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ORIGINAL ARTICLE

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Turoctocog alfa is safe for the treatment of Indian patients with hemophilia A: Guardian 10 trial results

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Abstract

Background: Hemophilia A is an X chromosome–linked bleeding disorder caused by the deficiency of coagulation factor VIII (FVIII). The majority of the Indian population with hemophilia A use plasma-derived clotting factors and, in some instances, fresh frozen plasma and cryoprecipitate. Safer and more efficient treatment options are needed for this group of patients.

Objectives: To assess the safety of turoctocog alfa, a third-generation recombinant FVIII molecule, for the treatment and prophylaxis of bleeding episodes in previously treated Indian patients with moderate or severe hemophilia A.

Patients/Methods: This single-country, multicenter, open-label, nonrandomized trial enrolled 60 patients who received prophylactic treatment with turoctocog alfa for 8 weeks, which corresponded to a minimum of 20 exposure days. Confirmed development of FVIII inhibitors during the 8-week treatment period was evaluated. Other assessments included frequencies of adverse drug reactions (ARs), serious adverse reactions, drug-related allergic reactions, and infusion reactions during the 12-week period after the first treatment; hemostatic effect of turoctocog alfa for the treatment of bleeding episodes; and total annualized dose of turoctocog alfa administered during the 8-week treatment period.

Results: No incidence of FVIII inhibitors was detected. No safety concerns such as ARs, serious ARs, or drug-related allergic reactions were noted. The hemostatic success rate for the treatment of bleeding episodes with turoctocog alfa was 81.6%.

Conclusions: The trial results demonstrated that turoctocog alfa is a safe treatment option for the prophylaxis and treatment of bleeding episodes in previously treated adolescent and adult patients with hemophilia A in the Indian population.

Clinical Trial: Registration number NCT03449342

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KEYWORDS

coagulation factor VIII, hemophilia, hemostatic, treatment, turoctocog alfa

Essentials

- Safer treatment options are necessary for Indian patients with hemophilia A.
- This study assessed the safety of turoctocog alfa in an Indian cohort.
- There was no development of coagulation factor VIII inhibitors during the trial period.
- The safety of turoctocog alfa was demonstrated in Indian patients with hemophilia A.

1 | INTRODUCTION

Hemophilia A, the most prevalent type of hemophilia, is an inherited disorder caused by mutations in the coagulation factor VIII (*FVIII*) gene on the X chromosome. Absent or significantly decreased FVIII activity prevents adequate clot formation, and patients with severe hemophilia A are at high risk for spontaneous bleeding or excessive bleeding following injury or during surgery, with subsequent development of arthropathy, chronic pain, and disability.[1,2] Treatment for hemophilia A has progressed from the use of blood transfusions to the use of cryoprecipitates in 1960, plasma-derived (pd) FVIII concentrate in the 1970s, and recombinant products in the 1990s. In many countries, FVIII replacement therapy remains the standard of care for patients with hemophilia A without inhibitors, and in some countries, on-demand therapy is the only available option for the patients.[2-4] The estimated number of patients with hemophilia in India is more than 70 000, many of whom are not diagnosed and registered.[5] In India, 17 606 patients with hemophilia A are registered, and the majority of these patients are treated on demand at hemophilia care centers.[6,7] As per the current standard of care, among the FVIII concentrates used in India in 2017, 76% of the consumption was pd-FVIII.[8] In some instances, even fresh frozen plasma and cryoprecipitates are used in the treatment of hemophilia A in India.[5] The use of pd products exposes patients with hemophilia A to an increased risk of transfusion-transmitted infections (TTIs), among which HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) infections are the most prevalent. Real-world data from Indian patients with hemophilia A indicates that the approximate prevalence rates of HIV, HBV, and HCV infections due to blood transfusions are 1%, 6%, and 30%, respectively.[9-11]

Turoctocog alfa is a third-generation FVIII molecule with a truncated B-domain.[12] Preclinical studies have documented that turoctocog alfa retains full procoagulant activity[13] and has a pharmacokinetic profile similar to that of octocog alfa.[14] No human or animal proteins are used in the manufacture of turoctocog alfa,[12] and it has been reported that turoctocog alfa can withstand variable storage conditions and can be stored for up to 3 months at temperatures of up to 40°C and for up to 9 months at temperatures of up to 30°C without loss of stability.[4,15] Turoctocog alfa is approved for the treatment of hemophilia A [16] and has been demonstrated to have favorable safety and efficacy in previously treated children and adults with severe hemophilia A in two phase III trials—guardian 1 and guardian 3.[17,18] A recent phase IIIb trial, the guardian 2 extension trial, demonstrated that the extended use of turoctocog alfa was safe and effective for the prevention and treatment of bleeding episodes in patients of all age groups.[19]

