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Turoctocog alfa pegol provides effective management for major and minor surgical procedures in patients across all age groups with severe haemophilia A: Full data set from the pathfinder 3 and 5 phase III trials

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Abstract

Introduction: Turoctocog alfa pegol is a glycoPEGylated recombinant factor VIII (FVIII) with an extended half-life developed for prophylaxis, treatment of bleeds and perioperative management in patients with haemophilia A.

Aim: Evaluate the efficacy and safety of turoctocog alfa pegol treatment for major and minor surgeries in the pathfinder 3 and 5 phase III trials.

Methods: Adults/adolescents aged ≥12 years with severe haemophilia A (FVIII <1%) received perioperative turoctocog alfa pegol treatment planned to achieve FVIII activity levels >80% during major surgery (pathfinder 3). The primary end point was haemostatic efficacy during surgery; secondary end points were blood loss, haemostatic effect postsurgery, consumption, transfusions, safety and health economics. Children (0-11 years) undergoing minor surgeries received 20-75 IU/kg turoctocog alfa pegol at Investigator's discretion (pathfinder 5).

Results: pathfinder 3 included 35 patients undergoing 49 major surgeries. Haemostasis was successful in 47/49 (95.9%) surgeries; two had moderate haemostatic responses. Median (mean) blood loss during major surgery was 75 (322.6) mL. Four bleeds were reported postsurgery; three were successfully treated with turoctocog alfa pegol (one was not evaluated). On the day of surgery, overall mean (median) dose was 75.5 (74.5) IU/kg and mean (median) number of doses was 1.7 (2.0). Five procedures required 11 transfusions on the day of surgery or days 1-6. No safety concerns or inhibitors were identified. Forty-five minor surgeries in 23 children were performed without complications.

Conclusion: Turoctocog alfa pegol was effective for perioperative haemostatic management of major and minor surgeries in patients across age groups with severe haemophilia A.

KEYWORDS

extended half-life, factor VIII, haemophilia A, haemostasis, surgery, turoctocog alfa pegol

1 | INTRODUCTION

Severe haemophilia A is associated with bleeding during surgery.[1-3] Treatment with factor VIII (FVIII) concentrates is required to provide haemostasis during the perioperative period.[2,4] Therapies enabling reduced dosing frequency and FVIII consumption compared with standard FVIII products may allow for modified treatment schedules during surgical procedures, including the potential for reduced hospitalisation times.[5]

Turoctocog alfa pegol (N8-GP; Novo Nordisk) is a glycoPEGylated recombinant FVIII (rFVIII) with an extended half-life (EHL). Turoctocog alfa pegol requires less frequent dosing and has a half-life of up to 1.6-fold longer compared with standard FVIII products.[6-8] Turoctocog alfa pegol was recently approved by the US Food and Drug Administration (adults/adolescents and children)[9] and the European Medicines Agency (adults/adolescents)[10] for prophylaxis, treatment of bleeds and perioperative management in patients with haemophilia. It has demonstrated safety and efficacy in the prophylaxis and treatment of bleeds in adults/adolescents and children with severe haemophilia A in the pivotal phase III pathfinder 2[6] and 5[7] trials. Data on the surgical haemostatic efficacy of rFVIII products with EHL are emerging for major and minor procedures in adults/adolescents[11] and children.[12] Turoctocog alfa pegol has been successfully used in the perioperative prevention and treatment of bleeding during major surgery and control of postoperative bleeds in a limited number of adults/adolescents aged ≥12 years with severe haemophilia A who participated in the pathfinder 3 trial.[5]

With even more patients treated with turoctocog alfa pegol, we now present results from a larger cohort evaluating the surgical haemostatic effect of turoctocog alfa pegol in the completed pathfinder 3 trial. We also report for the first time, results from minor surgeries in children who participated in the completed pathfinder 5 trial.

2 | MATERIALS AND METHODS

2.1 | Patients

Inclusion and exclusion criteria for pathfinder 3 and 5 are described in detail elsewhere.[5,7] In brief, pathfinder 3 included males aged ≥12 years old with severe congenital haemophilia A (FVIII activity <1%) and ≥150 exposure days (EDs) to any FVIII products, who were scheduled for major surgery requiring daily monitoring of FVIII activity and wound status for at least 3 days.[5] pathfinder 5 included males aged <12 years old with severe congenital haemophilia A (FVIII activity <1%) and >50 EDs to any FVIII products if aged ≤5 years old and >150 EDs if aged 6-11 years with a body weight ≥10 kg.[7] Children participating in pathfinder 5 could undergo minor surgeries, such as dental extractions and placement of central venous access ports during the trial.

