aged 6-11 years (0.93).[9,10] This observation may reflect the more active lifestyle of older children compared with that of younger children, or that older children may be more predisposed to rebleeding in a previously damaged joint.

Furthermore, one fifth of patients enrolled did not bleed during the entirety of this trial, with a higher proportion of younger children (nearly one quarter) experiencing no bleeding episodes. In comparison, during the main phase of the pathfinder5 trial, 43.2% of patients experienced no bleeding episodes. It should be noted that, similar to pediatric trials with other EHL FVIII replacement products,[9,10] patients in the pathfinder5 main phase were only treated for approximately 6 months. Nevertheless, nearly half of patients (47.1%) experienced no spontaneous bleeding events over a median of almost 5 years of N8-GP prophylaxis. Furthermore, the annual proportion of patients experiencing no bleeding episodes increased with long-term treatment. Fifty-six percent of patients experienced no bleeding episodes in the fourth year of treatment and nearly 70% of patients experienced no bleeding episodes during the fifth year of treatment, indicating a possible increase in patient confidence in the trial product and confirming the value of long-term standard prophylactic treatment.

An analysis of target joint resolution in the combined main and extension phases was possible. All target joints among patients that participated in both the main and extension phases of pathfinder5 were resolved. Most target joints (68.8%) were resolved within 12 months, the earliest possible evaluation time point according to the protocol definition of a target joint resolution. Furthermore, the pathfinder5 protocol was written prior to the publication of the ISTH definition of target joint resolution and hence is very stringent by comparison. The ISTH definition, published in 2014, defines target joint resolution as follows: "Where there have been ≤2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint."[7] Using the ISTH definition, 87.5% of target joints were resolved at 12 months, and all target joints were resolved within 2 years of treatment in pathfinder5, with no relapses observed. Target joint resolution has a dual benefit, directly improving long-term health outcomes of patients, while also reducing non-drug-related direct costs associated with severe hemophilia patient care.[11]

When bleeds did occur in pathfinder5, the efficacy of N8-GP was demonstrated by the estimated success rate of 81.6% for the treatment of bleeding episodes, with 88.2% of episodes treated with ≤2 injections and with no significant differences between the two age groups assessed. This represents an improvement compared with the main phase results, in which 79.0% of bleeds were treated with ≤2 injections,[4] possibly reflecting the consistent long-term efficacy of N8-GP. There were no noteworthy differences between the different age groups with regard to the hemostatic effect of N8-GP. The majority of bleeds were traumatic in origin (67.3%) and of mild or moderate severity, with three severe bleeds reported.

Results from the main phase single-dose pharmacokinetic assessment have been previously published.[4,8] However, samples were taken for trough level determination throughout the entire trial. Simple twice-weekly fixed-dose N8-GP prophylaxis maintained mean pre-dose trough levels of 1.6 IU/dL for patients aged 0-5 years and 2.4 IU/dL for patients aged 6-11 years, with a mean prophylaxis dose of approximately 65 IU/kg. These levels are above 1 IU/dL for both age groups, indicating that with this consumption of N8-GP, most children maintained the range of moderate hemophilia A throughout their time in the trial (median time of 4.9 years on regimen). Furthermore, pharmacokinetic predictions at steady state show that children aged 0-11 should have FVIII levels >5 IU/dL approximately 85% of the week.[8] Moreover, after dosing, children on replacement factor therapies, such as N8-GP, can achieve high peak levels of FVIII activity, a distinct advantage associated with replacement factor therapies over non-replacement therapies that may be beneficial when children are involved in high-risk activities.

In conclusion, the pathfinder5 trial followed pediatric patients treated with N8-GP for up to 5.5 years (4.9 median). A simple, fixed-dose regimen maintained adequate FVIII trough levels in both younger and older children. Nearly 20% of children experienced no bleeds during the trial, and the proportion of children that experienced no annual bleeds increased with time on regimen. Data from the completed pathfinder5 trial show that long-term N8-GP treatment was efficacious and well tolerated in previously treated pediatric patients with severe hemophilia A.

ACKNOWLEDGMENTS

The authors thank the patients who participated in the trial and their families, and acknowledge the contribution of all investigators, co-investigators, and trial nurses who were involved in the pathfinder5 trial. The authors would also like to thank Soraya Benchikh el Fegoun and Ekaterina Gresko from Novo Nordisk for their review and input to the manuscript. Medical writing support was provided by Physicians World Europe GmbH, Mannheim, Germany and was financially supported by Novo Nordisk A/S, Denmark. A full list of investigators and countries are provided in the supplementary material.

CONFLICTS OF INTEREST

SST received honoraria as a lecturer, symposium speaker, and/or advisory board member from Takeda, Roche, Octapharma, and Novo Nordisk. ME reports nothing to disclose. GK has received research support from Alnylam, Bayer, Opko Biologics, Pfizer, Shire, and honoraria for consultancy from Alnylam, Bayer, Novo

Nordisk, Pfizer, Roche, and Takeda. AL and CS are employees and stockholders of Novo Nordisk A/S. SK has received research funding from Novo Nordisk, Grifols, Bayer, Bioverativ, and Daichii Sankyo, and is on advisory boards of Novo Nordisk, Bayer, and Bioverativ.

AUTHOR CONTRIBUTIONS

S. Šaulytė Trakymienė, M. Economou, G. Kenet, A. Landorph, C. Shen, and S. Kearney contributed to the writing and review of the manuscript and approved the final version.

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SUPPORTING INFORMATION

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

How to cite this article: Šaulytė Trakymienė S, Economou M, Kenet G, Landorph A, Shen C, Kearney S. Long-term safety and efficacy of N8-GP in previously treated pediatric patients with hemophilia A: Final results from pathfinder5. *J Thromb Haemost*. 2020;18(Suppl. 1):15–25. https://doi.org/10.1111/jth.15036