CLINICAL INVESTIGATION



# Turoctocog alfa in the treatment of individuals with hemophilia A: review of quality of life data collected in Phase III trials

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Hemophilia A is an X-linked recessive hereditary bleeding disorder resulting from a deficiency in coagulation factor VIII. Difficulties due to hemophilia and its management present challenges for patient's quality of life. Turoctocog alfa, a recombinant, B-domain truncated factor VIII, is a recent US FDA- and EMA-approved replacement therapy shown to be an effective and safe option for the treatment of individuals with hemophilia A. Data collected throughout two Phase 3, multinational, open-label, non-randomized, non-comparative trials demonstrated that individuals with hemophilia A, particularly young adults experienced improvements in health-related quality of life when switched from an on-demand to a prophylactic regimen of turoctocog alfa.

**Keywords:** EQ-5D • factor VIII • health-related quality of life • hemophilia • HAEMO-QOL • questionnaires • turoctocog alfa

Hemophilia A is an X-linked recessive hereditary bleeding disorder resulting from a deficiency in coagulation factor VIII (FVIII). The annual incidence of hemophilia A is estimated at 1/5000 male births in the USA and in Europe [1,2]. The level of circulating coagulation factor determines the severity of hemophilia and this may be mild (5–40% of normal), moderate (1–5% of normal) or severe (<1% of normal) [3]. Hemophilia is characterized by bleeding episodes which may occur spontaneously or following an injury, trauma or surgical procedure. Recurrent bleeding episodes can lead to long-term musculoskeletal complications including synovitis, degenerative arthropathy and articular deformities [4]. Bleeding episodes are primarily treated by coagulation factor replacement as a bleed occurs (on-demand) or in a preventive manner (prophylaxis regimen). Current standards of care in severe hemophilia support regular prophylaxis, characterized by self-infusion of either recombinant or plasma-derived FVIII concentrate several times a week [5]. Prophylaxis, when compared with on-demand treatment, is associated with a reduced number of bleeds, a greater quality of life (QOL) and may potentially reduce the risk of developing long-term musculoskeletal complications. This has been observed both in adults and younger individuals with severe hemophilia [6–8]. Using the Standard Gamble method, Naraine *et al.* showed that scenarios with prophylaxis treatment regimens were preferred to scenarios with on-demand treatment regimens not only by individuals with hemophilia and their parents, but also by members of the general public [9].

The US FDA defines patient's health-related quality of life (HRQoL) as 'a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological and social aspects of life' [10]. Individuals living with hemophilia may experience several QOL issues, which may affect their physical, psychological, social and economic well being on a daily basis. Some individuals need to limit their activities due to the potential risk of a bleeding incident, whereas others are limited in mobility and functional status due to permanent and painful joint damage [11].

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Using standard generic HRQoL questionnaires, the Short Form 36 health survey (SF-36) and EuroQol (EQ-5D), Miners *et al.* showed that individuals with severe hemophilia who were not receiving primary prophylaxis with coagulation factor, reported poorer HRQoL scores compared with individuals with mild-to-moderate hemophilia and members of the UK general population [12].

Since the introduction of factor replacement therapy, life expectancy and reported HRQoL of individuals with hemophilia have seen noticeable improvements [13]. In addition, the promise of further potential benefits arises from a number of new drugs that are currently in development. Coagulation factor concentrates with prolonged bioavailability require less frequent injections and can therefore minimize venous access problems and infusion-related pain [14]. Patients may also benefit in the future from drugs that can overcome the barrier of immunogenicity, since the development of inhibitory antibodies to factor concentrates (inhibitors) continues to be a major complication in hemophilia treatment [15].

There is recognition that perceived benefits for patients, in particular the balance between therapeutic efficacy, treatment risks (such as experience of adverse events) and treatment constraints are of key concern for patients, physicians and health authorities, as they may impact adherence to treatment [16–18].

Turoctocog alfa (NovoEight®) is an FDA- and EMA-approved replacement therapy option for the treatment of individuals with hemophilia A. Turoctocog alfa is a human, recombinant, B-domain truncated FVIII, produced in Chinese hamster ovary cells without addition of any human- or animal-derived materials [19,20]. As part of its development, two Phase 3, multinational, open-label, non-randomized, non-comparative trials demonstrated that turoctocog alfa administered as a prophylaxis treatment was both effective and safe to treat bleeding episodes in 24 adolescents and 126 adults with hemophilia A (guardian™ 1) and in 63 children with hemophilia A (guardian 3) [21,22]. In these trials, most children received prophylaxis in the 12 months preceding the trial (68% in the 4–7 years; 67% in the 8–12 years groups). Among adolescents, 44% received on-demand regimen, 22% received prophylaxis and 33% received a mixed regimen. Among adults, 39% received on-demand regimen, 36% received prophylaxis and 26% received a mixed regimen. The observed success rate defined as 'excellent' or 'good' hamostatic response was 81% in guardian 1 and 92% in guardian 3. The estimated median annualized bleeding rates were 3.7 bleeds/patient/year in adolescents and adults, and 3.0 in children. None of the patients enrolled developed FVIII inhibitors during the trials.

