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ORIGINAL ARTICLE

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Zero incidence of factor VIII inhibitors and successful haemostatic response in previously factor VIII-treated patients with haemophilia A switching to turoctocog alfa in a noninterventional study

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Abstract

Introduction: Turoctocog alfa (NovoEight®) is a B-domain-truncated recombinant factor VIII (FVIII) approved for patients with haemophilia A.

Aim: To investigate the long-term safety and efficacy of turoctocog alfa in routine clinical practice.

Methods: Guardian 5 was a prospective, multinational, non-interventional, post-authorisation safety study. Male previously treated patients (> 150 exposure days [EDs]) of any age with severe/moderately severe haemophilia A (FVIII ≤ 2%) and a negative inhibitor test prior to first dosing (independent of FVIII-inhibitor history) were included to receive prophylaxis or on-demand treatment. The primary endpoint was the proportion of patients developing FVIII inhibitors (≥.6 Bethesda Units [BU]) after baseline visit, measured as per routine practice of each study site during clinic visits. Secondary endpoints included haemostatic effect, annualised bleeding rate (ABR), and adverse reactions assessment. The study concluded when 50 patients reached 100 EDs/patient minimum.

Results: Seventy patients were screened and 68 exposed to turoctocog alfa; 63 (92.6%) were on prophylaxis and five received on-demand treatment. Six (8.8%) patients reported a history of positive inhibitors. During the study, patients were exposed to turoctocog alfa for a mean (standard deviation) of 131.9 (99.0) days/patient. Fifty-five of 58 patients who completed the study were tested for FVIII inhibitors; no positive tests were reported. Overall success rate of turoctocog alfa for treatment of bleeds was 87.3%. Among patients receiving prophylaxis, median (range) ABR was 1.97 (.0–25.5) bleeds/year; estimated ABR (negative binomial model) was 3.65 (95% confidence interval: 2.53–5.25).

Conclusion: Turoctocog alfa was safe and efficacious for haemophilia A treatment in routine clinical practice.

KEYWORDS
factor VIII inhibitors, haemophilia A, prophylaxis, real-world evidence, recombinant factor VIII, turoctocog alfa

1 | INTRODUCTION

Haemophilia A is a congenital bleeding disorder characterised by a deficiency in coagulation factor VIII (FVIII) that results in an increased tendency for spontaneous or traumatic bleeding events.[1] Prophylaxis with clotting factor concentrates or other haemostatic agents is the standard of care for patients with severe haemophilia A to prevent bleeding.[1]

The major complication in the treatment of haemophilia A with clotting factor concentrates is the development of alloantibodies (inhibitors) against exogenous FVIII.[2] Inhibitors neutralise the clotting activity of FVIII therapy, which may result in an increased risk of severe bleeding and, subsequently, higher risk of morbidity, mortality and disability, and decreased quality of life.[3,4] Switching FVIII concentrates in previously treated patients (PTPs; > 75–150 exposure days [EDs]) is not associated with a higher risk of developing inhibitors[5]; however, data for PTPs with a history of inhibitors are sparse because they are usually excluded from Phase 1–3 clinical studies.[6,7]

Turoctocog alfa (NovoEight®) is a third-generation, recombinant, B-domain-truncated human coagulation FVIII molecule developed by Novo Nordisk A/S and approved for prophylaxis and treatment of bleeding episodes in haemophilia A in all age groups.[8–10] The safety and efficacy of turoctocog alfa have been demonstrated across several Phase 3 clinical studies in PTPs (guardian 1, 2, 3 and 7) and previously untreated patients (guardian 4) with haemophilia A.[6,7,11–13]

Real-world studies help to understand treatments in broader, more representative patient populations than those used in interventional clinical studies,[14] which may exclude patient groups such as those with a history of inhibitors. Additionally, treatment practices may vary in the real-world setting due to differences in regional procedures and prescribing patterns. Issues with adherence can arise outside a controlled clinical study setting.[14]

The aim of the guardian 5 study was to evaluate the real-world immunogenicity, safety and clinical efficacy of turoctocog alfa for prophylaxis, treatment of bleeding episodes and for surgery in PTPs with severe and moderately severe haemophilia A.

