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Improvement in pain-related quality of life in patients with hemophilia A treated with rFVIIIFc individualized prophylaxis: post hoc analysis from the A-LONG study

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Abstract

Background: Pain, a common symptom of hemophilia, begins early in life primarily due to joint bleeding. Recurrent bleeding adversely affects patients' pain-related physical functioning, which can negatively impact their quality of life (QoL).

Objective: Post hoc analysis of data from the A-LONG study (NCT01181128), to assess change over time in pain-related QoL in patients with severe hemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein (rFVIIIFc).

Methods: Patients who completed Haem-A-QoL (17–65 years) and EQ-5D-3L (≥12–65 years) questionnaires at baseline (BL) and end of study (EoS). Individual-level changes were assessed using three pain-related items of the Haem-A-QoL 'Physical Health' domain and the pain/discomfort item of EQ-5D-3L. Distributions of responses (EoS *versus* BL) were compared using McNemar's test.

Results: A significantly greater proportion of patients reported they did not experience painful swellings ($n = 87$; 66% *versus* 46%, $p < 0.01$) or pain in their joints ($n = 89$; 42% *versus* 27%; $p < 0.05$) at EoS *versus* BL. The proportion of patients who did not find it painful to move numerically increased at EoS *versus* BL ($n = 86$; 47% *versus* 38%; $p =$ NS). A significantly greater proportion of patients reported no pain/discomfort at EoS *versus* BL ($n = 116$; 45% *versus* 34%; $p < 0.05$).

Conclusion: This study reports the effect of FVIII prophylaxis on patient-reported measures of pain over time in patients with severe hemophilia A. The results of this post hoc analysis showed improvements in pain from BL to EoS in patients receiving rFVIIIFc individualized prophylaxis indicating effective pain management, a key component of patient care.

Keywords: factor VIII Fc fusion protein, health-related quality of life, hemophilia, pain, patient-reported outcomes, treatment outcome

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Introduction

Pain, which often starts early in life as a result of joint bleeding, plays an intrinsic role in the lives of patients with hemophilia.[1,2] Repeated bleeding episodes into the same joint can result in progressive irreversible joint damage and the development of hemophilic arthropathy, which is characterized by chronic pain, swelling, deformity, and disability.[3] Therefore, in the absence of appropriate management, hemophilia may adversely affect patients' physical functioning and negatively impact their health-related quality of life (HRQoL).[4,5]

The Haemophilia Experiences, Results, and Opportunities (HERO) survey reported that among adults with hemophilia who completed

the survey ($n = 675$), 89% experienced pain that interfered with activities in 4 weeks prior to study participation, with 26% citing that pain had interfered with daily life 'extremely' or 'quite a lot'.[6] In another survey of patients with hemophilia ($n = 685$), 86% of patients reported experiencing episodes of pain, with pain already present in 66% of children and adolescents.[7] Furthermore, joint pain was the most common type of pain and was present in 92% of adult respondents, and most notably, in 80% of young patients. Further patient surveys cite varying proportions of patients with hemophilia who experience pain, including 15–35% of adults with severe hemophilia suffering from chronic pain,[8,9] 71% from 'some or moderate pain', and 4% reporting extreme pain.[10] In addition, in a public meeting conducted by the US Food and Drug Administration (FDA), which was held to gather patient perspectives on their bleeding disorder, two-thirds of participants reported joint damage or pain as having the most significant impact on their daily life.[11]

Prevention of bleeds, and subsequent reduction in bleeding-related pain, is a major goal of treatment and compared with on-demand therapy, prophylaxis has been shown to prevent joint damage and reduce the frequency of joint and other hemorrhages, particularly when initiated early in life.[12,13] In patients with severe hemophilia A, primary prophylaxis with factor VIII (FVIII) replacement therapy is the recognized standard of care.[14] The majority of respondents at the FDA public meeting identified factor replacement as their primary treatment regimen and reported the positive impact of this treatment on their daily lives, in particular giving them greater control of their disease and flexibility in treatment schedules.[11]

