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Simoctocog alfa (Nuwiq®) in previously untreated patients with severe haemophilia A—Final efficacy and safety results from the NuProtect study

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Abstract

Introduction: Simoctocog alfa (Nuwiq®) is a 4th generation recombinant FVIII with proven efficacy for the prevention and treatment of bleeding episodes (BEs) in previously treated patients with severe haemophilia A. The NuProtect study assessed the immunogenicity, efficacy and safety of simoctocog alfa in 108 previously untreated patients (PUPs). The incidence of high-titre inhibitors was 16.2% and no patients with non-null *F8* mutations developed inhibitors.

Aim: To report the efficacy and safety results from the NuProtect study.

Methods: PUPs received simoctocog alfa for prophylaxis, treatment of BEs, or as surgical prophylaxis. The efficacy of prophylaxis (during inhibitor-free periods) was assessed using annualised bleeding rates (ABRs). The efficacy in treating BEs and in surgical prophylaxis was assessed using a 4-point scale. Adverse events were recorded throughout the study.

Results: Of 108 PUPs treated with simoctocog alfa, 103 received at least one prophylactic dose and 50 received continuous prophylaxis for at least 24 weeks. In patients on continuous prophylaxis, the median ABR was 0 (mean 0.5) for spontaneous BEs and 2.5 (mean 3.6) for all BEs. In 85 patients who had BEs, efficacy of BE treatment was excellent or good for 92.9% (747/804) of rated BEs; 92.3% of BEs were treated with 1 or 2 infusions. The efficacy of surgical prophylaxis was excellent or good for 94.7% (18/19) of rated procedures. There were no safety concerns and no thromboembolic events.

Conclusion: Simoctocog alfa was efficacious and well tolerated as prophylaxis, surgical prophylaxis and for the treatment of BEs in PUPs with severe haemophilia A.

KEYWORDS
FVIII inhibitors, haemophilia A, NuProtect, Nuwiq, simoctocog alfa

What is the new aspect of your work?

Data on the efficacy and safety of FVIII products in previously untreated patients (PUPs) with haemophilia A are limited; this work describes the efficacy and safety of simoctocog alfa in 108 PUPs.

What is the central finding of your work?

Simoctocog alfa was efficacious and well tolerated as prophylaxis, surgical prophylaxis and for the treatment of bleeding episodes in PUPs with severe haemophilia A.

What is (or could be) the specific clinical relevance of your work?

The results of this study can help inform treatment decisions in a population who require long-term treatment.

1 | INTRODUCTION

Patients receiving factor VIII (FVIII) treatment for haemophilia A are classified as previously treated patients (PTPs) or previously untreated patients (PUPs). It is well established that PUPs have a high risk for development of FVIII neutralising antibodies (inhibitors), which interfere with the haemostatic function of the treatment.[1–3] Inhibitors develop in up to 40% of PUPs with severe haemophilia A[4] and have a

negative impact on bleeding rates, morbidity, mortality, quality of life and treatment costs.[5–7]

Simoctocog alfa (Nuwiq®; Octapharma AG) is a fourth generation recombinant FVIII (rFVIII) product[8] produced in a human cell line without chemical modification or protein fusion with the aim of reducing inhibitor development by faithfully replicating the native human FVIII protein.[9–12] The efficacy and safety of simoctocog alfa have been demonstrated in studies of 310 PTPs with severe haemophilia A, including 82 children under 12 years of age, with no inhibitor development.[13–19]

The NuProtect study (NCT01712438, EudraCT 2012-002554-23) assessed the immunogenicity, efficacy and safety of simoctocog alfa in patients without any previous exposure to FVIII concentrates or blood products containing FVIII (i.e., true PUPs) who were treated with simoctocog alfa for 100 exposure days (EDs) or up to 5 years. The immunogenicity results have been reported separately and indicated a low incidence of high-titre inhibitors of 16.2% (26.7% for all inhibitors) and no inhibitor development in patients with non-null *F8* mutations.[20] Here we report the efficacy and safety data from the NuProtect study.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

The NuProtect study was a prospective, multicentre, multinational, open-label, non-controlled, phase III study. Male PUPs with severe haemophilia A (FVIII coagulant activity [FVIII:C] <1%) of any age and ethnicity were treated with simoctocog alfa. Details of the study design have been published previously.[20,21] The trial was approved by all relevant independent ethics committees and institutional review boards and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was provided by the parent/legal guardian of all participants.

