

# Safety and Efficacy of Turoctocog Alfa in the Prevention and Treatment of Bleeding Episodes in Previously Treated Patients from China with Severe Hemophilia A: Results from the Guardian 7 Trial

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**Purpose:** Hemophilia care in China is characterized by widespread use of on-demand regimens and low-dose prophylaxis. With a limited number of approved recombinant factor VIII (FVIII) products, the incidence of arthropathy and disability in hemophilia patients remains high in China. The purpose of this trial was to evaluate the safety and efficacy of turoctocog alfa for prophylaxis and treatment of bleeding episodes in patients from China with severe hemophilia A across all age groups.

**Patients and Methods:** In this Phase 3, open-label trial, previously treated males of all ages with severe hemophilia A from China received turoctocog alfa for prophylaxis or on-demand treatment of bleeds. The primary endpoint was hemostatic effect for the treatment of bleeds during the main phase of the trial. Secondary endpoints included annualized bleeding rate during prophylaxis and the frequency of FVIII inhibitor development.

**Results:** Overall, 42 pediatric patients (age <12 years) and 26 adolescent/adult patients (≥12 years) were dosed with turoctocog alfa; 51 patients initiated treatment with prophylaxis, while 17 patients initiated on-demand treatment. During the main phase of the trial (6 months), hemostatic success was 95.1%. During the full trial (up to 24 months), hemostatic success was 95.4%; the overall median ABR was 1.18 bleeds/patient/year for prophylaxis patients; and 25 (51.0%) of 49 patients with target joints at baseline had all target joints resolved. No FVIII inhibitors (≥0.6 BU) were reported.

**Conclusion:** Turoctocog alfa was safe and effective for prophylaxis and treatment of bleeding episodes and for surgery in patients from China with severe hemophilia A across all ages.

**Keywords:** hemophilia A, prophylaxis, recombinant factor VIII, turoctocog alfa, China

## Introduction

Hemophilia A is a congenital bleeding disorder characterized by a deficiency in coagulation factor VIII (FVIII) that results in increased tendency for spontaneous or traumatic bleeding events.<sup>1</sup> The international standard of care for hemophilia management is prophylactic administration of clotting factor concentrates, which aim to prevent and treat bleeding, and reduce the risk of hemophilic arthropathy.<sup>1-4</sup> Despite recent advances in care with the development of non-factor replacement products and gene therapy, prophylaxis with clotting factor concentrates remains the cornerstone of hemophilia treatment in many parts of the world, including China.<sup>3-5</sup>

Historically, the implementation of effective hemophilia care in China has been challenging, due to healthcare infrastructure, affordability of treatment and relatively low disease awareness.<sup>6</sup> Due to resource constraints, hemophilia A treatment in China is characterized by widespread use of on-demand treatment.<sup>7,8</sup> As the incidence of arthropathy and disability remains high in hemophilia patients from China, low-dose prophylaxis regimens are available mainly for younger patients.<sup>7,9,10</sup> Plasma-derived concentrates are the mainstay of treatment, and there is a limited number of approved recombinant FVIII (rFVIII) products and prospective trials in this population in recent years.<sup>8,11</sup>

Turoctocog alfa (NovoEight<sup>®</sup>, Novo Nordisk A/S, Bagsværd, Denmark) is a third-generation, B domain-truncated, human coagulation, rFVIII molecule approved for the prophylaxis and treatment of bleeding episodes in hemophilia A; the molecule design and characterization have been discussed in detail elsewhere.<sup>12–14</sup> Turoctocog alfa demonstrated favorable efficacy and safety in the long-term guardian 2 extension trial in previously treated adults and children with severe hemophilia A.<sup>15</sup> In a population of previously untreated pediatric patients, turoctocog alfa was also shown to be effective at preventing and controlling bleeding episodes.<sup>16</sup> It is the first rFVIII molecule to demonstrate stability and be approved for storage at up to 40°C,<sup>14,17</sup> offering patients greater flexibility to store their factor replacement without refrigeration, which is associated with fewer restrictions on daily activities and increased patient satisfaction.<sup>18</sup>

The aim of guardian 7 was to evaluate the safety, efficacy and pharmacokinetics (PK) of turoctocog alfa for prophylaxis, treatment of bleeding episodes and for surgery in previously treated patients (PTPs) of all ages from China with severe hemophilia A. At the time of the investigation, the trial was the first in China to prospectively investigate the efficacy of rFVIII prophylaxis in hemophilia patients from China of all ages, designed in accordance with European Medicines Agency (EMA) guidelines for the investigation of FVIII products.<sup>19</sup> It also had the longest treatment duration (up to 24 months) and the largest sample size of any phase 3 trial of its kind. (Watch [video abstract](#) in Chinese).

## Materials and Methods

### Trial Design

Guardian 7 was a Phase 3, multicenter, open-label, non-randomized safety and efficacy trial (NCT02938585). PTPs with severe hemophilia A (FVIII  $\leq 1\%$ ) of all ages were enrolled across 10 sites in mainland China ([Supplementary material](#)). The trial was conducted between 12 December

2016 (first patient first visit) and 12 December 2018 (last patient last visit) and consisted of a main phase and extension phase. Unless otherwise stated, data reported here are the combined results from both phases. The duration of participation in the trial was ~6 months (equaling ~50 exposure days [EDs] for prophylaxis patients) in the main phase and  $\leq 18$  months in the extension phase. Optional PK sessions took place for selected patients during the main phase. Patients who underwent surgery could receive treatment with turoctocog alfa before, during and after surgery according to the standard of practice at the trial site. The trial was approved by all relevant independent ethics committees and institutional review boards. All patients or their representatives provided written informed consent to participate in the trial, which was conducted in accordance with the Declaration of Helsinki<sup>20</sup> and Good Clinical Practice.<sup>21</sup>

### Participants

Male patients with severe congenital hemophilia A,  $\geq 50$  EDs (patients  $< 12$  years of age) or  $\geq 100$  EDs ( $\geq 12$  years) to any FVIII concentrates, Asian ethnicity and residency in China were enrolled. Patients with a known history or presence of inhibitor ( $\geq 0.6$  Bethesda Units [BU]), or immunocompromised patients (CD4+ T lymphocyte count  $\leq 200$   $\mu\text{L}$ ) were not eligible.

