Accepted: 1 September 2017

DOI: 10.1111/hae.13353

ORIGINAL ARTICLE

Clinical haemophilia

WILEY Haemophilia

Improved joint health in subjects with severe haemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein

J. Oldenburg[1] | R. Kulkarni[2] | A. Srivastava[3] | J. N. Mahlangu[4] | V. S. Blanchette[5] | E. Tsao[6] | B. Winding[7] | J. Dumont[6] | N. Jain[6]

[1]Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany

[2]Department of Pediatrics and Human Development, Michigan State University, East Lansing, MI, USA

[3]Department of Haematology, Christian Medical College, Vellore, Tamil Nadu, India

[4]Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa

[5]Department of Pediatrics, University of Toronto and Division of Hematology/Oncology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

[6]Bioverativ, Waltham, MA, USA

[7]Sobi, Stockholm, Sweden

Correspondence
Johannes Oldenburg, Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany.
Email: johannes.oldenburg@ukbonn.de

Funding information
Biogen/Bioverativ; Sobi

Introduction: Joint arthropathy is the long-term consequence of joint bleeding in people with severe haemophilia.

Aim: This study assessed change in joint health over time in subjects receiving recombinant factor VIII Fc fusion protein (rFVIIIFc) prophylaxis.

Methods: ALONG is the phase 3 pivotal study in which the benefit of rFVIIIFc as a prophylactic treatment for bleeding control was shown in previously treated severe haemophilia patients ≥12 years of age (arm 1: 25-65 IU/kg every 3-5 days, arm 2: 65 IU/kg weekly and arm 3: episodic). After completing ALONG, subjects had the option to enrol into the extension study (ASPIRE). This interim, post hoc analysis assessed changes in joint health over ~2.8 years in these patients.

Results: Forty-seven subjects had modified Haemophilia Joint Health Score (mHJHS) data at A-LONG baseline, ASPIRE baseline and ASPIRE Year 1 and Year 2. Compared with A-LONG baseline (23.4), mean improvement at ASPIRE Year 2 was −4.1 (95% confidence interval [CI], −6.5, −1.8; $P = .001$). Regardless of prestudy treatment regimen, subjects showed continuous improvement in mHJHS from A-LONG baseline through ASPIRE Year 2 (prestudy prophylaxis: −2.4, $P = .09$; prestudy episodic treatment: −7.2, $P = .003$). Benefits were seen in subjects with target joints (−5.6, $P = .005$) as well as those with severe arthropathy (−8.8, $P = .02$). The mHJHS components with the greatest improvement at ASPIRE Year 2 were swelling (−1.4, $P = .008$), range of motion (−1.1, $P = .03$) and strength (−0.8, $P = .04$).

Conclusions: Prophylaxis with rFVIIIFc may improve joint health over time regardless of prestudy prophylaxis or episodic treatment regimens.

KEYWORDS

arthropathy, factor VIII, haemarthrosis, haemophilia, joint health, prophylaxis

1 | INTRODUCTION

Haemophilia A is an X-linked hereditary bleeding disorder caused by a deficiency in plasma coagulation factor VIII (FVIII),[1] representing 85% of haemophilia cases. The severity of haemophilia A is defined by plasma levels of FVIII with levels of <1% considered severe.[1,2]

A common symptom in severe haemophilia is spontaneous musculoskeletal bleeding. The development of intra-articular bleeds (ie, haemarthrosis) results in synovial hypertrophy and damage to cartilage with gradual joint destruction (ie, haemophilic arthropathy).[1] Haemophilic arthropathy is the largest cause of morbidity and remains a challenge in the management of haemophilia.[2] Although

the mechanism of haemophilic arthropathy is complex and not fully understood, the process is multifactorial and associated with cartilage destruction and inflammation due to repeated blood effusions into the joints.[1,3] In patients treated on-demand, the most commonly affected joints are the knees (45%), elbows (30%), ankles (15%), shoulders (3%) and wrists (2%),[2] while ankles are the most affected joints in patients receiving prophylaxis.[4,5]

Standard treatment of haemophilia A is FVIII replacement, administered intravenously either on-demand or prophylactically.[1] Early use of prophylaxis is recommended following diagnosis of haemophilia A to maintain joint health and prevent joint destruction.[1,4,6] Addition of an Fc fusion protein to recombinant FVIII (rFVIIIFc) prolongs the half-life of rFVIII by redirecting the protein back into the circulation via the Fc receptor and endogenous IgG recycling pathway, thus delaying lysosomal degradation.[7-10] rFVIIIFc is produced using a human cell line, enabling a human pattern of post-translational modifications, potentially reducing the risk of inhibitor development relative to FVIII products produced from non-human cell lines.[11]

