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REVIEW ARTICLE

An overview of the pathfinder clinical trials program: Long-term efficacy and safety of N8-GP in patients with hemophilia A

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Abstract

N8-GP (turoctocog alfa pegol, Esperoct®; Novo Nordisk A/S, Bagsvaerd, Denmark) is a state-of-the-art, extended half-life factor VIII (FVIII) molecule used for prophylactic and on-demand treatment of patients with hemophilia A. The pathfinder clinical trial program, which began with the pathfinder1 trial in 2010, was developed to assess the long-term efficacy and safety of N8-GP in children, adolescents, and adults. The pivotal pathfinder2 (adolescents and adults) and pathfinder5 (children) trials were completed in late 2018, and comprehensive analyses of the end-of-trial results are published together with this article as part of an N8-GP Supplement. Furthermore, results from the pathfinder3 trial, which was designed to evaluate the safety and efficacy of N8-GP during major surgery, have also recently been finalized. Here, we provide an overview of the pathfinder clinical development program and summarize key data from the completed pathfinder trials. We also provide perspectives on the future of extended half-life FVIII molecules in the treatment of patients with hemophilia A and describe currently ongoing pathfinder trials.

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

1 | INTRODUCTION

N8-GP (turoctocog alfa pegol, Esperoct®; Novo Nordisk A/S, Bagsvaerd, Denmark) is a state-of-the-art, PEGylated recombinant coagulation factor VIII (FVIII) protein that exhibits a prolonged systemic half-life when compared with its unmodified parent molecule N8 (turoctocog alfa, NovoEight®; Novo Nordisk A/S).[1] The pathfinder clinical trial program was established by Novo Nordisk to assess the long-term efficacy and safety of N8-GP in children, adolescents, and adults with hemophilia A. It commenced in September 2010 with pathfinder1 and currently comprises five completed and two ongoing trials. Positive results from the pathfinder program have led to the recent approval of N8-GP for routine prophylaxis and on-demand treatment of acute bleeding in patients with hemophilia A in the EU, United States, Canada, Switzerland, and Japan.[2-6] The pivotal pathfinder2 (adolescents and adults [≥12 years old]) and pathfinder5 (children [<12 years old]) trials were concluded in late 2018, and the primary analysis of the end-of-trial (EOT) results encompassing the entire trial period has now been completed. Additionally, the pathfinder3 trial, which evaluated the hemostatic efficacy and safety of

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N8-GP during surgery, was concluded in December 2018.[7,8] Here, we provide an overview of the pathfinder program, summarize key results from the completed trials (final results from pathfinder2 and pathfinder5 are published together with this article as part of an N8-GP Supplement[9,10]), and discuss the future of extended half-life FVIII molecules in the treatment of patients with hemophilia A.

2 | THE N8-GP MOLECULE

As unmodified FVIII molecules have relatively short circulation half-lives of 8-12 hours,[11] patients with hemophilia on prophylactic treatment regimens require regular infusions three times weekly or every second day to maintain sufficient FVIII levels.[12] In order to reduce the treatment burden for these patients, N8-GP was developed as a modified FVIII molecule with an extended half-life to enable maintenance of higher FVIII levels for longer with fewer injections. N8-GP comprises a single branched 40-kDa polyethylene glycol (PEG) moiety attached to an *O*-linked glycan within the truncated FVIII B-domain of the unmodified parent FVIII molecule N8.[1] PEGylation acts to reduce renal excretion by increasing the size of the molecule and reducing binding to clearance receptors by shielding the protein surface, thereby prolonging circulation half-life.[13] While there is a concern that PEGylated molecules can exhibit reduced activity when compared with their unmodified forms, site-directed PEGylation can be used to target residues that minimize any unexpected negative effects on biological activity, enabling wild type activity levels to be maintained as well as allowing for creation of a chemically homogenous product.[14] Generally, the half-life of a PEGylated molecule can be further extended by increasing the size of the PEG moiety. While use of a 40-kDa PEG moiety improved pharmacokinetic (PK) parameters when compared with 10- or 20-kDa PEG, 80-kDa PEG showed no additional improvement.[1] During thrombin-mediated activation at the site of injury, the B domain harboring the PEG moiety is released from N8-GP to produce an activated FVIII with a primary structure that is identical to native FVIII. Nonclinical studies confirmed that the biochemical functions of N8-GP are maintained after PEGylation, and that the presence of PEG did not affect the hemostatic activity of N8-GP in animal bleeding models.[1,15] The production and formulation of N8-GP does not require the use of human- or animal-derived components.[16] N8-GP also allows for flexibility in storage and patient use. Unopened vials of N8-GP are stable at room temperature (≤30°C) for a single period of up to 12 months, and above room temperature (>30-40°C) for a single period for up to 3 months.[2]