The primary objective of this trial was to assess the safety of turoctocog alfa for the treatment and prophylaxis of bleeding episodes in previously treated Indian patients with moderate or severe hemophilia A. The trial was executed to fulfill the postapproval commitment requirements from the Indian Health Authority. The secondary objective of this trial was to assess the hemostatic efficacy of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated patients with moderate or severe hemophilia A. This article provides insights into the safety profile of turoctocog alfa in patients with severe or moderate hemophilia A in an Indian population.

2 | METHODS

2.1 | Patients

Males aged ≥ 12 years with moderate or severe congenital hemophilia A (FVIII ≤ 5%) with a documented history of at least 150 exposure days (EDs) to FVIII-containing products were eligible to participate in the trial. Patients with a history of FVIII inhibitors and those with a confirmed presence of FVIII inhibitors (≥0.6 Bethesda unit [BU]) at the time of screening were excluded from the trial. Additional exclusion criteria were known or suspected hypersensitivity to the trial product, participation in any clinical trial during the 1 month before screening, immunocompromised patients due to HIV infection, known congenital or acquired disorders other than hemophilia A, mental incapacity, unwillingness to cooperate, and language barrier. The trial was ethically approved by the institutional review boards at the respective trial sites. Written informed consent was obtained from all participants, and the trial was conducted according to the Declaration of Helsinki. For patients aged younger than 18 years, legally acceptable patient representatives provided written informed consent. The trial was registered at clinicaltrials.gov with a clinical trial registration number of NCT03449342.

2.2 | Trial design

Guardian 10 was a single-country, multicenter, open-label, nonrandomized, phase IV trial with a single treatment arm. Patients with moderate or severe hemophilia A who were previously treated with any FVIII-containing product, defined as those with ≥ 150 documented EDs, received prophylactic treatment with turoctocog alfa for 8 weeks, corresponding to at least 20 EDs on standard prophylaxis. Dosing for prophylaxis was based on the approved prescribing information. The frequency of dosing was either every second day or three times weekly at a dose range of 20-50 IU/kg. The trial design and visit schedule are presented in Figure 1. All patients were administered the first dose of turoctocog alfa at visit 2, which was the baseline visit. At the baseline visit, the trial product was administered intravenously by the patient or parent/legally acceptable representative at the trial site to ensure correct administration of the trial product. The trial product for home treatment was dispensed to the patient or parent/legally acceptable representative until next visit. The next visit, visit 3, involved review of the hemostatic efficacy of the trial product for the treatment of bleeding episodes, evaluation of the severity rating, and dispensing the trial product. Visit 4 was the final visit, at which time samples were collected to assess the presence of FVIII inhibitors, and all patients were instructed to cease FVIII treatment for 48 hours before visit 4. The patients' diaries were reviewed to assess the hemostatic efficacy of the trial product for the treatment of bleeding. The follow-up visit, visit 5, was scheduled for patients who completed the trial to assess any potential adverse events. Bleeding episodes were treated with one or more intravenous bolus injections of turoctocog alfa. The individual dose, determined by the investigator, was based on the World Federation of Hemophilia guidelines[20] and was according to the approved prescribing information using the formula: dose (IU) = weight (kg) × desired factor level (IU/dL) × 0.5.

2.3 | Trial end points

The primary end point was confirmed development of FVIII inhibitors during the 8-week treatment period. The secondary safety end points were frequencies of adverse drug reactions, serious adverse reactions, and allergic and infusion reactions associated with the trial product reported during the follow-up period of 12 weeks after the first treatment. The secondary efficacy end points were successful hemostatic effects of turoctocog alfa, which was based on a rating of "excellent" or "good" using a 4-point scale, for the treatment of bleeding episodes and total annualized dose of turoctocog alfa administered during the 8-week treatment period. The hemostatic effects of turoctocog alfa were jointly evaluated by the patients and investigators.