In both trials, HRQoL was a secondary endpoint. Patients completed two patient-reported questionnaires at baseline prior to treatment initiation and at the end-of-treatment visit: the EQ-5D and the hemophilia quality of life (HAEMO-QOL/HAEM-A-QOL) questionnaires.

The EQ-5D is a 5-dimensional generic standard utility instrument for measurement of health outcome [23]. The EQ-5D includes the following domains: Mobility; Self-Care; Usual Activity; Pain/Discomfort and Anxiety/Depression. In addition, a 10 cm visual analog scale (VAS) also enables recording of individual's rating for their current HRQoL; the VAS ranges from 0-worst to 100-best imaginable health state. The single index score is derived from application of country-specific value sets (the UK value set in the case of the guardian trials) to responses from each domain. An index score of 0.0 represents a state approximately as desirable as 'death' while an index score of 1.0 represents 'perfect health.'

The HAEMO-QOL is a disease-specific HRQoL family of questionnaires that consists of four age-specific instruments (4–7 years, 8–12 years, 13–16 years and the HAEM-A-QOL for 17 years and above) specifically designed to assess HRQoL in individuals with hemophilia [24,25]. HAEMO-QOL questionnaires cover various domains of HRQoL including: psychological, physical and social factors. For all HAEMO-QOL questionnaires, a score for each domain as well as a total score summarizing the global HRQoL of individuals with hemophilia can be calculated. Scores range from 0 to 100; lower scores indicate better HRQoL (and thus a negative change in this score should be interpreted as improvement).

The present review compiles existing available data complemented with as yet unpublished patient-reported outcome data collected throughout the turoctocog alfa development program (guardian trials) to provide a comprehensive picture of the impact of prophylactic turoctocog alfa in the treatment of individuals with hemophilia A.

## Individuals with hemophilia A treated with prophylactic turoctocog alfa maintained their level of HRQoL

Overall, the mean HAEMO-QOL/HAEM-A-QOL total score did not change between baseline and end-of-treatment assessments [26,27]. This indicated that in the overall population, individuals who were prophylactically administered turoctocog alfa maintained their level of HRQoL. As shown in Table 1, only children aged 4–7 years reported a small worsening (1.4, SD = 13.4) in the HEMO-QOL total score in the version completed by their parents between base-

line and the end-of-trial visit; all other age groups reported an improvement, -2.6 (SD = 10.7) for the 8–12 years, -5.8 (SD = 10.0) for the 13–16 years and -1.6 (SD = 8.9) for the adults. Only minor changes in HRQoL of patients treated with turoctocog alfa were observed, suggesting that the transition to this recombinant FVIII compound is not detrimental for patient HRQoL from the patients' perspective. Despite the absence of evidence of statistical significance of the change in scores from baseline to end-of-

Table 1. Baseline scores and mean changes from baseline to end of treatment for HAEMO-QOL dimension and total scores for all versions for all age groups.

| HAEMO-QOL/HAEM-A-QOL | Baseline mean score (SD) | Mean change (SD) |
|---|---|---|
| **Children 4–7 years (n = 25)** | | |
| Physical health | 27.8 (20.7) | -9.9 (31.9) |
| Feeling | 17.5 (23.9) | 10.8 (28.8) |
| View | 14.3 (16.9) | 5.6 (20.2) |
| Family | 47.0 (27.1) | 4.9 (27.5) |
| Friend | 25.0 (33.6) | 21.1 (30.3) |
| Others | 17.0 (21.0) | 1.3 (34.8) |
| Sport | 37.7 (25.4) | -6.3 (26.4) |
| Treatment | 40.5 (34.9) | -4.2 (47.9) |
| Total score | 30.0 (13.6) | 1.4 (13.4) |
| **Children 8–12 years (n = 21)** | | |
| Physical health | 27.0 (17.8) | -11.3 (19.3) |
| Feeling | 16.7 (14.7) | -5.4 (15.3) |
| View | 21.7 (12.5) | -1.4 (21.8) |
| Family | 33.1 (15.1) | 5.3 (16.6) |
| Friend | 38.4 (27.0) | 0.6 (33.4) |
| Perceived support | 44.6 (23.7) | -1.2 (25.6) |
| Others | 18.7 (16.6) | -3.0 (17.7) |
| Sport | 34.3 (15.7) | -4.2 (14.4) |
| Dealing | 22.8 (17.4) | 0.7 (19.3) |
| Treatment | 18.4 (17.3) | -3.2 (12.9) |
| Total score | 26.1 ( 8.9) | -2.6 (10.7) |
| **Adolescents (n = 18)** | | |
| Physical health | 33.7 (23.2) | -15.0 (18.4) |
| Feeling | 21.7 (16.5) | -7.3 (12.3) |
| View | 31.8 (19.6) | -7.5 (18.4) |
| Family | 35.2 (20.6) | -4.4 (17.9) |
| Friend | 51.7 (26.9) | -1.0 (29.1) |
| Perceived support | 43.3 (18.2) | 7.3 (26.4) |
| Others | 20.8 (20.2) | -5.9 (19.3) |
| Sport | 44.2 (17.8) | -14.1 (17.3) |
| Dealing | 24.8 (15.9) | -5.5 (18.6) |
| Treatment | 24.6 (15.2) | -8.1 ( 9.9) |
| Future | 30.0 (10.1) | 9.4 (25.8) |
| Relationship | 9.6 (14.6) | -5.0 (19.7) |
| Total score | 31.4 ( 9.6) | -5.8 (10.0) |