3 | OVERVIEW OF THE PATHFINDER CLINICAL TRIAL PROGRAM

The pathfinder clinical development program was initiated to investigate the PK and long-term efficacy and safety of N8-GP in patients with hemophilia A. The program was one of the first to be designed according to European Medicines Agency (EMA) guidance regarding clinical trials evaluating novel recombinant and plasma-derived FVIII products.[17] An overview of the completed trials, as well as the overall flow of patients through the pathfinder program, are provided in Figure 1. A total of 270 patients from the pathfinder program have been exposed to N8-GP with more than 882 patient years of exposure. Further information on ongoing trials (ie, pathfinder6 and pathfinder8) is provided in the Discussion section.

3.1 | pathfinder1 (first-in-human trial)

The phase I/II pathfinder1 dose-escalation trial (ClinicalTrials.gov identifier: NCT01205724) was initiated in September 2010 in previously treated patients (PTPs) ≥18 years old with severe hemophilia A (Figure 1).[18] Three dose levels were evaluated as part of the pathfinder1 study (25, 50, and 75 IU/kg). Patients were initially recruited to a 25 IU/kg dose cohort and were requested to attend three study visits. Single-dose PK of the patients' previous FVIII product (plasma-derived or recombinant) was assessed during the first study visit. PK properties were evaluated predose and at 30 minutes and 1, 4, 8, 12, 24, 30, and 48 hours postdose. Single-dose PK of N8-GP was then assessed during the second visit at the same dose level. For evaluation of N8-GP, samples were drawn at the same time points as with the patients' previous product, and at 72, 96, 120, 144, and 168 hours postdose. Antibody assessments were completed at visit 3. In subsequent cohorts (50 and 75 IU/kg), dosing with N8-GP was not performed until at least six patients had been treated at the previous dose level and data had been reviewed by a safety group. PK parameters were calculated using standard non-compartmental methods.

3.2 | pathfinder2 (pivotal trial; adolescents and adults)

Starting in January 2012, the phase III, pathfinder2 trial (NCT01480180) was initiated as a multi-center, multi-national, open-label, non-randomized trial evaluating long-term safety, PK, and efficacy of N8-GP when used for on-demand or prophylactic treatment of PTPs ≥ 12 years old with severe hemophilia A. The trial was conducted at 77 sites in 22 countries and comprised a main phase followed by a two-part extension phase (Figure 1). Of the 186 patients enrolled at the beginning of the main phase, 175 received prophylaxis treatment, and 12 were treated on-demand (one patient transferred from on-demand to prophylaxis treatment and is counted in both treatment arms). Most patients on prophylaxis were treated with 50 IU/kg every fourth day (Q4D), which was shortened to twice weekly at the discretion of the investigator.[19] Patients previously receiving on-demand treatment were eligible for inclusion in the on-demand arm in which bleeds were treated with an N8-GP dose of 20-75 IU/kg depending on severity and location. Two single-dose PK sessions were performed during the main phase in a subset of the trial population (after the first dose [visit 2a]