2.2 | Trial design

pathfinder 3 was a phase III, multinational, open-label, non-randomized, non-controlled trial evaluating the haemostatic efficacy and safety of turoctocog alfa pegol during major surgery in adults/adolescents with severe haemophilia A.[5] Patients from the pivotal pathfinder 2 trial who received turoctocog alfa pegol prophylaxis and scheduled for major surgery were eligible to participate. pathfinder 5 was a phase III, multinational, open-label, non-randomized, non-controlled trial evaluating the safety, efficacy and pharmacokinetics of turoctocog alfa pegol in children with severe haemophilia A.[7] In the paediatric trial, turoctocog alfa pegol was administered twice weekly as prophylaxis to all participants and only minor surgeries were permitted. Both trials were approved by independent ethics committees and institutional review boards and conducted in accordance with the Declaration of Helsinki[13] and Good Clinical Practice guidelines.[14] Written informed consent was obtained from all patients prior to any trial-related activity.

At the pathfinder 3 screening visit, patients received a single dose of turoctocog alfa pegol at 50 IU/kg in order to evaluate incremental FVIII recovery and inform the dosing decisions for the day in surgery in the context of World Federation of Hemophilia (WFH)-recommended FVIII levels for surgery: presurgery (day 0): 80%-100%; and postsurgery days 1-3: 60%-80%; days 4-6: 40%-60%; days 7-14: 30%-50%.[15] On the day of surgery, a planned preoperative loading dose of turoctocog alfa pegol was administered before the start of surgery. Intraoperative and postsurgery turoctocog alfa pegol dosing was at the investigator's discretion.[5] In pathfinder 5, the recommended turoctocog alfa pegol dosing for treatment of bleeds was 20-75 IU/kg, and total daily dose was ≤200 IU/kg body weight according to bleed location and severity; minor surgeries were performed by administering regular prophylaxis or an extra dose presurgery (equivalent to that for a severe bleeding episode or aligned to local practice) to prevent perioperative bleeding at the investigator's discretion.

Final results from the main and extension phases are presented for pathfinder 3 (completion date: 10 December 2018) and pathfinder 5 (completion date: 28 September 2018). Both trials are registered at www.clinicaltrials.gov as NCT01489111 and NCT01731600, respectively.

2.3 | Analytical methods

Blood samples in pathfinder 3 were collected to assess FVIII activity: daily during postoperative days 1-6, at least once during days 7-14 and once weekly thereafter.[5] On days when turoctocog alfa pegol had been administered (when hospitalized/at visits), samples were taken for assessment of predose and 30 minutes postdose FVIII activity; for scheduled visits when dosing did not occur, only FVIII activity was measured. FVIII activity was monitored to adjust the turoctocog alfa pegol dose and maintain WFH-recommended activity levels.[15] Plasma FVIII activity measured with the chromogenic assay with product

specific standard is reported. Inhibitors against FVIII (≥0.6 Bethesda unit [BU]) were measured at screening, presurgery and at trial end using a Nijmegen-modified FVIII Bethesda assay. Samples for measurement of FVIII inhibitors were analysed by the central laboratory.

2.4 | End points

The pathfinder 3 primary end point was haemostatic effect of turoctocog alfa pegol during surgery, evaluated by the investigator/surgeon on the day of surgery using a four-point scale (Table S1). Successful haemostasis was defined as 'excellent' or 'good'.

Secondary efficacy end points were estimated blood loss during surgery, average consumption during surgery and postoperative days 1-6, haemostatic effect of turoctocog alfa pegol for the treatment of bleeds during postoperative days 1-6 and 7-14, and the number of transfusions administered during postoperative days 1-6. Definitions of haemostatic response for the treatment of bleeds were described elsewhere.[16] Successful haemostasis was defined as a rating of 'excellent' or 'good'.

