rFIXFc prophylaxis improves pain and levels of physical activity in haemophilia B: Post hoc analysis of B-LONG using haemophilia-specific quality of life questionnaires

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Abstract
Introduction: Recurrent bleeding in severe haemophilia B causes painful hemarthroses and reduces capacity for physical activity. Recombinant factor IX Fc fusion protein (rFIXFc) prophylaxis results in low annualised bleeding rates, with the potential to improve patients’ health-related quality of life (HRQoL).
Aim: To present a post hoc analysis of data from B-LONG describing change over time in patient-reported outcomes associated with pain and physical activity.
Methods: Patients (≥12 years) who received weekly dose-adjusted or interval-adjusted rFIXFc prophylaxis and completed the Haemophilia-Specific QoL questionnaire for adolescents (Haemo-QoL) or adults (Haem-A-QoL) at baseline (BL) and end of study (EoS). Individual level changes in items of the ‘Physical Health’ and ‘Sports and Leisure’ domains, categorised as ‘never/rarely/seldom’ or ‘sometimes/often/all the time’, were analysed using McNemar’s test to compare distribution of responses at EoS versus BL.
Results: At EoS versus BL, a significantly greater proportion of patients did not experience painful swellings (64% vs. 44%; $P = .004$), painful joints (44% vs. 28%; $P = .003$) or pain when moving (54% vs. 41%; $P = .026$). Additionally, at EoS versus BL, patients were less likely to avoid participating in sports like football (30% vs. 8%; $P = .002$), avoid sports due to their haemophilia (47% vs. 27%; $P = .007$), or experience difficulty walking as far as they wanted (63% vs. 43%; $P = .001$). The proportion of patients who played sports as much as the general population was numerically increased (52% vs. 37%; $P = .033$) at EoS versus BL.
Conclusion: Results of the analysis suggest that over time, rFIXFc prophylaxis is associated with significant improvements in pain and physical functioning. This contributes to previous evidence of overall HRQoL improvements in patients with haemophilia B treated with rFIXFc.
INTRODUCTION

Severe haemophilia B is characterised by frequent and often spontaneous bleeding into joints and muscles. Recurrent bleeding into a joint causes progressive damage and may result in the development of haemophilic arthropathy, leading to impaired physical functioning characterised by limited range of motion, deformity, disability, and chronic pain. This plays an intrinsic role in the lives of patients from an early age, and reduced physical functioning and pain add to the burden of disease, impacting negatively on patients’ health-related quality of life (HRQoL). Recurrent and painful haemarthroses reduce a patient’s capacity to participate in physical activities. Furthermore, participation may be challenging due to an increased likelihood of suffering from joint and muscle bleeds, joint damage, and contact injuries ranging from bruising to life-threatening bleeds. Despite this, studies suggest that participating in physical activity provides not only physical benefits, such as improved joint, muscular and bone health, and a reduction in the perception of pain, but also supports the emotional and social well-being of patients with haemophilia and ultimately may lead to improved HRQoL. Physical activity is therefore recommended for patients with haemophilia to promote bone and joint health, muscle strengthening, coordination, physical functioning, healthy body weight, and positive self-esteem. The majority of healthcare professionals managing patients with haemophilia support the benefits of physical exercise and widely encourage their patients to participate.