Table 1. Baseline scores and mean changes from baseline to end of treatment for HAEMO-QOL dimension and total scores for all versions for all age groups (cont.).

| HAEMO-QOL/HAEM-A-QOL | Baseline mean score (SD) | Mean change (SD) |
|---|---|---|
| **Adults (n = 129)** | | |
| Physical health | 41.6 (24.5) | -4.9 (20.6) |
| Feeling | 26.9 (24.0) | -1.8 (17.6) |
| View | 37.4 (21.1) | -0.8 (16.7) |
| Family planning | 17.9 (26.7) | 3.0 (16.8) |
| Work | 26.8 (26.1) | -3.8 (18.0) |
| Sport | 54.5 (22.3) | -1.0 (18.7) |
| Dealing | 19.7 (18.9) | -1.7 (20.7) |
| Treatment | 32.7 (16.9) | -0.8 (15.2) |
| Future | 39.2 (24.4) | -1.9 (15.4) |
| Partnership | 18.2 (28.8) | -0.7 (18.5) |
| Total score | 33.4 (16.0) | -1.6 ( 8.9) |

treatment independently of age groups, improvement was systematically observed across all age groups for domains related to a physical activity. As indicated in Table 1, patients reported an improvement in the Physical health, Sport and Work domain scores. Physical health was the domain for which the patients reported the largest improvement: -9.9 (SD = 31.9) in the 4–7 years, -11.3 (SD = 19.3) in the 8–12 years, -15.0 (SD = 18.4) in the 13–16 years and -4.9 (SD = 20.6) in the adults aged 17 years and above. These results though should be interpreted cautiously in the absence of evidence of statistical significance and considering the limited sample size of the child population and the single arm open-label study design. The low bleeding rate that occurred following administration of prophylactic turoctocog alfa may have resulted in the observed impact of prophylaxis on patients' HRQoL. Decreased disruption due to bleeding may have led to an increase in their participation in everyday activities, enabling them to work and engage in sport more easily. Physical activity has been strongly associated with an increased risk of bleeding episodes in children and adolescents with moderate or severe hemophilia [26]. The present study suggests a link between a treatment ensuring a low bleeding rate and participation in physical activity.

## Benefits of switching from on-demand regimen to prophylaxis

The switch from prophylaxis to an on-demand regimen has been associated with not only an increase in the number of bleeds but also with a worsening in HRQoL [28]. The guardian trials provided the opportunity to compare the HRQoL of individuals who were following an on-demand regimen prior to enrolment and who subsequently switched to prophylactic turoctocog alfa with individuals who were already on a prophylactic regimen prior to entry. At study entry, 81 (42%) patients had been receiving only prophylaxis during the 12 months preceding the trial, and 70 (36%) had been receiving only on-demand treatment. Mean changes in HAEMO-QOL total score were always greater in absolute value (but no evidence of statistical significance published), indicating greater improvement in HRQoL in patients receiving on-demand therapy before the trial than in patients who had been receiving prophylactic therapy (Table 2): 3.0 (SD = 13.9) for prophylaxis versus -1.6 (SD = 13.0) for on-demand in the 4–7 years, -2.1 (SD = 12.4) versus -4.2 (SD = 6.9) in the 8–12 years, -0.8 (SD = 7.9) versus -4.2 (SD = 12.4) in the 13–16 years and 0.7 (SD = 7.2) versus -3.4 (SD = 9.6) in the adults [26,27]. These results suggest that switching from an on-demand regimen to prophylaxis with turoctocog alfa may be beneficial for the HRQoL of individuals with hemophilia regardless of the age group.

