Clinical haemophilia

Long-term safety and efficacy of turoctocog alfa in prophylaxis and treatment of bleeding episodes in severe haemophilia A: Final results from the guardian 2 extension trial

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Abstract

Introduction: Turoctocog alfa is a recombinant factor VIII (FVIII) molecule, approved for treatment and prophylaxis of bleeding in patients with haemophilia A. In the guardian 1 (adolescents/adults) and guardian 3 (children) phase 3 trials, turoctocog alfa demonstrated a favourable efficacy and safety profile. The guardian 1 or 3 completers could enrol in the guardian 2 extension. Final guardian 2 results are reported here.

Aim: Investigate long-term safety and efficacy of turoctocog alfa administered for prophylaxis and treatment of bleeds.

Methods: In this phase 3b open-label trial, previously treated males of all ages with severe haemophilia A received prophylaxis regimens of turoctocog alfa or on-demand treatment of bleeds. The primary safety endpoint was frequency of FVIII inhibitor development. Efficacy endpoints included annualized bleeding rate (ABR) during prophylaxis, haemostatic response in treatment of bleeds and number of injections required to treat bleeds.
INTRODUCTION

Standard therapy for haemophilia A involves administering FVIII concentrates, either plasma-derived or recombinant FVIII [rFVIII], to replace the deficient FVIII and restore haemostasis.1 Turoctocog alfa is a third-generation rFVIII molecule2,3 approved for the treatment and prophylaxis of bleeding in patients with haemophilia A.4 Turoctocog alfa demonstrated favourable efficacy and safety in the guardian 1 and guardian 3 pivotal phase 3 trials involving previously treated adults and children with severe haemophilia A.5,6 Here, final safety and efficacy results from the guardian 2 extension trial are reported.

MATERIALS AND METHODS

2.1 | Trial design

This was a phase 3b, non-randomized, open-label, multicentre, multinational, single-arm, safety and efficacy extension trial (NCT00984126). Previously treated patients (PTPs) with severe haemophilia A (FVIII activity ≤1%) and no history of FVIII inhibitors were enrolled. Patients who had completed guardian 1 or guardian 3 or phase 1 pharmacokinetics trials and who chose to continue prophylaxis with turoctocog alfa in the guardian 2 extension trial were eligible. A 6-month on-demand sub-trial was subsequently added to ensure collection of sufficient on-demand regimen data.

Patients were included at 52 sites in 19 countries (Table S1). The trial was approved by all relevant independent ethics committees and institutional review boards. All participants provided written informed consent.

2.2 | Patients and treatment

Patients received prophylaxis or on-demand treatment with turoctocog alfa. Prophylaxis was administered as standard (20-50 IU/kg once every second day or 20-60 IU/kg three times weekly) or as less-frequent prophylaxis (40-60 IU/kg twice weekly or once every third day). The dose and regimen were chosen by the investigator. For treatment of bleeds, the recommended dose level was 20-50 IU/kg. Switching regimens and adjusting the dosing schedule was permitted.

Trial participation continued until turoctocog alfa was commercially available in the patient’s country, until the predefined end of trial date or at the latest until 30 June 2016.

2.3 | Trial endpoints and clinical assessments

The primary safety endpoint was frequency of FVIII inhibitor development (≥0.6 BU). The secondary safety endpoint was frequency of adverse events (AEs) and of serious AEs (SAEs).

Efficacy endpoints were assessed by annualized bleeding rate (ABR) during prophylaxis, haemostatic response in treatment of bleeds, number of injections to treat each bleed, time to control each bleed and total consumption of turoctocog alfa (IU/kg body weight/bleeding episode).

Details of clinical assessments have been previously published.7,8

Statistical methods

No formal testing of statistical hypotheses was performed.

Haemostatic response was presented using a success/failure rate (bleeds with missing evaluations were excluded). Mean ABR was estimated using a Poisson model allowing for over-dispersion. Frequency of inhibitor development was calculated as number of patients with inhibitors during the trial divided by number of patients in the trial with a 95% one-sided upper confidence limit.

