Haemophilia

WILEY

Haemophilia WFH

ORIGINAL ARTICLE OPEN ACCESS

Clinical haemophilia

Impact of Systematic Joint Examination (Ultrasound, Functional and Physical) on Treatment Management Decisions in Patients With Haemophilia A in France: Final Data From the Prospective, Observational A-MOVE Study

Nicolas Drillaud[1] | Virginie Barbay[2] | Jean Baptiste Valentin[3] | Romain Jailler[4] | Aurélien Lebreton[5] | Brigitte Pan-Petesch[6] | Sabine Marie Castet[7] | Birgit Frotscher[8] | Laurent Frenzel[9] | Sandrine Jousse-Joulin[10] | Hervé Chambost[11] | Mikaela Alenäs[12] | Markus Fusser[12] | Corinne Gandossi[13] | Meriem Zidi[13] | Oussama Mahdout[13] | Yohann Repessé[14] | on behalf of the A-MOVE study group

[1]CRC-MHC, Haemophilia Treatment Centre, University Hospital, Nantes, France | [2]Haemophilia Treatment Centre, University Hospital of Rouen Normandie, Rouen, France | [3]CRC-MHC Tours, Tours, France | [4]CRC-Centre Hospitalier Métropole Savoie, Chambéry, France | [5]Centre de Ressource et de Compétence des Maladies Hémorragiques Constitutionnelles, CHU Clermont-Ferrand, Hôpital Estaing, Clermont-Ferrand, France | [6]CRC-MHC Brest – Service Hématologie, Unité Hémostase Clinique, Brest, France | [7]CRC-MHC, Haemophilia Treatment Centre, University Hospital of Bordeaux, Bordeaux, France | [8]Haemophilia Treatment Centre, University Hospital of Nancy, Nancy, France | [9]APHP-CHU Paris, Hôpital Necker-Enfants Malades, Paris, France | [10]CHRU de Brest, Brest, France | [11]AP-HM, Paediatric Haematology Oncology Department, Children's Hospital La Timone and Aix Marseille University, C2VN, Marseille, France | [12]Sobi, Stockholm, Sweden | [13]Sobi, Puteaux, France | [14]Haemophilia Treatment Centre CRC-MHC, University Hospital of Caen Normandie, Caen, France

Correspondence: Nicolas Drillaud (nicolas.drillaud@chu-nantes.fr)

Received: 18 September 2024 | **Revised:** 23 January 2025 | **Accepted:** 6 February 2025

Funding: This article was based on data from the A-MOVE study (ClinicalTrials.gov identifier: NCT04133883), sponsored by Sobi. Support for third-party writing assistance for this article, provided by Sana Yaar, PhD, and Riddhi Naik, MSci, Costello Medical, UK, was funded by Sobi in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Keywords: arthropathy | factor VIII | haemophilia | joints | prophylaxis | ultrasound

ABSTRACT

Background: Haemophilia management aims to prevent bleeding and preserve joint function. Changes in patients' joint health may influence physicians' decisions to adjust treatment. The Haemophilia Joint Health Score (HJHS) and Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) score assess joint health but are not routinely used.

Aim: To evaluate whether systematic joint examination with HJHS and/or HEAD-US had an impact on treatment management decisions in France, using final data from the A-MOVE study.

Methods: A-MOVE (NCT04133883) was a 12-month prospective, multicentre study, which enrolled persons with haemophilia A (all severities, aged 6–40 years) treated prophylactically or on demand with standard/extended half-life FVIII replacement. At baseline, 6 and 12 months, HJHS/HEAD-US and changes in patients' management were assessed.

Results: Eighty-six patients from 20 sites were included in the final analysis; 68 had HJHS/HEAD-US assessments at 12 months. Over 12 months, 24.4% (n = 21/86) of patients experienced an impact on their haemophilia management due to

For the study group's affiliations, please see pages 12–14 of the A-MOVE article supplementary appendix.

[Correction added on March 24, 2025, after first online publication: The figure legend and the A-MOVE study group affiliations was updated.]

HJHS/HEAD-US scores; these decisions were impacted by HJHS in about half of the patients (52.4%, $n = 11/21$) and HEAD-US in almost all patients (95.2%, $n = 20/21$). Both assessments contributed to a change in management decisions in about half of the patients (47.6%, $n = 10/21$). Twenty-nine patients (33.7%) had haemophilia management decisions impacted by factors other than HJHS/HEAD-US, including physical examination findings ($n = 9$) and the occurrence of bleeding episodes ($n = 8$).

