First report of safety and efficacy of a glycoPEGylated rFVIII (N8-GP) in previously treated pediatric patients with severe hemophilia A: results from the international phase 3 pathfinder™5 trial

P-T-103

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Objective

- To evaluate the safety, efficacy, and pharmacokinetics (PK) of N8-GP when used for prophylaxis and treatment of bleeds in pediatric patients with severe hemophilia A.

Conclusions

- Following twice-weekly N8-GP administration (50–75 IU/kg) for ≥50 exposure days, no patient developed an inhibitor, and no other significant clinical concerns were identified.
- The half-life of N8-GP was extended 1.97-fold compared with that of the patients' previous FVIII product.
- Similar to prior studies in adolescents/adults, the current pathfinder™5 trial demonstrates N8-GP was well tolerated and provided effective hemostatic treatment in pediatric patients.

Introduction

- The standard of care for patients with severe hemophilia A is prophylaxis with factor VIII (FVIII),[1] but repeated dosing can be challenging when treating young children because of the need for venous access.[2]
- To reduce treatment burden, recombinant FVIII (rFVIII) products with an extended half-life have been developed.[3]
- Turoctocog alfa pegol (N8-GP; Novo Nordisk, Bagsværd, Denmark) is an extended half-life glycoPEGylated rFVIII developed to prevent and treat bleeds in patients with hemophilia A.
- pathfinder™5 is a multinational, open-label, non-controlled, single-arm, phase 3 trial evaluating the safety, efficacy, and PK of N8-GP in previously treated pediatric patients.
- In the pivotal phase 3 trial (pathfinder™2), N8-GP was well tolerated and had a low annualized bleeding rate (ABR) when given for prophylaxis and on-demand treatment of bleeds in previously treated adolescent and adult patients with severe hemophilia A.[4]

Methods

- Key inclusion criteria were:
  - Boys aged <12 years with severe hemophilia A (<1% FVIII activity).
  - No history of inhibitors (≥0.6 Bethesda units [BU]).
  - Previously treated with FVIII products (>50 exposure days [EDs] for patients aged 0–5 years; >150 EDs for patients aged 6–11 years).
- Patients were recruited evenly into two age cohorts: 0–5 years and 6–11 years.
- N8-GP prophylaxis was approximately 60 IU/kg twice weekly for ≥50 EDs (dosing every third day was possible based on bleeding patterns).
- Bleeds were treated with 20–75 IU/kg N8-GP, based on bleeding severity/location.

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Primary endpoint

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU.

Secondary safety endpoint

- Frequency of adverse events (AEs), including serious AEs (SAEs).

Secondary efficacy endpoints

- Hemostatic effect for the treatment of bleeds (four-point categorical scale: excellent, good, moderate, and none).
- Hemostatic effect during prophylaxis (number of treatment-requiring bleeds, ABR).
- Half-life ratio between the patients' previous FVIII product (blood samples collected from 1–30 hours) and for N8-GP (blood samples collected from 6–96 hours) was calculated.

Results

- N8-GP dosed at 50–75 IU/kg was administered to 68 patients (Table 1). The per-protocol dose was approximately 60 IU/kg, with a dose range of 50–75 IU/kg to enable whole mL dosing.
- Most patients (80.9%) were Caucasian and 15 (22.1%) patients had a target joint (defined as ≥3 bleeds in a period of 6 months in a particular joint) at baseline.

Table 1 Patient demographics and baseline characteristics.

	Age 0–5 years	Age 6–11 years	Total
Number of patients	34	34	68
Age, years, mean (SD)	3.0 (1.3)	8.9 (1.7)	6.0 (3.3)
Weight, kg, mean (SD)	16.1 (3.4)	34.1 (11.5)	25.1 (12.4)
Race, N (%)			
Asian	1 (2.9)	4 (11.8)	5 (7.4)
Black/African American	2 (5.9)	1 (2.9)	3 (4.4)
Caucasian	30 (88.2)	25 (73.5)	55 (80.9)
Other	1 (2.9)	1 (2.9)	2 (2.9)
Not applicable	–	3 (8.8)	3 (4.4)

SD, standard deviation.

Table 2 Adverse events (AEs).

	Age 0–5 years			Age 6–11 years			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
All AEs	24	(70.6)	75	26	(76.5)	82	50	(73.5)	157
Mild	19	(55.9)	56	26	(76.5)	75	45	(66.2)	131
Moderate	10	(29.4)	17	5	(14.7)	6	15	(22.1)	23
Severe	2	(5.9)	2	1	(2.9)	1	3	(4.4)	3
Treatment-related	8	(23.5)	11	2	(5.9)	2	10	(14.7)	13
SAEs	3	(8.8)	4	1	(2.9)	1	4	(5.9)	5

%, percentage of patients with AEs; E, number of AEs; N, number of patients with AEs; SAEs, serious AEs.