### Treatment

Turoctocog alfa prophylaxis was administered every other day (EOD) or three times weekly as an intravenous (iv) injection. The prophylaxis dose for patients  $\geq 12$  years of age was 20–40 IU/kg (of body weight) EOD or 20–50 IU/kg three times weekly; patients  $< 12$  years were dosed with 25–50 IU/kg EOD, or 25–60 IU/kg three times weekly. These regimens were consistent with prescribing information,<sup>14</sup> with the individual regimen and dose chosen by the investigator. For the treatment of bleeding episodes, investigators determined the individual doses based on recommendations from the World Federation of Hemophilia (WFH).<sup>1</sup> Treatment could be administered at home, at the trial site, or at another clinic.

For PK assessment, a dose of  $50 \pm 5$  IU/kg was administered iv as a single bolus injection. The washout period before the PK session was dependent on the patient's age. Dosing guidance for surgery was provided in the trial protocol and followed WFH guidelines.<sup>1</sup> For prevention of surgical bleeding, the recommended FVIII level was 30–60 IU/dl (%) for minor surgery (including

tooth extractions) and 80–100 IU/dL (%) for major surgery.

## Study Endpoints and Clinical Assessments

The primary endpoint was the hemostatic effect of turoctocog alfa for treatment of bleeding episodes during the main phase. Secondary endpoints included hemostatic effect, annualized bleeding rate (ABR), consumption, incidence rate of inhibitory antibodies against FVIII ( $\geq 0.6$  BU) and frequency of adverse events (AEs), all of which were assessed during both the main phase and combined main and extension phases. PK endpoints included incremental recovery (IR) of FVIII, area under the curve (AUC), half-life ( $t_{1/2}$ ), clearance (CL) and highest measured FVIII activity ( $C_{max}$ ). Patient-reported outcomes included the change in total scores for health-related quality of life (HRQoL) parameters. Plasma FVIII activity (one-stage clotting assay), FVIII inhibitor testing, genotyping and clinical laboratory tests were performed in China at the central laboratory (Quintiles Limited, United Kingdom [now IQVIA]). Testing of FVIII activity with chromogenic assays and FVIII binding antibody analysis was performed in a specialized laboratory outside of China.

## Statistical Methods

The evaluation of data was based mainly on descriptive statistics. Hemostatic responses rated as “good” or “excellent” were classified as successful, and responses rated as “moderate”, “none” or “missing” were classified as failure. ABR was analyzed using a negative binomial model; as a sensitivity analysis, a Poisson model for over-dispersion was applied. Two separate criteria (study protocol and a more recent 2014 International Society on Thrombosis and Haemostasis Scientific and Standardization Committee [ISTH SSC] communication) were applied to define target joints and target joint resolution (Table 1).<sup>22</sup> The incidence rate of FVIII inhibitors ( $\geq 0.6$  BU) was calculated with a one-sided 97.5% upper confidence limit based on an exact calculation for a binomial distribution. Exceptional outlier PK profiles and/or individual plasma concentrations could be excluded. Only one PK datapoint was excluded in patients with several other data points missing. There was no tabulation of PK parameters, including outliers. Disease- and age-specific HRQoL data were collected using HAEM-A-QOL (adults) and HAEMO-QOL (children/adolescents and their parents) questionnaires.

**Table 1** Definition of Target Joints

	<b>Guardian 7 Protocol Definition</b>	<b>ISTH Definition (2014)<sup>22</sup></b>
Target joint	Three or more bleeds in a period of 6 calendar months in a particular joint	Three or more spontaneous bleeds in a period of 6 calendar months in a particular joint
Resolution of a target joint	A target joint is considered resolved, and no longer a target joint, when there have been no bleeds in the joint in the past 12 months	A target joint is considered resolved, and no longer a target joint, when there have been 2 or less bleeds into the joint within a consecutive 12 month period