2 | METHODS

2.1 | Study design

Guardian 5 was a prospective, multinational, non-interventional, post-authorisation safety study investigating the long-term safety and efficacy of turoctocog alfa in routine clinical practice (NCT02035384). The study design followed European Medicines Agency guideline recommendations for FVIII product investigation.[15] Patients received intravenous prophylaxis or on-demand treatment as per their and the treating physician's choice, and clinical assessment was done according to local practices. Patients were enrolled at 31 sites in 13 countries (12 European countries and the USA; see Supplementary Table **1**).

For each patient, data were planned to be collected until they reached a minimum of 100 EDs (counted from the baseline visit) with turoctocog alfa, or until at least 50 patients had a minimum of 100 EDs after inclusion in the study, whichever came first. The study was completed in 67.5 months between June 2014 and January 2020. The study was approved by all relevant independent ethics committees and institutional review boards and conducted in accordance with the Declaration of Helsinki,[16] Guidelines for Good Pharmacoepidemiology Practices[17] and Good Pharmacovigilance Practice.[18] All patients or representatives provided written consent.

2.2 | Participants

Patients were considered for inclusion if it had already been decided that they would switch from their previous FVIII product to turoctocog alfa, typically because of tendering. Patients were eligible if they were male, diagnosed with congenital severe or moderately severe haemophilia A (FVIII level ≤ 2%), previously FVIII treated with at least 150 EDs at the time of first dosing with turoctocog alfa, and had a negative FVIII inhibitor test not more than 4 weeks prior to first dosing.

Patients with a history of FVIII inhibitors were eligible for inclusion. Patients who had previously participated in any clinical study with turoctocog alfa were not eligible.

2.3 | Treatment

Product usage was in accordance with clinical daily practice and generally in agreement with the approved product label and national guidelines.[10] Commercially available product was used as part of this study.

2.4 | Study endpoints and clinical assessments

The primary endpoint was the proportion of patients developing FVIII inhibitors (≥.6 BU, or above the specific local laboratory reference range). The physician was encouraged to perform clinical evaluation and blood testing for FVIII inhibitors during visits to the clinic or when there was a lack of therapeutic effect. Inhibitor testing was in accordance with the local practice and not mandatory, due to the non-interventional nature of the study. Secondary safety endpoint was the

number of adverse reactions reported during the study period. Secondary efficacy endpoints included haemostatic effect of turoctocog alfa in the treatment of bleeds and during surgical procedures, annualised bleeding rate (ABR) for preventive and on-demand treatment, and consumption of turoctocog alfa.

Detailed information related to treatment and bleeding episodes was captured in a paper patient diary by the patient or parent/caregiver. If a patient was unable to enter a treatment or bleeding episode in the diary, or was hospitalised, information was reported by the physician. It was possible to use the patient's own diary to capture details of bleeding episodes (e.g. location, type, date of occurrence), where some of the data points (haemostatic response and severity of bleed) were not captured.

2.5 | Statistical methods

Data evaluation was mainly based upon descriptive statistics. The proportion (percentage) of patients developing FVIII inhibitors was calculated; a one-sided 97.5% upper confidence limit based on an exact calculation for a binomial distribution was provided. In the analysis, all patients with at least one inhibitor test performed after baseline visit were included.

Bleeds were classified as mild/moderate or severe; haemostatic responses for the treatment of bleeds and during surgery were evaluated on a four-point scale (see Supplementary Table 2). Haemostatic response assessment was repeated with the inclusion of missing responses (counted as treatment failure) in the sensitivity analysis. ABR was analysed using a negative binomial model and estimated ABR with confidence intervals (CIs). A Poisson model allowing for overdispersion was applied in the sensitivity analysis of ABR.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

In total, 70 patients were screened for this study (see Figure 1); 68 patients were exposed to FVIII during study participation and therefore included in the full analysis set and safety analysis set. One patient with FVIII level > 2% at inclusion could not be classified into 'severe haemophilia (FVIII level < 1%)' or 'moderately severe haemophilia (FVIII level 1–2%)' categories; however, this patient was included in the total number of patients in the analyses by severity of haemophilia A to represent the full analysis set.