Prevention of bleeding, and subsequent reduction of bleeding-related pain, constitutes a major therapeutic goal in patients with haemophilia B. Primary prophylaxis with recombinant factor IX (FIX) is the recognised standard of care and has been shown to prevent joint damage and reduce the frequency of haemorrhages, especially when initiated early in life, thus contributing to reduction of pain, physical dysfunction, long-term disability, and hospitalisation rates. Recombinant factor IX Fc fusion protein (rFIXFc) is an extended half-life FIX replacement therapy approved for the treatment and prophylaxis of patients of all ages with haemophilia B. The safety and efficacy of rFIXFc was demonstrated in three phase 3 trials of previously treated paediatric (<12 years; Kids B-LONG) and adolescent/adult patients (≥12 years; B-LONG), and previously untreated patients (<18 years; PUPs B-LONG) with severe haemophilia B (endogenous FIX ≤2 IU/kg). Prophylaxis with rFIXFc resulted in low annualised bleeding rates (ABRs) and was well tolerated, with the frequency and severity of adverse events consistent with those expected in the overall population of patients with haemophilia B. These results were confirmed in a long-term extension study (B-YOND), with low ABRs sustained for up to 5 years (with a cumulative duration up to 6.5 years). In addition, treatment with rFIXFc has been shown to provide HRQoL benefits in patients with severe haemophilia B. Changes observed in Haem-A-QoL key domains (‘Physical Health’ and ‘Sports and Leisure’), and ‘Total Score’ suggest that prophylaxis with rFIXFc results in meaningful improvements in HRQoL.

This study presents a post hoc analysis of data from the B-LONG study to describe changes over time in patient-reported outcomes (PROs) related to pain and physical activity in patients with severe haemophilia B treated with rFIXFc.

METHODS

Study design and patient population

The study design of B-LONG has been published previously. Briefly, previously treated patients (≥12 years of age, N = 123) with severe haemophilia B (defined as endogenous FIX ≤2 IU/dl) were assigned to one of four treatment arms: weekly dose-adjusted rFIXFc prophylaxis (group 1; 50 IU/kg starting dose, n = 63), interval-adjusted rFIXFc prophylaxis (group 2; 100 IU/kg every 10 days to start, n = 29), episodic treatment (group 3; 20–100 IU/kg for bleeding episodes, with the dose adjusted depending on bleeding severity, n = 27), or treatment as part of perioperative care (n = 12; enrolled for surgery only n = 4; enrolled from groups 1, 2, or 3, n = 8). Patients assigned to the weekly dose-adjusted or interval-adjusted prophylaxis groups could have the dose or interval adjusted, respectively, to maintain a trough level of 1-3 IU/kg.

This analysis included patients who received weekly dose-adjusted (n = 63) or interval-adjusted (n = 29) rFIXFc prophylaxis and completed the Haemophilia-Specific Quality of Life questionnaire for adolescents (Haemo-QoL; 12–17 years) or adults (Haem-A-QoL; ≥18 years) at baseline (BL) and end of study (EoS). A separate analysis evaluating overall change in physical activity during B-LONG included patients from the pooled prophylaxis arms, in addition to the episodic treatment arm (n = 27; Figure S1).

The primary objective of this post hoc analysis was to describe the change from BL to EoS in PROs related to pain and physical activity. Median duration of treatment was 51.6, 58.3 and 40.9 weeks in the weekly dose-adjusted or interval-adjusted prophylaxis groups, and the episodic treatment group, respectively. Data were analysed using a pooled prophylaxis group (weekly dose-adjusted and interval-adjusted prophylaxis arms) and according to prior treatment regimen (i.e., patients previously treated on-demand or previously treated with prophylaxis). All treatment arms (weekly dose-adjusted and interval-adjusted prophylaxis, and episodic treatment arms) were used to assess the overall change in physical activity during the study.

KEYWORDS

factor IX, haemophilia B, Pain, patient reported outcomes measures, physical activity, quality of Life, rFIXFc protein
2.2 Patient-reported outcome measures

The Haemo-QoL and Haem-A-QoL are disease-specific tools to assess HRQoL in paediatric, adolescent, and adult patients with haemophilia. Haemo-QoL consists of a varying number of items and domains for different age groups. The long version of Haemo-QoL, which is comprised of 77 items and 12 domains, was used in this analysis. Although it is validated for use in the 13–16 year age group, for this analysis it was used for patients aged 12–17 years. Haem-A-QoL consists of 46 items and 10 domains. In both questionnaires, items are rated on a 5-point Likert-type frequency scale (1 = ‘never’, 2 = ‘rarely/seldom’, 3 = ‘sometimes’, 4 = ‘often’, 5 = ‘all the time’).