2.2 | Study treatment

Patients received simoctocog alfa for prophylaxis, treatment of bleeding episodes (BEs), and for surgical prophylaxis. Patients could switch between prophylaxis and on-demand treatment during the study. The type of treatment and the dose/dosing frequency were determined by the investigator based on the clinical situation of the patient. The recommended dose for prophylaxis was 20–50 international units (IU) FVIII/kg. The dose and duration of treatment of BEs depended on the location and the extent of bleeding as well as the clinical situation of the patient. Dosing recommendations were as follows: minor haemorrhage (superficial muscle or soft tissue and oral bleeds): 20–30 IU FVIII/kg to achieve a target peak level of 40%–60% (dose repeated every 8–24 h until the BE was resolved); moderate-to-major haemorrhage (haemorrhage into muscles, into oral cavity, haemarthrosis, known trauma): 30–40 IU FVIII/kg to achieve a target peak level of 60%–80% (dose repeated every 6–24 h until BE was resolved); major to life-threatening haemorrhage (intracranial, intra-abdominal, gastrointestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma): initial dose of 40–60 IU FVIII/kg to achieve a target peak level of 100%–120% (dose of 20–50 IU FVIII/kg repeated every 6–12 h until BE was resolved). The severity of BEs was recorded by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment).

The dose and duration of treatment for surgical prophylaxis depended on the type of surgery and the patient's individual incremental FVIII recovery. Dosing recommendations were as follows: minor surgeries, including tooth extractions, 25–30 IU FVIII/kg starting within 3 h prior to surgery to achieve a target peak level of >30% (one dose repeated every 12–24 h if needed to maintain trough levels ≥30%); major surgeries, 40–60 IU FVIII/kg within 3 h prior to surgery to achieve a target peak level of approximately 100% (repeated if necessary after 6–12 h initially, and for at least 6–14 days until healing was complete and recurrence of regular treatment was possible) to maintain trough levels >50%.

2.3 | Outcome measures

Annualised bleeding rates (ABRs) were calculated for all patients who received at least one prophylactic dose. ABRs were also calculated for patients who received continuous prophylaxis (defined as prophylaxis for at least 169 calendar days [~24 weeks] without a mixture of on-demand and prophylaxis [except for a single course of on-demand treatment]).

The efficacy of simoctocog alfa in the treatment of BEs was assessed using a 4-point scale. Efficacy was rated at the end of a BE by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment) as follows: excellent (abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion); good (definite pain relief and/or improvement in signs of bleeding within approximately 8–12 h after an infusion requiring up to two infusions for complete resolution); moderate (probable or slight beneficial effect within approximately 12 h after the first infusion requiring more than 2 infusions for complete resolution); none (no improvement within 12 h, or worsening of symptoms, requiring more than 2 infusions for complete resolution).

The overall efficacy of surgical prophylaxis was assessed by the surgeon and haematologist, taking into account both the intra- and post-operative assessment. Major surgery was classified prospectively as requiring general or spinal anaesthesia, requiring opening into the great body cavities in the course of which severe haemorrhage was possible, requiring haemostatic therapy for ≥6 days, orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow and shoulder), third molar extraction or extraction of ≥3 teeth, or surgeries in which the patient's life was at stake. All other surgeries were classified as minor.