During the study, 68 patients were exposed to turoctocog alfa for a total of 87.8 patient-years and 8967 EDs. The mean EDs (standard deviation [SD]) per patient was 131.9 (99.0) days/patient; 50 patients reported 100 EDs. Of the 68 exposed patients, 63 patients were on a prophylaxis regimen (14 patients < 12 years; 49 patients ≥ 12 years) and five patients received on-demand treatment (all patients ≥ 12 years). No patients switched from on-demand to prophylaxis (or vice versa) after entering the study. A total of 58 (84.1%) patients (9 patients < 12 years; 49 patients ≥ 12 years) completed the study, of which eight patients (all ≥ 12 years) were considered as study completers without recording a minimum of 100 EDs but confirmed by the physician as completers.

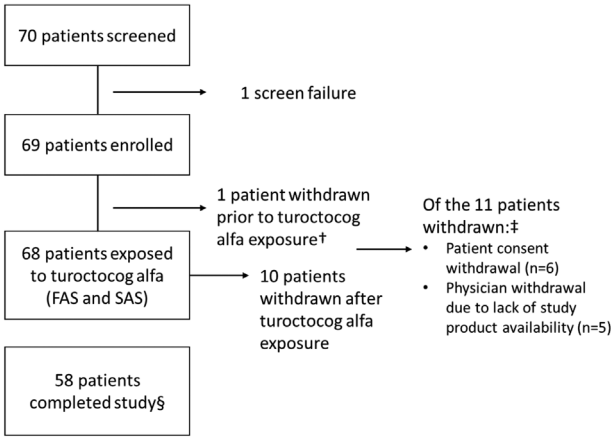

FIGURE 1 Participant flow. FAS, full analysis set; SAS, safety analysis set. [a]Patient forgot diary and did not wish to continue in study. [b]Evaluations until the moment of withdrawal were included in the analyses. [c]8 patients were considered as study completers without recording a minimum of 100 EDs but confirmed by the physician as completers.

The study population, disposition and baseline demographics are shown in Table 1. The study population included 14 paediatric patients (< 12 years) and 55 adolescent/adult patients (≥ 12 years), of which one patient was not exposed to turoctocog alfa. Before study entry, five patients (all ≥ 12 years) received an on-demand regimen. Overall, 63 patients (14 patients < 12 years; 49 patients ≥ 12 years) were on a prophylaxis regimen. Historical frequency of dosing for prophylaxis is reported in Table 1; prophylaxis dose before the trial was not collected.

Six patients (one patient < 12 years; five patients ≥ 12 years [oldest patient: 41 years old]) reported a history of clinical suspicion of inhibitors. Information on the historical inhibitor titre, duration and treatment was not consistently captured. Five of the six patients were tested for FVIII inhibitors during the study; one patient (< 12 years) was not tested. In total, 41 (60.3%) patients had a family history of haemophilia A. Fifty-one patients had a history of switching FVIII products.

3.2 | Safety

3.2.1 | FVIII inhibitor development

None of the 68 exposed patients was reported to be positive for FVIII inhibitor during treatment with turoctocog alfa (proportion of patients: 0%; 97.5% upper confidence limit: 6.5). Of the 68 exposed patients, 55 had at least one inhibitor test post-baseline; all of them reported negative FVIII inhibitor test results.