In two Phase 3 trials conducted in previously treated adolescents/adults (A-LONG) [12] and children (Kids A-LONG) [13] with severe haemophilia A, rFVIIIFc demonstrated good efficacy and was well tolerated. Long-term safety and efficacy of rFVIIIFc is being evaluated in the ongoing ASPIRE extension study in subjects who completed the A-LONG [12] or Kids A-LONG [13] studies. Interim data from ASPIRE supports the long-term safety and efficacy of rFVIIIFc for the prevention and treatment of bleeding episodes with extended-interval prophylaxis.[14] Effective prevention of bleeding episodes may be beneficial to long-term joint health.[15]

The development of haemophilic arthropathy can be quantified using the Haemophilia Joint Health Score (HJHS), a first-line assessment tool and the most widely used clinical joint score.[16] The HJHS is a validated, 11-item scoring tool used to assess joint impairment in children aged 4-18 years.[16,17] The HJHS grades joints by specific domains: swelling, swelling duration, muscle atrophy, axial alignment, crepitus on motion, flexion loss, extension loss, instability, joint pain, strength and global gait.[17] The International Hemophilia Prophylaxis Study Group is currently undertaking a project to validate the HJHS for adults. In the absence of a validated tool for quantifying joint heath in the adult population, Biogen modified the HJHS (mHJHS) for use in A-LONG. Modifications were minor and involved condensing certain response scales. These modifications were based on recommendations from the latest HJHS validation study.[16] Of note, the mHJHS is not validated, and the modifications may lead to a loss of sensitivity, with the mHJHS having a total score of 116 compared with a total score of 124 for the HJHS version 2.1.

Improvement in musculoskeletal outcomes is an important measure of the effectiveness of prophylactic treatment for haemophilia A.[18] The aim of this post hoc analysis was to evaluate musculoskeletal changes and changes in joint health in adults and adolescents with haemophilia A who received rFVIIIFc prophylaxis during the A-LONG and ASPIRE studies.

2 | MATERIALS AND METHODS

2.1 | Subjects

The analysis population included adults/adolescents (≥12 years of age) treated with rFVIIIFc prophylaxis who completed A-LONG and enrolled in the ASPIRE extension study (data cut off of December 8, 2014) with available mHJHS data.

A full description of subjects enrolled in the A-LONG study was previously reported.[12] Briefly, previously treated male adolescents or adults ≥12 years of age with severe haemophilia A, defined as endogenous FVIII activity <1 IU/dL (1%), and were enrolled in A-LONG. Patients were treated prophylactically (arm 1: individualized prophylaxis, rFVIIIFc 25-65 IU/kg every 3-5 days; arm 2: weekly prophylaxis, rFVIIIFc 65 IU/kg) or episodically (arm 3: rFVIIIFc 10-50 IU/kg as required), with episodic patients having a history of ≥12 bleeding events in the 12 months prior to study entry. Subjects with a history of inhibitors (ie, neutralizing antibodies), hypersensitivity to FVIII concentrate, intravenous immunoglobulin or other coagulation disorders were excluded. Subjects were enrolled in one of three treatment arms: individualized prophylaxis, weekly prophylaxis or episodic treatment.[12] All subjects who completed A-LONG were eligible to enrol in the ASPIRE extension, which included an additional modified prophylaxis treatment arm for subjects in whom optimal prophylaxis could not be achieved with individualized or weekly prophylaxis [14] (Fig. S1).

Study protocols were approved by the local institutional review board/ethics committees. The studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients, or parent guardians, gave written informed consent.

2.2 | mHJHS

Joint health was assessed using the mHJHS at A-LONG baseline, ASPIRE baseline and annually thereafter. Using this tool, the six joints most commonly affected in haemophilia (left ankle, right ankle, left elbow, right elbow, left knee and right knee) were scored on a scale from 0 to 19 according to the following domains: swelling duration, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain and strength. Gait was scored globally on a scale from 0 to 2 based on walking and climbing stairs. The total mHJHS was the sum of scores for all six joints plus the gait score.

Compared with the most recent HJHS (version 2.1), which defines peak severity by a maximal score of 124, the scoring range of the mHJHS is 0 (normal) to 116 (most severe disease) due to simplification in the crepitus of motion, joint pain and global gait domains and inclusion of the "instability" domain removed in the latest version of the HJHS (see Table 1). The mHJHS was modified by the study designers to adapt the HJHS scoring system to an adult haemophilia population and according to comments from a recent validation study by the International Haemophilia Prophylaxis Study Group.[16] The mHJHS will be further evaluated, modified if needed and validated for use in future trials.