Primary outcome and secondary safety outcomes

- No patients developed FVIII inhibitors during the trial.
- Five SAEs were reported (all patients recovered, Table 2).
  - Two treatment-related SAEs led to patient withdrawals: severe allergic reaction in one patient, and increasing moderate hemorrhagic symptoms (bruising associated with minimal trauma) in another patient.
- Five patients (7.4%, aged 0–5 years) withdrew:
  - Two SAEs (described above), one treatment-related allergic reaction, one patient with a FVIII inhibitor who was wrongly included, and one patient who was receiving high-dose treatment for synovitis.

Secondary efficacy outcomes

- N8-GP treatment was successful for 78.6% of bleeds in all patients (excellent/good hemostatic response); most bleeds (80.0%) were treated with ≤2 injections.
- A summary of bleeds is shown in Table 3. Twenty-nine (42.6%) patients receiving N8-GP for prophylaxis did not experience any bleeds during the trial.
  - Seventy bleeds were reported, all mild or moderate.
- A summary of ABR is shown in Table 4.
- The half-life ratio between N8-GP and the patients' previous FVIII product was 1.97.

Table 3 Summary of bleeds.

	Age 0–5 years	Age 6–11 years	Total
Number of patients (%)			
With bleeds	19 (55.9)	20 (58.8)	39 (57.4)
With target joints[a]	6 (17.6)	9 (26.5)	15 (22.1)
Without target joint bleeds[b]	4 (66.7)	7 (77.8)	11 (73.3)
Number of bleeds (%)	30	40	70
Spontaneous	9 (30.0)	10 (25.0)	19 (27.1)
Traumatic	20 (66.7)	30 (75.0)	50 (71.4)
After minor surgery	1 (3.3)	-	1 (1.4)
Number of injections to resolve bleeds (%)[c]			
1	18 (60.0)	26 (65.0)	44 (62.9)
2	5 (16.7)	7 (17.5)	12 (17.1)
3	2 (6.7)	6 (15.0)	8 (11.4)
>3	5 (16.7)	1 (2.5)	6 (8.6)

[a]A target joint was defined as ≥3 bleeds in a period of 6 months in a particular joint at baseline. [b]Percentage is out of the number of patients with target joints at baseline. [c]Age and Total columns show the number of bleeds and % of bleeds requiring N8-GP treatment.

Table 4 Annualized bleeding rates (ABR) in pathfinder™5.

	Age 0–5 years	Age 6–11 years	Total
Estimated mean ABR[a] (95% CI)	1.94 (1.10–3.42)	2.30 (1.40–3.75)	2.13 (1.48–3.06)
Median ABR (IQR)	1.94 (0–2.08)	1.97 (0–3.91)	1.95 (0–2.79)

CI, confidence interval; IQR, interquartile range. [a]Poisson regression model.

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Conflict of interest disclosure

SM has received honoraria from Baxalta, Baxter, Novo Nordisk and Pfizer, investigator support from Biogen Sobi, CSL Behring, Novo Nordisk and Pfizer, is a consultant for Baxalta, Baxter and Novo Nordisk, and is a Study Data Monitoring Committee member for Baxalta. **JA** has received speaker fees from BPL and CSL, and travel grants from Baxalta and Grifols, and attended an advisory board for SOBI. **SE** is a full-time employee of Novo Nordisk A/S. **HH** has attended advisory boards for Novo Nordisk, Baxalta, KaketsuKen, and Biogen and has received honoraria from Novo Nordisk, Baxalta, Bayer, Pfizer, Biogen, Kaketsuken, and Chugai. **KK** received research support from and acted as a consultant for Baxalta, Bayer, Novo Nordisk, and Pfizer. **MK** is a full-time employee of Novo Nordisk A/S. **JS** has received honoraria from Baxalta and Emergent Biosolutions. **DLY** has been a local principal investigator for several Novo Nordisk clinical trials and has served on advisory boards for Octapharma. **FA-K**, **OS**, and **LR** have no COI to declare.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT01731600).
The authors acknowledge the medical writing assistance of Jo Fetterman (PAREXEL).
Presented at the World Federation of Hemophilia (WFH) World Congress, July 24–28, 2016, Orlando, FL, USA.

PosterSessionOnline.com
Poster Presented at:
WFH 2016 World Congress
DOI: 10.3252/pso.eu.WFH2016.2016
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