Long-term patterns of safety and efficacy of bleeding prophylaxis with turoctocog alfa (NovoEight®) in previously treated patients with severe haemophilia A: interim results of the guardian™2 extension trial

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Haemophilia A (factor VIII deficiency) is the most common type of haemophilia [1], affecting approximately 1 in 5000 males, although its prevalence varies globally [2]. Restoration of haemostasis with FVIII concentrates is the standard therapy. Turoctocog alfa (NovoEight®; Novo Nordisk A/S, Bagsvaerd, Denmark) is a third generation human recombinant B domain-truncated FVIII molecule [3] that in Phase 3 trials – guardian™1 (adolescent and adult patients ≥12 years) [4] and guardian™3 (paediatric patients <12 years) [5] – demonstrated favourable efficacy and safety profiles; there were no inhibitors and no safety concerns were observed. Subjects who completed the guardian™1 or guardian™3 trials could choose to continue treatment with turoctocog alfa by enrolling in the open-label, non-controlled guardian™2 extension trial (www.clinicaltrials.gov: NCT00984126) that investigates the long-term safety and efficacy of turoctocog alfa administered as prophylaxis and for treatment of bleeds.

This letter presents a preplanned interim analysis of data collected up to September 1, 2012 for the guardian™2 extension trial. The primary objective is to assess the safety of turoctocog alfa for prevention and treatment of bleeds. The primary endpoint is the frequency of developing FVIII inhibitors. Key efficacy endpoints are haemostatic effect during treatment of bleeding, number of infusions needed to treat a bleeding episode and annualized bleeding rate (ABR).

The guardian™2 extension trial enrolled 188 male patients [27 children (≤5 years), 28 children (6–11 years), 23 adolescents (12–17 years) and 110 adults (≥18 years)] with severe haemophilia A (FVIII level ≤1%) who had no history of FVIII inhibitors. The trial included 51 sites in 18 countries (Brazil, Croatia, Germany, Israel, Italy, Japan, Lithuania, Macedonia, Malaysia, Poland, the Russian Federation, Serbia, Spain, Switzerland, Taiwan, Turkey, the UK and USA).

Patients received turoctocog alfa as prophylactic treatment (20–50 IU kg<sup>−1</sup> every second day or 20–60 IU kg<sup>−1</sup> three times weekly) and for treatment of bleeds. Turoctocog alfa was in most cases administered at home by the patient or a caregiver. FVIII inhibitors were analysed at a central laboratory (Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany) using the Nijmegen modification of the Bethesda assay [6,7]. In accordance with EMA guidance [8], a patient was considered to have a FVIII inhibitor if he tested positive [≥0.6 Bethesda units (BU)] in two consecutive samples.

Joint bleeds were categorized as target joint bleeds (target joint defined as ≥3 bleeding episodes in the same joint within a 6-month period prior to the trial) or non-target joint bleeds. The haemostatic effect of turoctocog alfa was self-assessed by the patient using a predefined 4-point scale (excellent, good, moderate and none; definitions are provided in the footnote of Table 1). The ratings ‘excellent’ and ‘good’ were considered treatment successes; ratings of ‘moderate’ and ‘none’ were considered treatment failures.

Evaluation of data was based on descriptive statistics. Data were evaluated for four predefined patient age groups (≤5 years; 6–11 years; 12–17 years; ≥18 years). ABR was estimated by cause of bleed (‘spontaneous’; ‘traumatic’) and by location (‘joint’;
As of 1 September 2012, the guardian\textsuperscript{2} full analysis set comprised 188 patients, 1–61 years of age, with severe haemophilia A (133 adults and adolescents; 55 children). As of the cut-off date, 18 patients had been withdrawn during guardian\textsuperscript{2} for: withdrawn consent (4 patients); treatment with another factor (4 patients); adverse event (AE) (3 patients); non-compliance (2 patients); transfer to another trial (2 patients); treatment with an anticoagulant agent (1 patient); unplanned surgery (1 patient); treatment for hepatitis C (1 patient).

This interim analysis includes approximately 3 years of data for the first patient in guardian\textsuperscript{2}, and a total of 255.9 patient-years exposure. The mean number of exposure days (EDs) was 205. Safety was assessed in all 188 patients exposed to turoctocog alfa; none developed FVIII inhibitors. Turoctocog alfa was considered to be well tolerated, with no unexpected patterns seen in AEs or serious adverse events (SAEs).