TABLE 1 Patient demographics and baseline characteristics

	Age at inclusion		Haemophilia severity at inclusion[a]		
Full analysis set	**< 12 years**	**≥ 12 years**	**Severe**	**Moderately Severe**	**Total**
Number of patients	14	54	58	9	68[a]
Age (years)					
Mean (SD)	7.4 (2.3)	33.6 (15.5)	26.2 (15.5)	38.6 (24.8)	28.2 (17.4)
Severity of haemophilia, N (%)					
Severe (< 1%)	13 (92.9)	45 (83.3)	58 (100.0)	–	58 (85.3)
Moderately severe (1–2%)	1 (7.1)	8 (14.8)	–	9 (100.0)	9 (13.2)
FVIII level > 2%	–	1 (1.9)	–	–	1 (1.5)
Current treatment prior to study, N (%)					
On-demand	–	5 (9.3)	3 (5.2)	1 (11.1)	5 (7.4)
Prophylaxis	14 (100.0)	49 (90.7)	55 (94.8)	8 (88.9)	63 (92.6)
FVIII product given as prophylaxis or on-demand, N (%)[b]					
N	13	53	56	9	66
Plasma FVIII product	1 (7.7)	6 (11.3)	5 (8.9)	2 (22.2)	7 (10.6)
Recombinant FVIII	12 (92.3)	47 (88.7)	51 (91.1)	7 (77.8)	59 (89.4)
Average number of bleeds per year (prophylaxis regimen)					
N	14	44	51	7	58
Mean (SD)	3.2 (6.2)	5.3 (7.8)	4.6 (7.3)	5.9 (9.0)	4.8 (7.5)
Average number of bleeds per year (on-demand)					
N	0	5	3	1	5
Mean (SD)	– (–)	22.6 (11.2)	17.6 (11.0)	36.0 (–)	22.6 (11.2)
Dose level for patients on prophylaxis at inclusion					
N	14	49	55	8	63
Mean (SD)	30.2 (12.1)	27.0 (12.2)	28.2 (12.2)	24.1 (11.7)	27.7 (12.1)
Frequency of dosing for patients on prophylaxis at inclusion					
N	14 (100.0)	48 (100.0)	55 (100.0)	7 (100.0)	62 (100.0)
Once weekly	1 (7.1)	5 (10.4)	5 (9.1)	1 (14.3)	6 (9.7)
Every second day	1 (7.1)	10 (20.8)	9 (16.4)	2 (28.6)	11 (17.7)
Three times weekly	11 (78.6)	23 (47.9)	30 (54.5)	4 (57.1)	34 (54.8)
Other	1 (7.1)	10 (20.8)	11 (20.0)	–	11 (17.7)

Severe: FVIII level < 1%, Moderately Severe: FVIII level 1–2%. FVIII, factor VIII; SD, standard deviation.
[a]One patient with FVIII activity > 2% at inclusion is included in the 'Total' column to represent the full analysis set.
[b]Patients can consume more than one product.

Six patients completed the study without any inhibitor test taken, and for seven patients an inhibitor test result was reported only at baseline visit; therefore, these 13 patients were not included in the primary analysis. For these patients, reported data did not indicate clinical signs of possible inhibitor development, such as an increase in bleeding frequency, increased consumption for prophylaxis and bleed treatment, or lack of response to hemostatic treatment. Four patients did not have an inhibitor test done within the 4 weeks prior to starting treatment with turoctocog alfa. Of these, three patients had an inhibitor test taken during the study (these patients were included in the primary analysis).

3.2.2 | Adverse events

One serious adverse reaction of angina pectoris was reported. A 38-year-old patient (body mass index 40.1 kg/m^2) with severe haemophilia was enrolled into the study and treated with a mean dose regimen

TABLE 2 Annualised bleeding rates by age and haemophilia severity for patients on prophylaxis