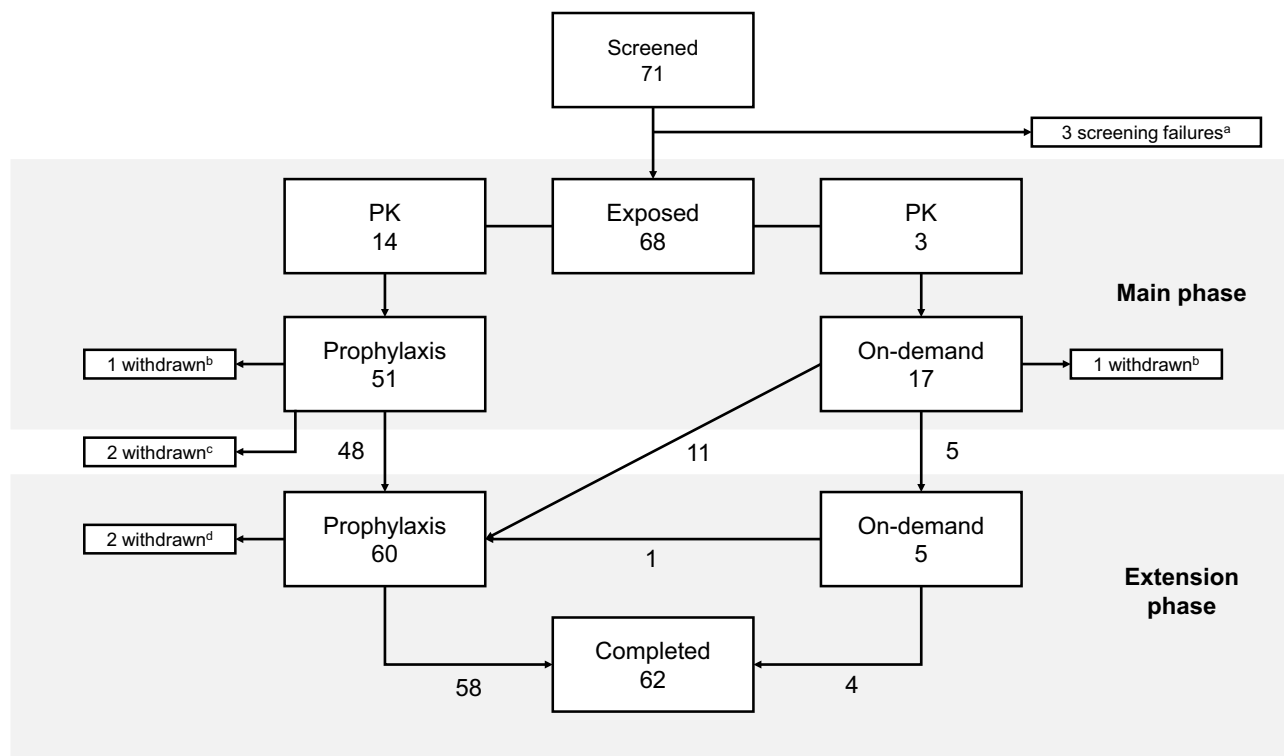
## Results

### Patient Disposition and Baseline Characteristics

In total, 42 pediatric patients (<12 years) and 26 adolescent/adult patients ( $\geq 12$  years) received treatment with turoctocog alfa during the combined main and extension phase, for a cumulative total of 99.7 patient years and 15,240 EDs. Of these, 51 patients initiated the trial with prophylaxis, while 17 patients initiated the trial with on-demand treatment (Figure 1). Of the 17 patients treated on-demand, one withdrew from the main phase and the majority ( $n=11$ ) switched to prophylaxis at the start of the extension phase. The remaining five patients continued with on-demand treatment in the extension period, of which one also later switched to prophylaxis.

Overall, mean exposure was 63.6 EDs (range: 2–136) in the main phase, and 224.1 EDs (range: 2–345) in the combined main and extension phase. A total of 66 patients completed the main phase. Of the 64 patients who entered the extension phase, two patients withdrew and the remaining 62 patients completed the extension phase.

Baseline demographics are shown in Table 2. The overall mean (SD) age was 13.9 (11.0) years. In the year prior to trial participation, 40 patients reported receiving prophylactic treatment at some time, and 32 patients reported receiving intermittent on-demand treatment at some time, with either recombinant or plasma-derived FVIII used. Dosing schedules for previous prophylaxis varied in frequency and only 14/40 (35.0%) patients reported receiving standard prophylaxis (three times weekly or more) in the previous year. The mean (SD) historical weekly prophylaxis dose was 33.0 (15.4) IU/kg. Based on the reported bleeding frequency, the mean historical ABR was 24.57 bleeds/patient/year and 53.67 bleeds/patient/year for patients receiving prophylaxis or on-demand treatment, respectively.



**Figure 1** Participant flow.

**Notes:** <sup>a</sup>3 screening failures: 1 patient did not meet the inclusion criteria (severe congenital hemophilia A with FVIII  $\leq 1\%$ ) and 2 patients had inhibitors to FVIII ( $\geq 0.6$  BU) at screening. <sup>b</sup>2 patients (one from each regimen) withdrew at will from the main phase. <sup>c</sup>2 patients in the prophylaxis regimen withdrew before starting the extension phase (1 due to refusal to participate in the extension and the other for personal reasons). <sup>d</sup>2 patients withdrew during the extension phase (1 due to medical insurance and the other for personal reasons) and the remaining 62 patients completed the extension period. A total of 5 patients were switched from their original prophylaxis dosing frequency during the trial: 1 small child, 1 older child and 1 adult switched from three times weekly to EOD, and 1 older child and 1 adult switched from EOD to three times weekly. **Abbreviations:** BU, Bethesda Units; EOD, every other day; PK, pharmacokinetics.

## Treatment of Bleeding Episodes

A total of 611 bleeds that required treatment were reported in 47 patients during the main phase; the success rate for the treatment of bleeds was 95.1% ( $n=581$ ), including missing values ( $n=1$ ) as failure. A total of 925 bleeds that required treatment were reported in 54 patients in the combined main and extension phase (Table 3); the success rate for the treatment of bleeds was 95.4% ( $n=882$ ), including missing values ( $n=1$ ) as failure. Of the 925 bleeds that required treatment, 693 (74.9%) were reported in 17 patients treated on-demand, and 232 (25.1%) in 44 patients exposed to prophylaxis. The majority (98.3%) of the 925 bleeds were classed as mild/moderate. All severe bleeds ( $n=16$ , 1.7%) were joint bleeds, of which 14 involved target joints. Joint bleeds accounted for the majority of bleeding episodes in older children (64.2%), adolescents (92.5%) and adults (80.1%). A total of 872 (94.3%) bleeds were resolved with 1–2 infusions of turoctocog alfa (Table 3). The mean (SD) number of injections used to treat a bleed was 1.3 (1.0).

