Safety and efficacy of turoctocog alfa for prophylaxis and treatment of bleeding episodes in patients with severe hemophilia A: results from the guardian™2 trial

P-T-97

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Objective

- To report an analysis of new long-term safety and efficacy results (over 5 years for some patients) from the guardian™2 trial.

Conclusions

- As of the interim cut-off date (March 25, 2015), no patient had developed factor VIII inhibitors and no other clinically significant safety concerns had been identified.
- The median annualized bleeding rate for spontaneous bleeds in patients on prophylactic treatment was 0.52 bleeds/year. The overall success rate for treatment of bleeds was 89.7%; 89.9% of bleeds were resolved with ≤2 infusions of turoctocog alfa.
- New data from the guardian™2 trial demonstrate the long-term safety and efficacy of turoctocog alfa for the prevention and treatment of bleeds in patients of all ages with severe hemophilia A.

Introduction

- Turoctocog alfa, a B-domain truncated recombinant factor VIII (rFVIII) product, has been licensed for use by some countries for the prevention and treatment of bleeds in patients with hemophilia A.
- In the pivotal phase 3 trials, guardian™1 and guardian™3, turoctocog alfa provided well-tolerated and effective prophylaxis in previously treated adults or adolescents (aged 12–65 years), and children (aged <12 years).[1,2]
- The multi-national guardian™2 trial, an extension to the guardian™1 and guardian™3 trials, was conducted at 52 sites in 19 countries. The main objectives of guardian™2 were to assess the long-term safety and efficacy of turoctocog alfa for the prevention and treatment of bleeds.
- Here we report the results from guardian™2 as assessed at the interim cut-off date on March 25, 2015.

Methods

Patients and trial design

- guardian™2 was a prospective, non-randomized, open-label, multi-center, multi-national, single treatment arm, safety and efficacy extension trial.
- Previously treated male patients aged 6 months to 70 years, with severe hemophilia A (FVIII activity ≤1%) and no history of inhibitors, were eligible for inclusion in guardian™2 if they had completed guardian™1, guardian™3, one of the preceding pharmacokinetics trials, or the on-demand sub-trial of guardian™2.
- Participants received turoctocog alfa prophylactically (20–50 IU/kg once every second day, or 20–60 IU/kg three times weekly), and on-demand (20–200 IU/kg/day [dose levels up to 200 IU/kg/day could be used depending on severity/location of the bleed]) for treatment of bleeds.

Endpoints

- The primary endpoint was FVIII inhibitor development (≥0.6 Bethesda units [BU]/mL).
- The efficacy endpoints were:
  - Annualized bleeding rate (ABR) reported during the prevention period (only applicable for subjects in the preventive regimen).
  - Hemostatic success when treating bleeds (assessed on a predefined four-point scale [excellent/good/moderate/none]).
  - Number of turoctocog alfa infusions required to stop bleeds.
  - Turoctocog alfa consumption.
- The safety endpoint was frequency of adverse events (AEs) and serious AEs.
- Descriptive statistics were used to evaluate all safety endpoints and efficacy during treatment of bleeds.

Results

- At the guardian™2 interim cut-off (March 25, 2015), 199 patients had been treated prophylactically with turoctocog alfa for a total of 589 patient-years.
- Total exposure to turoctocog alfa was 476.9 days per patient and a mean of 466.0 infusions per patient were used for prophylaxis.

Efficacy

- The ABRs for patients receiving prophylactic treatment are shown in Table 1.
- In total, 1508 bleeds in 162 (81.4%) patients on prophylaxis were treated with turoctocog alfa. The majority of bleeds were spontaneous (56.2%), and 43.6% were caused by trauma. The most frequent location of the bleeds was in a joint (74.9%).
- Treatment was successful ('excellent' or 'good') for 89.7% of bleeds, and was similar across all age groups.

Table 1 Annualized bleeding rates (bleeds/patient/year) reported in guardian™2.