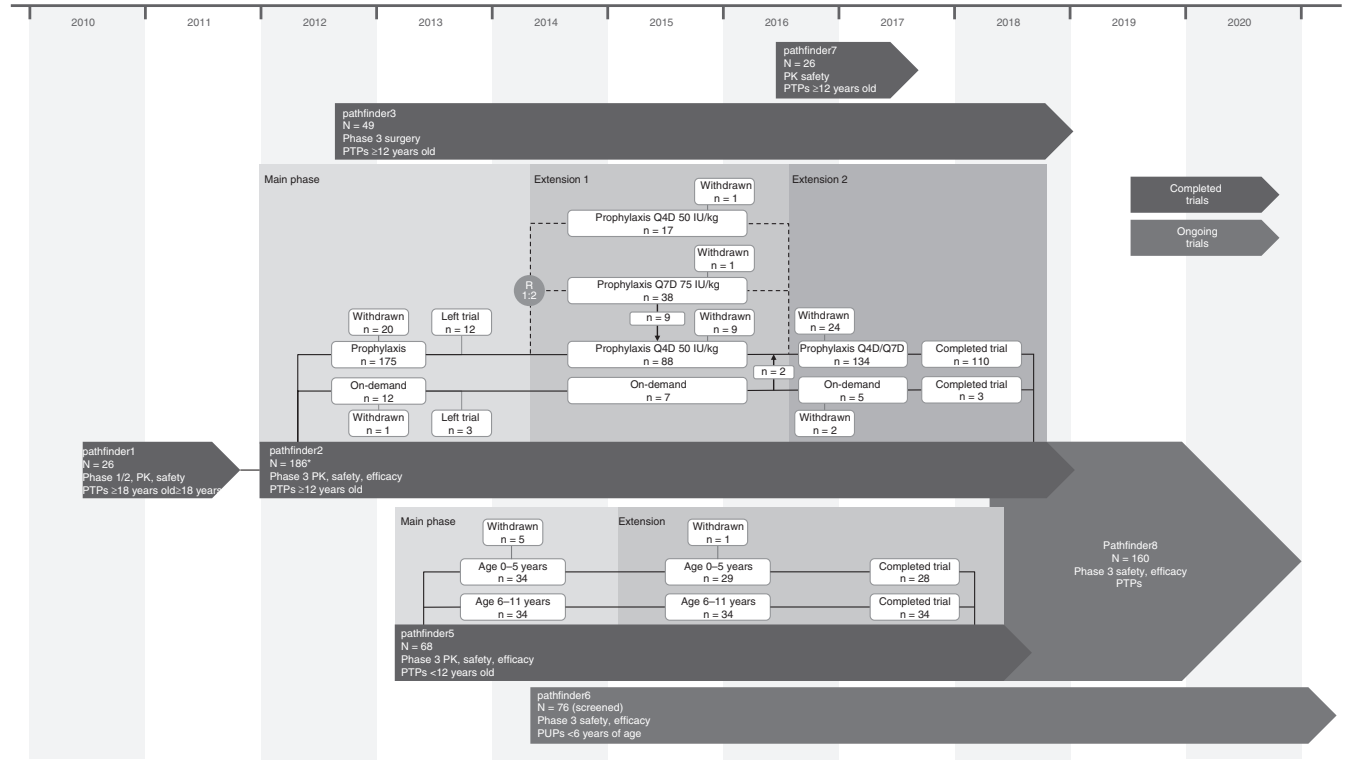

FIGURE 1 Patient disposition during the pathfinder program. Ten patients transferred from pathfinder1 to pathfinder2. Thirty-five patients transitioned between the pathfinder3 surgery trial and pathfinder2. *One patient changed treatment regimen from on-demand to prophylaxis during the main phase and is counted as exposed in both the prophylactic and on-demand arms, but counted only once in the total. PK, pharmacokinetic; PTP, previously treated patient; PUP, previously untreated patients; Q4D, every 4 days; Q7D, every 7 days; R, randomized

and after ~28 weeks of prophylactic treatment [visit 7]). Both sessions were performed after a wash-out period of at least 96 hours and are therefore considered single-dose PK evaluations. An analysis of the main phase results of pathfinder2 has been described previously.[19]

An alternative prophylactic regimen with dosing every 7 days (Q7D) was investigated in part 1 of the extension phase of pathfinder2 in a subset of patients that previously demonstrated low bleeding rates (ie, 0-2 bleeding episodes in the 6-month period preceding the extension phase). Patients were temporarily randomized to one of two N8-GP regimens for 24 weeks; 50 IU/kg Q4D or 75 IU/kg Q7D.[20] Patients progressing into part 2 of the extension phase could transfer to Q4D or Q7D prophylaxis regimens according to predefined criteria, or at the investigator's discretion. Patients on Q4D dosing with 0-2 bleeding episodes in the prior 6 months could switch to a less frequent Q7D regimen. Patients on Q7D who experienced ≥2 spontaneous bleeds or one severe bleed over an 8-week period were switched back to the Q4D regimen.