TABLE 1 Scoring comparison between the HJHS (v2.1) and mHJHS

Domain	Scoring range	
	HJHS	mHJHS
Duration	0-1	0-1
Swelling	0-3	0-3
Muscle atrophy	0-2	0-2
Flexion loss	0-3	0-3
Extension loss	0-3	0-3
Strength	0-4	0-4
Crepitus of motion	0-2	0-1
Joint pain	0-2	0-1
Instability[a]	-	0-1
Global gait[b]	0-4	0-2
Total score[c]	0-124	0-116

HJHS, Haemophilia Joint Health Score; mHJHS, modified Haemophilia Joint Health Score.
[a]Instability was scored the same as in the old version of the HJHS as 0 = none and 1 = significant pathologic joint laxity.
[b]Global gait scored as follows: 0 = no difficulty with walking or climbing up/down stairs; 1 = no difficulty with walking, but difficulty with stairs; 2 = difficulty with walking and with stairs.
[c]Joint scoring performed separately for six joints (left and right ankle, left and right elbow, left and right knee) with a score range of 0-19 plus the gait score (0-2). Score of 0 = normal; score of 116 = most severe disease.

2.3 | Assessments

Change in mHJHS from A-LONG baseline to follow-up visits was summarized using total score, with negative values indicating improvement. In addition to comparing individual mHJHS domains, different factors, such as target joints, weight-bearing and non–weight-bearing joints and prestudy dosing regimen, were assessed for impact on mHJHS. In this study, a target joint was defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) into which ≥3 bleeding episodes occurred in a consecutive 6-month period.[19] Changes in target joints were assessed using the sum of all questions for a single target joint (range, 0-19). Changes in weight-bearing and non–weight-bearing joints were assessed using the sum of the right and left joints of a single location (range, 0-38).

2.4 | Statistics

The primary analysis population comprised subjects who received prophylaxis during A-LONG and ASPIRE and had mHJHS data at four major time points (A-LONG baseline, ASPIRE baseline and ASPIRE Year 1 and Year 2). A sensitivity analysis of subjects with mHJHS data at A-LONG baseline and at least one post-baseline data point was also conducted. The change in total mHJHS from A-LONG baseline to subsequent study visits was summarized using descriptive statistics. The change from baseline to ASPIRE Year 2 was analysed using a paired *t* test, with a *P*-value of .05 considered to be statistically significant. A subgroup analysis of total mHJHS was conducted by prestudy regimen (ie, prior enrolment in A-LONG; prophylactic vs episodic), severity of functional impairment based on initial mHJHS quartile, age and presence of target joints at baseline. The total mHJHS was excluded from the analysis if all nine questionnaires were not assessed for each of the six joints or if total mHJHS was collected within 2 weeks of a bleed. Scores for joints that underwent surgical interventions were imputed using the last-observation-carried-forward technique from final visit scores prior to surgery.

As a sensitivity analysis, a linear mixed-effects model with random intercept and slope, adjusting for baseline mHJHS, age, body mass index (BMI), and weight was used to estimate annual change in total mHJHS in all subjects with a total mHJHS at baseline and at least one data point post-baseline.

3 | RESULTS

3.1 | Study population

Seventy-four subjects with mHJHS data at A-LONG baseline enrolled in the ASPIRE extension study; of those, 47 subjects had mHJHS data at all four time points (A-LONG baseline; ASPIRE baseline, Year 1 and Year 2). Mean follow-up was 2.8 years (range, 2.5-3.3 years). Baseline characteristics were similar between subjects enrolled in ASPIRE and those completing 2 years on-study (Table 2).

3.2 | Longitudinal joint health

Compared with the mHJHS at A-LONG baseline, continuous improvement in total mHJHS was observed over time. Mean (± standard error of the mean [SEM]) mHJHS at A-LONG baseline for subjects with data at all time points (n = 47) was 23.4 ± 2.7 (Figure 1). Between A-LONG baseline and ASPIRE baseline, change in mean mHJHS was −1.6 ± 0.8, which increased to −3.0 ± 1.1 at ASPIRE Year 1. The total change in mHJHS from A-LONG baseline to ASPIRE Year 2 was −4.1 ± 1.2 (95% confidence interval [CI], −6.5, −1.8; *P* = .001). Regardless of prestudy treatment regimen (prophylactic, n = 30 vs episodic, n = 17), the reduction in mHJHS over time was continuous (Figure 2). Subjects with prestudy prophylactic treatment had an mHJHS of 21.0 ± 3.5 at A-LONG baseline and experienced a total change of −2.4 ± 1.4 (95% CI, −5.2, 0.4; *P* = .09) at ASPIRE Year 2. Subjects treated episodically prestudy had an mHJHS of 27.6 ± 3.9 at A-LONG baseline and experienced a total change of −7.2 ± 2.1 (95% CI, −11.7, −2.8; *P* = .003) at ASPIRE Year 2.