Individual level changes in pain over time were assessed using three items of the ‘Physical Health’ domain in both Haemo-QoL and Haem-A-QoL: ‘My swellings hurt’, ‘I had pain in my joints’, ‘It was painful for me to move’. Individual level changes in physical activity over time were assessed using three items of the ‘Sports and Leisure’ domain in Haem-A-QoL: ‘I had to avoid sports that I like because of my haemophilia’, ‘I played sports just as much as others’, and one item of the ‘Physical Health’ domain in both Haemo-QoL and Haem-A-QoL: ‘I had difficulty walking as far as I wanted to’. A summary of items used in each of the questionnaires is shown in Table 1. For this analysis, item responses were merged into two categories ‘never/rarely/seldom’ versus ‘sometimes/often/all the time’. In addition, for assessment of the pain items, merged categories were further defined as ‘no pain’ and ‘pain’, respectively.

In addition, at each study visit (weeks 4, 16, 26 and 39, and at EoS) after their first rFIXFc dose, patients were asked to report any changes in physical activity levels by choosing one of the following statements: ‘I am doing more physical activities (or more intensive physical activities) since last study visit’, ‘I am doing about the same amount and intensity of physical activities as last study visit’, or ‘I am doing fewer physical activities (or less intensive physical activities) since last study visit’.

### TABLE 1 Summary of items analysed in the Haemo-QoL and Haem-A-QoL questionnaires

| Domain               | Item evaluated                                      | Haemo-QoL (12–17 years) | Haem-A-QoL (≥18 years) |
|----------------------|-----------------------------------------------------|--------------------------|-------------------------|
| Physical Health      | My swellings hurt                                  | ✓                        | ✓                       |
|                      | I had pain in my joints                            | ✓                        | ✓                       |
|                      | It was painful for me to move                      | ✓                        | ✓                       |
|                      | I had difficulty walking as far as I wanted to     | ✓                        | ✓                       |
| Sports and Leisure   | I had to avoid sports like football                 | ·                        | ✓                       |
|                      | I had to avoid sports that I like because of my haemophilia | ·                        | ✓                       |
|                      | I played sports just as much as others              | ·                        | ✓                       |

Haemo-QoL is validated for use in the 13–16-year age group; in this analysis it was used for patients aged 12–17 years.

### 2.3 Statistical analysis

For discrete variables, frequencies and percentages are displayed for categorical data. Distribution of responses to the Haemo-QoL and Haem-A-QoL pain and physical activity items at EoS versus BL were compared using McNemar’s test. Odds ratio and 95% confidence interval (CI) were computed to assess the change from BL to EoS for each of the Haemo-QoL and Haem-A-QoL pain and physical activity items.

Statistical analysis was performed using SAS software version 9.4.

### 3 RESULTS

#### 3.1 Patient population

Patient demographics have been published previously. The analysis population comprised all patients who received weekly dose-adjusted or interval-adjusted prophylaxis with rFIXFc in B-LONG (n = 92). Assessment of overall change in physical activity included this pooled prophylaxis group, in addition to the episodic treatment arm (n = 112; Figure S1). The four items of the ‘Physical Health’ domain of the Haemo-QoL/Haem-A-QoL questionnaire were available, both at BL and EoS, for 73, 78, 76, and 76 patients, respectively. The three items of the ‘Sports and Leisure’ domain of Haem-A-QoL only were available, both at BL and EoS, for 50, 62, and 54 patients, respectively. Reasons for non-completion of the questionnaires were not recorded. A comparison of characteristics (mean age, mean target joints at BL, and proportion of patients who previously received prophylaxis) and bleeding rates of patients with missing data versus those without missing data showed no significant differences (P > .05).

#### 3.2 Pain items

##### 3.2.1 All patients (pooled prophylaxis arm)

A statistically significant greater proportion of patients did not experience painful swellings (P = .004), painful joints (P = .003), or pain when moving (P = .026) at EoS versus BL (Figure 1).