	Age at inclusion, N (%)		Haemophilia severity at inclusion, N (%)		
	Baseline age < 12 years	Baseline age ≥ 12 years	Severe	Moderately Severe	Total
Number of patients	14	49	55	8	63
N[a]	14	48	54	8	62
Number of patients with bleeds	8 (57.1)	32 (66.7)	35 (64.8)	5 (62.5)	40 (64.5)
Mean observation period per patient (years)	.89	1.24	1.20	.96	1.17
Observation period per patient, min.; max. (years)	.21; 1.71	.21; 5.06	.21; 5.06	.21; 1.97	.21; 5.06
Total observation period (years)	12.52	59.73	64.61	7.64	72.25
Annualised bleeding rate					
Negative binomial analysis	2.75	3.90	3.67	3.37	3.65
95% CI	1.35, 5.61	2.57, 5.92	2.47, 5.46	1.41, 8.06	2.53, 5.25
Poisson estimate	2.56	3.48	3.36	3.01	3.32
95% CI	1.36, 4.82	2.29, 5.29	2.25, 5.00	1.43, 6.36	2.31, 4.78
Median (IQR)	1.34 (4.02)	2.14 (6.56)	1.93 (6.19)	2.76 (7.04)	1.97 (6.19)

Severe: FVIII level < 1%, Moderately Severe: FVIII level 1–2%. CI, confidence interval; FVIII, factor VIII; IQR, interquartile range; max., maximum; min., minimum; SD, standard deviation.

[a]Number of patients with more than one exposure day reported: only these patients are included in the analysis.

of 16.2 IU/kg every alternate day. The patient had a medical history of heart disease and non-ST segment elevation myocardial infarction. Concomitant medication included platelet aggregation inhibitors, antihypertensive and cholesterol-lowering therapy. After reaching 110 EDs in the study, 2 hours after a prophylactic injection of turoctocog alfa, the patient developed symptoms of angina pectoris and elevated troponin. A coronary angiography with percutaneous transluminal coronary angioplasty and right coronary artery stent (bare metal) was performed. The serious adverse reaction was reported to be possibly related to the study drug by the physician because of the temporal relationship. It was resolved, and the patient continued with turoctocog alfa. No other adverse reactions were reported during the study.

3.3 | Efficacy

3.3.1 | Prevention of bleeding episodes

Of the 63 patients who received prophylaxis, 62 had > 1 ED reported and were included in the bleeding rate calculation. Additionally, one patient reported one bleeding episode during treatment with turoctocog alfa with unknown number of EDs and was excluded from the ABR analyses. Eight patients had missing diary periods; those periods were not accounted in the ABR analyses. Overall, the negative binomial estimates of ABR among patients on prophylaxis regimens and on-demand treatment were 3.65 (95% CI: 2.53–5.25) bleeds/patient/year and 20.28 (12.09–34.01) bleeds/patient/year, respectively. Overall median (interquartile range) ABR was 1.97 (6.19) (Table 2). Estimated ABR on prophylaxis regimen for spontaneous bleeds was 2.39 (95% CI: 1.50–3.81) bleeds/patient/year and for traumatic bleeds was 1.15 (95% CI: .76–1.73) bleeds/patient/year.

3.3.2 | Treatment of bleeding episodes

Overall, 469 bleeds were reported in 46/68 patients (Table 3). Most were mild or moderate (n = 387, 82.5%) in severity. The most frequent location was in the joints (69.7% of bleeds). Of the 469 bleeds, 308 (65.7%) were spontaneous, 103 (22.0%) were traumatic and 58 (12.4%) bleeds had unknown cause.

Of the 469 reported bleeds, 333 (71.0%) bleeds were stopped with one to two injections of turoctocog alfa. The mean (median) number of injections required from start to stop of a bleed were 2.6 (2.0) injections/bleed. Haemostatic evaluation ratings were available for 361 bleeds in 37 patients. The overall success rate of turoctocog alfa for the treatment of bleeds was 87.3% (excluding bleeds with no outcome reported). Patients who had not used the Novo Nordisk diary provided and for whom the haemostatic effect was not captured for any episodes were excluded from the haemostatic effect analysis.