When assessing change in total mHJHS from A-LONG baseline by quartile of initial total mHJHS, subjects with the highest quartile of total mHJHS (ie, greatest impairment in joint function) at A-LONG baseline showed the greatest improvement in total mHJHS (Figure 3). The group in the highest (fourth) quartile (mHJHS >34 at A-LONG baseline; n = 12) showed a mean change between A-LONG

TABLE 2 Demographic and baseline characteristics

	A-LONG baseline and enrolled in ASPIRE (n = 74)[a]	A-LONG and ASPIRE 2-year completer (n = 47)[b]
Age, y, mean (SD)	31.6 (11.9)	32.3 (12.8)
Weight at parent study entry, kg, mean (SD)	72.7 (15.1)	73.5 (15.7)
BMI, kg/m^2, mean (SD)	23.8 (4.3)	24.0 (4.1)
Baseline mHJHS, mean (SD)	22.1 (18.0)	23.4 (18.3)
Subjects with ≥1 target joint, %	55.4	51.1
Prestudy (pre–A-LONG) treatment, %		
Prophylaxis	68.9	63.8
On-demand	31.1	36.2
Prestudy (pre-A-LONG) ABR, mean (SD)	15.8 (20.0)	16.5 (18.4)

ABR, annualized bleeding rate; BMI, body mass index; FVIII, factor VIII; mHJHS, modified Haemophilia Joint Health Score; rFVIIIFc, recombinant factor VIII Fc fusion protein; SD, standard deviation.
[a]74 subjects on rFVIIIFc prophylaxis enrolled in A-LONG, have mHJHS data and subsequently entered ASPIRE.
[b]47 subjects on prophylaxis reached Year 2 in ASPIRE with data available at A-LONG baseline, ASPIRE baseline and ASPIRE Year 1 and Year 2.

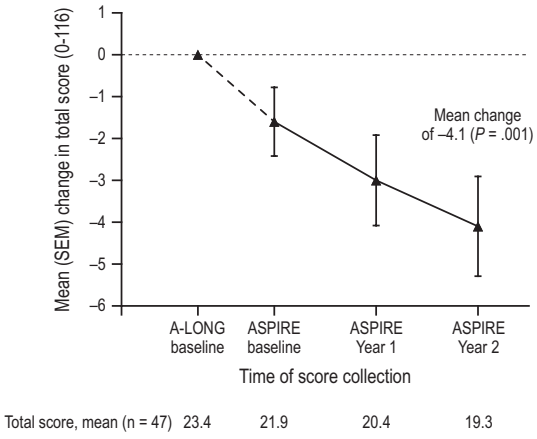


FIGURE 1 Change in total mHJHS from A-LONG baseline (n = 47). [a,b] mHJHS, modified Haemophilia Joint Health Score; SEM, standard error of the mean. [a]Dashed line between A-LONG baseline and ASPIRE baseline indicates variable follow-up time between the two time points across subjects (6.6-13.6 mos, with a median of 8.2 mos). [b]*P* value compares A-LONG baseline with ASPIRE Year 2 using a paired *t* test

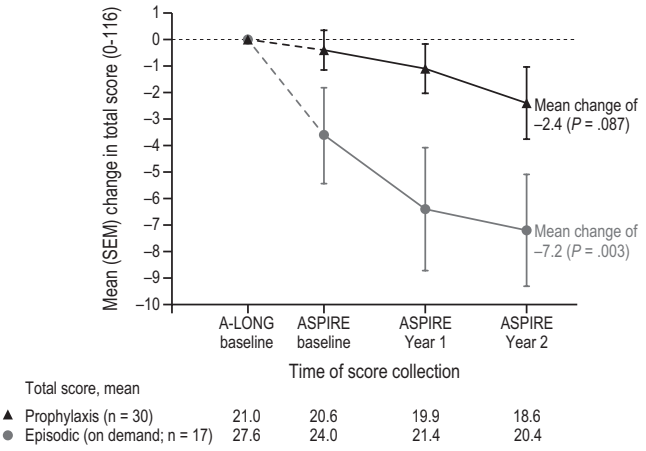
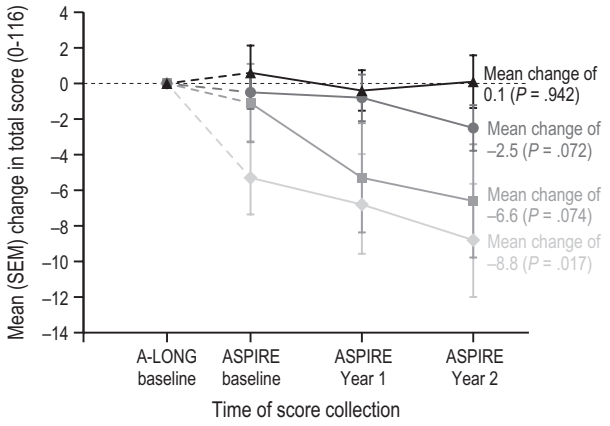