##### 3.2.2 Data split by prior treatment (on-demand or prophylaxis)

In the subgroup of patients treated on-demand prior to enrolment in B-LONG, a statistically significant greater proportion of patients did not experience painful swellings (P = .002) or painful joints (P = .034) at EoS versus BL (Figure 2). Similarly, the proportion of patients who did not experience pain when moving was numerically increased (P = .058) at EoS versus BL but the difference was not statistically significant (Figure 2).

In the subgroup of patients on prophylaxis prior to enrolment in B-LONG, a statistically significant greater proportion of patients did not experience painful swellings (P = .002) or painful joints (P = .034) at EoS versus BL (Figure 2). Similarly, the proportion of patients who did not experience pain when moving was numerically increased (P = .058) at EoS versus BL but the difference was not statistically significant (Figure 2).
3.3 | Physical activity items

3.3.1 | All patients (pooled prophylaxis arm)

A statistically significant greater proportion of patients never/rarely/seldom avoided participating in sports like football ($P = .002$), avoided sports that they like due to their haemophilia ($P = .007$), or experienced difficulty walking as far as they wanted to ($P = .001$) at EoS versus BL (Figure 4). A statistically significant lower proportion of patients reported never/rarely/seldom playing sports as much as others ($P = .033$) at EoS versus BL (Figure 4).

3.3.2 | Data split by prior treatment (on-demand or prophylaxis)

In the subgroup of patients treated on-demand prior to enrolment in B-LONG, a significantly greater proportion of patients never/rarely/seldom avoided participating in sports like football ($P = .008$) or experienced difficulty walking as far as they wanted to ($P = .020$), and a statistically significant lower proportion of patients reported never/rarely/seldom playing sports as much as others ($P = .034$) at EoS versus BL (Figure 5). Similarly, the proportion of patients who did not experience painful joints ($P = .034$) at EoS versus BL (Figure 3). Likewise, the proportion of patients without painful swellings ($P = .166$) or pain when moving ($P = .206$) was numerically increased at EoS versus BL; however, the differences were not statistically significant (Figure 3).
My swellings hurt

OR 1.68
(95% CI 0.81–3.48)

P = .195

I had pain in my joints

OR 1.88
(95% CI 1.07–3.28)

P = .034

It was painful for me to move

OR 1.49
(95% CI 0.67–2.37)

P = .206

FIGURE 3  Individual level changes in pain items at EoS versus BL in patients treated with prophylaxis prior to enrolment in B-LONG.† BL, baseline; CI, confidence intervals; EoS, end of study; OR, odds ratio. †Item responses were merged in two categories ‘never/rarely/seldom’ (no pain) versus ‘sometimes/often/all the time’ (pain).

I had to avoid sports like football

OR 4.93
(95% CI 1.77–13.74)

P = .002

I had to avoid sports that I like because of my haemophilia

OR 2.33
(95% CI 1.28–4.23)

P = .007

FIGURE 4  Individual level changes in physical activity items at EoS versus BL in patients treated with weekly dose-adjusted and interval-adjusted prophylaxis. BL, baseline; CI, confidence intervals; EoS, end of study; OR, odds ratio.
avoid sports that they like due to their haemophilia was numerically increased at EoS versus BL; however, the difference was not statistically significant (\(P = .317\); Figure 5).

In the subgroup of patients on prophylaxis prior to enrolment in B-LONG, a statistically significant greater proportion of patients did not avoid participating in sports like football (\(P = .025\)), avoid sports that they like due to their haemophilia (\(P = .007\)), or experience difficulty walking as far as they wanted to (\(P = .021\)) at EoS versus BL (Figure 6). There was no significant difference in the proportion of patients who reported never/rarely/seldom playing sports as much as others at EoS versus BL (\(P = .414\); Figure 6).

3.4 Overall change in physical activity levels

Most patients maintained or increased their physical activity levels during the study (Figure S1). Of patients assigned to weekly dose-adjusted and interval-adjusted prophylaxis, 77% and 76%, respectively, reported more or the same amount of physical activity over time versus 56% of patients assigned to episodic treatment.