3.4 | Surgery

Eight patients underwent 11 surgeries. Haemostatic response was available for seven surgeries (four surgeries in three patients with severe haemophilia, two surgeries in two patients with moderately severe haemophilia and one surgery in a patient with FVIII level > 2%). Of these surgeries, haemostatic response for five surgeries was rated as 'Excellent' and for two surgeries was rated as 'Good'. Overall

TABLE 3 Details of bleeding episodes and haemostatic response to turoctocog alfa treatment

	Age at inclusion, N (%)		Haemophilia severity at inclusion, N (%)		
	Baseline age < 12 years	Baseline age ≥ 12 years	Severe	Moderately Severe	Total
Number of patients with bleeding episodes	8	38	39	6	46
Number of bleeding episodes	32	437	412	50	469
Cause of bleed, N (%)	32 (100.0)	437 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Spontaneous	8 (25.0)	300 (68.6)	283 (68.7)	19 (38.0)	308 (65.7)
Traumatic	24 (75.0)	79 (18.1)	97 (23.5)	5 (10.0)	103 (22.0)
Missing	–	58 (13.3)	32 (7.8)	26 (52.0)	58 (12.4)
Site of bleed, N (%)	32 (100.0)	437 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Joint	18 (56.3)	309 (70.7)	294 (71.4)	29 (58.0)	327 (69.7)
Mucocutaneous	4 (12.5)	33 (7.6)	35 (8.5)	2 (4.0)	37 (7.9)
Muscular	3 (9.4)	48 (11.0)	38 (9.2)	11 (22.0)	51 (10.9)
Other/unknown	7 (21.9)	47 (10.7)	45 (10.9)	8 (16.0)	54 (11.6)
Classification of bleed, N (%)	32 (100.0)	437 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Mild/moderate	27 (84.4)	360 (82.4)	335 (81.3)	45 (90.0)	387 (82.5)
Severe	1 (3.1)	12 (2.7)	9 (2.2)	4 (8.0)	13 (2.8)
Unknown	4 (12.5)	65 (14.9)	68 (16.5)	1 (2.0)	69 (14.7)
Infusions to treat the bleed, from start to stop of the bleed, N (%)	32 (100.0)	437 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
1 infusion	12 (37.5)	222 (50.8)	206 (50.0)	28 (56.0)	234 (49.9)
2 infusions	12 (37.5)	87 (19.9)	93 (22.6)	3 (6.0)	99 (21.1)
≥ 3 infusions	8 (25.0)	128 (29.3)	113 (27.4)	19 (38.0)	136 (29.0)
Number of patients with bleeding episode with diary data [a]	7	30	31	5	37[b]
Haemostatic response, [c] **N (%)**	23 (100.0)	338 (100.0)	331 (100.0)	23 (100.0)	361 (100.0)
Excellent	15 (65.2)	77 (22.8)	84 (25.4)	2 (8.7)	92 (25.5)
Good	8 (34.8)	215 (63.6)	207 (62.5)	15 (65.2)	223 (61.8)
Moderate	–	37 (10.9)	32 (9.7)	5 (21.7)	37 (10.2)
None	–	9 (2.7)	8 (2.4)	1 (4.3)	9 (2.5)
Success rate, N (%)	23 (100.0)	338 (100.0)	331 (100.0)	23 (100.0)	361 (100.0)
Success	23 (100.0)	292 (86.4)	291 (87.9)	17 (73.9)	315 (87.3)
Failure	–	46 (13.6)	40 (12.1)	6 (26.1)	46 (12.7)

Severe: FVIII level < 1%, Moderately Severe: FVIII level 1–2%. FVIII, factor VIII.

[a]Haemostatic response was calculated for 37 patients with bleeding episodes for whom there was diary data.

[b]One patient with FVIII activity > 2% at inclusion is included in the 'Total' column to represent the full analysis set.