FIGURE 2 Change in total mHJHS from A-LONG baseline by prestudy treatment subgroups. [a-c] mHJHS, modified Haemophilia Joint Health Score; SEM, standard error of the mean. [a]Dashed line between A-LONG baseline and ASPIRE baseline indicates variable follow-up time between the two time points across subjects (6.6-13.6 mos, with a median of 8.2 mos). [b]Cannot compare between the prophylactic and episodic (on-demand) groups because the follow-up duration differed. [c]*P* value compares A-LONG baseline with ASPIRE Year 2 using a paired *t* test

baseline and ASPIRE Year 2 of −8.8 ± 3.2 points (95% CI, −15.8, −1.9; *P* = .02), while subjects in the third quartile (>22-34; n = 9) and second quartile (>10-22; n = 13) experienced progressively smaller changes (−6.6 ± 3.2 [95% CI, −13.9, 0.8; *P* = .074] and −2.5 ± 1.3 [95% CI, −5.3, 0.3; *P* = .07] respectively). The group in the first quartile (≤10; n = 9) had the least amount of impairment at baseline and showed no improvement between A-LONG baseline and ASPIRE Year 2 (0.1 ± 1.5; 95% CI, −3.3, 3.5; *P* = .94). Overall, the observed trend suggests a positive relationship between severity of haemarthrosis at baseline and degree of improvement over time.

Subjects with/without target joints at A-LONG baseline showed continued improvement in total mHJHS (Table 3). For subjects without target joints at baseline (n = 23), mean total mHJHS changed −2.7 ± 1.6 points (95% CI, −5.9, 0.6; *P* = .1) between A-LONG baseline and ASPIRE Year 2. Subjects with target joints at baseline (n = 24) showed a change of −5.6 ± 1.8 (95% CI, −9.2, −1.9; *P* = .005) in total mHJHS for the same time period. Among subjects with target joint(s), the change in the target joint(s) score from A-LONG baseline to ASPIRE Year 2 was −1.7 ± 0.6 (95% CI, −2.8, −0.5; *P* = .007; Table 3).

Changes in total mHJHS over time were also evaluated by age subgroups. Improvements were observed over time in both the ≥18–<50-year (n = 38) and ≥50-year (n = 6) age groups. No marked improvement was observed in 3 subjects 12-17 years of age (Table 4). Continuous improvement was observed in both weight-bearing and non–weight-bearing joints. Similar results were found in individual joints of the elbow, ankle and knee (Table 4).



Total Score, mean				
▲ Q1 (≥1–10; n = 9)	6.2	6.8	5.8	6.3
● Q2 (>10–22; n = 13)	14.9	14.5	14.2	12.4
■ Q3 (>22–34; n = 9)	30.0	28.9	24.7	23.4
◆ Q4 (>34–37; n = 12)	48.4	43.1	41.6	39.6

FIGURE 3 Change in total mHJHS from A-LONG baseline by quartile of initial total mHJHS. [a,b] mHJHS, modified Haemophilia Joint Health Score; Q, quartile; SEM, standard error of the mean. [a]Dashed line between A-LONG baseline and ASPIRE baseline indicates variable follow-up time between the two time points across subjects (6.6-13.6 mos, with a median of 8.2 mos). [b]*P* value compares A-LONG baseline with ASPIRE Year 2 using a paired *t* test

Of all components of the mHJHS, swelling (combination of questions "Swelling" and "Duration of swelling" of all joints; range, 0-24), range of motion (combination of questions "Extension loss [dorsiflexion of ankles]" and "Flexion loss [plantarflexion of ankles]" of all joints; range, 0-36) and strength (sum of all joints; range, 0-6) had the largest effect on total score (Table 4). Between A-LONG baseline and ASPIRE Year 2, swelling improved by −1.4 ± 0.5 points (95% CI, −2.5, −0.4; *P* = .008), range of motion by −1.1 ± 0.5 points (95% CI, −2.0, −0.1; *P* = .03) and strength by −0.8 ± 0.4 points (95% CI, −1.6, 0; *P* = .04). Comparing A-LONG baseline with ASPIRE Year 2, the number of joints with pain decreased or remained the same in 39 (83%) subjects and increased in 8 (17%) subjects. Additional mHJHS components showed an overall trend toward improvement over time (see Table S1).

3.3 | Estimated mean annual change

Of the 74 subjects with a total mHJHS at A-LONG baseline who entered ASPIRE, 73 had some post-baseline mHJHS data and thus were included in a linear mixed-effects model to estimate the annual change in mHJHS. There was an estimated mean (SEM) annual improvement in total mHJHS of −1.4 ± 0.4 (95% CI, −0.58, −2.16; *P* < .001) controlling for baseline total mHJHS, age, BMI, and weight.