2.4 | Safety assessments

To assess the primary trial end point, the FVIII inhibitor levels were evaluated at the first and final trial visits. FVIII inhibitor levels were analyzed at Q^2 Solutions Laboratory, Singapore, using the Nijmegen-modified Bethesda assay.[21,22] A positive inhibitor test result was

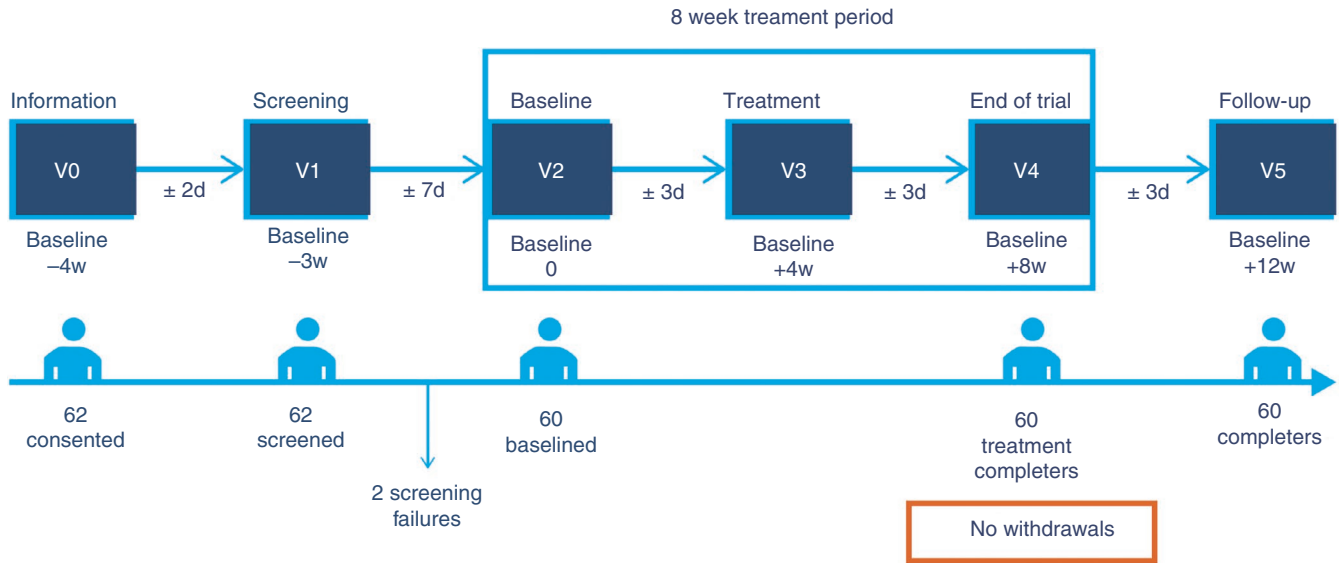

FIGURE 1 Trial design and study flow. A total of 62 patients were screened, and finally, 60 patients, including 10 adolescents and 50 adults, were enrolled in the trial. V0, information visit; V1, screening visit; V2, baseline visit, during which the first dose of turoctocog alfa was administered; V2-V4, 8-week treatment period; V5, final follow-up visit at 12 weeks after baseline visit

defined as a FVIII inhibitor level of ≥ 0.6 BU in accordance with the European Medicines Agency guidelines.[23] Other safety assessments included physical examination, evaluation of adverse events, medication errors, and clinical laboratory tests, including hematologic, biochemical, and antibody tests for the identification of FVIII inhibitors.

2.5 | Efficacy assessments

The hemostatic effect was assessed based on patient ratings using the following predefined 4-point scale: excellent, good, moderate, none, and missing.[24] An excellent or good hemostatic response was defined as success, whereas a rating of moderate, none, or missing for hemostatic response was defined as failure. Relevant details regarding treatment of bleeding episodes (location, severity, cause, and number of injections needed to manage a bleeding episode) were recorded in the medical records.

2.6 | Statistical analysis

The sample size was based on the requirements of the Indian Health Authorities. Novo Nordisk was mandated by the health authorities to perform a trial with 50 patients. The incidence rate of inhibitors (≥ 0.6 BU) was calculated, and a one-sided 97.5% upper confidence limit based on an exact calculation for a binomial distribution was provided. For the calculation of the incidence rate, the numerator included all patients with confirmed inhibitors any time after baseline visit, while the denominator included the number of patients in the safety analysis set. Additional safety and efficacy end points and the total annualized dose of turoctocog alfa administered were summarized using descriptive statistics.

2.7 | Drug product

The trial product turoctocog alfa was provided by Novo Nordisk A/S (Denmark). The drug was supplied in powder form in single-use sterilized vials with 2000 IU/vial and was reconstituted with 0.9% sodium chloride before intravenous injection.