3.3 | pathfinder3 (surgery trial)

Patients who had received at least five doses of N8-GP and required major surgery at any stage during the pivotal pathfinder2 trial could switch to a separate surgery trial (pathfinder3, NCT01489111; Figure 1).[7] This trial aimed to assess hemostatic efficacy and safety of N8-GP in patients undergoing major surgery. Patients could return to pathfinder2 upon completion or withdrawal from the surgery trial.

3.4 | pathfinder5 (pivotal trial; children)

In February 2013, the first patient visit was completed for the pediatric pathfinder5 trial (NCT01731600), a multi-national, open-label, single-arm, non-controlled trial to assess the safety, efficacy, and PK of N8-GP in pediatric (<12 years old) PTPs. The pathfinder5 trial was conducted at 36 sites in 15 countries. Out of 68 children treated in total, 34 were 0-5 years old at enrollment, and 34 were 6-11 years old. Patients received approximately 60 IU/kg of N8-GP twice weekly. The trial comprised a main phase lasting approximately 26 weeks and an extension phase that was completed in September 2018 (Figure 1). Single-dose PK of the patients' previous FVIII product (plasma-derived or recombinant) and N8-GP were investigated in a subset of patients 0-5 and 6-11 years of age after administration of 50 IU/kg. Results from the pathfinder5 main phase analysis were published in 2017.[21]

3.5 | pathfinder7 (PK trial)

Patients continuing into part 2 of the extension phase of pathfinder2 could also participate in a separate single-dose PK trial (pathfinder7;

NCT02920398), designed to evaluate the PK of an N8-GP molecule produced using an optimized commercial manufacturing process (Figure 1).

4 | OVERVIEW OF KEY RESULTS FROM THE PATHFINDER PROGRAM

Both pathfinder2 (adolescents and adults) and pathfinder5 (children) trials concluded in 2018, and final EOT results covering the entire study periods (main and extension phases) are presented in the accompanying articles within this Supplement.[9,10] In pathfinder2, 186 patients in total (25 adolescents and 161 adults) were exposed to N8-GP for a total of 66 577 exposure days (EDs), with a total trial time of 785 years. In pathfinder5, a total of 68 PTPs (34 younger children [0-5 years old] and 34 older children [6-11 years old]) had 32 138 EDs with N8-GP in a total trial time of 306 years. Final results from the pathfinder3 surgery trial were also recently published by Tosetto et al.[8] Below, we provide a comprehensive overview of the key results from the pathfinder program that confirm the long-term efficacy and safety of N8-GP in children, adolescents, and adults with hemophilia A. A discussion on the potential implications of these results for treatment with N8-GP in the future follows.

4.1 | Efficacy

4.1.1 | Annualized bleeding rates (ABRs) for patients receiving N8-GP prophylaxis

ABRs (number of all bleeds per patient per year) observed during prophylactic treatment with N8-GP were reported as key efficacy endpoints in pathfinder2 and pathfinder5. In the pathfinder2 (adolescents and adults) EOT analysis,[9] estimated ABRs (observed data without imputation) were 2.14 (95% confidence interval [CI]: 1.73-2.65) for patients treated with the Q4D regimen, and 1.31 (95% CI: 0.89-1.92) for patients receiving the Q7D regimen. Imputed ABRs, in which missing data for patients withdrawing prematurely were replaced with projected values to calculate ABRs as if the patients had remained in the study, are reported in the pathfinder2 EOT analysis.[9] In the pathfinder5 (children) EOT analysis,[10] the estimated ABR (observed data without imputation) was 1.08 (95% CI: 0.81-1.44) for patients on a twice-weekly regimen. A comparison of ABR values calculated for the entire trial period with historical ABR data confirmed the prophylactic effect of N8-GP in both trials. When comparing results from the main phases of both pivotal pathfinder trials to EOT data, lower ABRs were observed in the final analysis.[19,21] In addition, overall ABRs were shown to reduce gradually over the duration of both trials (Figure 2).[9,10]