In guardian 1, adults who were treated on-demand within the 12 months preceding the trial tended to show greater improvements (without evidence of statistical significance) than adults who were on prophylaxis. Adults who received an on-demand regimen within the 12 months preceding the trial reported a greater improvement in the Physical health, Sport, Work, Dealing, Feeling and Treatment scores than those who were already receiving a prophylaxis regimen (Table 2, [guardian trials, Unpublished data]). This indicates that even at a late stage, adults with hemophilia treated on-demand, and who likely have poor joint status and poor HRQoL, may still benefit from switching from an on-demand to a prophylaxis regimen. Assessment of joint status at baseline

in patients treated with on-demand versus prophylaxis prior to study start is missing. No other relevant data were available in the original articles reporting HRQL data or reporting clinical findings. Such information could have supported the aforementioned assumption, which thus remains hypothetical.

Table 2. Baseline scores and mean changes from baseline to end of treatment for HAEMO-QOL dimension [unpublished data] and total scores for all versions for all age groups, for adolescents and adults, according to previous regimen received before the trials.

| HAEMO-QOL/ HAEM-A-QOL | Baseline mean score (SD) | | Mean change (SD) | |
|---|---|---|---|---|
| | On-demand | Prophylaxis | On-demand | Prophylaxis |
| **Children 4–7 years** | n = 8 | n = 17 | | |
| Physical health | 37.5 (18.9) | 22.3 (20.3) | -12.5 (43.3) | -8.3 (25.2) |
| Feeling | 26.2 (25.2) | 12.8 (22.7) | 0.0 (29.8) | 16.7 (27.9) |
| View | 14.3 (19.7) | 14.3 (16.2) | 8.3 (12.9) | 4.2 (23.4) |
| Family | 58.9 (23.6) | 41.1 (27.5) | 16.7 (10.2) | -1.0 (31.7) |
| Friend | 18.8 (37.2) | 28.6 (32.3) | 14.3 (37.8) | 25.0 (26.1) |
| Others | 21.9 (24.8) | 14.3 (18.9) | -7.1 (31.3) | 6.3 (37.1) |
| Sport | 47.9 (24.3) | 30.3 (24.5) | -4.8 (23.0) | -7.4 (30.2) |
| Treatment | 43.8 (39.5) | 38.5 (33.3) | -3.6 (50.9) | -4.5 (48.5) |
| Total score | 38.1 (16.8) | 25.6 ( 9.7) | -1.6 (13.0) | 3.0 (13.9) |
| **Children 8–12 years** | n = 5 | n = 14 | | |
| Physical health | 30.4 ( 5.9) | 25.5 (20.0) | -17.5 (10.9) | -12.5 (19.3) |
| Feeling | 23.6 (10.6) | 13.8 (16.4) | -14.3 ( 8.7) | -1.8 (16.9) |
| View | 21.1 ( 8.9) | 23.0 (14.2) | -0.6 ( 6.3) | -2.9 (25.3) |
| Family | 43.0 ( 7.6) | 27.5 (14.9) | 9.0 (17.5) | 3.9 (17.3) |
| Friend | 23.8 (15.6) | 48.7 (25.6) | -10.0 (23.6) | 3.1 (37.2) |
| Perceived support | 38.8 (16.2) | 51.3 (23.3) | -10.0 (16.3) | 1.3 (29.7) |
| Others | 7.5 ( 1.9) | 19.3 (16.4) | 5.8 (15.8) | -2.7 (16.9) |
| Sport | 46.3 ( 9.7) | 31.6 (16.3) | -8.1 (17.5) | -2.6 (14.1) |
| Dealing | 13.6 (16.2) | 25.3 (17.1) | 4.3 ( 8.1) | 1.9 (22.2) |
| Treatment | 15.0 ( 9.9) | 18.1 (18.4) | -0.7 (13.5) | -2.8 (11.1) |
| Total score | 25.7 ( 6.1) | 26.4 (10.4) | -4.2 ( 6.9) | -2.1 (12.4) |
| **Adolescents** | n = 4 | n = 8 | | |
| Physical health | 45.2 (23.5) | 17.9 (15.6) | -23.1 (20.2) | 6.0 ( 2.1) |
| Feeling | 14.0 (11.5) | 19.0 (18.7) | -2.8 (10.6) | -1.3 (11.3) |
| View | 26.4 (11.4) | 21.7 (23.2) | -7.5 (20.6) | -1.9 (19.9) |
| Family | 30.6 ( 6.0) | 32.6 (44.8) | -6.0 (18.6) | 10.1 (21.7) |
| Friend | 42.0 (29.9) | 47.9 (23.7) | 10.0 (13.0) | -20.8 (15.7) |
| Perceived support | 32.1 (15.5) | 43.8 (21.7) | 5.0 (23.6) | 10.4 (26.0) |
| Others | 19.0 (16.3) | 33.3 (36.3) | -5.0 (18.0) | -11.1 (34.7) |
| Sport | 48.1 (20.5) | 27.8 (13.9) | -11.1 (13.4) | -9.3 (10.5) |
| Dealing | 19.4 (13.0) | 20.2 ( 5.5) | -4.3 (25.1) | 0.0 (25.3) |
| Treatment | 21.0 (18.2) | 25.1 ( 3.4) | -6.3 (12.5) | -3.3 ( 5.5) |
| Future | 27.7 ( 8.0) | 22.9 ( 9.5) | 7.5 (15.6) | 20.8 (41.6) |
| Relationship | 1.8 ( 4.7) | 12.5 ( 0.0) | 7.5 (16.8) | -12.5 ( 0.0) |
| Total score | 28.1 ( 4.5) | 26.9 (14.5) | -4.2 (12.4) | -0.8 ( 7.9) |