3 | RESULTS

3.1 | Patients

Sixty-two male adults and adolescents with severe and moderate hemophilia A were screened for participation in the trial. Finally, 60 patients were enrolled in the trial, as there were two screening failures. Among the trial population, 10 patients were adolescents with ages ranging from 12 to <18 years. The demographic data and patient characteristics are presented in Table 1. The median age of adult patients was 26 years, whereas that of adolescent patients was 13.5 years. The trial population included 3 patients with moderate hemophilia A and 57 patients with severe hemophilia A. Among them, 53.3% of patients were on prophylaxis sometime within the previous 12 months before the start of the trial for a mean period of 9.10 months. On the other hand, 75% of patients were treated on demand within the previous 12 months before the start of the trial for a mean period of 9.46 months. All patients received turoctocog alfa prophylaxis for 8 weeks, which corresponded to at least 20 EDs on standard prophylaxis. The total number of EDs in the trial was 1523.

3.2 | Safety

No incidence of confirmed FVIII inhibitor development was observed during the trial period. A total of nine treatment-emergent adverse events were observed in 6 patients. The most common adverse events were upper respiratory tract infection (n = 4) and pyrexia (n = 2). Other adverse events were cough (n = 1), headache (n = 1), and nasopharyngitis (n = 1). All observed adverse events were either mild or moderate in severity. There was no adverse event with possible or probable relationship with the trial product. There were no fatalities or medication errors. One allergic reaction (cough) was observed, occurring at the same EDs as pyrexia and nasopharyngitis, with an unlikely relationship reported with turoctocog alfa. No surgeries were recorded in any of the patients.

3.3 | Efficacy

A total of 49 treated bleeding episodes were reported in 19 patients, of which 3 bleeding episodes were in the adolescent group and 46 bleeding episodes were in the adults.Of the 49 treated bleeding episodes, only 1 was classified as severe, and the remaining 48 were classified as mild or moderate. The most frequent bleeding location was the joints in both the adult and adolescent patients. The majority of the bleeding episodes were spontaneous (81.6%), which accounted for 82.6% in adults and 66.7% in adolescents (Table 2). The

TABLE 1 Demographic and baseline characteristics of the trial cohort

	Adolescents (12 to <18 years)	Adults (≥18 years)	Total
Number of patients	10	50	60
Age at baseline, years			
Mean (SD)	13.90 (1.91)	27.10 (7.28)	24.90 (8.32)
Median	13.50	26.00	25.00
Min; Max	12.00; 17.00	18.00; 50.00	12.00; 50.00
Severity of hemophilia A, N (%)			
Moderate	-	3 (6.00)	3 (5.00)
Severe	10 (100.0)	47 (94.00)	57 (95.00)

overall hemostatic success rate of turoctocog alfa bleed treatment was 81.6%. Finally, 81.6% of the treated bleeding episodes required one to two injections. The mean total annualized dose of turoctocog alfa administered per patient was 6086 IU/kg body weight for the adult patients and 7030 IU/kg body weight for the adolescent patients.

4 | DISCUSSION

In the guardian 10 trial, 60 Indian patients received prophylactic treatment with turoctocog alfa for 8 weeks, which corresponded to a minimum of 20 EDs. This time frame provided the opportunity to detect development of FVIII inhibitors after initiation of turoctocog alfa prophylaxis in previously treated patients. The patient population included patients with severe and moderate hemophilia A. Turoctocog alfa was well tolerated, and there were no safety concerns with its use in Indian patients. FVIII inhibitor development was not observed in the patients. The absence of FVIII inhibitor development along with no ARs and no drug-related allergic reactions observed in the present trial demonstrate the safe use of turoctocog alfa in patients with hemophilia A in an Indian population. The majority of the 49 treated bleeding episodes reported in the trial were mild or moderate in severity. The most frequent bleeding location was the joints (93.9%), and the major cause of bleeding episodes was spontaneous (81.6%). The overall percentage of spontaneous bleeding episodes in the patients was higher than that reported in other trials using turoctocog alfa.[17,18] The possible reasons for this could be that some patients previously received on-demand treatment and some of them may have had a joint disease. The hemostatic success rate was 81.6% for the treatment of bleeding episodes, and 81.6% of the bleeding episodes were treated using one to two injections of turoctocog alfa.