Conclusions: Final data from the A-MOVE study show that systematic joint assessments, through functional/physical examination (HJHS) and ultrasound (HEAD-US), may impact treatment management decisions in persons with haemophilia A.

1 | Introduction

Haemophilia A can result in bleeds into muscles and joints if inadequately managed; one joint bleed alone can cause permanent joint damage with recurrent joint bleeds leading to long-term musculoskeletal damage [1–3]. Most bleeds occur in mechanical or weightbearing joints (knees, elbows and ankles) [4, 5].

Prophylaxis with factor VIII (FVIII) replacement therapy, or other non-factor agents, is currently the standard of care for the prevention of bleeding and preservation of long-term joint health in haemophilia A [3, 6, 7]. However, prophylactic treatment may not completely prevent joint bleeds; occasional clinical and subclinical bleeds may occur, resulting in progressive joint disease [3, 6].

Careful and regular joint health monitoring and patient follow-up are crucial in the long-term management of haemophilia [3]. Changes in a patient's joint health may influence their physician's decision to adjust their haemophilia treatment and, importantly, can help identify early joint damage [8].

Joint health can be assessed using several techniques, including functional/physical examinations (Haemophilia Joint Health Score; HJHS) and imaging examinations, such as ultrasound scoring systems (Haemophilia Early Arthropathy Detection with Ultrasound; HEAD-US) [8, 9]. The HEAD-US method allows direct examination of joint health, including the detection of soft tissue damage and peripheral cartilage pathology in early arthropathy, in conjunction with medical history and physical examination [8, 9]. However, these scoring tools are not used routinely in clinical practice, so it remains to be determined whether systemic joint examination using HJHS and/or HEAD-US influences a physician's decisions on haemophilia management in persons with haemophilia A [8]. Furthermore, the sensitivity of each tool to detect clinical and subclinical bleeds has not been directly compared [3, 6, 8, 9].

Here, we report final data from the multicentre, prospective, low-interventional A-MOVE study (NCT04133883), which aimed to evaluate whether systematic joint examination with HJHS and/or HEAD-US had an impact on treatment management decisions in persons with haemophilia A in France.

2 | Methods

2.1 | Study Design and Participants

The A-MOVE (NCT04133883) study, conducted across 20 haemophilia treatment centres in France, aimed to prospectively evaluate if and how haemophilia treatment management decisions are impacted by systematic joint examination (ultrasound, functional and physical) in patients with haemophilia A over a 12-month period from January 2020 to July 2022.

Eligible patients were aged between 6 and 40 years, had haemophilia A of all severities, and were treated prophylactically or on demand with any FVIII product, plasma-derived or recombinant (standard [SHL] or extended [EHL] half-life), according to routine clinical practice in France. All patients had ≥1 joint bleeding episode in the 12 months prior to inclusion. Patients were excluded if they had inhibitors ≥0.6 BU/mL at the latest available inhibitor test, had joint surgery in the past year prior to inclusion, >1 joint replacement and/or were participating in another interventional study.

See Supplementary Methods for further information on the study design, sites and eligibility criteria.

2.2 | Outcome Measures

The primary objective was to investigate if systematic joint examination with HJHS and HEAD-US had an impact on haemophilia management decisions. The primary endpoint was assessed by investigating the change in haemophilia management decisions based on systematic joint examination of ankles, knees and elbows (as judged by the investigator), according to the following key questions: changes in haemophilia management (Yes/No); HJHS findings impacted the decision (Yes/No); and HEAD-US findings impacted the decision (Yes/No).

Patients from the Full Analysis Set (FAS; consisting of all patients enrolled in the study without major protocol violations) with changes in their haemophilia management due to HJHS and/or HEAD-US examinations comprised the primary interest group. In these patients, the following secondary endpoints supporting the primary objective were assessed: main joint examination findings leading to a haemophilia management decision (Supplementary Methods) and changes to haemophilia management, including treatment regimen (on demand or prophylaxis), FVIII product used, prescribed FVIII product dose/dosing interval and other changes (physical therapy, contact with healthcare professional [HCP], pain and/or anti-inflammatory medication, intra-articular injections and surgical intervention).