Secondary safety end points were incidence of inhibitors against FVIII (≥0.6 BU), adverse events (AEs) and serious AEs (SAEs). Medical event(s) of special interest (MESI) were collected as part of safety reporting; MESI included medication errors, inhibitors against FVIII, allergic reactions including anaphylaxis, thromboembolic events and suspected transmission of infections via a trial product. Thromboprophylaxis with heparin was allowed if clinically warranted. Health economic end points were length of hospital stay and intensive care days assessed at trial end.

Key efficacy end points in pathfinder 5 relating to minor surgeries were the number of presurgery turoctocog alfa pegol injections and dose (IU/kg) required to resolve bleeds. Haemostatic response was evaluated for treatment-requiring bleed.[7] Safety end points included frequency of AEs/SAEs and occurrence of inhibitors.

2.5 | Statistical methods

For pathfinder 3, no formal sample size calculation was performed, but a sample size of 10-15 patients with severe haemophilia A undergoing at least 15 major surgeries in total was based on European Medicines Agency guidelines.[17] Descriptive statistics were summarized for primary and secondary end points, and all enrolled patients were included in the analyses. For pathfinder 5, no formal sample size calculations were performed; data were analysed descriptively.

3 | RESULTS

3.1 | Patients

In pathfinder 3, 53 surgeries were planned in 36 adults/adolescents (Table 1); all 36 were exposed to turoctocog alfa pegol (Table 1). Of these 36, 35 underwent 49 major surgeries; some underwent more than one surgery. Procedures were cancelled or postponed for four patients; of these, three were performed later. In pathfinder 5, 23 children underwent 45 minor surgeries (Table 1).

TABLE 1 Patient disposition and baseline patient demographics (pathfinder 3 and pathfinder 5)

Characteristics	Adults/adolescents (pathfinder 3)	Children (pathfinder 5)
Full analysis set, n (%)	36 (100.0)	23 (100.0)
Safety analysis set, n (%)	36 (100.0)	23 (100.0)
Withdrawals, n (%)	4 (7.5)	0 (0)
Age at baseline, y		
Median (range)	39.0 (15-69)[a]	8.6 (3-14)
Race, n (%)		
White	30 (83.3)	19 (82.6)
Asian	5 (13.9)	2 (8.7)
Black/African American	1 (2.8)	1 (4.3)
NA	–	1 (4.3)
Body mass index at baseline, kg/m^2		
Mean (SD)	25.5 (4.4)[a]	16.7 (2.1)
Median (range)	24.9 (18.4-36.7)[a]	16.8 (13-21)

Abbreviations: n, number of patients; NA, not applicable; SD, standard deviation.

[a]Based on the number of planned surgeries (n = 53). One patient was aged <18 y (for one surgery), and the rest were aged ≥18 y.

3.2 | Types of surgical procedures

Forty-nine major surgeries in pathfinder 3 were completed in adults/adolescents; 31 of these have not been reported previously.[5] Among 44 orthopaedic procedures, 16 were joint replacements, 11 were arthroscopic interventions and 17 were other orthopaedic interventions; five patients underwent non-orthopaedic surgeries (one bilateral mastectomy, two cholecystectomies, one circumcision and one pseudotumour removal; Figure 1).

Forty-five minor surgeries were reported in 23 children in pathfinder 5: 29 tooth extractions and other minor dental procedures, seven Port-a-Cath-related procedures and nine other minor procedures (Table S2).

3.3 | Haemostatic response during surgery and on the day of surgery

All major surgeries in adults/adolescents were effectively performed with turoctocog alfa pegol treatment per protocol. Haemostasis was successful (rated 'excellent' or 'good') during major surgery in adults/adolescents in 47/49 (95.9%) procedures (Table 2; Table S3). In two surgeries, haemostasis was rated 'moderate'; one was a total hip replacement in a patient with comorbidities