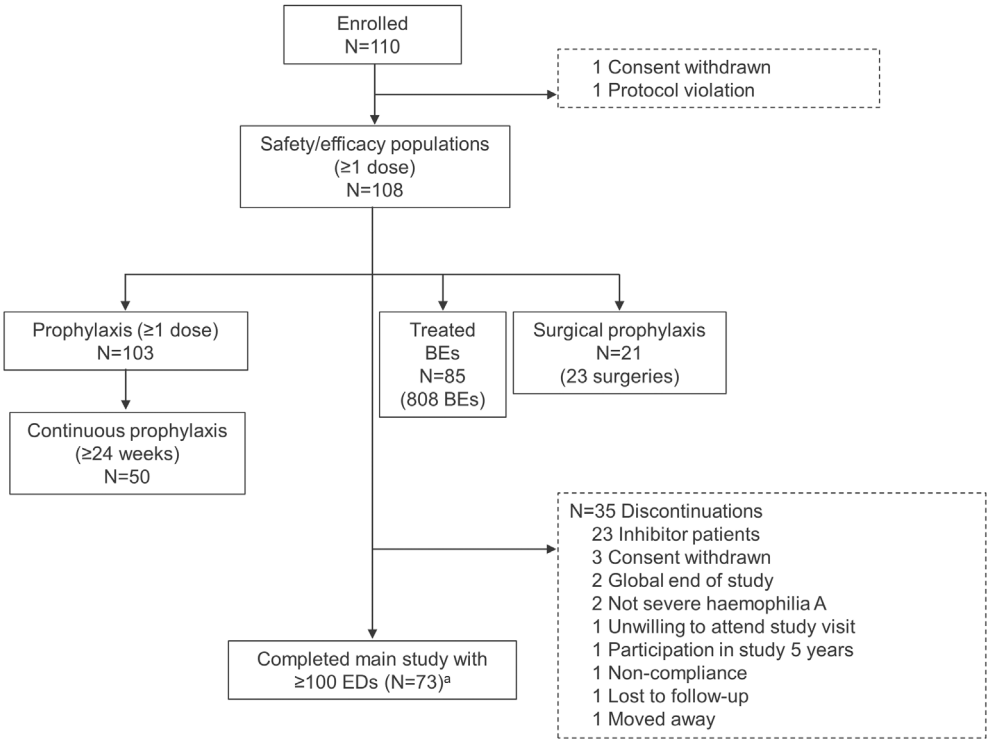

FIGURE 1 Patient disposition and analysis groups. [a]Includes five patients who developed low-titre inhibitors that disappeared without a change in prophylactic treatment and five patients who completed the study with 97–99 EDs due to miscounting of the EDs. BE, bleeding episode; ED, exposure day.

Safety was assessed based on the incidence of adverse events (AEs) during the treatment period. The treatment relatedness of AEs was assessed by the investigator and by the sponsor. Any AEs that occurred within 24 h of simoctocog alfa administration were classified as treatment-related AEs by the sponsor unless concurrent conditions existed that would have been a more likely cause of the AE.

2.4 | Statistical analyses

Statistical analyses of all outcome measures were exploratory. Median (range, interquartile range [IQR]) and mean ± standard deviation (SD) ABR values for all (total), spontaneous, joint (all/spontaneous/traumatic) BEs were calculated. ABRs and 95% confidence intervals (CIs) for all, spontaneous and traumatic BEs were also estimated using a Poisson model. All statistical analyses were performed by Clinipace (Marburg, Germany).

3 | RESULTS

3.1 | Patients

The study was conducted at 38 sites in 17 countries. A total of 110 patients were enrolled, and 108 treated with simoctocog alfa (Figure 1). Baseline demographics are shown in Table 1. Of the 108 treated patients, 103 (95.4%) received at least one prophylactic dose of simoctocog alfa and 50 received continuous prophylaxis. Eighty-five patients received treatment for BEs, and 21 patients underwent 23 surgical procedures. During the study, 28 patients developed inhibitors, of whom five developed transient low-titre inhibitors and continued in the study. For patients who developed inhibitors, efficacy data documented during inhibitor-free periods only were included in the analysis (i.e., the periods before and after inhibitor positive results in the five patients who developed transient low-titre inhibitors and continued in the study, and the period before inhibitor development in the other 23 patients who developed inhibitors were included). AEs were analysed for all 108 treated patients.

The reason for first treatment was to treat bleeding in 46 (42.6%) patients, as prophylaxis in 54 (50.0%) patients, for recovery investigations in 7 (6.5%) patients, and as surgical prophylaxis in 1 (0.9%) patient. In the 10 children under 6 months of age at first treatment, the reason for first treatment was to treat bleeding in 7 (70%), prophylaxis in 2 (20%), and recovery investigation in 1 (10%) patient.