The use of pd products for the treatment of patients with hemophilia A imposes a risk of TTIs.[9] A recent retrospective study from a regional blood transfusion center in northern India demonstrated the prevalence of contagious pathogens such as HIV (0.32%), HBV (1.61%), HCV (0.73%), syphilis (1.62%), and malaria (0.06%) in the blood supply from donors.[25] The seroprevalence of pathogens such as HIV, HBV, HCV, and syphilis were also reported in blood donors from a rural Indian population.[26] The manufacturing process for turoctocog alfa uses an advanced purification technique for the inactivation and removal of contagious pathogens, and potential viral pathogens are eliminated by solvent/detergent inactivation and nanofiltration using a filter with a 20-nm pore size.[27] These purification steps strengthen the safety of turoctocog alfa against known

TABLE 2 Details of bleeding episodes and hemostatic response to turoctocog alfa treatment

	Adolescents (12 to <18 years)	Adults (≥18 years)	Total
Number of patients	10	50	60
Number of patients with bleeds, N (%)	2 (20.0)	17 (34.0)	19 (31.7)
Number of bleeding episodes	3	46	49
Site of bleeding, N (%)			
Joint	2 (66.7)	44 (95.7)	46 (93.9)
Muscle	1 (33.3)	2 (4.3)	3 (6.1)
Classification of bleeding, N (%)			
Mild/moderate	3 (100.0)	45 (97.8)	48 (98.0)
Severe	-	1 (2.2)	1 (2.0)
Site of severe bleeding, N (%)			
Joint	-	1 (100.0)	1 (100.0)
Cause of bleeding, N (%)			
Spontaneous	2 (66.7)	38 (82.6)	40 (81.6)
Traumatic	1 (33.3)	8 (17.4)	9 (18.4)
Hemostatic response, N (%)			
Excellent	1 (33.3)	10 (21.7)	11 (22.4)
Good	1 (33.3)	28 (60.9)	29 (59.2)
Moderate	1 (33.3)	8 (17.4)	9 (18.4)
None	-	-	-
Missing	-	-	-
Success/failure, N (%)			
Success	2 (66.7)	38 (82.6)	40 (81.6)
Failure	1 (33.3)	8 (17.4)	9 (18.4)

as well as unknown pathogens. The improved safety of turoctocog alfa provides a safer treatment alternative to blood transfusions and eliminates the risk of TTIs in Indian patients with hemophilia A.

Turoctocog alfa was extensively evaluated in one of the largest clinical development programs for clotting factors. In the guardian clinical trial program, guardian 1 included previously treated adolescent and adult patients with severe hemophilia,[17] whereas guardian 3 included previously treated pediatric patients.[18] Additionally, guardian 2 was a phase IIIb long-term extension trial involving patients from both the guardian 1 and 3 trials.[19] The results of the present trial are consistent with those of guardian 1,[17] guardian 3,[18] and guardian 2 [19] and demonstrate the absence of the development of FVIII inhibitor in previously treated patients and an overall favorable safety profile of turoctocog alfa.

One of the limitations of the trial was the short study duration, which limited the collection of meaningful data on the efficacy of bleeding prevention. However, the results of this first phase IV postapproval trial of an FVIII compound in India will provide the basis for future clinical research in hemophilia. Future research will focus on examining the effects of short-term secondary prophylaxis on the study population by characterizing the degree of existing joint damage and frequency of bleeding and assessing the benefit of this prophylaxis on the quality of life, mobility, and bleeding frequency after the study.

In summary, the present trial demonstrated the favorable safety profile of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated adult and adolescent patients with hemophilia A in an Indian population. The guardian 10 trial provides additional documentation of the safety of turoctocog alfa and supports its addition to the available treatment options for patients with hemophilia A in India.

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AUTHOR CONTRIBUTIONS

PC contributed to the conception and design of the study, recruitment of patients, and development of the study protocol. MJJ was the chief investigator of the study and contributed to the analytical plan. TH contributed to data interpretation and the analytical plan. All authors were involved in the critical review of the manuscript during the draft development and approved the final manuscript for submission.

RELATIONSHIP DISCLOSURE

TH and RK are employees of Novo Nordisk. JMJ is an advisory board member of Roche, Shire, and Novo Nordisk and has also received grants for inhibitor screening in northern India. PC has participated in an advisory board meeting of Novo Nordisk and has accepted speaker fees from Novo Nordisk and Pfizer Rare Disorders. AA has received travel and accommodation support during conferences from Novo Nordisk. All other authors declare no conflict of interest.

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