The Q7D dosing regimen was also deemed to be appropriate for adult and adolescent patients exhibiting lower bleeding rates during the pathfinder2 trial. A subanalysis of the pathfinder2 trial by Curry et al indicated that "low bleeders" randomized to N8-GP 50 IU/kg Q4D or 75 IU/kg Q7D dosing regimens in part 1 of the extension phase of pathfinder2 had comparable observed mean ABRs (1.66 versus 1.65 bleeds/patient/year, respectively).[20]

4.1.2 | Hemostatic response to bleeding

The hemostatic effect of N8-GP for treatment of bleeding episodes was confirmed in both the pathfinder2 and pathfinder5 trials.[9,10] In adolescents and adults, 83.2% of all bleeds were successfully treated with N8-GP, and 94.9% were treated with ≤2 doses. In children, 81.6% of all bleeds were successfully treated with N8-GP, and 88.2% were treated with ≤2 doses.

4.2 | Safety

4.2.1 | FVIII inhibitors

The incidence rate of FVIII inhibitors ≥0.6 Bethesda units (BU) was investigated in both pathfinder2 and pathfinder5. As described in the published analysis of the pathfinder2 main phase,[19] one adolescent patient developed FVIII inhibitors to N8-GP (1.3 BU) after 93 EDs. This resulted in an estimated FVIII inhibitor development rate of 0.6%, which is within the expected range for PTPs with hemophilia A.[19] This patient was retested 2 weeks later at a central laboratory, resulting in a FVIII inhibitor measurement of 1.9 BU. While this patient initially continued in the trial, he was eventually withdrawn during the first extension phase (approximately 4 months after the initial discovery of FVIII inhibitors) due to an increasing inhibitor titer of 13.5 BU. FVIII inhibitors disappeared 5 months after withdrawal from treatment with N8-GP, and the patient returned to their previous FVIII treatment with no further issues reported. No other neutralizing antibodies were reported in either adolescents or adults over the course of pathfinder2, and no other patients have developed FVIII inhibitors in the pathfinder program.

4.2.2 | Antidrug and anti-PEG antibodies

Overall, patients enrolled in the pathfinder program demonstrated a low rate of antidrug/anti-PEG antibody development. In pathfinder2 (adolescents and adults), four patients tested positive for non-neutralizing anti-N8-GP antibodies. Of these patients, three had pre-existing antibodies, and one patient tested positive once at a single visit (visit 5) during the main phase. In pathfinder5 (children), two patients were positive for non-neutralizing anti-N8-GP antibodies; one before the first exposure and throughout the trial, and one only at visit 5 (patient was negative between subsequent visits 6-8).

In pathfinder2 (adolescents and adults), 23 patients tested positive for anti-PEG antibodies during the trial. Of these 23 patients, 12