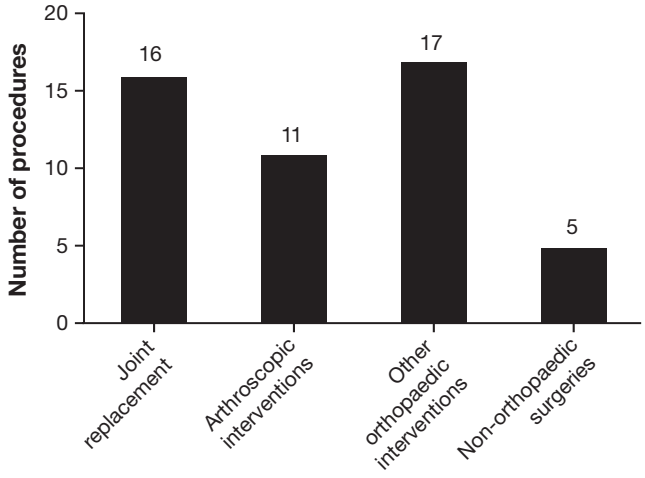

FIGURE 1 Surgical procedures completed in the pathfinder 3 trial (n = 49 procedures in 35 adults/adolescents). Among the 49 major surgeries, three were emergencies and the remaining 46 were elective

(including liver cirrhosis and hypertension) that has been described previously: this patient was both HCV- and HIV-positive and had other multiple comorbidities. He had a platelet count <60 000 on the day of surgery and received a single planned platelet autologous transfusion (see below).[5] The other was a right ankle arthroscopic and open debridement with chondroplasty lasting 1 hour 52 minutes; despite the 'moderate' response, surgery went well (Table S3). Six patients (17.1%) received concomitant tranexamic acid treatment during surgery.

All 45 minor procedures in children during pathfinder 5 were performed with regular prophylaxis or an extra turoctocog alfa pegol dose, without complications (see Safety section below).

3.4 | Haemostatic response postsurgery

During pathfinder 3, four bleeds (all in joints) were reported following major surgeries in adults/adolescents; two during days 1-6 and two during days 7-14 (Table S4). All four of these bleeds were treated with turoctocog alfa pegol. Haemostatic efficacy was rated 'good' or 'excellent' for three, and efficacy was not evaluated for the other, a traumatic bleed treated with extra doses (Table 2; Table S4). FVIII activity levels around the time of each bleed were within the WFH-recommended levels (Table S4).[15]

One of four patients with postoperative bleeds received one blood transfusion (prior to the bleeding episode) on postoperative day 3. The remaining three did not require a transfusion.

Haemostatic response postsurgery in children was not evaluated.

3.5 | Blood loss and transfusions

During pathfinder 3, median (mean) estimated blood loss during major surgery was 75 mL (322.6); range: 0-4520 mL. Estimated blood loss during major surgery for individuals in pathfinder 3 is shown in Figure 2. The patient with comorbidities who underwent a total hip replacement (lasting 2 hours 21 minutes), previously described,[5] had a moderate haemostatic response and blood loss of 4520 mL during surgery, markedly higher than other patients (Figure 2). The median

TABLE 2 Summary data of haemostatic efficacy of turoctocog alfa pegol during surgery and postsurgery, and days in hospital (pathfinder 3)

Parameter	Value
Number of patients	36[a]
Number of patients undergoing surgery	35[b]
Number of surgical procedures	49
Number of bleeds postsurgery	4
Haemostatic response during surgery[c], number of surgical procedures (%)	
N	49
Excellent	25 (51.0)
Good	22 (44.9)
Moderate	2 (4.1)
None	0 (0)
Haemostatic response to treatment of postsurgical bleeding, days 1-6, number of bleeds (%)	
N	2
Good	1 (50.0)
Missing[d]	1 (50.0)
Haemostatic response to treatment of postsurgical bleeding, days 7-14, number of bleeds (%)	
N	2
Excellent	1 (50.0)
Good	1 (50.0)
Postsurgical drainage on day of surgery, mL	
Mean (SD)	435.9 (533.1)
Median (range)	200.0 (5-2200)
Number of days in hospital	
Mean (range)	10.0 (0-39)
Number of days in intensive care[e]	
Mean (range)	0.02 (0-1)

Abbreviation: SD, standard deviation.

[a]Four patients withdrew due to postponement or cancellation of their procedure; three of these then re-entered the trial and underwent surgery.

[b]Eight patients underwent more than one surgery.

[c]'During surgery' is the time from 'knife to skin' until 'last stitch'.

[d]Patient bled into the right knee for several days after surgery and did not receive 'treatment of bleed' doses (even though the bleed was classified as 'severe') because the bleed was classified as a postsurgical bleed. The patient continued with a postsurgical dose and not with a 'bleeding treatment' dose. This is the same patient who suffered two serious adverse events (SAEs) after a total right knee replacement, and these SAEs were rated severe (haemorrhage and surgical wound ischaemia, See Safety section).