Recombinant FVIII Fc fusion protein (rFVIIIFc) is an extended half-life FVIII replacement therapy approved for the treatment of bleeding and prophylaxis in patients with hemophilia A.[15,16] The safety and efficacy of rFVIIIFc was demonstrated in two phase 3 studies of previously treated adult/adolescent (A-LONG) and pediatric (Kids A-LONG) patients with severe hemophilia A who received prophylactic or episodic factor replacement regimens.[17,18] These results were confirmed in the phase 3 long-term extension study (ASPIRE), with low annualized bleeding rates sustained for a cumulative treatment duration in A-LONG and ASPIRE of up to ~6 years of treatment.[19] Safety and efficacy of rFVIIIFc has also been shown in previously untreated patients (PUPs) with severe hemophilia A aged < 6 years (PUPs A-LONG).[20]

In A-LONG, HRQoL was assessed as a secondary endpoint via the Haemophilia-specific Quality of Life (Haem-A-QoL) and EuroQoL 5-dimension-3 Level (EQ-5D-3L) questionnaires.[21,22] Haem-A-QoL has strong measurement properties (validity, reliability, and sensitivity to change) and contains a 'Physical Health' domain, which assesses the most clinically relevant symptoms of hemophilia, such as joint pain, painful swellings, and reduced physical functioning.[21,22] Changes in the Haem-A-QoL key domains 'Physical Health' and 'Sports and Leisure', and the 'Total Score', suggest that prophylaxis with rFVIIIFc leads to meaningful improvements in HRQoL.[21] However, to our knowledge, there are limited data reporting the effect of FVIII replacement therapy on patient-reported measures of pain over time.

Here we present a post hoc analysis of data from A-LONG, a phase 3 study that evaluated the efficacy and safety of rFVIIIFc in adults and adolescents with severe hemophilia A, to assess pain-related QoL in this patient population.

Methods

Study design and patient population

The detailed study design of A-LONG (NCT01181128), a phase 3 open-label, multicenter, partially randomized study of rFVIIIFc in patients with severe hemophilia A (< 1 IU/dl endogenous FVIII activity), has been described previously.[17] Briefly, previously treated patients ≥ 12 years of age, treated prophylactically, or episodically with a history of ≥ 12 bleeding episodes in 12 months prior to the study ($n = 165$) were assigned to one of three treatment arms; arm 1: individualized prophylaxis (25–65 IU/kg every 3–5 days, $n = 118$); arm 2: weekly prophylaxis (65 IU/kg; $n = 24$); or arm 3: episodic regimen (10–50 IU/kg depending on bleeding severity, $n = 23$). Patients on a prophylaxis regimen prior to study entry were enrolled into arm 1 and patients on an episodic regimen had the option to enter arm 1 or be randomized into arms 2 or 3. In the individualized prophylaxis arm, to maintain good control of breakthrough bleeding, each patient's pharmacokinetic parameters were used to guide individual adjustments to dosing

interval to target a steady-state FVIII trough level of 1–3 IU/dL.

Of the 164 adult/adolescent patients exposed to rFVIIIFc in A-LONG, this analysis included only those patients in the weekly prophylaxis ($n = 24$) and individualized prophylaxis ($n = 117$) arms who completed the Haem-A-QoL (patients aged 17–65 years) and EQ-5D-3L (≥12–65 years) questionnaires at baseline and end of study. In the weekly prophylaxis and individualized prophylaxis arms, 100% and 26.3% of patients were receiving episodic treatment prior to study entry.[17]

The primary objective of this post hoc analysis was to assess the change from baseline to end of study in patient-reported outcomes (PROs) associated with pain-related QoL. Secondary objectives were to explore the association between the presence of at least one bleed or absence of any bleeds and PROs associated with pain-related QoL, and to assess the change from baseline to end of study in PROs associated with pain-related QoL in patients with and without target joints at baseline and according to prior treatment regimen (i.e. patients previously treated on-demand or previously treated with prophylaxis). The median durations of treatment with rFVIIIFc in the weekly and individualized prophylaxis arms were 32.1 and 28.0 weeks, respectively.[17]