3.2 | Prophylaxis

For the 103 patients who received at least one prophylactic dose, the mean (SD) prophylactic dose was 38.1 (16.1) IU/kg per ED and 67.5 (62.6) IU/kg per week during the study. The mean (SD) number of EDs for prophylaxis was 70.4 (36.8) over 10.5 (6.0) months. The dosing frequency was at the discretion of the treating physician and varied both between patients and over time. The most frequent dosing frequencies were once or twice weekly, accounting for 47% and 23% of patients, respectively, at the start of prophylaxis and 22% and 47% of patients, respectively, at the end of the study. The median (IQR)

TABLE 1 Baseline demographics of all patients treated with simoctocog alfa in the NuProtect study.

Parameter	*n* (%) of patients (unless stated otherwise), *N* = 108
Age at first treatment, months, median (IQR)	12.0 (8.0–23.5)
Age at first treatment	
<1 month	1 (0.9)
1–6 months	9 (8.3)
>6–12 months	47 (43.5)
>12–24 months	25 (23.1)
>24 months	26 (24.1)
Race	
White	89 (82.4)
Asian	14 (13.0)
Native American/Alaska Native	1 (0.9)
Other	4 (3.7)
F8 genotype[a]	
Null mutations	90 (83.3)
Non-null mutations	12 (11.1)
No mutation	2 (1.9)
Missing	4 (3.7)
Family history	
Haemophilia	42 (38.9)
Inhibitors	13 (31.0[b])

Abbreviation: IQR, interquartile range.
[a]*F8* gene mutation data were available for 102 patients. Null mutations were intron 22 inversions (*N* = 47), intron 1 inversions (*N* = 3), nonsense mutations (*N* = 11), splice site mutations (*N* = 4), small duplications (*N* = 6), small deletions (excluding in-frame and within a poly-A run; *N* = 14) and large deletions (*N* = 5). Non-null mutations were missense mutations (*N* = 12).
[b]Percentage of those with a family history of haemophilia.

ABR was 2.8 (0–7) for all BEs and 0 (0–1) for spontaneous BEs (Table 2). For joint BEs, the median (IQR) ABR was 0 (0–1.8) for all joint BEs and 0 (0–0) for spontaneous joint BEs.

In patients who received continuous prophylaxis with simoctocog alfa, the mean (SD) prophylactic dose per ED was 38.2 (16.0) IU/kg and 80.2 (69.2) IU/kg per week. The mean (SD) number of EDs for continuous prophylaxis was 95.7 (8.8) over 12.8 (4.5) months. The median (IQR) ABR was 2.5 (1.1–4.8) for all BEs and 0 (0–0.9) for spontaneous BEs (Table 2). The median (IQR) ABR was 0 (0–1.7) for all joint BEs and 0 (0–0) for spontaneous joint BEs.

3.3 | Treatment of BEs

Of 808 BEs treated with simoctocog alfa, 196 (24.3%) were spontaneous, 584 (72.3%) were traumatic, 4 (0.5%) post-operative and 24 (3.0%) other or unknown. The severity of BEs was classified as follows: 524 (65.1%) were minor, 274 (34.0%) were moderate-to-major, 7 (0.9%) were major to life-threatening BEs and 3 (0.4%) were of unknown severity.

The efficacy of treatment was rated as excellent or good for 747 of 804 (92.9%) BEs with an efficacy rating (Table 3); an efficacy rating was not available for 4 BEs (1 minor BE and 3 BEs of unknown severity). Of 805 BEs with data on the duration of treatment, 754 (93.7%) were controlled within 1 or 2 EDs. Considering that some of the 808 BEs were treated in parallel with other bleeding sites, 756 BEs were included in dosing calculations for which data were available for 753 BEs. The mean dose per BE was 51.3 IU/kg and 695 of 753 (92.3%) BEs were treated with 1 (81.1%) or 2 (11.2%) infusions.

3.4 | Surgical prophylaxis

Twenty-one children underwent 23 surgical procedures for which simoctocog alfa was given as surgical prophylaxis (Table 4). Thirteen procedures were minor and 10 were major.