Table 2. Baseline scores and mean changes from baseline to end of treatment for HAEMO-QOL dimension [unpublished data] and total scores for all versions for all age groups, for adolescents and adults, according to previous regimen received before the trials (cont.).

| HAEMO-QOL/ HAEM-A-QOL | Baseline mean score (SD) | | Mean change (SD) | |
|---|---|---|---|---|
| | On-demand | Prophylaxis | On-demand | Prophylaxis |
| **Adults** | n = 47 | n = 44 | | |
| Physical health | 47.5 (21.3) | 35.5 (25.2) | -9.1 (21.8) | -0.8 (16.7) |
| Feeling | 27.9 (21.5) | 24.4 (24.1) | -4.5 (17.0) | 1.1 (15.5) |
| View | 34.7 (19.4) | 38.3 (22.0) | 1.8 (17.3) | -3.2 (16.9) |
| Family planning | 19.0 (26.3) | 17.8 (28.0) | 3.9 (18.3) | 4.5 (15.5) |
| Work | 32.1 (27.6) | 21.7 (24.0) | -7.4 (20.0) | 2.8 (16.5) |
| Sport | 61.7 (20.6) | 44.3 (21.7) | -4.2 (21.2) | 4.2 (17.0) |
| Dealing | 20.7 (18.5) | 14.9 (19.0) | -4.9 (22.3) | 4.2 (22.6) |
| Treatment | 32.6 (16.8) | 33.0 (16.8) | -4.3 (17.6) | 0.1 (12.3) |
| Future | 34.8 (23.2) | 42.6 (24.6) | -0.7 (14.4) | -2.1 (16.4) |
| Partnership | 18.5 (28.8) | 18.0 (30.5) | 2.7 (22.5) | -0.4 (14.7) |
| Total score | 34.8 (15.6) | 31.2 (15.9) | -3.4 ( 9.6) | 0.7 ( 7.2) |

## Young adults may particularly benefit from the switch to prophylactic turoctocog alfa

Early adulthood is a transitional period for all individuals characterized by physical, psychological and social developmental changes. This period is particularly critical for individuals with chronic diseases as the changes naturally affect individuals' attitudes toward their condition and its management. Maslow *et al.* reported that young adults, 18–28 years of age, with chronic diseases may have an increased risk for poor educational and financial outcomes compared with healthy young adults in USA [29]. However, the same authors further reported that young adults aged 24–32 years, with a chronic disease did not differ in their social outcomes (living with parents, having been married and having children) compared with healthy young adults [30]. For individuals with hemophilia, little information is available on the health status of young adults. As suggested by interviews conducted with adolescents in the UK [31], higher risk of bleeds and subsequent joint and muscle pains can reasonably be assumed to be detrimental at an age when physical activity is often of primary importance, and an age when compliance to treatment may not be optimal due to questions raised around the benefit of taking the treatment [32]. guardian 1 enabled the health status of young adults aged 16–29 years to be compared with both the full analysis set of the trial, and to the gender and age-specific reference values from the UK general population using data from the EQ-5D. Young adults (16–29 years, n = 83) and older adults (30–60 years, n = 51) with hemophilia A reported more problems in all EQ-5D domains and in particular for the Mobility and Pain/Discomfort domains than young adults and adults in the respective reference populations [33,34]. For all EQ-5D domains, adults 30–60 years of age reported more problems than young adults, supporting the degenerative nature of hemophilia. The overall health status of the young adults with hemophilia (78.0, SD = 18.1) as evaluated by the EQ-5D VAS was poorer than that of the young adults in the reference population (87.3, SD = 13.9), and quite similar to the full analysis set of the trial (75.0, SD = 18.8). For the full analysis set of the trial as well as for the adults aged 30–60 years, the change from baseline in EQ-5D VAS did not differ according to the treatment regimen received within the 12 months preceding the trial [33]. In the young adults, as indicated in Figure 1, the baseline EQ-5D VAS was comparable between the group who had received prophylaxis and the group who had received on-demand prior to the trial; mean change in EQ-5D VAS from baseline to the end-of-treatment visit showed an improvement (no information on statistical significance available) for both groups, however the improvement was greater in the individuals previously treated with on-demand regimen before the trial (5.2 point improvement, SD = 10.3) than individuals previously treated with prophylaxis (1.2 point improvement, SD = 18.5).