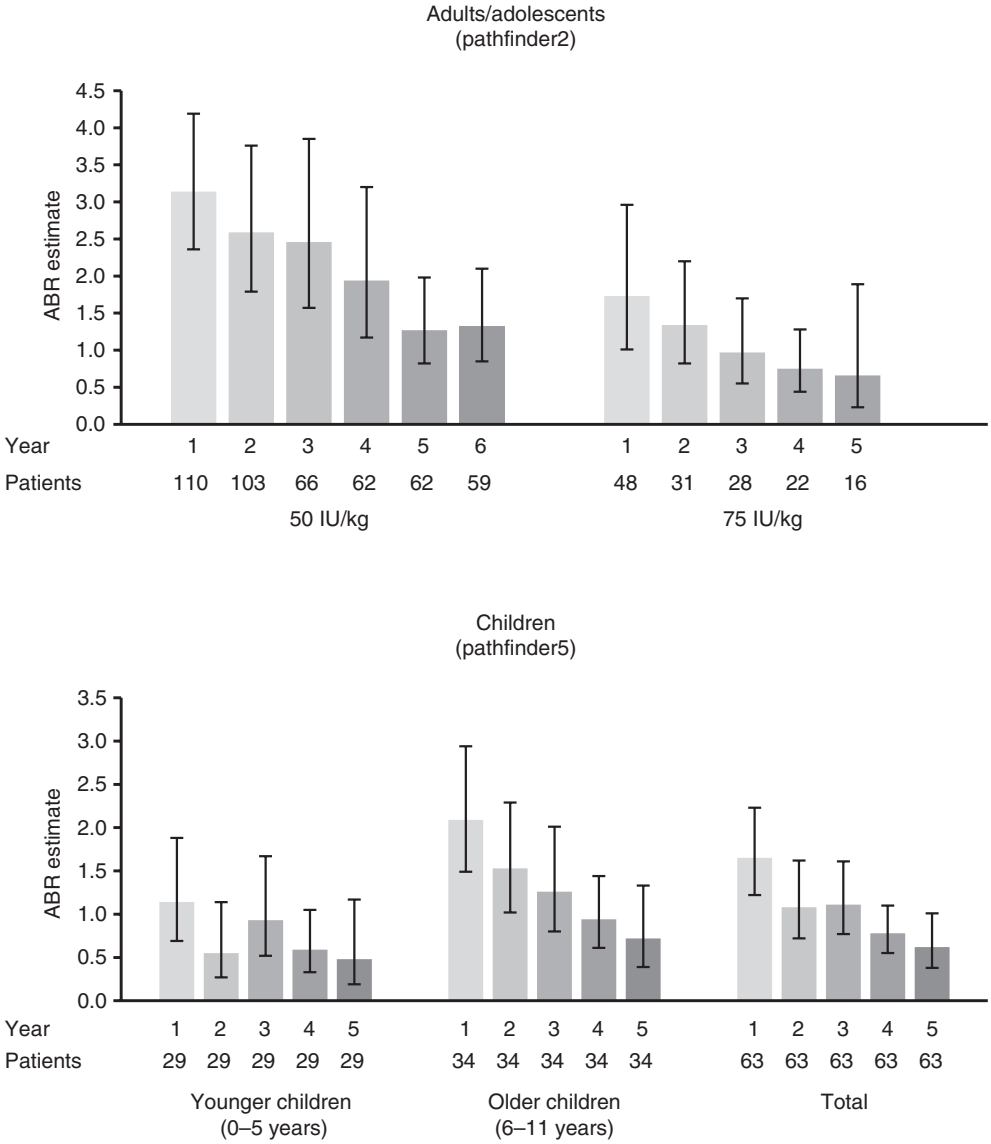

FIGURE 2 Observed ABRs over the duration of pathfinder2 (adults/adolescents) and pathfinder5 (children). ABRs were estimated using a Poisson regression model with log (prophylaxis duration) as offset and allowing for over-dispersion by Pearson's scale. Error bars show 95% confidence intervals. The x-axis represents the amount of time patients were exposed to N8-GP as part of either trial. For pathfinder2, only patients that had continuously received N8-GP on Q4D (50 IU/kg) or Q7D (75 IU/kg) treatment regimens were included in each column. For pathfinder5, only patients who attended both main and extension phases were included. ABR, annualized bleeding rate; Q4D, every 4 days; Q7D, every 7 days

were positive at baseline before being exposed to N8-GP (five were still positive at the last visit, and seven became negative during the trial). There was no consistent pattern to the incidence of anti-PEG antibodies; they occurred at isolated visits, and no pattern in terms of adverse events was noted in relation to the positive anti-PEG antibody tests. Of the 174 patients who tested negative for anti-PEG antibodies at baseline, 163 remained negative throughout the trial. In pathfinder5 (children), 20 patients were positive for anti-PEG antibodies at baseline (visit 1), and 47 were negative. Four patients were positive for low-titer anti-PEG antibodies after exposure to N8-GP, three of whom were also positive prior to N8-GP exposure. Forty-six patients remained negative throughout the trial.

4.2.3 | PK

PK analyses were initially conducted as part of the pathfinder1 trial.[18] Mean terminal half-life was prolonged with N8-GP compared with the patients' previous FVIII standard half-life (SHL) products (19 versus 12 hours). The time to 1% FVIII activity with a 50 IU/kg dose also increased with N8-GP treatment (6.5 versus 3.7 days with FVIII SHL product). Estimated mean incremental recovery at 30 minutes ($IR_{30\,min}$) was 0.025 (U/mL)/(U/kg), and clearance (CL) was 1.79 (mL/h/kg).