Patient-reported outcome measures

Haem-A-QoL is a disease-specific assessment tool, which assesses HRQoL in adults ≥17 years of age, comprising 46 items and 10 domains: 'Physical Health', 'Feelings', 'View of Yourself', 'Sports and Leisure', 'Work and School', 'Dealing with Hemophilia', 'Treatment', 'Future', 'Family Planning', and 'Partnership and Sexuality'. All questions are rated on a 5-point Likert-type scale (1 = 'never' to 5 = 'all the time'); for each domain and the 'Total Score', scores are transformed to range from 0 to 100, with higher scores representing greater impairment in HRQoL. Previous studies have established strong measurement properties (validity, reliability, and sensitivity to change) of the Haem-A-QoL questionnaire.[21,22] EQ-5D-3L, a frequently used generic tool for assessing HRQoL, consists of two parts, the first of which includes five domains ('Mobility', 'Self-Care', 'Usual Activities', 'Pain/Discomfort', and 'Anxiety/Depression') with responses rated on an ordinal scale of 1 = 'no problems' to 3 = 'severe problems'.[4] A utility score based on the UK-specific value set ranging from 1 ('perfect health') to −0.594 (states 'worse than dead') is derived from the overall response.[23] The second part is a visual analogue scale that rates overall health on the day of assessment based on a scale of 0 ('worst health imaginable') to 100 ('best possible health'). 'Pain/Discomfort' is an EQ-5D-3L item that has been deemed particularly relevant to the hemophilia population.[4]

Outcomes and assessments

Primary outcome measures included change in pain from baseline to end of study as assessed by Haem-A-QoL pain items and the EQ-5D-3L pain domain. Change in pain from baseline was assessed using the following three items of the 'Physical Health' domain of the Haem-A-QoL questionnaire relating to pain: 'My swellings hurt', 'I had pain in my joints', and 'It was painful for me to move'. For this analysis, item responses were merged into two categories 'never/rarely' *versus* 'sometimes/often/all the time' and defined as 'no pain' and 'pain', respectively. For the 'Pain' domain of the EQ-5D-3L questionnaire, level of severity was rated as follows: 1 = 'no pain or discomfort', 2 = 'moderate pain or discomfort', and 3 = 'extreme pain or discomfort'. For this analysis, levels 2 and 3 were grouped as moderate/extreme pain or discomfort. Both Haem-A-QoL and EQ-5D-3L questionnaires were administered at baseline, week 14, week 28, and end of study; here we report results of patients who completed the questionnaires at both baseline and end-of-study visits.

Statistical analysis

For discrete variables, frequencies and percentages are displayed for categorical data. Distribution of responses to the Haem-A-QoL pain items at end of study *versus* baseline were compared using McNemar's test and the association between presence/absence of bleeds and the EQ-5D-3L pain domain was tested using Fisher's exact test.

Results

Patient population

Patient demographics and clinical characteristics have been published previously.[17] For the

primary objective and subgroup analyses in patients with and without target joints at baseline, the analysis population comprised all patients who received individualized prophylaxis in A-LONG ($n = 117$); the association between the presence of bleeds and pain-related items was assessed using a pooled group comprising patients from both the individualized and weekly prophylaxis treatment arms ($n = 141$). For the analysis according to prior treatment regimen, patients were grouped into those who were previously treated on-demand ($n = 31$) and those who were previously treated with prophylaxis ($n = 86$).

Data for the three items of the 'Physical Health' domain of the Haem-A-QoL questionnaire, 'My swellings hurt', 'I had pain in my joints', and 'It was painful for me to move' were available for 87, 89, and 86 patients, respectively, both at baseline and end of study. For the analysis based on prior treatment regimen, data for the three items described above were available for 21 patients previously treated on-demand (all three items) and for 66, 68, and 65 patients who were previously treated with prophylaxis, respectively, both at baseline and end of study.

Reasons for non-completion of the questionnaire were not recorded. However, a comparison of patient characteristics (including mean age, proportion of patients with target joints at baseline, 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 (chi-square test; $p = $ NS) except for mean age, where patients with at least one missing value were younger compared with those without missing data (Wilcoxon test; $p = 0.0001$). Therefore, any selection bias due to lack of response is thought to be minimal.

Haem-A-QoL

Pain items. At end of study compared with baseline, a statistically significant greater proportion of patients reported they did not experience painful swellings ($n = 87$; 66% *versus* 46%, $p < 0.01$) or pain in their joints ($n = 89$; 42% *versus* 27%, $p < 0.05$; Figure 1(a) and (c)). The proportion of patients who did not find it painful to move numerically increased at end of study *versus* baseline ($n = 86$; 47% *versus* 38%; $p = $ NS; Figure 1(a) and (c)).

In the subgroup of patients who had target joints at baseline, a statistically significant greater proportion of patients reported they did not experience painful swellings ($n = 52$; 62% *versus* 38%, $p < 0.05$) or pain in their joints ($n = 53$; 42% *versus* 21%, $p < 0.05$) at end of study *versus* baseline (Supplementary Figure 1(a, b)). The proportion of patients who had no pain when moving numerically increased at end of study *versus* baseline ($n = 52$; 48% *versus* 37%, $p = $ NS; Supplementary Figure 1(a, b)).