[e]One patient was admitted to intensive care for observation.

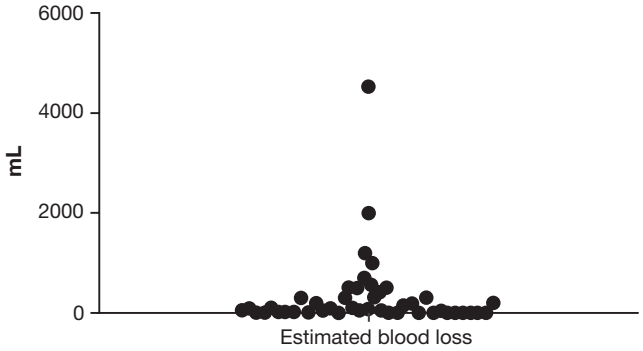

FIGURE 2 Estimated blood loss during major surgery for individuals in the pathfinder 3 trial. Estimated blood loss was reported for the surgery in general and not distinctly during the time from 'knife to skin' until 'last stitch'. One patient with multiple comorbidities and a moderate haemostatic response had markedly higher blood loss (4520 mL) than the other patients[5]

postsurgical drainage on the day of surgery was 200 mL; range: 5-2200 mL (Table 2).

Four patients undergoing five procedures received 11 transfusions (Table 3); all patients who received transfusions had an excellent/good haemostatic response during surgery, except the patient with a hip replacement who had a moderate response, as described.[5]

Blood loss in children undergoing minor surgical interventions was not evaluated.

3.6 | Turoctocog alfa pegol consumption

On the day of major surgery in adults/adolescents, mean (median) preoperative turoctocog alfa pegol dose was 55.7 (51.2) IU/kg (n = 49), postoperative dose was 30.7 (26.2) IU/kg (n = 31) and total dose was 75.5 (74.5) IU/kg (n = 49; Table 4). Only one patient (with the moderate haemostatic response)[5] required an additional intraoperative dose (20.7 IU/kg). After surgery, dosing was at the investigator's discretion. Mean (median) number of doses on the day of surgery was 1.7 (2.0) (Table 4).

For postoperative days 1-6 and 7-14, mean (median) turoctocog alfa pegol daily dose was 33.0 (30.6) and 20.3 (19.3) IU/kg (both n = 49), respectively. Mean (median) number of doses across postoperative days 1-6 and 7-14 was 5.8 (6.0) and 4.5 (4.0), respectively (Table 4).

For minor surgeries in children (pathfinder 5), one turoctocog alfa pegol dose per surgery was given and the mean (median) dose was 65.3 (68.4; for the n = 18 surgeries which received an extra turoctocog alfa pegol dose presurgery).

3.7 | FVIII activity

During pathfinder 3, FVIII activity levels (chromogenic assay results) were within WFH-recommended levels pre, during and postsurgery

TABLE 3 Blood transfusions during and after major surgery (pathfinder 3)

	Transfusion		
Surgery	**Product transfused**	**Quantity**	**Timing**
Left and right knee prosthesis insertion[a]	RBC	2 units	Day of surgery
	RBC	1 unit	Day 1
	RBC	2 units	Day 4
Removal of infected right knee prosthesis[a]	RBC	1 unit	Day 1
	RBC	1 unit	Day 2
Total hip replacement[b]	Autologous blood transfusion	800 mL	Day of surgery
	RBC	2 units	Day 1
	RBC	4 units	Day 3
Laparotomy and excision of psoas pseudotumour[c]	RBC	1 unit	Day 1
	RBC	1 unit	Day 2
Total knee replacement[d]	RBC	1 unit	Day 3

Note: A total of 49 surgical procedures were performed. Four patients undergoing five procedures received 11 transfusions.

RBC, red blood cells.

[a]One patient with epigastralgia, hypertension and osteoporosis underwent two procedures (left and right knee prosthesis insertion; removal of infected right knee prosthesis), both with an excellent haemostatic response.

[b]Patient with multiple comorbidities underwent a total hip replacement, as described previously,[5] with a moderate haemostatic response.

[c]One patient with chronic hepatitis C and right iliopsoas haematoma underwent a laparotomy and excision of psoas pseudotumour with a good haemostatic response.