Additional post hoc analyses were performed in the remaining patients from the FAS as two subgroups: patients with haemophilia management changes based on factors other

than HEAD-US/HJHS, and those with no changes in their haemophilia management during the study (only baseline characteristics were analysed). Secondary endpoints for the FAS population included assessment of HJHS and HEAD-US scores at baseline, 6 and 12 months, other factors impacting haemophilia management decisions, annualised bleeding rate (ABR), target joints and pain. Pre-specified secondary endpoints are listed in the Supplementary Methods.

2.3 | Data Collection

At baseline, patient demographics and medical, surgical and haemophilia history were collected. At each study visit (baseline, 6 and 12 months), investigators performed systemic joint assessments using HJHS v2.1 (six index joint scores, range 0–20, total score range 0–120) and HEAD-US protocol (six joint scores, range 0–8, total score range 0–48) [6, 8]. Investigators also performed a general physical examination according to routine clinical practice (recorded as 'normal' or 'abnormal' as per the investigators' discretion), and patients completed patient-reported outcomes (PROs) questionnaires for pain (brief pain inventory [BPI]) and functional ability (Haemophilia Activities List [HAL]/Paediatrics HAL [PedHAL]) at each study visit. Additionally, investigators documented if any changes were made to the patient's haemophilia management (Yes/No), the factors that impacted the change (HEAD-US, HJHS or other) and the specific changes to their haemophilia management decision (including change in treatment regimen [on-demand/prophylaxis] and dosing frequency).

Further data regarding patients' FVIII product prescription, bleeding episodes, pain, functional ability, general physical health and adverse events were also collected to support the joint assessment data.

2.4 | Statistical Analysis

All endpoints were evaluated using descriptive statistics; no formal statistical analyses were performed. Outcomes were summarised using descriptive statistics (mean, median, interquartile range [IQR] and range); no inferential statistics were performed. The sample size was based on feasibility and practical considerations.

3 | Results

3.1 | Study Population

Overall, the A-MOVE study enrolled 92 persons with haemophilia A of all severities, across 20 haemophilia treatment centres in France from 13 January 2020 to 13 July 2022; participating centres are listed in the Supplementary Appendix. Overall, 86 male patients were included in the FAS ($n = 6$ patients excluded due to major protocol deviation); 68 had HJHS/HEAD-US assessments at 12 months, and 66 patients completed the study. Of the 20 patients who discontinued the study, five were due to switch to non-factor therapy (Table S1). In the FAS, most patients had severe haemophilia A (64.0%, $n = 55$) and the median (range) age was 19 (7–40) years; 38 patients (44.2%) were <18 years (Table 1).

At enrolment, 64 patients (74.4%) received prophylaxis ($n = 52$ severe, $n = 11$ moderate, $n = 1$ mild haemophilia); 22 patients (25.6%) received on-demand treatment (Table 1). In the 3 months prior to baseline, 17 patients (19.8%) received pain and/or anti-inflammatory medication.

The subgroups in this analysis included 20 patients (23.3%) with changes in haemophilia management due to joint assessments (HJHS/HEAD-US), 19 (22.1%) with changes in haemophilia management due to findings other than joint assessments, and 42 (48.8%) with no changes in haemophilia management. Baseline demographics and characteristics of the overall population and subgroups are reported in Table 1.

3.2 | Impact of HJHS/HEAD-US and Other Factors on Haemophilia Management

Over the evaluation period, 21/86 patients (24%) experienced an impact on their haemophilia management due to functional or physical examination (HJHS) and/or ultrasound examination (HEAD-US; Table 2).

Overall, 11/21 patients (52.4%) experienced haemophilia management changes based on HJHS results over the total evaluation period ($n = 4$ changes at baseline, $n = 5$ at 6 months and $n = 7$ at 12 months); five patients experienced changes due to global gait scores, and eight were due to joint score items ($n = 2$ patients experienced changes due to both components). In total, 20/21 (95.2%) patients experienced changes based on HEAD-US ($n = 12$ at baseline, $n = 7$ at 6 months and $n = 6$ of the patients at 12 months). Of these, 13/20 (65.0%) scored for synovial hypertrophy, 10/20 (50%) for cartilage degeneration and 2/20 (10.0%) for bone irregularities. Joint health evaluation using HJHS and HEAD-US together had an impact on management decisions in 47.6% of patients ($n = 10/21$).