In the subgroup of patients without target joints at baseline, at end of study compared with baseline, the proportion of patients who reported they did not experience painful swellings numerically increased ($n = 35$; 71% *versus* 57%; $p = $ NS), and the proportion of patients who reported no pain in their joints ($n = 36$; 42% *versus* 36%; $p = $ NS) or pain when moving ($n = 34$; 44% *versus* 41%; $p = $ NS) was similar (Supplementary Figure 2(a, b)).

In the analysis according to prior treatment regimen, a statistically significant greater proportion of patients who were previously treated on-demand reported no painful swellings ($n = 21$; 71% *versus* 33%; $p < 0.05$) or pain in their joints ($n = 21$; 43% *versus* 14%; $p < 0.05$) at end of study compared with baseline. The proportion of patients who did not report pain when moving numerically increased ($n = 21$; 57% *versus* 43%; $p = $ NS; Supplementary Figure 3(a, b)).

For the patients who were previously treated with prophylaxis, a statistically significant greater proportion of patients reported no painful swellings ($n = 66$; 64% *versus* 50%; $p < 0.05$) at end of study compared with baseline. The proportion of patients who reported no pain in their joints ($n = 68$; 41% *versus* 31%; $p = $ NS) or pain when moving ($n = 65$; 43% *versus* 37%; $p = $ NS) was numerically higher (Supplementary Figure 4 (a, b)).

EQ-5D- 3L

Pain or discomfort domain. A statistically significantly greater proportion of patients reported no pain or discomfort at end of study compared with baseline ($n = 116$; 45% *versus* 34%, $p < 0.05$; Figure 1(b) and (c)). In the subgroup of patients who had target joints at baseline, a statistically significantly greater proportion of patients reported no pain or discomfort at end of study compared with baseline