[d]One patient with gastric reflux, hypertension and eczema underwent total knee replacement with a good haemostatic response.

TABLE 4 Turoctocog alfa pegol consumption (pathfinder 3)

	Presurgery[a] (Day 0)	Postsurgery[b,c]	Day of surgery (total)	Postsurgery days 1-6 (total)[d]	Postsurgery days 7-14 (total)[d]
N	49	31	49	49	49
Turoctocog alfa pegol consumption (IU/kg)					
Mean (SD)	55.7 (10.8)	30.7 (13.7)	75.5 (24.0)	33.0 (10.2)	20.3 (8.7)
Median (range)	51.2 (27.2-86.2)	26.2 (10.1-58.8)	74.5 (27.2-136.2)	30.6 (15.5-59.6)	19.3 (6.5-41.4)
Number of doses received					
Mean (SD)	1.0 (0.0)	1.0 (0.2)	1.7 (0.6)	5.8 (1.4)	4.5 (2.2)
Median (range)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	6.0 (3.0-9.0)	4.0 (1.0-8.0)

Note: One patient who had surgery with a haemostatic effect rated 'moderate' received a single dose of turoctocog alfa pegol (20.7 IU/kg) during the procedure. For this patient, preoperative on day 0, postoperative on day 0, postoperative on days 1-6 and postoperative on days 7-14 turoctocog alfa pegol total doses were 51.8, 20.7, 357.5 and 305.7 IU/kg, respectively. The second patient who had surgery with a haemostatic effect rated 'moderate' received preoperative on day 0 (no postoperative dose on day 0 was given), postoperative on days 1-6 and postoperative on days 7-14 turoctocog alfa pegol doses were 52.0, 183.9 and 104.8 IU/kg, respectively.

Abbreviations: N, number of surgeries requiring turoctocog alfa pegol; SD, standard deviation.

[a]The time from midnight before day of surgery until 'knife to skin'.

[b]The time from last stitch until midnight at day of surgery.

[c]Excluding surgeries in which the patients did not get any doses.

[d]Mean per day per surgery.

(Figure S1). FVIII activity levels were not collected for minor surgeries in pathfinder 5.

3.8 | Safety

No new safety observations were reported with turoctocog alfa pegol treatment in adults/adolescents during major surgeries, and no symptomatic thromboembolic events (or laboratory indications of thromboembolic events) or inhibitor development were reported. During 40 surgeries, 127 AEs were reported (75.5%): 20 AEs in six surgeries (11.3%) were evaluated as being possibly/probably related to turoctocog alfa pegol by the investigator. Most possibly/probably related events (17/20) were mild/moderate in severity, and the outcome was recovered/recovering. Table S5 gives details of these AEs. One non-serious AE (bone pain) was rated severe and judged as possibly related to trial product; two additional SAEs in one patient who underwent a total right knee replacement were rated severe (haemorrhage and surgical wound ischaemia, Table 5).

Five SAEs and two MESI were reported (Table 5). No patients were withdrawn due to AEs. Eight patients received thromboprophylaxis, one of whom experienced a spontaneous bleed in the left knee on days 1-6 (Table S4). In general, AEs seen in pathfinder 3 were considered typical for patients with severe haemophilia A undergoing surgical procedures.

In pathfinder 5, there were eight AEs during minor surgery, all were non-serious, mild/moderate in severity and unlikely to be related to study treatment. All patients recovered except one with pectus carinatum (a congenital disorder diagnosed during the trial); the AE was moderate and considered unlikely related to study treatment. No inhibitors developed during pathfinder 5. All patients with AEs did not change their turoctocog alfa pegol dose.

3.9 | Health economic end point

Mean (range) number of hospital days and intensive care days were 10 (0-39) days and 0.02 (0-1) days, respectively (Table 2 and Table S3).