The mean (SD) number of EDs for surgery was 4.1 (2.5) and 7.6 (2.3) for minor and major procedures, respectively, and the mean (SD) number of infusions was 7.4 (5.0) and 18.1 (8.0), respectively. The mean (SD) pre-surgery dose was 54 (36) IU/kg and 53 (40) IU/kg for minor and major procedures, respectively. The initial dose was administered during surgery in three major procedures. The mean (SD) total dose was 310 (273) and 1049 (430) IU/kg for minor and major procedures, respectively.

Of the 23 procedures, 19 were rated by both the surgeon and haematologist. Efficacy was excellent (15, 78.9%) or good (3, 15.8%) in 18 (94.7%) procedures and moderate in 1 procedure (5.3%).

3.5 | Safety

The 108 patients received a total of 8863 infusions and a mean (SD) total dose of 3125 (2129) IU/kg.

In addition to inhibitor development (28 patients), AEs considered possibly or probably related to the treatment by the investigator and/or the sponsor were pyrexia (18 patients), hypersensitivity (8 patients [2 hypersensitivity, 4 rash, 2 ecchymosis]), anaemia (1 patient), and haemorrhagic anaemia (1 patient). For the 18 patients with pyrexia, all were recorded by the sponsor and only one of these cases was recorded by the investigator. Pyrexia was mild (13 patients) or moderate (5 patients) in intensity and considered possibly related to treatment in 17 patients and probably related to treatment in one patient. The intensity of hypersensitivity was mild in all eight patients (single cases in seven patients, and three cases in 1 patient). Topical corticosteroids were used to treat two cases of rash, and antihistamine therapy was used to treat one case of rash and one case of hypersensitivity. With the exception of one patient with ecchymosis, in whom inhibitors were detected at the time, treatment was continued with no change to the regimen and no further incidences of

TABLE 2 Annualised bleeding rates in patients receiving simoctocog alfa prophylaxis.

	ABR		
Type of BE	**Median (IQR)**	**Mean (SD)**	**Estimated, Poisson (95% CI)**
Any prophylaxis ($N = 102$)[a]			
All BEs	2.8 (0.0–7.3)	4.7 (5.4)	4.4 (3.9, 4.8)
Spontaneous	0.0 (0.0–1.0)	1.0 (2.8)	0.8 (0.7, 1.1)
Traumatic	2.0 (0.0–4.6)	3.3 (4.3)	3.3 (3.0, 3.8)
Continuous prophylaxis ($N = 50$)			
All BEs	2.5 (1.1–4.8)	3.6 (3.8)	3.5 (3.0, 4.1)
Spontaneous	0.0 (0.0–0.9)	0.5 (1.1)	0.5 (0.3, 0.8)
Traumatic	2.1 (0.0–3.4)	2.8 (3.6)	2.8 (2.4, 3.3)

Abbreviations: ABR, annualised bleeding rate; BE, bleeding episode; CI, confidence interval, IQR, interquartile range; SD, standard deviation.
[a]Data were missing for one patient.

TABLE 3 Efficacy of simoctocog alfa in the treatment of BEs.

	Efficacy rating ($N = 804$)[a], *n* (%) of BEs		
Type/severity of BE	**Excellent or good**	**Moderate**	**None**
Any ($N = 804$)	747 (92.9)	51 (6.3)	6 (0.7)
Minor ($n = 523$)	506 (96.7)	13 (2.5)	4 (0.8)
Moderate-to-major ($n = 274$)	237 (86.5)	35 (12.8)	2 (0.7)
Major to life-threatening ($n = 7$)	4 (57.1)	3 (42.9)	0 (0.0)
Joint ($n = 218$)	197 (90.4)	18 (8.3)	3 (1.4)
Non-joint ($n = 586$)	550 (93.9)	33 (5.6)	3 (0.5)

Abbreviation: BE, bleeding episode.
[a]Efficacy ratings were not available for four BEs (1 minor BE and 3 BEs of unknown severity).

hypersensitivity were recorded. The cases of anaemia and haemorrhagic anaemia were of moderate and severe intensity, respectively; both cases were considered related to treatment by the investigator but were considered unrelated to treatment by the sponsor and indicative of haemophilia A.