On HAEM-A-QOL data for young adults a switch from an on-demand to prophylaxis regimen resulted in improvement from baseline assessment to end-of-trial assessment (mean HAEM-A-QOL total score decrease

of 5.3 [SD = 8.2]). Young adults who were previously treated with prophylaxis and remained on prophylaxis during the trial showed no improvement from baseline assessment to end-of-trial in HAEM-A-QOL total score (Table 3, [Guardian trials, Unpublished data]). On the HRQoL domain level, young adults receiving prophylaxis regimen before the trial reported at the end-of-treatment visit an improvement in 4 of the 10 domains (Physical health, View, Treatment and Partnership), whilst those receiving on-demand before the trial reported an improvement in 8 of the 10 domains (Physical health, Feeling, View, Sport, Work, Dealing, Treatment and Future) (Table 3, [unpublished data]). These improvements in the on-demand group were greatest for the Work score (mean change = -8.3, SD = 14.7) and the Dealing score (mean change = -11.8, SD = 16.5).

In light of these findings, guardian 1 data suggested that among adults, young adults in particular benefited from the switch from on-demand treatment to prophylactic turoctocog alfa. In addition to trends observed toward improvement in their overall health status and almost all the HRQoL domains, greater improvements were reported in their ability to work and their ability to deal with their hemophilia (management of bleeds). All individuals with hemophilia will likely not remain adherent to prophylaxis throughout adolescence and young adulthood [32], but the guardian 1 study suggests that these individuals could benefit from reverting back to prophylaxis. Similarly, as the