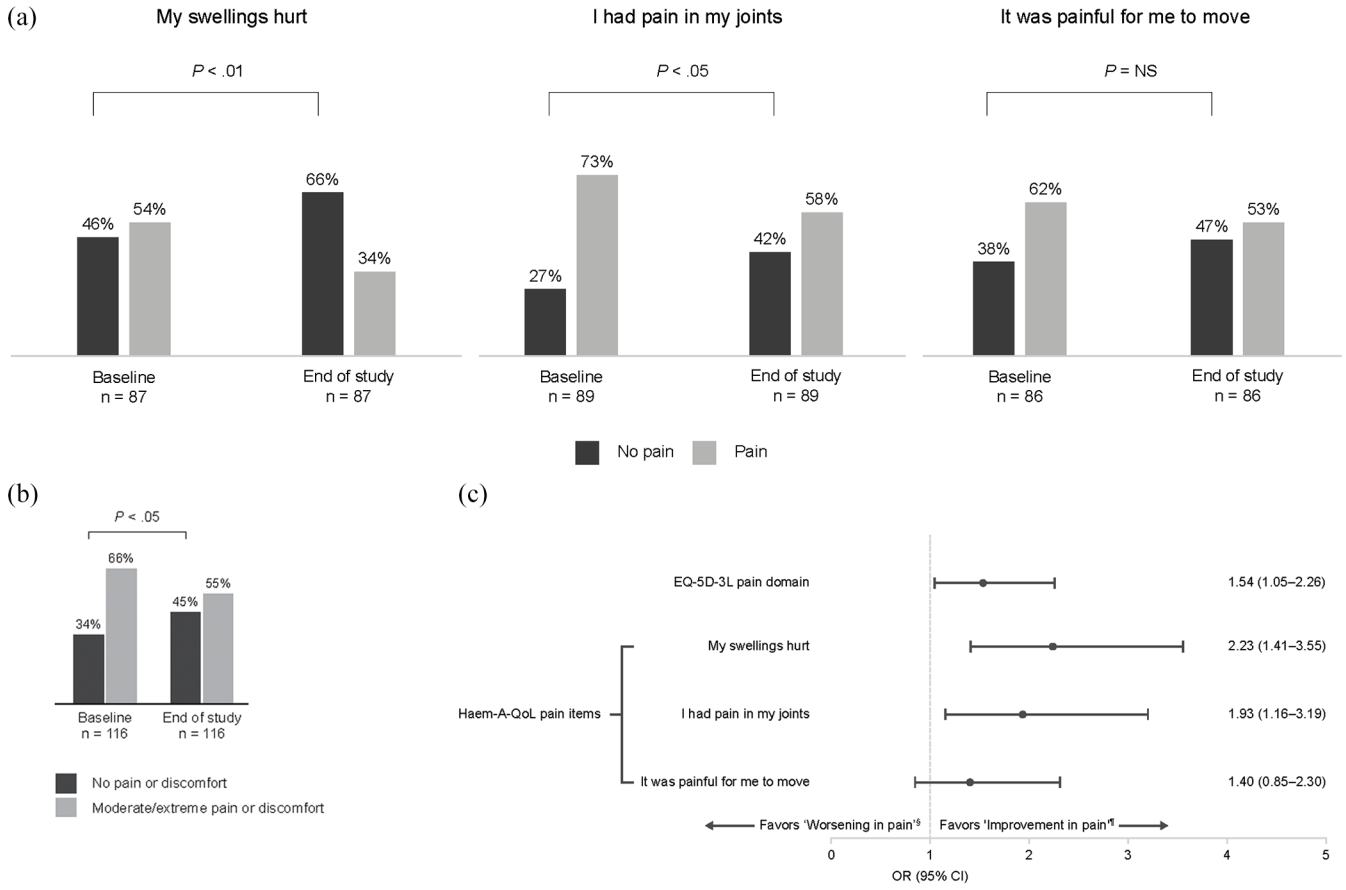

Figure 1. Change in pain from baseline to end of study in patients treated with rFVIIIFc individualized prophylaxis as assessed by Haem-A-QoL pain items† (a) and EQ-5D-3L pain domain‡ (b); forest plot represents relative treatment effects presented as OR with 95% CI (c).

†McNemar's test comparing proportions at each visit *versus* baseline, item responses were merged in two categories 'never/rarely' (no pain) *versus* 'sometimes/often/all the time' (pain) for the test; ‡Fischer's exact text comparing proportions at each visit *versus* baseline; §Favors increase in proportion of patients reporting pain with rFVIIIFc individualized prophylaxis; ¶Favors decrease in proportion of patients reporting pain with rFVIIIFc individualized prophylaxis.

CI, confidence interval; OR, odds ratio.

($n = 72$; 49% *versus* 31%, $p < 0.05$; Supplementary Figure 5(a, c)). In the subgroup of patients without target joints at baseline, the proportion of patients reporting no pain or discomfort at end of study *versus* baseline was similar (39% *versus* 41%, $p =$ NS; Supplementary Figure 5(b, c)).

Association between bleeding events and EQ-5D-3L pain/discomfort dimension

In the pooled analysis population, the proportion of patients with no bleeding events was 40.3% (Table 1). At end of study, the proportion of patients who reported pain or discomfort was significantly greater in patients with at least one

Table 1. Effect of patient bleeds on EQ-5D-3L pain dimension at end of study (pooled analysis population).

Level of severity	Presence/absence of bleeding events	
	0 (%) $n = 56$	**⩾1 (%) $n = 83$**
No pain or discomfort	32 (57.1)	29 (34.9)
Moderate pain or discomfort	23 (41.1)	49 (59.0)
Extreme pain or discomfort	1 (1.8)	5 (6.0)
p value (Fisher's exact test)	<0.05	

EQ-5D-3L: EuroQoL 5-dimension-3 level.

bleeding event compared with those with no bleeding events (65.0% *versus* 42.9%, $p < 0.05$; Table 1).

Discussion

This study presents data showing improvements in patient-reported measures of pain from baseline in patients with hemophilia A treated prophylactically with an extended half-life rFVIII therapy. This post hoc analysis of data from the A-LONG clinical study demonstrated that individualized prophylaxis with rFVIIIFc results in significant improvements in pain from baseline to end of study in patients with severe hemophilia A. Data were derived from both generic and condition-specific preference-based health status measures. A significantly greater proportion of those patients who reported no pain had zero bleeds compared with those with at least one bleed during the study period.