A recent publication examined PK data encompassing 108 PK profiles from 69 pediatric, adolescent, and adult patients included

in pathfinder1, 2, 5, and 7.[22] Single-dose geometric mean half-lives were reported for different age groups as 13.6 hours (0-5 years old), 14.2 hours (6-11 years old), 15.8 hours (12-17 years old), and 19.9 hours (≥18 years old). In children, FVIII activity and incremental recovery tended to be lower, the half-life shorter, and the dose-adjusted clearance higher when compared with values for adolescents and adults. Measured mean trough FVIII activity levels were 1.2 IU/dL (95% CI: 0.8-1.6 IU/dL) and 2.0 IU/dL (95% CI: 1.5-2.7 IU/dL) in children 0-5 and 6-11 years old, respectively, receiving 60 IU/kg twice weekly, and 3.0 IU/dL (95% CI: 2.6-3.5 IU/dL) and 2.7 IU/dL (95% CI: 1.8-4.0 IU/dL) in adults and adolescents, respectively, receiving 50 IU/kg Q4D. PK modelling was used to show that children (0-11 years old) receiving 60 IU/kg N8-GP maintain FVIII levels >5 IU/dL for the majority of a 7-day dosing period with both Q3/4D (twice weekly) and Q3D (every third day) dosing regimens (72% and 85% of the time, respectively). Adults and adolescents (≥12 years of age) receiving 50 IU/kg N8-GP were predicted to have FVIII activity >5 IU/dL for 90% of the time with the Q4D (every fourth day) regimen, and 95% of the time with the Q3/4D (twice weekly) regimen. Interestingly, a positive linear relationship was observed between the half-life of N8-GP and von Willebrand factor levels in treated patients.[22]

4.3 | Surgery

A recent publication from Tosetto et al described surgery data from pathfinder3 (adolescents and adults) and pathfinder5 (children).[8] In the pathfinder3 trial, the hemostatic efficacy of N8-GP was rated on a four-point scale as "good" or "excellent" in 95.5% of orthopedic surgical procedures (n = 42/44), and 95.9% of all major surgeries (n = 47/49). A total of 45 minor surgical procedures were also performed during pathfinder5, with no reported complications. No safety concerns were identified over the course of pathfinder3, and no patients tested positive for FVIII inhibitors.

4.4 | Quality of life

Quality of life was assessed in the pivotal pathfinder trials using the HAEM-A-QOL and HAEMO-QOL questionnaires (in adults and children, respectively).[23,24] A lower score in these questionnaires indicates a better quality of life, meaning that negative-score changes from baseline represent an improvement in quality of life over time. Results from the main phase quality of life analysis from both trials have been published previously.[25] For pathfinder2, there were minor improvements in quality of life scores with long-term N8-GP treatment. For patients ≥17 years of age participating in part 2 of the extension phase, the mean change in the overall HAEM-A-QOL score from baseline (ie, visit 1) was −3.1 after 5–<6 years, and −3.5 after 6–<7 years. For pathfinder5, HAEMO-QOL questionnaires were provided to children of different age groups (4-7 years [HAEMO-QOL I] and 8-11 years [HAEMO-QOL II]). Proxy versions of both questionnaires were also provided to the parents of children treated in the trial. There was an overall improvement in the total HAEMO-QOL score as assessed by patients aged 4-7 years (−18.7) and their parents (−9.7), as well as patients aged 8-11 years (−7.6) and their parents (−10.0).

5 | DISCUSSION

5.1 | Concentrations of PEG in plasma

In general, PEGylated molecules can be considered to comprise two distinct moieties: the active protein (in this case rFVIII) and the PEG moiety. In the case of N8-GP, upon activation by thrombin, the PEG moiety is cleaved from the molecule and released back into the circulation intact where it is subsequently excreted in the urine and feces.[26] As PEG and the active component exhibit different kinetics, they are therefore eliminated from the body at different rates. Systemic PEG levels are expected to reach steady state in patients receiving regular N8-GP infusions when the rate of input (dose and frequency of dosing) is in equilibrium with the rate of output (elimination from the body). However, hypothetical concerns have been raised regarding long-term exposure to PEGylated drugs and the potential for PEG to accumulate beyond steady-state levels in some tissues.[27] Recently, a study conducted by Novo Nordisk examined the plasma concentration of PEG in children, adolescents, and adults receiving long-term prophylactic treatment with N8-GP as part of the pathfinder program.[28] This study demonstrated that PEG levels reach steady state in plasma and do not accumulate further beyond expected steady-state levels.