4 | DISCUSSION

This analysis included results from the largest available data set of surgical procedures in patients of all ages with severe haemophilia A using an EHL FVIII product for haemostasis. Although 18 of the major surgeries in adults/adolescents described here have been previously published,[5] our aim in the current article was to present the complete data set of surgical procedures managed to date with turoctocog alfa pegol in the clinical trial setting. Our results further establish the surgical haemostatic efficacy and safety of turoctocog alfa pegol with an additional 31 major surgeries. In these 49 total surgeries, successful haemostasis was achieved in 95.9% of major procedures in adults/adolescents; two surgeries had a moderate drug response but required no treatment change. Turoctocog alfa pegol provided protection from bleeding during surgery and in the postoperative period in a wide variety of major procedures in adults/adolescents. Importantly, mean (median) number of injections on the day of surgery was 1.7 (2.0), and 5.8 (6.0) and 4.5 (4.0) for postoperative days 1-6 and 7-14, respectively, with potential to decrease treatment burden whilst

TABLE 5 Summary of SAEs and MESI (pathfinder 3)

Type of AE	Description	Severity	Relatedness to trial product	Resolution
SAEs				
Haemorrhage in right leg[a]	Postsurgery days 1-6	Severe	Possible	Recovered with sequelae
Wound ischaemia[a]	Postsurgery days 7-14	Severe	Possible	Recovered
Acute pancreatitis	Before day of surgery	Severe	Unlikely	Recovered
Decreased mobility of right thumb	Postsurgery days 7-14	Moderate	Unlikely	Recovering
Tooth extraction	Before day of surgery	Mild	Unlikely	Recovered
MESI				
Allergic dermatitis	Postsurgery days 1-6	Mild	Unlikely	Recovered
Blister	Postsurgery days 1-6	Mild	Unlikely	Recovered

Abbreviations: AE, adverse events; MESI, medical event(s) of special interest; SAE, serious adverse event.

[a]Both these events were reported at the site of surgery and are related to one surgery. The 'haemorrhage' was described by the investigator as 'major bleeding in the right leg (knee, calf and thigh)' on postsurgery days 1-6. The N8-GP dose was increased, and the event recovered with sequelae. The 'wound ischaemia' was described by the investigator as 'important cutaneous ischaemia (skin near the surgical wound, right knee)' on postsurgery days 7-14. The N8-GP dose was not changed, and the event recovered.

achieving desired therapeutic predose FVIII levels. Minor surgeries in children, the largest data set available, were also successfully managed with regular prophylaxis or an extra turoctocog alfa pegol dose.

Direct comparisons with surgical studies investigating rFVIII products are not feasible due to the limited number of patients, as well as differences in methodologies and parameters. The surgical haemostatic effects of several rFVIII products with EHL have been previously reported, including rFVIIIFc, Eloctate®; Bioverativ Therapeutics Inc), BAX 855 (PEGylated rFVIII, rurioctocog alfa pegol, Adynovate®; Shire), and BAY 94-9027 (PEGylated rFVIII, Jivi®; Bayer). rFVIII Fc was investigated in a phase III trial of 23 major and 52 minor procedures in adults (no major and 10 minor in children) in the perioperative setting.[12] Haemostasis was rated excellent/good in 100% of those assessed for haemostatic response (22 major and 32 minor); 95.7% of procedures could be performed with one rFVIIIFc injection during most major surgeries.[12] Twenty-one major and five minor procedures were reported with BAX 855 treatment, with haemostasis successful in all procedures.[11] Similarly, haemostasis was rated effective for all 26 major surgeries undertaken in adults/adolescents using BAY 94-9027.[18]

In pathfinder 3, postoperative bleeds were reported in 8.2% (n = 4/49) of procedures. In other studies, postoperative bleeds were reported with rFVIIIFc in 4.3% (n = 1/23),[12] with BAX 855 in 23.8% (n = 5/21)[11] and with BAY 94-9027 in 7.7% (n = 2/26)[18] of major/minor surgeries, respectively. A variety of major orthopaedic/non-orthopaedic procedures were successfully performed with turoctocog alfa pegol. Similarly, surgical studies with other EHL products have demonstrated they could be used in a range of procedures, establishing their efficacy irrespective of procedure type.[11,12]

In pathfinder 5, minor procedures were performed in children with regular prophylaxis or an extra turoctocog alfa pegol dose based on the investigator's discretion (mean/median doses were close to the prophylactic doses used in the main phase[7]) administered pre-surgery, which were managed without safety complications. rFVIII products with EHL have shown good efficacy and safety profiles in the treatment of children with haemophilia A.[7,19,20] EHL products have successfully been used in minor procedures, both in adults/adolescents and children. rFVIIIFc was used with 100% success in minor procedures; median number of injections was one in adults/adolescents and two in children.[12]

Due to the heterogeneity of the patient populations, surgeries performed and reporting consumption data, comparisons of the latter between products are not feasible. In the present trial, turoctocog alfa pegol dose was similar on the day of surgery, but the postoperative daily dose and frequency of injections was lower, compared to standard products.[21-23] As such, postoperatively, most patients who received major surgery only needed once-daily turoctocog alfa pegol dosing/one dose ~24 hours and monitoring (from two blood samples) for FVIII activity levels. In addition, mean number of hospital days was 10.0 with 0.02 intensive care days following surgery.