SAEs considered possibly or probably related to the treatment by the investigator and/or the sponsor were inhibitor development (28 patients), pyrexia (2 patients) and hypersensitivity (rash; 1 patient).

No thromboembolism or severe allergic reaction was recorded. There were no deaths during the study.

4 | DISCUSSION

We present here the final efficacy and safety results of the NuProtect study with simoctocog alfa, a fourth generation human cell-line-derived rFVIII, in PUPs. Simoctocog alfa was effective in the prevention and treatment of BEs, and as surgical prophylaxis, in this patient population. The median ABR during continuous prophylaxis was 0 for spontaneous BEs and 2.5 for all BEs. On-demand/breakthrough treatment was rated as excellent or good for 93% of BEs and 92% of BEs were treated with 1 or 2 infusions, which limited high intensity exposure and may have contributed to the previously reported relatively low inhibitor rate with simoctocog alfa in the NuProtect study.[20] Simoctocog alfa as surgical prophylaxis was rated as excellent or good for 95% of procedures. These data are consistent with data from studies of simoctocog alfa in previously treated adults and children.[13–18]

There are no studies directly comparing different FVIII products in PUPs. Although efficacy data in PUPs for individual FVIII products have been published,[22–24] comparison of data across studies is limited by the fact that all studies were designed primarily to evaluate immunogenicity. The treatment regimens used and study methodology varied considerably across the studies. Haemostatic efficacy of turoctocog alfa prophylaxis was evaluated in 58 PUPs in a prospective study that comprised a main study (≥50 EDs) and an extension phase of up to 100 EDs.[22] The mean duration of prophylaxis was 168 EDs at a mean weekly dose of 68 and 104 IU/kg during the main ($N = 58$) and extension ($N = 49$) phases, respectively. The Poisson-estimated ABR during prophylaxis was 5.5 in the main study and 3.6 in the extension phase. In a prospective study of moroctocog alfa, 45 PUPs who received primary prophylaxis experienced an average of 6 BEs per year.[23] In a recent prospective study of efmoroctocog alfa, median overall ABR was 1.49 in 89 PUPs who received prophylaxis for a median of 91 EDs and with a mean weekly dose of 101 IU/kg.[24] The subject's response to infusions was considered excellent or good for 80% of prophylaxis and 85% of on-demand infusions, and most physician assessments (97%) of the response to treatment were excellent or effective.[24] The efficacy of FVIII in the treatment of bleeds was excellent or good in approximately

TABLE 4 Description of surgical procedures undertaken with simoctocog alfa as surgical prophylaxis.

Surgery severity	Surgery	No. of infusions (EDs)	Pre-surgery dose (IU/kg)	Total dose (IU/kg)	Intraoperative efficacy (surgeon)	Postoperative efficacy (haematologist)	Overall efficacy (surgeon and haematologist)
Minor	Insertion of CVAD	13 (5)	112	1045	Excellent	Excellent	Excellent
	Circumcision	1 (1)	NR	91	Excellent	Excellent	Excellent
	Insertion of CVAD	8 (3)	50	217	ND	ND	ND
	Revision of CVAD	13 (5)	21	271	ND	ND	ND
	Insertion of CVAD	6 (4)	65[d]	237	ND	Excellent	ND
	Circumcision	6 (3)	31	156	Excellent	Moderate	Moderate
	Tooth extraction	1 (1)	21	21	Excellent	Excellent	Excellent
	Scalp haematoma incision	3 (3)	36	107	Excellent	Excellent	Excellent
	Circumcision	7 (6)	63	313	Excellent	Excellent	Excellent
	Insertion of CVAD	13 (6)	89[e]	580	Excellent	Excellent	Excellent
	Insertion of CVAD	2 (1)	125[f]	125	Excellent	ND	ND
	Insertion of CVAD	16 (10)	43	494	Excellent	Excellent	Excellent
	Insertion of CVAD	7 (5)	53	372	Good	Excellent	Good
Major	Insertion of CVAD[a]	12 (5)	0[g]	1348	Excellent	Excellent	Excellent
	Insertion of CVAD[a]	16 (7)	100	1320	Excellent	Excellent	Excellent
	Insertion of CVAD[a]	17 (6)	0[h]	1399	Excellent	Excellent	Excellent
	Insertion of CVAD[a]	18 (7)	58	1047	Good	Good	Good
	Orchiopexy[a,b]	22 (8)	63	1203	Excellent	Moderate	Good
	Ileus surgery[a]	7 (6)	0[i]	271	Excellent	Excellent	Excellent
	Adenoidectomy followed by postectomy[a]	30 (11)	83	1292	Excellent	Excellent	Excellent
	Insertion of CVAD[a,c]	32 (11)	95[j]	1491	Excellent	Excellent	Excellent
	Insertion of CVAD[a,b]	16 (10)	52	647	Excellent	Excellent	Excellent
	Insertion of CVAD[a]	11 (5)	79	472	Excellent	Excellent	Excellent