RESULTS

A total of 214 patients were enrolled, 213 dosed with turoctocog alfa and 130 completed the main trial (Figure S1). Patient demographic and baseline characteristics are shown in Table S2.
A total of 207 patients were treated prophylactically (27 on the less-frequent regimen) and 19 were treated on-demand. Trial sequences (ie, switching between treatment regimens) are detailed in Table S3.

Accumulated number of patient-years for all 207 patients on prophylaxis was 730.8; for the 27 patients on less-frequent prophylaxis was 16.9; and for those treated on-demand was 16.3 (including in the on-demand sub-trial).

3.1 | Safety

No FVIII inhibitors were reported, with a 95% one-sided confidence upper limit of 1.4%. A total of 1260 AEs were reported in 183 (85.9%) patients (Table S4), corresponding to 1.7 AEs per patient-year of exposure. The most common AE (% of total patients) was nasopharyngitis (14.6%; Table S5).

Forty-seven SAEs occurred in 39 (18.3%) patients (Table S4); all except one event were judged “unlikely” related to turoctocog alfa treatment.

There was one fatal event in a 57-year-old patient on prophylaxis, which the investigator considered “unlikely” related to turoctocog alfa.

3.2 | Efficacy

3.2.1 | Prevention of bleeding episodes

In those on prophylaxis, 1782 bleeds were reported in 170/207 patients. Overall Poisson-estimated mean ABR among patients on prophylaxis was 2.44 bleeds/patient/y (95% confidence interval [CI]: 2.06-2.89 bleeds/patient/y); overall median ABR was 1.37 bleeds/y (range 0.00-17.82; Table S6). ABR by cause of bleed and location is shown in Figures S2 and S3.

In those on less-frequent prophylaxis, 34 bleeds were reported in 13/27 patients. Overall Poisson-estimated mean ABR among patients on less-frequent prophylaxis was 2.01 bleeds/patient/y (95% CI: 1.21-3.33 bleeds/patient/y); overall median ABR was 0.00 bleeds/y (range 0.00-9.91; Table S7).

Mean per-patient consumption of turoctocog alfa for prophylaxis overall was 5094 IU/kg/y, with a mean dose level of 32.5 IU/kg; corresponding figures for the less-frequent prophylaxis regimen were 5432 IU/kg/y and 48.2 IU/kg.

3.2.2 | Treatment of bleeding episodes

A total of 2173 bleeds were reported: 88.7% were classified as mild/moderate and 11.2% as severe. In total, 1607 (74.0%) bleeds were stopped with one injection of turoctocog alfa and 336 (15.5%) with two injections. A mean (SD) of 1.6 (2.4) injections was required to stop the bleed, the median (range) time from first administration of turoctocog alfa until the bleed stopped was 7.7 (0.0-671.0) hours, and the mean consumption of turoctocog alfa from start to stop of the bleed was 58.9 IU/kg. Overall, the success rate for the treatment of bleeds was 91.4%.

Of the 1782 bleeds during prophylaxis, 1572 (88.2%) were stopped with 1-2 injections. A mean (SD) of 1.7 (2.6) injections was required to stop the bleed. Success rate for the treatment of bleeds was 90.2% (Table S8).

Of the 34 bleeds during the less-frequent prophylaxis regimen, 26 (76.5%) were stopped with one injection of turoctocog alfa. A mean (SD) of 1.3 (0.6) injections was required to stop the bleed. Success rate for the treatment of bleeds was 94.1%.

In the on-demand regimen, 391 bleeds were reported in 19 patients. Overall Poisson-estimated mean ABR was 24.02 bleeds/patient/y (95% CI: 16.90-34.15 bleeds/patient/y); overall median ABR was 30.44 bleeds/y (range 2.21-73.05).