5.2 | Monitoring of N8-GP activity

One-stage (OS) activated partial thromboplastin time (aPTT)-based clotting and chromogenic substrate (CS) assays are commonly used in clinical laboratories to monitor FVIII activity in patients with hemophilia A. A recent field study examining N8-GP in spiked plasma samples demonstrated that all CS assays tested and most OS aPTT assay reagents can be used to accurately measure FVIII activity after administration of N8-GP; however, three OS aPTT assay reagents that contain silica as a contact activator (APTT-SP, TriniCLOT™, STA® PTT Automate) underestimate FVIII activity.[29] A detailed review listing appropriate assay reagents for measurement of N8-GP activity was published recently.[30]

5.3 | Future of N8-GP in clinical practice

Results from the pathfinder program have confirmed the long-term efficacy and safety of N8-GP in PTPs (children, adolescents, and adults). ABR and hemostatic response data show that N8-GP is an efficacious prophylactic treatment for patients with hemophilia A of all ages. Approximately 30% of adolescents/adults from pathfinder2

receiving the Q4D regimen and approximately 19% of all children from pathfinder5 experienced zero bleeds during the trials. In pathfinder5, all baseline target joints resolved during the trial. N8-GP was well tolerated, and there were no unexpected safety concerns reported during the pathfinder program reviewed here. N8-GP can be used safely and effectively in patients undergoing surgical procedures. In addition, patients are able to maintain a good quality of life while receiving N8-GP.

The pathfinder program established that a fixed regimen with an appropriate dose can avoid the need for personalization and PK-tailored regimens. While prophylactic treatment regimens with SHL molecules require intravenous injections approximately 3-4 times per week, results from the pathfinder trials show that less frequent Q4D, twice-weekly, and Q7D regimens with N8-GP are possible and effective in the majority of patients with hemophilia A. Half-life extension was observed throughout the entire population of patients with severe hemophilia A without inhibitors treated with N8-GP. Thus, all patients could potentially benefit from either less frequent injections or the higher trough levels achieved with N8-GP compared with SHL FVIII molecules. Special-interest patient groups, including those requiring very intense prophylaxis with SHL molecules, could potentially benefit from N8-GP in more intense regimens, eg, every other day, based on individual needs.

5.4 | Potential further analyses

While data on younger PTPs have already been obtained from the pathfinder5 trial, additional data are needed for previously untreated patients (PUPs) below 6 years of age. A phase III trial in PUPs <6 years of age with hemophilia A, which will be the final N8-GP trial in children, is currently enrolling by invitation (pathfinder6; NCT02137850). However, it is important to note that due to the concurrent development of several different hemophilia products, limited numbers of PUPs are available for inclusion in clinical trials. While formal trials in PUPs are no longer required by the EMA for recombinant or plasma-derived FVIII products,[17] data are currently being collected to address this patient population.

The phase III pathfinder8 trial (NCT03528551) is also currently active in a number of countries worldwide. pathfinder8 aims to investigate the following dosing regimens over a 2-year period in previously treated children, adolescents, and adults: once weekly (Q1W; 75 IU/kg), twice weekly (50 or 60 IU/kg), and three times weekly (50 IU/kg). Patients <12 years old allocated to receive twice weekly treatment will receive a 60 IU/kg dose, and patients ≥12 years old will receive 50 IU/kg N8-GP. Patients enrolled in pathfinder8 were participating in pathfinder2 or pathfinder5 at the time of transfer. The pathfinder8 trial, which is expected to be completed in December 2020, will provide further long-term follow-up on the use of N8-GP.

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CONFLICTS OF INTEREST

TM: consultancy for Bayer; funding to attend meetings or honorarium by/from Bayer, Takeda/Shire, Novo Nordisk, Bioverative/Sanofi, CSL-Behring, and Chugai. SM: consultancy for Roche, Takeda, Novo Nordisk; funding to attend meetings SOBI, Octapharma, Novo Nordisk, Shire, and Roche/Chugai.

AUTHOR CONTRIBUTIONS

T. Matsushita and S. Mangles contributed to the writing and review of the manuscript and approved the final version.

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