## Prevention of Bleeding Episodes

In total, 63 patients were treated prophylactically during the trial, of which the majority ( $n=57$ ; 90.5%) initiated treatment three times weekly. Of these 63 patients, 19 (30.2%) had no bleeds that required treatment while receiving prophylaxis. Overall, the Poisson estimate of ABR was lower for patients receiving prophylaxis versus on-demand treatment (2.62 vs 65.75 bleeds/patient/year, respectively). The overall median ABR for prophylaxis patients was also lower compared with those treated on-demand (1.18 vs 74.40 bleeds/patient/year, respectively) (Table 4).

## Resolution of Target Joints

A total of 49 patients had target joints at trial baseline, with up to 6 target joints observed in patients. Per the protocol definition, 25 (51.0%) of these 49 patients had all target joints resolved at the end of the trial. Of the 63 patients exposed to prophylaxis, a total of 111 target joints were reported by 50 patients at prophylaxis baseline (defined as the start of the prophylaxis regimen in the main or extension phase). During prophylaxis treatment,

**Table 2** Demographics and Baseline Characteristics

	<b>Small Children (0–&lt;6 Years)</b>	<b>Older Children (6–&lt;12 Years)</b>	<b>Adolescents (12–&lt;18 Years)</b>	<b>Adults (≥18 years)</b>	<b>Total</b>
<b>Number of patients</b>	9	33	11	15	68
Age at baseline (years), mean (SD)	4.00 (1.12)	8.70 (1.91)	14.55 (1.92)	31.00 (11.20)	13.94 (10.99)
Body weight (kg), median (Min.; max.)	16.4 (15.0; 21.3)	28.5 (16.5; 55.0)	50.0 (26.5; 65.1)	62.0 (41.5; 79.8)	39.0 (15.0; 79.8)
<b>BMI (kg/m<sup>2</sup>)</b>					
N <sup>a</sup>	0	0	11	15	26
Mean (SD)	–	–	17.68 (2.43)	20.92 (3.87)	19.55 (3.66)
<b>Prophylaxis in the last year – frequency of dosing</b>					
N <sup>a</sup> (%)	8 (100)	19 (100)	5 (100)	8 (100)	40 (100)
Once daily, n (%)	–	2 (10.5)	–	–	2 (5.0)
Every two days, n (%)	1 (12.5)	2 (10.5)	–	2 (25.0)	5 (12.5)
Three times weekly, n (%)	2 (25.0)	5 (26.3)	–	–	7 (17.5)
Every three days, n (%)	1 (12.5)	2 (10.5)	–	4 (50.0)	7 (17.5)
Twice weekly, n (%)	6 (75.0)	8 (42.1)	1 (20.0)	2 (25.0)	17 (42.5)
Every four days, n (%)	–	–	1 (20.0)	–	1 (2.5)
Once weekly, n (%)	2 (25.0)	5 (26.3)	2 (40.0)	–	9 (22.5)
NA, n (%)	–	2 (10.5)	1 (20.0)	–	3 (7.5)
<b>ABR during prophylaxis in the last year</b>					
N <sup>a</sup>	8	19	5	8	40
Mean (SD)	7.67 (6.30)	25.76 (39.20)	33.33 (40.66)	33.19 (27.93)	24.57 (33.32)
Median (Min.; max.)	6.55 (0.00; 19.64)	9.98 (0.00; 156.0)	12.00 (0.00; 83.01)	30.86 (0.00; 82.32)	10.85 (0.00; 156.0)
<b>ABR during on-demand in the last year</b>					
N <sup>a</sup>	3	16	6	7	32
Mean (SD)	44.15 (65.86)	45.59 (35.82)	61.82 (35.06)	69.20 (50.76)	53.67 (41.32)
Median (Min.; max.)	10.90 (1.54; 120.0)	38.49 (5.97; 120.0)	69.85 (11.94; 96.00)	49.23 (20.10; 156.0)	45.75 (1.54; 156.0)
Patients with baseline target joints, <sup>b</sup> N <sup>a</sup>	3	24	9	13	49
Number of baseline target joints, <sup>b</sup> N	3	45	19	38	105
Bleeds in target joints during the last year per patient, mean (SD)	5.33 (1.15)	36.63 (38.55)	53.33 (37.39)	41.92 (42.55)	39.18 (38.89)

**Notes:** <sup>a</sup>N, number of patients with reported outcome in each category. <sup>b</sup>Per protocol definition of target joints.

**Abbreviations:** ABR, annualized bleeding rate; BMI, body mass index; max., maximum; min., minimum; SD, standard deviation.

26 (52.0%) of these 50 patients and 78 (70.3%) of the 111 target joints at prophylaxis baseline had no bleeds that required treatment. A total of 36 (72.0%) patients had ≥1 baseline target joint resolved and 24 (48.0%) had all baseline target joints resolved. The Poisson estimate of ABR for target joints was 1.32 bleeds/patient/year.

Per the 2014 ISTH definition, 36 (73.5%) of the 49 patients with target joints at trial baseline had all baseline target joints resolved during the trial. During prophylaxis treatment, 45 (90.0%) of the 50 patients with target joints at prophylaxis baseline had ≥1 baseline target joint resolved and 38 (76.0%) had all baseline target joints resolved.