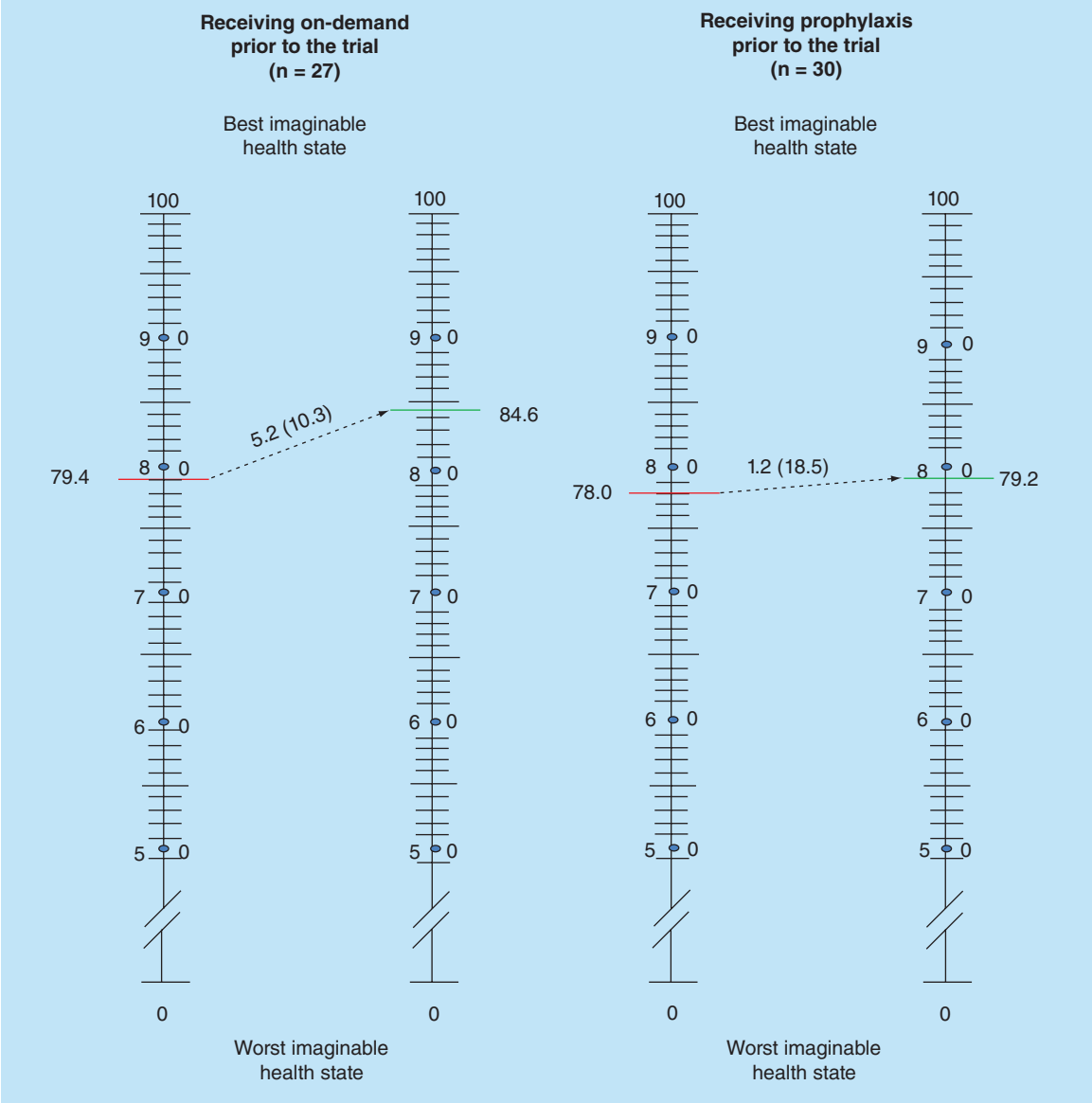


**Figure 1. Mean (and SD) change in EQ-5D VAS from baseline (red line) to end of trial (green line) in young adults according to the regimen received during the 12 months preceding the trial.**

Table 3. Baseline scores and mean changes from baseline to end of treatment for HAEM-A-QOL dimension and total scores for young adult groups (17 years and above) according to previous regimen received before the trial.

| HAEM-A-QOL | Baseline mean score (SD) | | Mean change (SD) | |
|---|---|---|---|---|
| | On-demand (n = 24) | Prophylaxis (n = 29) | On-demand | Prophylaxis |
| Physical health | 38.8 (18.8) | 30.9 (24.7) | -7.3 (24.4) | -1.2 (16.9) |
| Feeling | 22.0 (20.3) | 25.2 (28.2) | -6.0 (16.1) | 0.4 (15.8) |
| View | 31.7 (20.2) | 34.4 (22.4) | -3.2 (16.3) | -1.3 (18.4) |
| Family planning | 11.7 (17.8) | 20.4 (31.3) | 2.5 (15.9) | 6.1 (18.8) |
| Work | 29.4 (26.8) | 22.8 (25.2) | -8.3 (14.7) | 2.7 (16.9) |
| Sport | 52.7 (21.4) | 42.9 (21.6) | -5.2 (20.6) | 3.4 (18.8) |
| Dealing | 23.7 (19.2) | 11.0 (12.8) | -11.8 (16.5) | 9.9 (15.2) |
| Treatment | 31.7 (17.8) | 35.5 (19.9) | -4.9 (13.0) | -1.9 (14.0) |
| Future | 29.2 (22.6) | 37.9 (26.0) | -4.1 (16.4) | 0.4 (11.9) |
| Partnership | 11.7 (20.4) | 18.8 (34.1) | 0.4 (12.9) | -2.2 ( 8.8) |
| Total score | 30.3 (15.0) | 29.9 (18.2) | -5.3 ( 8.2) | 1.2 ( 5.3) |

use of prophylaxis in adults with hemophilia is frequently discussed [35,36], the guardian 1 study suggests that switching to prophylaxis in adulthood can still be beneficial to individuals with hemophilia. Prophylaxis treatment regimen therefore would appear to be an appropriate treatment option for individuals with hemophilia A at every age.

## Conclusion

Prophylaxis is increasingly recognized as the treatment option of choice for individuals with hemophilia. In addition to the benefits conferred in terms of established clinical outcomes, significant improvements are evident from direct patient reports, in particular in HRQoL. The guardian trials provide further evidence supporting the value of switching from an on-demand regimen to a prophylaxis treatment of hemophilia with clear trends toward improvements in physical outcomes, including the ability to play sports and to work. These findings indicate that prophylaxis is also a viable treatment option for adults with hemophilia who have been previously treated on an on-demand basis since a switch to a prophylaxis regimen was shown to lead to improvement in several meaningful aspects of their lives.

Switch from an on-demand regimen to prophylaxis with turoctocog alfa demonstrated additional benefit for young adults. Where an individual with hemophilia A is not already being treated prophylactically at the time of adolescence, early adulthood with all the corresponding life changes associated with the period may be a particularly suitable time to initiate a switch. This would allow young adults to experience meaningful benefits in major area of their lives such as the ability to play sports and even in their work or educational activities.