4 | DISCUSSION

Subjects with severe haemophilia A received rFVIIIFc prophylaxis during an approximately 28-week Phase 3 study (A-LONG) and an additional 2 years of the associated ongoing long-term extension study (ASPIRE). During A-LONG, rFVIIIFc was determined to be well tolerated and resulted in low bleeding rates when dosed one to two times per week.[12]

TABLE 3 Summary of mean (SEM) change in mHJHS total score, target joint score and component score from A-LONG baseline

	A-LONG baseline	ASPIRE baseline		ASPIRE Year 1		ASPIRE Year 2		
	Score	Score	Change[a]	Score	Change[a]	Score	Change[a]	*P* value[b]
Total score								
With target joint[c] (n = 24)	26.3 ± 3.3	24.4 ± 3.0	−1.8 ± 1.1	22.4 ± 3.2	−3.9 ± 1.4	20.7 ± 2.7	−5.6 ± 1.8	.005
No target joint[c] (n = 23)	20.5 ± 4.2	19.2 ± 3.9	−1.3 ± 1.2	18.4 ± 3.5	−2.1 ± 1.7	17.8 ± 3.6	−2.7 ± 1.6	.103
Target joint score								
With target joint[c] (n = 24)	7.0 ± 0.7	6.1 ± 0.5	−0.8 ± 0.5	5.5 ± 0.7	−1.5 ± 0.6	5.3 ± 0.7	−1.7 ± 0.6	.007
Component score								
Swelling (n = 47)[d]	3.3 ± 0.6	2.6 ± 0.6	−0.7 ± 0.4	2.0 ± 0.4	−1.2 ± 0.5	1.8 ± 0.5	−1.4 ± 0.5	.008
Range of motion (n = 47)[e]	10.6 ± 1.2	10.5 ± 1.2	−0.0 ± 0.4	10.2 ± 1.2	−0.3 ± 0.4	9.5 ± 1.2	−1.1 ± 0.5	.028
Strength (n = 47)[f]	2.8 ± 0.5	2.3 ± 0.5	−0.5 ± 0.3	2.0 ± 0.4	−0.8 ± 0.3	2.0 ± 0.4	−0.8 ± 0.4	.041

mHJHS, modified Haemophilia Joint Health Score; SEM, standard error of the mean.
[a]Versus A-LONG baseline.
[b]*P* values are based on a paired *t* test for change from A-LONG baseline to ASPIRE Year 2.
[c]A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeding occurred (frequency of 3 or more bleeding episodes into the same joint in a consecutive 6-month period).
[d]Swelling is the combination of questions "Swelling" and "Duration of swelling" (range, 0-24).
[e]Range of motion is the combination of questions "Extension loss (dorsiflexion of ankles)" and "Flexion loss (plantarflexion of ankles)" (range, 0-36).
[f]Range, 0-6.

TABLE 4 Summary of mean (SEM) change in mHJHS from A-LONG baseline, by age and joint type

	A-LONG baseline	ASPIRE baseline		ASPIRE Year 1		ASPIRE Year 2		
	Score	Score	Change[a]	Score	Change[a]	Score	Change[a]	*P* value[b]
Age group[c]								
≥12 to 17 y (n = 3)	1.7 ± 1.7	2.3 ± 1.9	0.7 ± 0.3	1.7 ± 1.2	0.0 ± 0.6	2.0 ± 1.2	0.3 ± 0.9	.742
≥18 to <50 y (n = 38)	21.8 ± 2.7	20.2 ± 2.4	−1.6 ± 1.0	18.7 ± 2.3	−3.1 ± 1.3	18.2 ± 2.4	−3.6 ± 1.2	.005
≥50 y (n = 6)	44.8 ± 6.0	42.2 ± 4.8	−2.7 ± 1.8	40.7 ± 6.5	−4.2 ± 2.4	35.0 ± 4.1	−9.8 ± 5.0	.107
Joint type (n = 47)								
Weight-bearing[d]	8.0 ± 0.9	7.6 ± 0.9	−0.4 ± 0.3	7.2 ± 0.9	−0.8 ± 0.3	6.8 ± 0.8	−1.2 ± 0.4	.006
Non-weight-bearing[d]	6.7 ± 1.0	6.0 ± 0.9	−0.7 ± 0.5	5.2 ± 0.8	−1.5 ± 0.6	4.8 ± 0.8	−1.9 ± 0.6	.002
Ankle (L+R)[e]	9.6 ± 1.2	9.4 ± 1.2	−0.2 ± 0.5	8.8 ± 1.2	−0.8 ± 0.6	8.4 ± 1.1	−1.2 ± 0.6	.044
Knee (L+R)[e]	6.5 ± 1.1	5.8 ± 1.0	−0.7 ± 0.3	5.7 ± 1.1	−0.8 ± 0.3	5.3 ± 1.0	−1.2 ± 0.4	.008
Elbow (L+R)[e]	6.7 ± 1.0	6.0 ± 0.9	−0.7 ± 0.5	5.2 ± 0.8	−1.5 ± 0.6	4.8 ± 0.8	−1.9 ± 0.6	.002