Abbreviations: CVAD, central venous access device; ED, exposure day; IU, international unit; ND, not done; NR, not reported.
[a]Major classification due to requirement for general or spinal anaesthesia.
[b]Major classification due to requirement for haemostatic therapy for at least 6 days.
[c]Major classification due to possibility of severe haemorrhage.
[d]One dose of 21.6 IU/kg 24 h prior to surgery and one dose of 43.1 IU/kg 45 min before surgery.
[e]One dose of 44.6 IU/kg 4.5 h before surgery and one dose of 44.6 IU/kg 2.5 h before surgery.
[f]One dose of 75 IU/kg 1.5 h before surgery and one dose of 50 IU/kg immediately before surgery.
[g]A dose of 112 IU/kg was administered during surgery.
[h]A dose of 69 IU/kg was administered during surgery.
[i]A dose of 67 IU/kg was administered during surgery.
[j]One dose of 47.6 IU/kg 3.5 h before surgery and one dose of 47.6 IU/kg 1.25 h before surgery.

90% of BEs in studies of turoctocog alfa,[22] moroctocog alfa[23] and octocog alfa.[25,26]

The safety profile of simoctocog alfa in PUPs in the NuProtect study was consistent with that previously reported in PTPs treated with simoctocog alfa,[13–18] with the exception of pyrexia. In NuProtect, treatment-related pyrexia was reported in 18 (16.7%) patients according to the sponsor's assessment and in 1 (0.9%) patient according to the investigator's assessment. In most cases, pyrexia was mild, and classified as possibly related to treatment. In general, pyrexia is expected in young children in a long-term trial. The higher percentage of patients who had pyrexia that was rated as related by the sponsor is likely due to the fact that any AE occurring within 24 h of administration was classified as related unless concurrent conditions existed that would have been a more likely cause of the AE. Overall, treatment was well tolerated, with no thromboembolic AEs or severe allergic reactions.

This analysis has some limitations. Treatment was at the discretion of the investigator and switching between prophylaxis and on-demand regimens was permitted. Thus, it was not possible to pre-specify analyses of different treatment regimens. However, 50 patients received at least 24 weeks of continuous prophylaxis. A Poisson model without correction for overdispersion was used to estimate ABRs. The close agreement between mean ABRs and Poisson-estimated ABRs suggests that any effects of overdispersion were likely to be small. Furthermore, there was no control arm in the

study. The main strength of the analysis is the sample size; the study is the largest prospective study of a single FVIII product in PUPs.

5 | CONCLUSION

Efficacy and safety data from the NuProtect study demonstrate that simoctocog alfa was well tolerated and efficacious for the prevention and treatment of BEs in PUPs. These results, taken together with the low rate of inhibitor development in PUPs[20] and the extensive data on the efficacy and safety in PTPs,[13–18] make simoctocog alfa an appealing option for PUPs as a first and ongoing treatment for patients with severe haemophilia A.

AUTHOR CONTRIBUTIONS

Mary Mathias wrote the first draft of the manuscript. All authors provided input, reviewed and approved the manuscript.

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This study was supported by the Octapharma AG.