4 DISCUSSION

This post hoc analysis of B-LONG data evaluated the effect of prophylactic treatment with rFIXFc on pain and levels of physical activity in patients with severe haemophilia B. Our results demonstrated that over time, rFIXFc prophylaxis resulted in improvements in pain and levels of physical activity in this patient population. Importantly, patients reported improvements in both pain and physical activity irrespective of their prior treatment regimen. Furthermore, the proportion of patients assigned to rFIXFc prophylaxis reporting more or the same amount of physical activity over the duration of the study was greater than in patients assigned to episodic treatment. These results are
consistent with a previous analysis of B-LONG data, whereby participants treated with rFIXFc weekly prophylaxis showed meaningful improvements in two key Haem-A-QoL domains (‘Physical Health’ and ‘Sports and Leisure’) and ‘Total Score’ over time, with greater improvements experienced by patients receiving pre-study on-demand therapy.17 These improvements were maintained over 24 months of follow-up in the long-term extension study (B-YOND).20

A reduced capacity to carry out activities due to impairment in physical functioning accompanied by chronic pain, negatively impacts HRQoL in patients with severe haemophilia.3,17 Therefore, effective pain management and improved physical functioning to facilitate participation in physical activities are of critical importance to reduce the burden on HRQoL.121 Not surprisingly, after controlling for age, disease severity, and body mass index, adult patients with haemophilia B reported a marginally non-significant improvement in HRQoL when engaged in high levels of physical activity compared with those who engaged in moderate/low physical activity.22 Participation in sports and physical activities contributes to improved HRQoL in patients with haemophilia by providing numerous multidimensional benefits, including physical (e.g., improved joint, muscular, and bone health), psychological (e.g., increased relaxation and self-esteem) and sociological (e.g., integration within a group of peers and feeling of belonging) benefits.6

Taken together, the changes over time in the pain and physical activity items assessed in this analysis, suggest that prophylaxis with rFIXFc may provide meaningful and relevant improvements in HRQoL in patients with severe haemophilia B. Of note, patients treated with prior prophylaxis were also able to demonstrate improvement in several pain- and physical activity-related items. There are few data on extended half-life (EHL) products and HRQoL in patients with haemophilia B.23 Previous studies in paediatric populations have shown mixed results; substantial improvements,23 and towards improvement in HRQoL have both been reported, although the latter study included a small sample size.24 Data from an adult patient population have shown significant improvements in overall HRQoL.
following prophylactic treatment with an EHL recombinant FIX. The current analysis is the first study to specifically evaluate pain- and physical activity-related HRQoL in patients with haemophilia B, thus complementing previous studies related to overall HRQoL. Further research is required to ascertain the effects of prophylaxis with rFIXFc on other HRQoL specific aspects in patients with haemophilia B. This post hoc analysis was conducted using a relatively large sample size, taking into consideration the rarity of haemophilia B, and clinically relevant endpoints, and thus contributes to the evidence supporting the benefits of EHL products to improve HRQoL in patients with haemophilia B. In addition to rFIXFc treatment, the improvements in PROs related to pain and physical activity may also be attributed to the presence of other potential confounding variables, such as patients reporting less pain due to improved acceptance, and this should be taken into consideration when interpreting the results. The analysis uses McNemar’s test to report individual level changes in the pain and physical activity items of the ‘Physical health’ and ‘Sports and Leisure’ domains. It is a non-parametric test, and is appropriate even considering the small number of participants. However, due to the small sample size analysed, the power of the test may be low, which means that there is a relatively high-risk of failing to detect a significant change. To address study limitations caused by potential higher adherence to treatment regimens within the robust setting of a clinical trial, our data should be further complemented with observational studies where adherence may be lower.

5 | CONCLUSIONS

The results of this analysis suggest that over time, rFIXFc prophylaxis is associated with significant improvements in PROs related to pain and physical activity. This contributes to previous evidence of overall HRQoL improvements in patients with haemophilia B treated with rFIXFc.

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AUTHOR CONTRIBUTIONS

M.E., S.A., Z.H. and J.N. collected and interpreted the data. J.A., C.H., and E.S. interpreted the data. All authors contributed to drafting and revising the article, provided their final approval of all content and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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