[c]Haemostatic response for the treatment of bleeds was evaluated on a four-point scale where 'excellent' (abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection) and 'good' (definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection for complete resolution) responses were classified as successful, and responses rated as 'moderate' (probable or slight beneficial effect within approximately 8 hours after the first injection; usually requiring more than one injection), 'none' (no improvement, or worsening of symptoms within approximately 8 hours after the first injection; usually requiring more than one injection) or 'missing' were classified as failure.

success rate for haemostatic effect during surgical procedures was 100%. Details of surgeries and invasive procedures with haemostatic response are shown in Supplementary Table 3.

3.5 | Consumption of turoctocog alfa for prophylaxis

The mean (SD) average dose of turoctocog alfa for prophylaxis regimen per patient per ED was 30.1 (11.4) IU/kg/ED. The mean (SD) consumption of turoctocog alfa per patient per month (including all doses given as prophylaxis regimen and for the treatment of bleed or surgery) was 309.0 (191.8) IU/kg (n = 68). The mean (SD) consumption of turoctocog alfa for prophylaxis per patient per month was 302.9 (165.1) IU/kg. The average number of prophylaxis doses per week was 2.6. For children < 12 years, monthly consumption for prophylaxis was higher (376 IU/kg) than for the older patients (282 IU/kg). This difference resulted from a slightly higher mean prophylaxis dose (33.0 vs 29.2 IU/kg) as well as more frequent dosing for prophylaxis in the younger age group (data on file). The mean (SD) average dose of turoctocog alfa per bleed per injection was 23.8 (10.4) IU/kg/bleed. The mean (SD) consumption of turoctocog alfa per bleed was 58.0 (99.0) IU/kg/bleed (see Supplementary Table 4).

4 | DISCUSSION

During guardian 5, turoctocog alfa was well tolerated and no inhibitors against turoctocog alfa were detected during the study period. Turoctocog alfa was effective for the prevention and treatment of bleeding episodes, and for haemostatic management during surgery in patients with severe and moderately severe haemophilia A.

The development of inhibitors against FVIII remains a major complication of haemophilia A treatment.[2] Importantly, guardian 5 is one of the first clinical studies to include patients with a history of inhibitors switching to a new recombinant FVIII concentrate (turoctocog alfa). In this study, 55 of 68 exposed patients were tested for an inhibitor post-baseline; none of these patients reported FVIII inhibitor development (≥.6 BU) during treatment with turoctocog alfa. This included six patients with history of inhibitors. The real-world data reported here are consistent with clinical study data of PTPs without a history of inhibitor development, in the guardian 1, 2 and 3 studies, where turoctocog alfa was well tolerated and no patients developed inhibitors.[6,7,11]

One patient in guardian 5 had a history of a high-titre inhibitor (30 BU) successfully treated with an immune tolerance induction with plasma-derived FVIII (personal communication). Due to fear of relapse, the patient was kept on plasma-derived FVIII until study start when he was switched to turoctocog alfa. Regular inhibitor tests performed during the study were negative and a FVIII half-life of slightly more than 6 hours was maintained.

One patient with multiple cardiovascular risk factors developed angina pectoris 2 hours after turoctocog alfa injection and was subsequently diagnosed with a myocardial infarction. Cases of myocardial infarction and acute coronary syndromes in patients with haemophilia occurring during or immediately after the administration of coagulation factor have been reported previously,[19] including one case of myocardial infarction from a clinical trial with turoctocog alfa.[20] Conditions predisposing to arterial occlusion, such as obesity, hypertension and hypercholesterolemia as observed in this patient, play an important role in the pathogenesis of myocardial infarction. It is noteworthy that the patient continued treatment with turoctocog alfa after the event.