From a statistical point of view, limitations linked to the sample size and missing data could be discussed. Indeed, given the small samples and distributional characteristics of the HRQoL scores, the statistics used and reported in the publications on HRQoL data of turoctocog alfa trials were mainly descriptive. No multivariable analyses were performed in the reported analyses, but this seems reasonable given the features of the studies (in particular small sample size). Moreover, missing data are certainly a critical question for analyses of HRQoL data. In this context, missing data can be at two levels: a patient might not complete some questions within a questionnaire (missing data at the item level) or a full questionnaire might be missing for a given visit for a patient (missing assessment). Missing data at the item level can be important since, if too many items are missing, scores cannot be calculated, which leads to a missing assessment. However, in the case of the HRQoL data of turoctocog alfa trials, issues related to missing data were limited. First, very little missing data at the item level were reported [27]. Second, by protocol, when a patient drop out, they were asked to complete the HRQoL questionnaires, and changes in HRQoL scores that were reported for turoctocog alfa trials were calculated between baseline and last assessment (i.e., either end of study or drop out). Thus, if the hypothesis that patient with poor HRQoL would drop out is correct, this would be captured by the analyses. If the opposite hypothesis (the patient with high HRQoL would drop out) is correct, this would also be captured by the analyses. Incidentally, very few patients did not complete the study (4 out of 150 patients (3%) in guardian 1; 5 out of 63 patients (8%) in guardian 3) [21,22]. These elements supported a limited impact of missing data on the published results.

In conclusion, turoctocog alfa has been shown to be a safe and effective option for prophylactic treatment of individuals with hemophilia A. Data from the guardian 1 and 3 trials further supported its value in demonstrating a positive profile from the patient perspective as shown by the maintenance in the HRQoL of patients treated by turoctocog alfa.

## Future perspective

In order to obtain a comprehensive picture of the HRQoL benefits associated with prophylactic turoctocog alfa, further investigations could be conducted to confirm the findings from exploratory analyses of clinical trial data (which are in particular characterized by limited statistical power). By conducting studies, possibly including an active comparator, and primarily designed to assess HRQoL of patients on prophylaxis treatment these findings could be confirmed. It would also be worth assessing the specific benefit of prophylaxis treatment in terms of HRQoL in young children (4–7 years) since published evidence so far in relation to young children is limited and inconclusive. Another potential topic of interest is the sustainability of HRQoL benefit over longer time periods. Indeed, decrements in HRQoL of individuals with hemophilia are often linked to long term effects of repeated bleeding episodes (e.g., synovitis, degenerative arthropathy and articular deformities). Future studies could also further explore the impact of common comorbidities (e.g., hepatitis, HIV) on patient-reported outcomes in individuals with hemophilia.

One question of interest which remains pending is whether the effect of prophylaxis as perceived by the patients may be influenced by the type of FVIII received. Based on some data collected in guardian 1, adults treated with recombinant factors seemed to have higher baseline HRQoL scores than those previously treated with plasma-derived factors, however, the small sample size available for these analyses prevented any robust conclusions [37]. However, it is reasonable to assume that the benefits of treatment attributed to turoctocog alfa can be generalizable to all third generation recombinant FVIII products for which the use of human blood from the production process has been removed. Gaining a better understanding on the relative benefits of prophylaxis with different FVIII products, in particular from the perspective of the patients themselves, would certainly be of interest to improve the management of individuals with hemophilia.

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### Executive summary

- Hemophilia A is an X-linked recessive hereditary bleeding disorder resulting from a deficiency in coagulation factor VIII (FVIII).
- Current standard of care supports regular prophylaxis, characterized by self-infusion of either recombinant or plasma-derived FVIII concentrate several times a week.
- Prophylaxis regimen when compared with on-demand regimen is associated with a reduced number of bleedings.
- Turoctocog alfa, a recombinant, B-domain truncated FVIII, is an effective and safe treatment option for individuals with hemophilia A as demonstrated in two Phase 3, multinational, open-label, non-randomized, non-comparative trials conducted in adolescents and adults with hemophilia A (guardian™ 1) and in children with hemophilia A (guardian 3).
- Individuals with hemophilia A treated with prophylactic turoctocog alfa maintained their level of HRQoL: overall, HRQol was maintained from baseline to end-of-treatment visit in patients receiving prophylactic turoctocog alfa.
- Benefits of switching from on-demand regimen to prophylaxis: adult patients following an on-demand regimen during the 12 months prior to the trials reported an improvement in their HRQoL following the switch to prophylactic turoctocog alfa.
- Young adults may particularly benefit from the switch to prophylactic turoctocog alfa: among the adults, young adults 16–29 years of age benefited from the switch from an on-demand regimen to prophylactic turoctocog alfa in terms of HRQoL and in particular reported improvements in their ability to work and their ability to deal with their hemophilia.

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