For patients treated on-demand, 35 target joints were reported in 11 patients at baseline. Per the protocol definition, two (18.2%) patients had no target joint bleeds. Per the protocol definition and ISTH definition, one (9.1%) patient had all baseline target joints resolved.

## Consumption of Turoctocog Alfa

The mean prophylaxis dose of turoctocog alfa was 40.5 IU/kg; the mean annual and monthly consumptions for prophylaxis were 6288 IU/kg/patient/year and 524.0 IU/kg/month/patient, respectively. The mean

**Table 3** Details of Bleeding Episodes and Hemostatic Response to Turoctocog Alfa Treatment (Combined Main and Extension Phase)

	<b>Small Children (0–&lt;6 Years)</b>	<b>Older Children (6–&lt;12 Years)</b>	<b>Adolescents (12–&lt;18 Years)</b>	<b>Adults (≥18 Years)</b>	<b>Total</b>
<b>Number of patients with bleeding episodes, N</b>	7	24	8	15	54
Number of bleeding episodes, N	65 (100)	405 (100)	53 (100)	402 (100)	925 (100)
<b>Cause of bleed, N (%)</b>					
Spontaneous	36 (55.4)	332 (82.0)	43 (81.1)	360 (89.6)	771 (83.4)
Traumatic	29 (44.6)	70 (17.3)	10 (18.9)	39 (9.7)	148 (16.0)
NA/NK	–	3 (0.7)	–	3 (0.8)	6 (0.6)
<b>Site of bleed, N (%)</b>					
Joint <sup>a</sup>	19 (29.2)	260 (64.2)	49 (92.5)	322 (80.1)	650 (70.3)
– Target joint	9 (13.9)	183 (45.2)	35 (66.0)	251 (62.4)	478 (51.7)
Mucosal	7 (10.8)	50 (12.4)	3 (5.7)	37 (9.2)	97 (10.5)
Muscular <sup>a</sup>	9 (13.9)	63 (15.6)	1 (1.9)	39 (9.7)	112 (12.1)
Subcutaneous	28 (43.1)	29 (7.2)	–	3 (0.8)	60 (6.5)
Other	2 (3.1)	3 (0.7)	–	1 (0.3)	6 (0.7)
<b>Classification of bleed, N (%)</b>					
Mild/moderate	65 (100)	403 (99.5)	52 (98.1)	389 (96.8)	909 (98.3)
Severe	–	2 (0.5)	1 (1.9)	13 (3.2)	16 (1.7)
<b>Hemostatic response,<sup>b</sup> N (%)</b>					
Excellent	45 (69.2)	275 (67.9)	42 (79.2)	272 (67.7)	634 (68.5)
Good	18 (27.7)	103 (25.4)	11 (20.8)	116 (28.9)	248 (26.8)
Moderate	2 (3.1)	26 (6.4)	–	14 (3.5)	42 (4.5)
None	–	–	–	–	–
Missing	–	1 (0.2)	–	–	1 (0.1)
<b>Success,<sup>b,c</sup> N (%)</b>					
Success	63 (96.9)	378 (93.3)	53 (100)	388 (96.5)	882 (95.4)
Failure	2 (3.1)	27 (6.7)	–	14 (3.5)	43 (4.6)
<b>Infusions to treat the bleed (from start to stop of the bleed) N (%)</b>					
1 infusion	47 (72.3)	341 (84.2)	48 (90.6)	337 (83.8)	773 (83.6)
2 infusions	15 (23.1)	36 (8.9)	5 (9.4)	43 (10.7)	99 (10.7)
3 infusions	2 (3.1)	14 (3.5)	–	8 (2.0)	24 (2.6)
≥4 infusions	1 (1.5)	14 (3.5)	–	14 (3.5)	29 (3.1)
Mean (SD)	1.3 (0.6)	1.3 (0.9)	1.1 (0.3)	1.3 (1.2)	1.3 (1.0)

**Notes:** <sup>a</sup>Data include multiple location bleeds; <sup>b</sup>hemostatic 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; <sup>c</sup>Including missing responses as failure.

**Abbreviations:** NA, data not available; NK, not known; SD, standard deviation.

(SD) on-demand dose of turoctocog alfa for treatment of bleeds was 27.8 (13.2) IU/kg; the annual and monthly consumptions used for on-demand treatment of bleeds were 2999 IU/kg/patient/year and 249.9 IU/kg/month/patient, respectively. Overall, the mean (SD) consumption of turoctocog alfa for the treatment of a bleed across both regimens was 30.95 (13.1) IU/kg.

## Surgery

Turoctocog alfa was used for bleeding prevention in four major and five minor surgeries that took place during the trial (Table 5). Hemostatic response to turoctocog alfa was successful (“excellent” and/or “good”) during and after all eight surgeries for which responses were recorded, and none of the patients received a blood transfusion.

**Table 4** Annualized Bleeding Rates

	Small Children (0–<6 Years)	Older Children (6–<12 Years)	Adolescents (12–<18 Years)	Adults (≥18 Years)	Total
<b>ABR (prophylaxis regimen)</b>					
N	9	31	11	12	63
Median (IQR)	1.71 (2.12)	1.18 (3.37)	1.15 (2.14)	1.54 (10.02)	1.18 (3.38)
Poisson estimate (95% CI)	2.15 (1.14; 4.09)	2.74 (1.56; 4.80)	1.93 (0.79; 4.70)	3.75 (1.57; 8.95)	2.62 (1.79; 3.82)
<b>ABR (on-demand regimen)</b>					
N	1	7	1	8	17
Median (IQR)	74.4 (–)	64.73 (34.88)	44.72 (–)	85.61 (42.26)	74.40 (43.49)
Poisson estimate (95% CI)	–	61.41 (45.55; 82.80)	–	70.70 (53.05; 94.22)	65.75 (54.52; 79.28)

**Abbreviations:** ABR, annualized bleeding rate; CI, confidence interval; IQR, interquartile range; N, number of patients with reported outcome in each category.