Seven AEs (peripheral oedema, increased aspartate aminotransferase, increased alanine aminotransferase,
musculoskeletal pain, pain in extremity and two cases of arthropathy) in 4/188 (2.1%) patients were considered by the investigator to be ‘possibly’ or ‘probably’ related to turoctocog alfa. These events were non-serious and of mild or moderate severity. Three patients were withdrawn due to AEs: one for fatal trauma caused by alleged assault involving subdural haemorrhage, one for paranoid-type schizophrenia (patient had history of psychiatric disorders), and one for increased hepatic enzymes that developed at the end of the guardian™1 trial and precluded participation in the guardian™2 trial. No thromboembolic events or hypersensitivity reactions against turoctocog alfa were reported and no other safety concerns were identified.

The mean per-patient consumption of turoctocog alfa for prophylaxis was 404 IU kg⁻¹ per month, with a mean dose level of 31.5 IU kg⁻¹. Approximately 84% of patients entered the extension trial on three times weekly dosing. The mean dose for adults and adolescents increased slightly (27.4–31.0 IU kg⁻¹) during the extension. For paediatric patients, dose remained stable during guardian™2 (approximately 40 IU kg⁻¹).

The overall median ABR was 1.7 (interquartile range [IQR]: 3.6) bleeds/patient/year and the estimated mean ABR was 3.1 (95% CI 2.6–3.8) bleeds/patient/year. Small differences in overall ABR were observed among the four age groups: adults (median 1.9 [IQR: 3.6], estimated mean 3.4 [95% CI 2.7–4.3]); adolescents (median 1.6 [IQR: 3.3], estimated mean 2.8 [95% CI 1.7–4.5]); older children (median 1.4 [IQR: 4.3], estimated mean 2.8 [95% CI 1.9–4.2]); younger children (median 1.4 [IQR: 3.1], estimated mean 2.3 [95% CI 1.5–3.5]). Interestingly, these ABRs are lower than the ABRs reported in the guardian™1 and guardian™3 trials [4,5]. It may be that prolonging prophylaxis during the extension trial may have progressively decreased ABR. Additional
differences were observed when ABR was classified by type of bleed among the age groups. Traumatic bleeding rates were highest among patients aged 6–11 years and lowest in adults, with the opposite pattern observed for spontaneous bleeding rates (Fig. 1a). Joint bleeding rates were higher than non-joint bleeding rates in all ages except children aged ≤5 years, for whom non-joint ABR was higher (rates were not compared statistically). Target joint bleeds comprised slightly more than half of joint ABR totals, across age groups, except 0–5 years (Fig. 1b).

A total of 752 bleeding episodes occurred in 142 (76%) patients during guardian™2; (Table 1). The majority (88%) of bleeding episodes were classified as mild or moderate. Twenty-four percent (24%) of patients did not experience a bleeding episode. However, some patients had a limited duration of exposure in the extension trial (exposure ranged from 1–492 days).

In all age groups, the majority of bleeds were joint bleeds (78%, overall); of these, 61% were in target joints. No non-traumatic intracranial haemorrhages occurred. Treatment was considered to be successful for 664/752 (88%) of overall bleeding episodes with minimal variation among age groups (Table 1). A total of 678 (90%) episodes were resolved with 1–2 infusions of turoctocog alfa. The overall mean consumption of turoctocog alfa to treat a bleed was 57.5 IU kg⁻¹ body weight per episode, with slight variation observed among age groups.

In conclusion, this interim analysis demonstrated that the extended use of turoctocog alfa is safe and effective in prevention and treatment of bleeding episodes in adult, adolescent and paediatric patients. Turoctocog alfa was well tolerated and no patients developed FVIII inhibitors. In accordance with previously published studies, a prophylactic regimen with turoctocog alfa was shown to be beneficial in the treatment of severe haemophilia A.

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Author contributions

Margareth Ozelo, Steven R. Lentz, Mudi Misgav, Elena Santagostino, Monica Martin-Salces and Faraizah Abdul Karim enrolled and cared for patients. Irina Matytsina was involved in the design of the trial and interpretation of the data. Trine Saugstrup contributed to the interpretation of the data, the statistical analysis and manuscript outline. All authors gave input, reviewed and approved the manuscript.

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