Approximately a third of patients in the FAS (33.7%; $n = 29$) had haemophilia management decisions impacted by factors other than HJHS/HEAD-US (Table 2), including physical examination findings on extremities and joints ($n = 9$), the occurrence of bleeding episodes ($n = 8$) and physical activity levels ($n = 8$).

Total joint scores, as well as by individual joints (ankle, knee and elbow), are presented in Table S2.

3.3 | Changes to FVIII Treatment Impacted by HJHS/HEAD-US

Of the patients with treatment changes impacted by HJHS/HEAD-US, 7/20 (35.0%) had changes to their FVIII treatment including the regimen, product, dose or dosing interval.

3.3.1 | Treatment Regimen

Most patients with treatment changes impacted by HJHS/HEAD-US received FVIII prophylaxis during the whole study period ($n = 15$ [75.0%] at baseline and 6 months, $n = 12$ [70.6%] at 12 months). Most patients received primary or secondary prophylaxis (for

TABLE 1 | Baseline demographics and characteristics.

n (%) unless otherwise specified	Overall population (*N* = 86)	Subgroup analysis[a]		
		Patients with treatment changes due to joint assessments (*n* = 20)[b]	Patients with treatment changes due to other findings (*n* = 19)	Patients with no treatment changes (*n* = 42)
Age (years) at enrolment, median (range)	19.0 (7–40)	25.5 (12–39)	21.0 (7–40)	17.0 (7–35)
Age category (years) at enrolment				
<18	38 (44.2)	7 (35.0)	7 (36.8)	23 (54.8)
≥18	48 (55.8)	13 (65.0)	12 (63.2)	19 (45.2)
Severity of haemophilia				
Severe	55 (64.0)	13 (65.0)	11 (57.9)	27 (64.3)
Moderate	21 (24.4)	5 (25.0)	5 (26.3)	11 (26.2)
Mild	10 (11.6)	2 (10.0)	3 (15.8)	4 (9.5)
Treatment regimen at enrolment				
Prophylaxis	64 (74.4)	15 (75.0)	13 (68.4)	32 (76.2)
On demand	22 (25.6)	5 (25.0)	6 (31.6)	10 (23.8)
FVIII product at baseline				
EHL rFVIIIFc	53 (61.6)	—	—	—
SHL FVIII[c]	33 (38.4)	—	—	—
Joint bleeds within the last 12 months prior to inclusion				
0 bleeds	55 (64.0)	16 (80.0)	13 (68.4)	25 (59.5)
≥1 bleeds	28 (32.6)	4 (20.0)	5 (26.3)	15 (35.7)
Missing	3 (3.5)	0 (0.0)	1 (5.3)	2 (4.8)
≥1 target joint at enrolment[d]				
Yes	3 (3.5)	0 (0.0)	0 (0.0)	2 (4.8)
No	83 (96.5)	20 (100.0)	19 (100.0)	40 (95.2)
History of joint surgery				
Yes	8 (9.3)	3 (15.0)	3 (15.8)	2 (4.8)
No	78 (90.7)	17 (85.0)	16 (84.2)	40 (95.2)
History of inhibitors at enrolment[e,f]				
Yes	16 (18.6)	N/A	N/A	N/A
No	70 (81.4)	N/A	N/A	N/A
HJHS total joint score, mean (SD) [*n*]	4.4 (8.0) [*n* = 84]	6.1 (6.4) [*n* = 20]	5.3 (9.8) [*n* = 19]	3.2 (8.3) [*n* = 40]
HEAD-US total joint score, mean (SD) [*n*]	3.3 (6.0) [*n* = 84]	4.8 (5.1) [*n* = 20]	4.1 (7.7) [*n* = 18]	2.3 (5.8) [*n* = 41]

Note: Percentages may not sum to 100% due to rounding.

Abbreviations: BU, Bethesda Unit; EHL, extended half-life; FVIII, factor VIII; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound; HJHS, Haemophilia Joint Health Score; rFVIIIFc, recombinant factor VIII Fc fusion protein; SD, standard deviation; SHL, standard half-life.

[a]The subgroup analysis excludes *n* = 5 patients of which *n* = 4 experienced treatment changes during the study, but no impact (joint assessment or other factors) was documented and *n* = 1 patient had a joint assessment impact documented but no details on the treatment change were recorded.