**Table 5** Hemostatic Response and Surgery Details

Surgery	Patient Age, Years	Duration, hh:mm	Hemostatic Response During <sup>a</sup>	Hemostatic Response After <sup>b</sup>	Blood Loss, mL (Actual/Estimated)
Pseudocarcinoma excision (major)	44	1:40	Excellent	Excellent	200/300
Tooth extraction (minor)	26	NA	Excellent	Excellent	1/2
Gingival debridement (minor)	14	NA	Good	Excellent	3/3
Correction of hypospadias (major)	11	3:10	Good	Excellent	20/20
Urethral dilation (minor)	11	0:15	Excellent	Excellent	–
Genitourinary transposition (major)	11	1:15	Good	Good	5/5
Tooth extraction (minor)	5	NA	Excellent	Excellent	–
Femoral fracture fixation (major)	17	2:20	Good	Good	100

**Notes:** <sup>a</sup>Hemostatic response during surgery was evaluated on a four-point scale, where “excellent” (blood loss less than expected) and “good” (blood loss as expected) responses were classified as successful, and responses rates as “moderate” (blood loss more than expected), or “none” (uncontrolled bleeding) were classified as failure. <sup>b</sup>Hemostatic response after surgery was evaluated on a four-point scale, where “excellent” (better than expected/predicted in this type of procedure) and “good” (as expected in this type of procedure) responses were classified as successful, and responses rated as “moderate” (less than optimal for the type of procedure, but hemostatic response maintained without change of treatment regimen), or “none” (bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required) were classified as failure.

**Abbreviation:** NA, data not available.

## Pharmacokinetics

A total of 17 patients were included in the PK assessment (age range: 3 to 44 years). PK parameters based on FVIII activity measured using a chromogenic assay are presented (Table 6; Figure 2). The 17 patients evaluated had a mean (SD) IR of 0.023 (0.006) (IU/mL)/(IU/kg) at the time of the assessment. The  $t_{1/2}$  of turoctocog alfa was similar in children <12 years and adults; the overall mean (SD) terminal  $t_{1/2}$  was 9.0 (2.4) hours.

## Safety

The safety analysis set included all 68 patients exposed to turoctocog alfa. No FVIII inhibitors ( $\geq 0.6$  BU) were reported. A total of 143 AEs were reported in 46 (67.6%) patients. The majority (99.3%) of events were of mild to moderate severity. The most commonly reported AEs were upper respiratory tract infections (27.9% of patients), nasopharyngitis (14.7%), pyrexia (8.8%) and diarrhea (7.4%). Four serious AEs (lung infection, asthma, femur fracture and hand-foot-and-mouth

disease) were reported. The serious AEs all occurred in three patients on prophylaxis and were evaluated as unlikely related to turoctocog alfa. The investigator evaluated two AEs of acne in one adolescent patient as possibly related to turoctocog alfa. The dose was not changed as a result of these AEs and both were resolved. No patients were withdrawn due to AEs, and no fatalities, hypersensitivity reactions or allergic reactions occurred during the trial.

## Patient-Reported Outcomes

Improvements in total HAEM-QOL scores (demonstrated by a negative change in value) from baseline to the end of trial were reported across all age groups. Changes in total HAEM-QOL scores were –10.1 (8–12 years), –4.9 (13–16 years), and –6.3 ( $\geq 17$  years), as reported by patients. Patients  $\geq 17$  years of age reported the greatest improvement in HAEM-A-QOL scores for “physical health” (–23.1) and “work and school” (–11.3). Patients 13–16 years of age reported the greatest improvement in HAEMO-QOL scores for “future” (–18.8) and “physical

**Table 6** Pharmacokinetic Parameters

Mean (SD)	Small Children <sup>a</sup> (0–<6 Years)	Older Children (6–<12 Years)	Adolescents (12–<18 Years)	Adults (≥18 Years)	Total
N	4	6	3	4	17
AUC <sub>0–inf</sub> (IU* <i>h</i> /mL)	16.4 (3.5)	17.7 (7.3)	11.2 (4.7)	16.9 (1.5)	16.0 (5.3)
AUC <sub>0–inf log</sub> (IU* <i>h</i> /mL)	68.9 (13.0)	70.5 (28.4)	72.0 (11.3)	69.4 (10.3)	70.2 (18.2)
<i>t</i> <sub>1/2</sub> (h)	8.5 (1.4)	8.3 (3.1)	11.6 (0.6)	8.4 (1.9)	9.0 (2.4)
IR (IU/mL)/(IU/kg)	0.022 (0.003)	0.026 (0.005)	0.014 (0.007)	0.026 (0.004)	0.023 (0.006)
CL (mL/h/kg)	3.7 (0.9)	3.5 (1.2)	5.5 (2.2)	3.5 (0.3)	3.9 (1.4)
C <sub>max</sub> (IU/mL)	1.2 (0.2)	1.4 (0.3)	0.9 (0.5)	1.6 (0.2)	1.3 (0.3)

**Notes:** <sup>a</sup>For one small child, the terminal rate constant could not be estimated, and therefore the AUC<sub>0–inf</sub>, AUC<sub>0–inf log</sub>, CL and *t*<sub>1/2</sub> were not calculated.