L, left; mHJHS, modified Haemophilia Joint Health Score; R, right; SEM, standard error of the mean.
[a]Versus A-LONG baseline.
[b]*P* values are based on a paired *t* test for change from A-LONG baseline to ASPIRE Year 2.
[c]Total score range: 0-116.
[d]Range of 0-38, with 0 indicating no damage and 38 indicating most severe damage. A score was first derived as the sum of per-joint scores for a pair of right and left joints (ankle, knee or elbow), then weight-bearing joint score was calculated as the average of the scores for the ankle and knee, and the non-weight-bearing joint score was the same as the score for the elbow.
[e]Per-joint score is the sum of the scores for all the questions for a specific joint (either L or R), with the range of 0-19. The sum of L+R range: 0-38.

The overall findings from the current analysis demonstrated a trend toward continued improvement in joint health during the ASPIRE extension study, as reflected by changes in mHJHS from A-LONG baseline to ASPIRE Year 2. The improvements observed in the completer population (n = 47) were also reflected in the larger population of subjects who had a total mHJHS at baseline and at least one post-baseline data point (n = 73; mean annual reduction in 1.4 points).

Improvements in mHJHS were observed among subjects aged ≥18-<50 years and 50 + . The improvement was greater among subjects with worse A-LONG baseline joint health. Greater improvements were observed in subjects on prestudy episodic treatment compared with prestudy prophylaxis and in subjects with target joints compared with those without target joints. Both weight-bearing and non–weight-bearing joints demonstrated improvement. For subjects with target joints, mHJHS of the individual target joint improved significantly, consistent with the findings that 97% of target joints in the overall A-LONG/ASPIRE population were resolved with rFVIIIFc prophylaxis.[20] Components of the mHJHS that contributed most to improvements in total score were swelling, range of motion and strength. Improvements in joint health may have been related to treatment with rFVIIIFc over an extended time period, low bleeding rates compared with prestudy rates and/or increased adherence to prophylaxis during ASPIRE.[14] Furthermore, it will be interesting to better understand the contributions to joint health provided by the Fc domain of rFVIIIFc, either by extended half-life or potential anti-inflammatory properties of IgG Fc mediated through the inhibitory Fc receptor FcγRIIB.[21-23]

Use of the mHJHS tool to evaluate joint health may have advantages over self-report questionnaires limited by a lack of objective measures and reliance on patient reporting. The HJHS, administered by a physical therapist, was developed to evaluate the functional well-being of people with haemophilia and objectively assess the presence or absence of joint swelling, flexion and extension and gait changes [24] with high inter-observer reliability.[17]

There are several limitations to the study. The small sample size, particularly in the 12-17 years age group, and lack of a control group limited the analysis of the results. Joint health was first evaluated in the A-LONG study using the Gilbert score, but following a protocol amendment, the mHJHS was employed in its place. Regarding the mHJHS, the study protocol did not mandate that the same assessor administer the mHJHS at each visit, leading to issues of inter-observer variability. Assessors were given a guide to direct assessments; however, no information is available relating to assessors in this study. Also, the mHJHS is a simplified and modified version of the HJHS that is not yet validated, so results cannot be compared with other studies. Use of the modified version reduced the burden for the assessor, but might have impacted on measurement properties previously reported for the HJHS.[15,16] Furthermore, use of additional objective methodologies for the quantification of joint health (eg, imaging) will be beneficial in future validation studies. Finally, this was a post hoc analysis and not powered to show statistical significance. Further studies will be needed to confirm these findings as well as the effect of improvements in joint health on overall improvements in quality of life.

5 | CONCLUSION

This study is the first to demonstrate continuous improvement in joint health with extended half-life factor replacement prophylaxis in haemophilia. Improvements in joint health were most marked in subjects with poor joint health. These data suggest that subjects treated long-term with rFVIIIFc, including those already on a prestudy prophylactic regimen with conventional FVIII products, and those with poor joint health, experienced improvements in joint health. Findings from this study are limited based upon the small number of subjects but suggest that joint health can be improved in subjects with severe haemophilia treated long-term with rFVIIIFc prophylaxis, and the majority of improvements can be attributed to benefits associated with decreased swelling and increased strength and range of motion. Future studies will be needed to confirm these findings.

ACKNOWLEDGEMENTS

J. Oldenburg, R. Kulkarni, A. Srivastava, J. Mahlangu and V. Blanchette contributed to the acquisition and interpretation of the data. E. Tsao contributed to the analysis and interpretation of the data. B. Winding, J. Dumont and N. Jain contributed to the research design and analysis and interpretation of the data. All authors contributed to the drafting and revision of the manuscript. Biogen/Bioverativ and Sobi reviewed and provided feedback on the paper. The authors had full editorial control of the paper and provided their final approval of all content.