Of the 391 bleeds during the on-demand regimen, 94.1% were classified as mild/moderate and 5.9% as severe. In total, 310 (79.3%) bleeds were stopped with one injection of turoctocog alfa and 61 (15.6%) with two injections. A mean (SD) of 1.3 (0.6) injections was required to stop the bleed. Median (range) time from first administration of turoctocog alfa until the bleed stopped was 8.5 (0.4-120.8) hours. Success rate for the treatment of bleeds was 96.7%.

4 | DISCUSSION

The guardian 2 trial is one of the largest clinical trials to date conducted in patients with haemophilia A; 213 patients were exposed to turoctocog alfa, with 753 patient-years in the trial. The final results of guardian 2 are consistent with data from previous interim analyses.7,8 Turoctocog alfa was well tolerated, with no unexpected safety signals and no development of FVIII inhibitors. Thus, throughout the guardian 1, 2 and 3 trials, 238 PTPs with severe haemophilia A were exposed to turoctocog alfa for 856 patient-years and received a total of 136 471 injections without the occurrence of inhibitors.9

The guardian 2 trial also evaluated a less-frequent dosing regimen (twice weekly or every third day) in selected patients, which demonstrated efficacy, with an overall median ABR of 0.00 (Poisson-estimated mean ABR 2.01), and a treatment success rate of 94.1%. These data suggest a subset of patients might be well managed with less-frequent dosing.

In conclusion, extended use of turoctocog alfa is safe and effective in the prevention and treatment of bleeding episodes across all age groups of PTPs with severe haemophilia A.

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CONFLICT OF INTERESTS

SRL has acted as a paid consultant to Novo Nordisk and has received research funding; DJ received reimbursement for attending a symposium and fee for speaking from Novo Nordisk; KK received speaking fees, reimbursement for scientific congresses, funding as a study investigator, and has advisory board membership with/ from the sponsor (Novo Nordisk); PM acted as a paid investigator in the guardian 2 extension trial, funded by Novo Nordisk; JO has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or consulting, and/or funds for research from Shire, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum; MO has received grant/ research support from Biogen, Novo Nordisk and Shire; has served on advisory boards for Shire, Novo Nordisk, Pfizer, CSL Behring and Roche; and has served on speakers’ bureau for Shire, Novo Nordisk, Pfizer, Grifols and Roche; ES has received speaker and/ or consulting fees for: Bayer, Shire, CSL Behring, Novo Nordisk, Pfizer, Roche, SOBI, Bioverativ, Grifols, Octapharma and Kedrion; TS has received speaker fees from Novo Nordisk, Bayer, Baxalta, Bioverative, Pfizer, CSL Behring, Chugai, Sekisui Medical, Kaketsuken, Nihon Pharmaceutical, Werfen, and consultant fees from Novo Nordisk, CSL Behring and Chugai; SZS has received reimbursement for attending symposia/congresses and honoraria for speaking from Octapharma, Shire and Novo Nordisk; KK performed the research, analyzed the data and wrote the paper; PM designed the research study, performed the research and wrote the paper; JO performed the research, analyzed the data and reviewed the paper; ES performed the research, analyzed the data and reviewed the paper; AT reports grants and personal fees for lectures and consultancy from Alnylam, Bayer, Biogen Idec, Biotest, Boehringer Ingelheim, CSL Behring, Leo Pharma, Novo Nordisk, Octapharma, Pfizer, Portola, Roche, Shire and SOBI.

AUTHOR CONTRIBUTIONS

SRL performed the research, analyzed the data and revised the paper; DJ performed the research and reviewed the paper; KK performed the research, analyzed the data and wrote the paper; PM designed the research study, performed the research and wrote the paper; JO performed the research, analyzed the data and reviewed the paper; MO performed the research and reviewed the paper; ES performed the research, recruited subjects, interpreted the data and wrote the paper; TS performed the research and reviewed the paper; SZS designed the research study, analyzed the data and reviewed the paper; LK analyzed the data and wrote the paper; IM designed the research study, performed the research, analyzed the data and reviewed the paper; AT performed the research and reviewed the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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