**Abbreviations:** AUC, area under the curve; CL, clearance; C<sub>max</sub>, maximal FVIII activity; IR, incremental recovery; N, number of patients; *t*<sub>1/2</sub>, terminal half-life; SD, standard deviation.

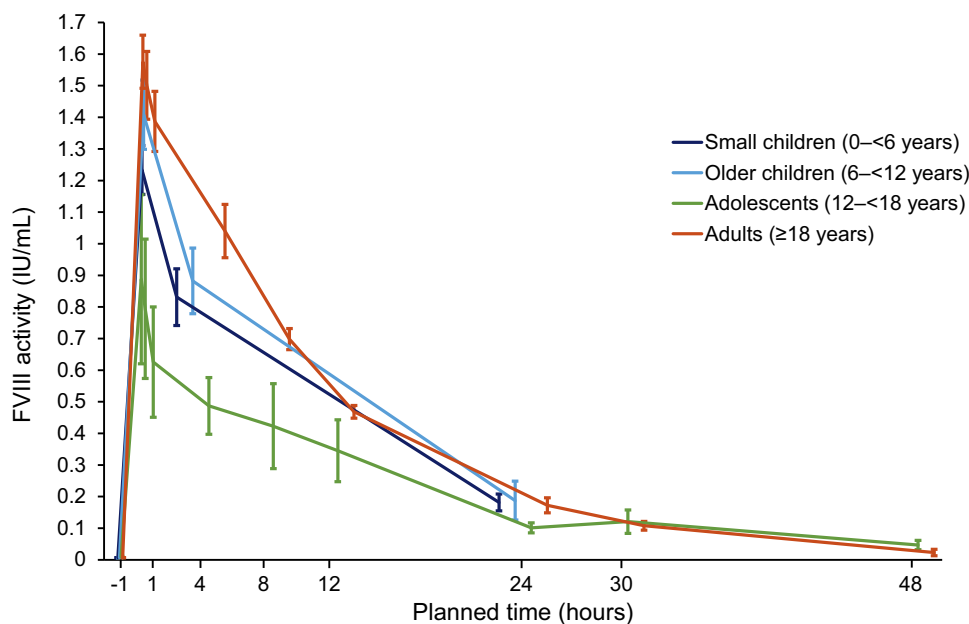
health” (–14.9). Patients 8–12 years of age reported the greatest improvement in HAEMO-QOL scores in “physical health” (–22.3) and “sports and school” (–13.5).

## Discussion

Guardian 7 is the first prospective, confirmatory safety and efficacy trial conducted in PTPs from China in accordance with EMA guidelines for the investigation of FVIII products,<sup>19</sup> and the first trial to have investigated the efficacy of standard prophylaxis (three times weekly or more) at full dose (up to 50 or 60 IU/kg) in patients from China of all age groups. It comprised a robust study design with a larger patient population and longer duration of follow-up compared with previous

studies of rFVIII products in patients from China. Furthermore, it included the assessment of a relatively high number of pediatric hemophilia A patients (<12 years, n=42) to demonstrate the safety and efficacy of turoctocog alfa as primary and secondary prophylaxis.

Haemophilia treatment in China is characterised by sub-optimal treatment with low-dose, low-frequency prophylaxis regimens,<sup>7,10,23</sup> which was observed in the guardian 7 patient population in the year prior to joining the trial, where the mean reported ABR for patients with prophylaxis treatment was 24.57 bleeds/patient/year, and only 35.0% patients reported receiving standard prophylaxis. During the trial, patients who received prophylaxis demonstrated a lower ABR compared

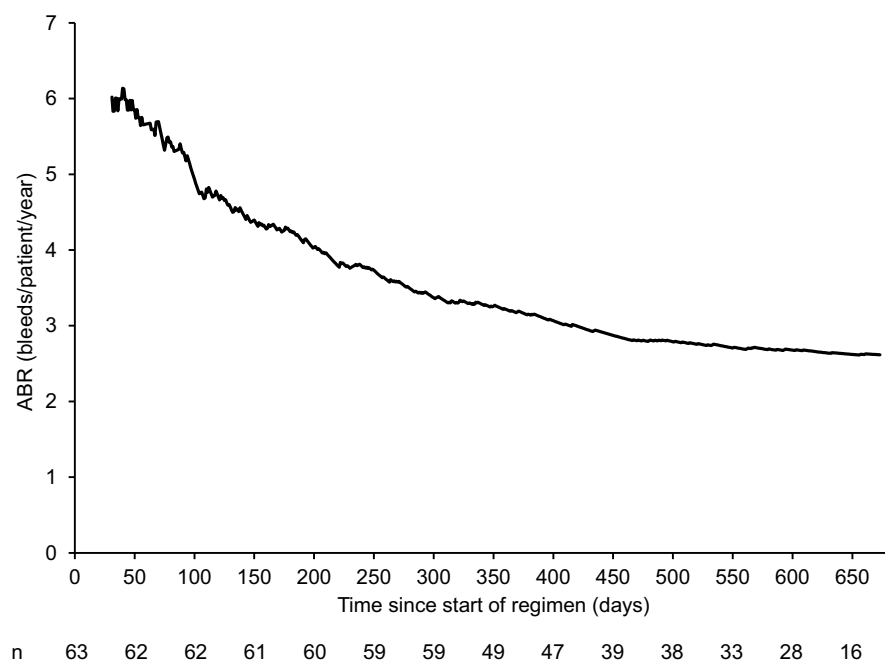


**Figure 2** Mean FVIII activity profile following administration of turoctocog alfa, by age group.

**Notes:** Chromogenic assay (linear scale), excluding outliers; bars show the standard error of the mean. A total of 17 patients were included in the PK assessment (small children, n=4; older children, n=6; adolescents, n=3; adults, n=4). Sampling frequency per patient for PK assessment varied between age groups (0–11 years, n=5 samples; ≥12 years, n=11 samples).