This study was funded by Biogen/Bioverativ and Sobi. Editorial support was provided by Kelly Burns, of Fishawack Communications, Santo D'Angelo, PhD, MS, CMPP, of Fishawack Communications, and was funded by Biogen/Bioverativ and Sobi.

DISCLOSURES

J. Oldenburg has received grant/research support from, served in a speakers bureau for and/or served as a consultant for Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum. R. Kulkarni has received grant/research support from Biogen, Baxter, Bayer and Novo Nordisk and served on advisory boards for Baxter, Bayer, Novo Nordisk, Pfizer, Kedrion, BPL, Hoffman LaRoche/Genentech and HEMA Biologics. A. Srivastava has received grant/research support from Bayer, Baxter and Novo Nordisk and served on advisory boards for Biogen, Baxter, Bayer, Novo Nordisk, Roche Genentech and BioMarin. J. Mahlangu has received grant/research support from Bayer, CSL, Novo Nordisk, Biogen and Roche and has served on a speakers bureau for Amgen, Biotest, Bayer, CSL, Novo Nordisk and Biogen. V. Blanchette has received grant/research support from Biogen and Shire, served on data safety monitoring boards for Octapharma and Shire and received honoraria for participation in educational symposia/advisory boards from Amgen, Bayer, Novo Nordisk, Pfizer and Shire. E. Tsao, J. Dumont and N. Jain are employees of and hold equity interest in Bioverativ. B. Winding is an employee of Sobi.

ORCID

J. Oldenburg http://orcid.org/0000-0003-3038-2145
R. Kulkarni http://orcid.org/0000-0001-9372-3184
A. Srivastava http://orcid.org/0000-0001-5032-5020

REFERENCES

1. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. *J Blood Med*. 2014;5:207–218.
2. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1:51–59.
3. Wyseure T, Mosnier LO, von Drygalski A. Advances and challenges in hemophilic arthropathy. *Semin Hematol*. 2016;53:10–19.
4. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125:2038–44.
5. Oldenburg J, Zimmermann R, Katsarou O, et al., Cross-sectional MRIsi. Controlled, cross-sectional MRI evaluation of joint status in severe haemophilia A patients treated with prophylaxis vs. on demand. *Haemophilia*. 2015;21:171–179.
6. 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.
7. Dumont JA, Liu T, Low SC, et al. Prolonged activity of a recombinant factor VIII-Fc fusion protein in hemophilia A mice and dogs. *Blood*. 2012;119:3024–3030.
8. Rath T, Baker K, Dumont JA, et al. Fc-fusion proteins and FcRn: structural insights for longer lasting and more effective therapeutics. *Curr Opin Biotechnol*. 2013;35:235–254.
9. Peters RT, Toby G, Lu Q, et al. Biochemical and functional characterization of a recombinant monomeric factor VIII-Fc fusion protein. *J Thromb Haemost*. 2013;11:132–141.
10. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood*. 2012;119:3031–3037.
11. McCue J, Kshirsagar R, Selvitelli K, et al. Manufacturing process used to produce long-acting recombinant factor VIII Fc fusion protein. *Biologicals*. 2015;43:213–219.
12. 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.
13. 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.
14. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. *Haemophilia*. 2016;22:72–80.
15. Fischer K, Steen Carlsson K, Petrini P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood*. 2013;122:1129–1136.
16. Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res (Hoboken)*. 2011;63:223–230.
17. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12:518–525.
18. Blanchette VS, Manco-Johnson M, Santagostino E, Ljung R. Optimizing factor prophylaxis for the haemophilia population: where do we stand? *Haemophilia*. 2004;10(Suppl 4):97–104.
19. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, Van Den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935–1939.

20. Pasi KJ, Pabinger I, Kerlin BA, et al. Long-term Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) Prophylaxis in Paediatric, Adolescent, and Adult Subjects With Target Joints and Severe Haemophilia A. Presented at: the 9th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), February 3-5, 2016, Malmo, Sweden, 2016.
21. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatoryactivity of IVIG mediated through the inhibitory Fc receptor. *Science*. 2001;291:484–486.
22. Debre M, Bonnet MC, Fridman WH, et al. Infusion of Fcgamma fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet*. 1993;342:945–949.
23. Nimmerjahn F, Ravetch JV. Fc gamma receptors as regulators of immune responses. *Nat Rev Immunol*. 2008;8:34–47.
24. Simpson ML, Valentino LA. Management of joint bleeding in hemophilia. *Expert Rev Hematol*. 2012;5:459–468.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Oldenburg J, Kulkarni R, Srivastava A, et al. Improved joint health in subjects with severe haemophilia A treated prophylactically with recombinant factor VIII Fc fusion protein. *Haemophilia*. 2018;24:77–84. https://doi.org/10.1111/hae.13353