CONFLICT OF INTEREST STATEMENT

Mary Mathias is, or has been, an investigator for studies sponsored by Octapharma, Roche, Sanofi, Novo Nordisk, Takeda and Swedish Orphan Biovitrum, carried out consultancy work for Freeline, received lecture/symposia fees from Octapharma, Roche, CSL Behring, Takeda, and received support to attend meetings from Roche, Novo Nordisk, CSL Behring, Takeda and Octapharma. Aby Abraham received a travel grant from Novo Nordisk and research grants from Roche and Novo Nordisk. Mark J. Belletrutti has received speaker fees from Octapharma Canada, consultant fees from Takeda Canada, and participated in advisory boards for advisory boards for Sanofi Canada, Bayer Canada, Roche Canada, and Takeda Canada. Manuel Carcao has been an investigator on clinical trials sponsored by Novartis, Novo Nordisk, Octapharma, Roche and Sanofi, and has received support for attending scientific meetings and honoraria (speaker fees/consultant in advisory boards) from Baxalta/Shire (now Takeda), Bayer, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi and Swedish Orphan Biovitrum. Manuela Carvalho has been an investigator on clinical trials sponsored by CSL Behring, Novo Nordisk, Octapharma and Roche, and has received support for attending scientific meetings and honoraria (speaker fees/consultant in advisory boards) from Baxalta/Shire (now Takeda), Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum. Hervé Chambost has received honoraria for consulting from BioMarin, LFB, Novo Nordisk, Octapharma, Pfizer, Roche/Chugaï and Swedish Orphan Biovitrum, and is Principal Investigator in clinical studies sponsored by Baxalta/Shire, BioMarin, Octapharma, Pfizer, Roche and Sanofi/Swedish Orphan Biovitrum/Bioverativ. Anthony K. C. Chan has been an investigator on clinical trials for Bayer, Novo Nordisk, Pfizer, Sanofi and Takeda, and has received honoraria for attending advisory boards from Bayer, Novo Nordisk, Roche and Takeda. Jonathan Ducore serves on advisory boards for Bayer. Paolo Gresele has received speaker fees from Roche and Sanofi. Yves Gruel has received support for attending meetings or honoraria (speaker fees or consultant) from Aguettant, Alexion, Bayer HealthCare, LFB, Octapharma, Roche, Stago and Swedish Orphan Biovitrum. Benoit Guillet has acted as a paid consultant to CSL Behring, Novo Nordisk, Octapharma, Roche-Chugaï, Swedish Orphan Biovitrum and Takeda. Victor Jiménez-Yuste has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Bayer, Biomarin, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum and Takeda. Lidija Kitanovski has received reimbursement or honoraria (advisory board, scientific meetings) from Octapharma, Swedish Orphan Biovitrum, Novo Nordisk, Roche, Takeda and Bayer. She has been an investigator for studies sponsored by Octapharma and co-investigator for studies sponsored by Swedish Orphan Biovitrum and Bayer. Anna Klukowska has received speakers fees from CSL Behring, Novo Nordisk and Takeda, and support for attending scientific meetings from Roche and Takeda. Maria Elisa Mancuso has acted as a paid consultant/advisor/speaker for Bayer, Biomarin, CSL Behring, Grifols, Kedrion, LFB, Octapharma, Novo Nordisk, Pfizer, Roche, Sanofi, Swedish Orphan Biovitrum, Takeda, Spark Therapeutics and UniQure. Johannes Oldenburg has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugaï Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum and Takeda. Marianne Sigaud has worked as a consultant for Roche and Takeda. Martina Jansen is a full-time employee of Octapharma Pharmazeutika Produktionsges m.b.H., Vienna, Austria. Larisa Belyanskaya, Olaf Walter and Sigurd Knaub are employees of Octapharma AG, Lachen, Switzerland. Ellis J. Neufeld has received honoraria from Octapharma and Takeda. He has been a consultant to Pfizer, Genentech and Dispersol/Austin. During the course of the NuProtect study, he participated in advisory boards for Novo Nordisk, Genentech and Saliogen. He has served on data and safety monitoring boards for Bayer, Dova/Swedish Orphan Biovitrum, Agios and Acceleron Pharma/Merck. Michael Gattens, Leonid Dubey, Sunil Lohade, Berardino Pollio, Kateryna Vilchevska and John K. M. Wu reported no competing financial interests other than being a study investigator.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available within the article.

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