The overall estimated negative binomial ABR for patients on prophylaxis regimen was 3.65 bleeds/patient/year, which was lower than the reported historical ABR (4.8 bleeds/patient/year). The overall success rate for the treatment of bleeds reported in the guardian 5 study was comparable to the reported success rate in previous guardian studies.[6,7,11,13] Despite advances in treatment of haemophilia A with the development of novel non-factor replacement therapies,[21] the present data suggest that regular prophylaxis with turoctocog alfa – a standard half-life FVIII replacement molecule – is efficacious for the prevention and management of bleeding episodes, and leads to a reduction in ABR. The ABR of 3.6 observed in the setting of routine clinical practice was achieved with a relatively moderate consumption and prophylactic dosing frequency below that considered standard prophylaxis. The mean (SD) turoctocog alfa consumption for prophylaxis per patient per month was 302.9 (165.1) IU/kg in this study, notably lower than observed in a long-term clinical trial with turoctocog alfa, guardian 2 (424.5 [126.7] IU/kg/month) (data on file). The difference can be explained by the lower dosing frequency in guardian 5 (2.6 vs 3 injections/week), as well as lower mean preventive dose (30.1 vs 32.5 IU/kg) [data on file].[11] Guardian 2 was a clinical trial in which most patients adhered to standard prophylaxis with three injections a week, and compliance with treatment administration and reporting was expectedly high. Turoctocog alfa usage in guardian 5 likely reflects administration in a real-world setting, where strict adherence to the prescribed regimen may be lower than in a clinical trial, although limitations of treatment data collection in a non-interventional study must be taken into account.

Because this is a non-interventional post-authorisation safety study, there were several potential confounding factors that are normally controlled in clinical studies. The requirement for use of a diary resulted in selection bias of patients willing/able to cooperate in a study with a diary. Patient diary use introduced an increased risk of recording the administered dose and bleed severity evaluation incorrectly. However, this was minimised via diary review by the physician. Due to the observational nature of the study, results from assessments and laboratory sampling were reported upon availability. Data were missing for various reasons, including limited on-site monitoring when transferring clinical data from medical records, patients being allowed to use their own diaries for recording bleeding episodes and the patients not being discontinued if they did not maintain their diary. Although physicians were encouraged to perform inhibitor tests as a routine practice during visits, practices varied between countries. At some sites, inhibitor testing was done only when there was a suspicion of inhibitor

development and not as a routine practice. As a result, 13 patients were excluded from the primary analysis because they were not tested for inhibitors. It is likely that these patients were not tested because there was no clinical suspicion of an inhibitor; however, this cannot be confirmed. The study ended when 50 patients were exposed for 100 EDs to study product; therefore, some patients were observed for less than 100 EDs.

In conclusion, the safety of turoctocog alfa in PTPs with haemophilia A in routine clinical practice has been demonstrated in this study. The reported ABR, surgical procedure outcomes, bleed resolution and monthly consumption data are supportive of the efficacy profile of turoctocog alfa. Turoctocog alfa remains an effective treatment option for patients with haemophilia A in the rapidly evolving treatment landscape.

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CONFLICTS OF INTEREST

Carmen Escuriola Ettingshausen: acted as a consultant, received speaker's fees and/or research funding from Bayer, Biomarin, Biotest, CSL Behring, Freeline, Grifols, Kedrion, Octapharma, Novo Nordisk, Shire/Takeda, Sobi, Roche/Chugai; Olga Katsarou: received speaker and consulting fees from Novo Nordisk; Irina Matytsina, Sohan Dey: employees of Novo Nordisk; Rudolf Schwarz: board membership, reimbursement for attending symposia for Novo Nordisk. Annie Borel Derlon, Barbara Faganel Kotnik, Paula F. Ypma, Roger E.G. Schutgens: stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and US will be shared with bona fide researchers submitting a research proposal requesting access to data. The access request proposal form and the access criteria can be found at novonordisk-trials.com. Data will be available permanently after research completion and approval of product and product use in both the EU and US on a specialised Statistical Analysis System data platform. The analyses available for use will be those as approved by the Independent Review Board according to the IRB Charter (see novonordisk-trials.com). Individual participant data will be shared in data sets in a de-identified/-anonymised format. In addition, the study protocol and redacted Clinical Study Report will be available according to Novo Nordisk data sharing commitments.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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