**Abbreviation:** PK, pharmacokinetic.





**Figure 3** Development of individual ABR over time for patients in the prophylaxis regimen.

**Notes:** Only treatment-requiring bleeds and periods in which a patient was at risk are included. Results for the first month and periods where there are less than 10 patients on a regimen have been excluded for stability purposes.

**Abbreviations:** ABR, annualized bleeding rate; n, number of patients.

with those treated on demand. A reduction in ABR over time for patients on standard prophylaxis was observed across all age groups (Figure 3), and the resulting Poisson estimate of ABR and mean ABR for prophylaxis patients was 2.62 and 2.91 bleeds/patient/year, respectively. These findings suggest that long-term treatment with standard prophylaxis offers improved ABR outcomes compared with those observed with the low-dose, low-frequency regimens frequently used in China.<sup>9,24</sup>

Guardian 7 results suggest a benefit of standard prophylaxis for reducing joint bleeds and resolving target joints following long-term treatment, which is in agreement with conclusions from other studies.<sup>8,25,26</sup> The limited use of primary prophylaxis in China suggests that many adult patients would have received turoctocog alfa as tertiary prophylaxis treatment.<sup>7,27</sup> Considering up to 70% of hemophilia patients in China are expected to develop arthropathy in adulthood,<sup>28</sup> the reduction of joint bleeds and resolution of target joints observed during guardian 7 suggests that even tertiary prophylaxis with standard doses and frequency can help to rehabilitate joints.

Hemostatic success of turoctocog alfa for the treatment of bleeds during guardian 7 was comparable with other turoctocog alfa trials investigating PTPs.<sup>15,29,30</sup> Despite differences in patient ethnicity, similarities in hemostatic success

between turoctocog alfa trials may be attributed to similarities in the treatment guidelines and evaluation instruments. Furthermore, hemostatic success with turoctocog alfa was similar to that observed in other hemophilia clinical trials of approved treatments in China, including Advate<sup>®</sup> (100%; Shire/Takeda) and Kogenate<sup>®</sup>FS (100%; Bayer), although in those studies the population size was slightly smaller and the majority of patients had mild/moderate hemophilia.<sup>31,32</sup>

Turoctocog alfa provided successful bleeding prevention in several major surgeries performed during guardian 7, including complex procedures such as removal of a pseudotumor, a corrective genitourinary surgery and fixation of a femoral fracture. Despite the presence of hemophilic arthropathy in many patients, no orthopedic procedures or joint replacements were performed, perhaps due to a relatively young study population and patients having to finance the procedures.

The safety of turoctocog alfa in guardian 7 was well tolerated in all age groups and comparable with other turoctocog alfa trials investigating PTPs.<sup>15,29,30</sup> No patient developed FVIII inhibitors, as expected for this population of PTPs.

PK results in pediatric patients (>12 years) and adults were consistent with previous observations in other turoctocog alfa clinical trials with PK assessments.<sup>30,33</sup>

Mean FVIII activity following administration of turoctocog alfa was lower in adolescent patients, which may partly be influenced by the small sample size ( $n=3$ ). Furthermore, mean IR and AUC were lower, and mean CL was higher in adolescent patients compared with the overall PK population. For patients undergoing PK assessment, mean body mass index (BMI) was lower in adolescents than adults ( $15.3 \text{ kg/m}^2$  versus  $21.1 \text{ kg/m}^2$ ), which could explain the difference in PK results, as BMI has previously been shown to be positively correlated with IR and AUC, and negatively correlated with CL.<sup>34</sup> There was no positive correlation with age for any of the PK parameters assessed. This differs from results observed in a global trial of turoctocog alfa, which suggested that IR,  $t_{1/2}$  and AUC increase with age whereas CL decreases.<sup>33</sup>

During guardian 7, HAEM-QOL scores improved with time until the end of the trial for all age groups. Previous analysis of HAEM-QOL data has identified substantial impairments in the “physical health” domain for hemophilia patients, with HAEM-A-QOL scores strongly influenced by the presence of arthropathy and target joints.<sup>35,36</sup> In this trial, patients of all ages reported substantial improvements in the “physical health” domain – which may in part be due to a reduction in joint bleeds and resolution of target joints – suggesting that long-term prophylaxis with turoctocog alfa offers the opportunity to improve QoL.

## Conclusion

In conclusion, turoctocog alfa was safe and effective for prophylaxis and treatment of bleeding episodes in patients from China with severe hemophilia A across all ages. Furthermore, findings suggest that maintaining standard prophylaxis with FVIII aids the resolution of target joints in this population, providing the opportunity to improve QoL and reduce the long-term burden of care.

## Data Sharing 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](http://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](http://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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## 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.

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## Disclosure

RW has received consulting fees from Novo Nordisk, is a steering committee member for Bayer, and is a member of the speakers' bureaus for Novo Nordisk. IM is an employee of Novo Nordisk A/S. SZ is an employee of Novo Nordisk (China) Pharmaceuticals Co., Ltd. MP is a paid consultant to and reports personal fees from Novo Nordisk A/S. RY has received speaker/consultancy fees from Bayer, Novo Nordisk, Pfizer, Roche and Takeda, outside the submitted work. The authors report no other conflicts of interest in this work.

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