Although we do not have sufficient data on dose interval and number of hospital days for standard products, the reduced injection frequency could have implications for early hospital discharge.[5]

Turoctocog alfa pegol provided FVIII activity levels comparable with other EHL products during surgery and postoperatively; activity levels were consistent with WFH-recommended levels.[15] Adequate FVIII activity levels are important for joint replacement surgeries,[24] which was possible without depending on continuous infusion.[25]

No safety concerns were observed with turoctocog alfa pegol in these trials. Among the five SAEs, two (haemorrhage and wound ischaemia) reported in one surgery were evaluated as possibly related to trial product. Surgery increases the risk of inhibitor development in patients with haemophilia due to the intensive nature of treatment[26]; however, no inhibitor development or thromboembolic events were reported. Other EHL products (BAX 855, rFVIIIFc and BAY 94-9027) were also shown to be well tolerated in the perioperative setting with no inhibitor development,[11-12,18] suggesting that EHL products seem to have a low immunogenicity potential when used during surgery in previously treated patients.[27]

4.1 | Study limitations

Patients' heterogeneity reflects clinical practice and inclusion of patients with comorbidities predisposed to bleeding may be considered a potential limitation. However, the current analysis represents a large collection of data on major/minor procedures in adults/adolescents and children with severe haemophilia A. In pathfinder 5, the analysis was not preplanned and was limited to minor procedures (children in need of major surgery had to be withdrawn from pathfinder 5 as prespecified in the protocol).

5 | CONCLUSIONS

The results from these completed trials provide further evidence for the haemostatic efficacy and safety of turoctocog alfa pegol in the perioperative management and treatment of bleeds during major surgeries in adults/adolescents with haemophilia A, in a simplified dosing frequency and monitoring schedule. Also, turoctocog alfa pegol can be used to manage minor procedures successfully in children without safety complications.

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DISCLOSURES

AT has participated in advisory boards for the following: Novo Nordisk, Roche and Werfen; and Speaker Bureaux of the following: Bayer, Novo Nordisk, Roche, Stago and Werfen. AN has participated in advisory boards for Baxalta (Shire), Genentech, HEMA Biologics and Novo Nordisk; a data and safety monitoring board for Pfizer. SRL has received grant support/personal fees and has served as a paid consultant for Novo Nordisk. ES has participated in advisory boards for Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire/Takeda, SOBI, Spark and Uniqure; and Speaker Bureaux of the following: Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire/Takeda and SOBI. LN has received honoraria from Baxalta (Shire), Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma and Pfizer, and acted as a consultant for Baxalta (Shire), Bayer, CSL Behring and Pfizer. JS has received speaker fees for Bayer, LEO Pharma and Novo Nordisk. KM has received research support from Bayer, Pfizer and Sanquin; speaker fees from Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Sanquin; and consulting fees from Uniqure. PC has received grants/research support from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer and SOBI; and acted as a consultant for Bayer, Baxalta (Shire), Baxter, Bioverativ, Chugai, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Shire and SOBI. CS is an employee of Novo Nordisk A/S. AL is an employee of Novo Nordisk A/S and holds shares with Novo Nordisk A/S. KH has participated in advisory boards for Bayer, Novo Nordisk and Octapharma.

AUTHORS' CONTRIBUTIONS

AT, AN, SRL, ES, LN, JS, KM, PC and KH were the clinical investigators during the trials; CS and AL were involved in the conduct of the trial, in interpretation of trial results and the statistical analysis of the data. All authors directed the data analysis, and the development of the manuscript and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Novo Nordisk's policy on data sharing may be found at https://www.novonordisk-trials.com/how-access-clinical-trial-datasets.

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SUPPORTING INFORMATION

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

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