	Children 0–<6 years	Children 6–<12 years	Adolescents 12–<18 years	Adults ≥18 years	Total
Patients, n	27	28	23	121	199
All bleeds, median (IQR) Poisson estimate, mean (95% CI)	1.08 (3.03) 1.95 (1.19–3.18)	1.57 (4.39) 3.09 (2.16–4.41)	1.48 (2.62) 2.05 (1.37–3.07)	1.49 (3.21) 2.69 (2.13–3.40)	1.48 (3.21) 2.56 (2.16–3.03)
Spontaneous bleeds, median (IQR) Poisson estimate, mean (95% CI)	0 (1.03) 0.64 (0.30–1.38)	0 (0.78) 0.75 (0.34–1.65)	0.53 (2.33) 1.15 (0.70–1.89)	0.82 (2.65) 1.89 (1.47–2.44)	0.52 (2.11) 1.44 (1.15–1.80)
Traumatic bleeds, median (IQR) Poisson estimate, mean (95% CI)	0.90 (2.42) 1.31 (0.84–2.03)	1.52 (2.95) 2.34 (1.68–3.25)	0.75 (0.99) 0.89 (0.58–1.35)	0.29 (0.86) 0.79 (0.60–1.06)	0.53 (1.49) 1.12 (0.92–1.35)
Joint bleeds, median (IQR) Poisson estimate, mean (95% CI)	0.28 (1.49) 0.89 (0.43–1.86)	0.83 (3.60) 2.15 (1.38–3.35)	1.40 (2.50) 1.6 (1.13–2.26)	0.87 (2.95) 2.21 (1.7–2.88)	0.82 (2.75) 1.93 (1.58–2.37)
Non-joint bleeds, median (IQR) Poisson estimate, mean (95% CI)	0.60 (1.81) 1.06 (0.65–1.71)	0.55 (1.24) 0.92 (0.65–1.31)	0.00 (0.53) 0.45 (0.20–1.00)	0.00 (0.65) 0.47 (0.36–0.61)	0.28 (0.85) 0.62 (0.51–0.76)

CI, confidence interval; IQR, interquartile range.

- Of the 1508 reported bleeds, most (89.9%) were resolved after one or two infusions of turoctocog alfa (74.4% and 15.5%, respectively).
- Mean turoctocog alfa consumption for patients receiving prophylaxis was 5098 IU/kg/year/patient, with an average dose of 32.2 IU/kg.

Safety

- No FVIII inhibitors were detected.
- Overall, for patients on prophylaxis, a total of 1051 AEs were reported for 172 (86.4%) patients (1.8 events per patient-year of exposure).
- The most frequently reported AEs were headache, nasopharyngitis, upper respiratory tract infection, pharyngitis, and fall.
- Eight events (local swelling, increased aspartate aminotransferase, increased alanine aminotransferase, pain in extremity, musculoskeletal pain, arthropathy [two cases], and lichenoid keratosis) in five of 199 patients (2.5%) were judged to be possibly or probably related to turoctocog alfa; all were mild or moderate in severity and not serious.
- Thirty-six serious AEs were reported in patients on prophylaxis; all were judged by the investigator unlikely to be related to turoctocog alfa.
- No thromboembolic events, hypersensitivity reactions, allergic events, or other safety concerns were reported.

References

1. Lentz SR, *et al. Haemophilia* 2013;19:691–697.
2. Kulkarni R, *et al. Haemophilia* 2013;19:698–705.

Conflict of interest disclosure

ES received speaker fees from Kedrion, was a paid consultant to Baxalta, Baxter, Bayer, Biogen Idec, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, and Sobi, and received a research grant from Pfizer. **DJ** received speaker fees from Baxter, Bayer, Novo Nordisk, Octapharma, and Pfizer. **IM** is a Novo Nordisk employee. **MO** received research support from Baxter, Bayer, CSL Behring, Biogen, and Novo Nordisk, and speaker fees from Baxter, Novo Nordisk, Biogen, and Pfizer. **AT** reports grants and fees for lectures/consultancy from Bayer, Baxter/Baxalta, Biogen Idec, Biotest, Boehringer Ingelheim, CSL Behring, Leo Pharma, Novo Nordisk, Octapharma, Pfizer, and Sobi. **JO** received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Sobi, Pfizer, and Roche. **FAK** and **AS** have no conflicts of interest.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT00984126). The authors acknowledge the medical writing assistance of Katherine Ayling-Rouse (PAREXEL). Presented at the World Federation of Hemophilia (WFH) World Congress, July 24–28, 2016, Orlando, FL, USA.