The Haem-A-QoL 'Physical Health' domain records patient experiences of pain associated with swelling in joints and muscles, overall joint pain, and the effect of pain on mobility. Our analysis showed that rFVIIIFc individualized prophylaxis resulted in significantly fewer patients reporting painful swellings and instances of joint pain at end of study *versus* baseline as assessed by the Haem-A-QoL. A numerical benefit in the proportion of patients who experienced no pain during movement at the end of treatment *versus* baseline was also observed. Among the patients treated with prior prophylaxis, significantly fewer patients demonstrated painful swellings and a numerically lower proportion of patients experienced joint pain or pain during movement, over time. Meanwhile, significantly fewer patients treated with prior on-demand reported painful swellings or joint pain, while a numerically higher proportion of patients did not experience pain during movement. As expected, improvements in patient-reported pain were greater for patients previously treated on-demand but were not always significant given the small sample size. Significant improvements in the EQ-5D-3L pain/discomfort domain score were also recorded at end of treatment compared with baseline, confirming the improvement in patient-reported pain observed with Haem-A-QoL. In addition, it was observed that patients with at least one target joint at baseline derived greater benefit from rFVIIIFc individualized prophylaxis than those patients with no target joints at baseline, as shown by significantly fewer patients with target joints reporting painful swellings and instances of joint pain at end of study *versus* baseline.

Previous studies on HRQoL in patients with hemophilia A report that limitations to physical health and sports activities lead to the greatest impairment in HRQoL.[5,24] In addition, prophylaxis with rFVIIIFc has been shown to provide meaningful improvements in HRQoL as shown by changes in the Haem-A-QoL key domains, 'Physical Health', 'Sports and Leisure', and 'Total Score'.[21] The results from our analysis suggest that prevention of bleeds is key to reducing patient pain. A recently published study observed improvements in overall HRQoL of patients who switched to rFVIIIFc, while those who remained on standard half-life products reported no change in their Haem-A-QoL scores.[25] No improvements in chronic pain were observed among those who switched to rFVIIIFc or those who did not, which is likely a result of patients being well controlled on prophylaxis with their standard half-life FVIII.[25] However, the results are based on a small sample size and therefore, the accuracy and power of the study are limited. In addition, the groups may not be directly comparable due to selection biases between switchers and non-switchers.

Reduction in pain has the potential to improve overall HRQoL through improved physical functioning, which may lead to increased participation in physical activity. Effective pain management in hemophilia is therefore a key component of patient care.[2] Primary prophylaxis with replacement FVIII is the recognized standard of care for individuals with severe hemophilia A,[26] and has been shown to prevent joint damage and reduce the frequency of joint and other bleeds.[12,13] Thus, an effective prophylaxis regimen provides relief from bleed-related pain and plays a role in the maintenance of normal joint function.[2] rFVIIIFc is approved for the treatment of bleeding and prophylaxis in patients with hemophilia A of all ages, and the recommended dose can be adjusted based on a patient's response, thus providing an opportunity to dose according to each individual patient's requirements.[15,16]

A-LONG was a phase 3 study in a relatively large population of patients with severe hemophilia A, offering a robust data set with efficacy evaluated using widely used and clinically relevant outcomes. However, this is a post hoc analysis of

clinical trial data and the very nature of clinical trials means regular visits and patient monitoring leading to high treatment adherence and potentially better outcomes. Generalizability of these results needs to be verified by real-world observational studies, where treatment adherence may be lower and changes in HRQoL measures may be different from the observations in this study. An analysis based on the age of the patients was not conducted; however, the study reported results according to the presence of target joints, which is correlated with age and arthropathy.[27] In addition, the short duration of treatment is a limitation of this analysis and confirmation with longer-term data would be beneficial.

Conclusion

The results of this post hoc analysis showed improvements in pain from baseline to end of study in patients with severe hemophilia A receiving rFVIIIFc individualized prophylaxis indicating effective pain management, a key component of patient care.

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Conflict of interest statement

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Compliance with ethics guidelines

This analysis was based on data from a previously published phase III trial (A-LONG). The A-LONG study was conducted in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients. Informed consent for this analysis was not required given the use of anonymized data from the previously published A-LONG study.

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Supplemental material

Supplemental material for this article is available online.

References

1. Rambod M, Sharif F, Molazem Z, *et al*. Pain: the voiceless scream in every haemophilia patient's life. *J Haem Pract* 2016; 3: 8–13.
2. Auerswald G, Dolan G, Duffy A, *et al*. Pain and pain management in haemophilia. *Blood Coagul Fibrinolysis* 2016; 27: 845–854.
3. Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. *J Thromb Haemost* 2010; 8: 1895–1902.
4. O'Hara J, Walsh S, Camp C, *et al*. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes* 2018; 16: 84.
5. Santagostino E, Lentz SR, Busk AK, *et al*. Assessment of the impact of treatment on quality of life of patients with haemophilia A at different ages: insights from two clinical trials on turoctocog alfa. *Haemophilia* 2014; 20: 527–534.
6. Forsyth AL, Witkop M, Lambing A, *et al*. Associations of quality of life, pain, and self-reported arthritis with age, employment, bleed rate, and utilization of hemophilia treatment center and health care provider services: results in adults with hemophilia in the HERO study. *Patient Prefer Adherence* 2015; 9: 1549–1560.
7. Kalnins W, Schelle G, Jost K, *et al*. Pain therapy in haemophilia in Germany. Patient survey (BESTH study). *Hamostaseologie* 2015; 35: 167–173.
8. Holstein K, Klamroth R, Richards M, *et al*. Pain management in patients with haemophilia: a European survey. *Haemophilia* 2012; 18: 743–752.
9. Witkop M, Lambing A, Divine G, *et al*. A national study of pain in the bleeding disorders community: a description of haemophilia pain. *Haemophilia* 2012; 18: e115–e119.
10. Gringeri A, Mantovani LG, Scalone L, *et al*. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; 102: 2358–2563.
11. Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. The voice of the patient. Hemophilia A, hemophilia B, von Willebrand disease and other heritable bleeding disorders, 2016, https://www.fda.gov/media/99237/download (accessed 10 December 2020).
12. Manco-Johnson MJ, Abshire TC, Shapiro AD, *et al*. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; 357: 535–544.
13. Gringeri A, Lundin B, von Mackensen S, *et al*. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; 9: 700–710.
14. Srivastava A, Santagostino E, Dougall A, *et al*. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020; 26(Suppl. 6): 1–158.
15. Bioverativ Therapeutics Inc. Eloctate® prescribing information, 2019, https://www.fda.gov/media/88746/download (accessed 10 December 2020).
16. Swedish Orphan Biovitrum AB (publ). Elocta® summary of product characteristics, 2019, https://www.ema.europa.eu/en/documents/product-information/elocta-epar-product-information_en.pdf (accessed 10 December 2020).
17. Mahlangu J, Powell JS, Ragni MV, *et al*. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014; 123: 317–325.
18. Young G, Mahlangu J, Kulkarni R, *et al*. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Haemost* 2015; 13: 967–977.
19. Nolan B, Mahlangu J, Pabinger I, *et al*. Recombinant factor VIII Fc fusion protein for the treatment of severe haemophilia A: final results from the ASPIRE extension study. *Haemophilia* 2020; 26: 494–502.
20. Königs C, Ozelo MC, Dunn A, *et al*. Final results of PUPs A-LONG study: evaluating safety and efficacy of rFVIIIFc in previously untreated patients with haemophilia A. *Res Pract Thromb Haemost* 2020; 4(Suppl. 1): 8 (Abstract OC 03.02).
21. Wyrwich KW, Krishnan S, Auguste P, *et al*. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. *Haemophilia* 2016; 22: 866–872.
22. Wyrwich KW, Krishnan S, Poon JL, *et al*. Interpreting important health-related quality of life change using the Haem-A-QoL. *Haemophilia* 2015; 21: 578–584.
23. Mulhern B, Feng Y, Shah K, *et al*. Comparing the UK EQ-5D-3L and English EQ-5D-5L value sets. *Pharmacoeconomics* 2018; 36: 699–713.

24. Von Mackensen S. Quality of life and sports activities in patients with haemophilia. *Haemophilia* 2007; 13(Suppl. 2): 38–43.

25. Sun H, Yang M, Poon M, *et al*. The impact of extended half-life factor concentrates on patient reported health outcome measures in persons with hemophilia A and hemophilia B. *Res Pract Thromb Haemost* 2021; 5: e12601.

26. Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al*. Guidelines for the management of hemophilia. *Haemophilia* 2013; 19: e1–e47.

27. Chang CY, Li TY, Cheng SN, *et al*. Prevalence and severity by age and other clinical correlates of haemophilic arthropathy of the elbow, knee and ankle among Taiwanese patients with haemophilia. *Haemophilia* 2017; 23: 284–291.