[b]Patients may also have other findings impacting their treatment management.

[c]SHL FVIII products included octocog alfa, lonoctocog alfa, octocog alfa, octocog alfa, turoctocog alfa and simoctocog alfa.

[d]A joint in which ≥3 spontaneous bleeds occurred within a consecutive 6-month period in the previous year.

[e]Presence of current FVIII inhibitors (≥0.60 BU/mL) at the latest available inhibitor test led to exclusion from enrolment.

[f]History of inhibitors at enrolment by subgroups was not recorded in this analysis.

TABLE 2 | Treatment decision impacted by HJHS/HEAD-US scores and other factors.

	A-MOVE study visit[a]			
	Baseline (*n* = 86)	**6 months (*n* = 77)**	**12 months (*n* = 68)**	**Total evaluation period (*N* = 86)**
Patients whose treatment decision was impacted by systematic joint assessments, *n* (%)				
HJHS	4 (4.7)	5 (6.5)	7 (10.3)	11 (12.8)
HEAD-US	12 (14.0)	7 (9.1)	6 (8.8)	20 (23.3)
HJHS and/or HEAD-US	12 (14.0)	8 (10.4)	8 (11.8)	21 (24.4)[b]
Patients whose treatment decision was impacted by other factors, *n* (%)				
n	10 (11.6)	14 (18.2)	10 (14.7)	29 (33.7)
Occurrence of bleeding episodes	0 (0.0)	5 (6.5)	3 (4.4)	8 (9.3)
FVIII activity level	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)
Physical activity level	3 (3.5)	5 (6.5)	1 (1.5)	8 (9.3)
Physical examination findings	3 (3.5)	4 (5.2)	3 (4.4)	9 (10.5)
Change in body weight	1 (1.2)	1 (1.3)	1 (1.5)	3 (3.5)
Other	5 (5.8)	6 (7.8)	4 (5.9)	14 (16.3)

Note: Percentages are calculated from total patients in each column.

Abbreviations: FVIII, factor VIII; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound; HJHS, Haemophilia Joint Health Score.

[a]Some patients experienced an impact of joint assessments or other factors on their treatment management at multiple visits.

[b]One patient had an impact of HJHS or HEAD-US results on haemophilia treatment management recorded; however, no actual change was recorded so this patient was excluded from the post hoc subgroup analysis.

both, $n = 7$ [46.7%] at baseline and 6 months, $n = 6$ [50.0%] at 12 months); some patients received on-demand treatment ($n = 5$ [25.0%] at baseline and 6 months, $n = 4$ [23.5%] at 12 months). One patient experienced a change in treatment regimen due to systematic joint assessment at the baseline visit. This patient was switched from on-demand to once-weekly prophylactic treatment with the same SHL FVIII product (turoctocog alfa). No other changes to the treatment regimen occurred due to systematic joint assessment.

3.3.2 | FVIII Product

Of patients with treatment changes impacted by HJHS/HEAD-US, 13 (65.0%) received rFVIIIFc ($n = 11$ prophylactic, $n = 2$ on demand) and the remaining seven received SHL FVIII products. Of the seven patients with changes in FVIII treatment due to HJHS/HEAD-US, six received prophylactic treatment ($n = 5$ with rFVIIIFc), and one patient received on-demand treatment (with turoctocog alfa) at baseline. There was no product change among these patients due to systematic joint assessments.

3.3.3 | Prescribed Dose and Dosing Interval

For the five patients treated with rFVIIIFc, the prescribed weekly dose ranged from 61 to 130 IU/kg/week. The mean (SD) prescribed dose per injection of rFVIIIFc prophylaxis was 40.5 (11.5) IU/kg at baseline, mostly administered twice weekly.

The prescribed weekly dose for the one patient treated with turoctocog alfa ranged from 26 to 31 IU/kg/week, and 86 to 117 IU/kg/week for the one patient treated with octocog alfa.

Six patients had changes in dosing and frequency of FVIII products, all due to systematic joint assessment at baseline; further details are provided in the Supplementary Results.

3.4 | Other Changes to Haemophilia Management

In the subgroup of patients with haemophilia management changes impacted by HJHS/HEAD-US ($n = 20$), the most frequent changes other than to FVIII treatment were increased physical therapy regimen ($n = 8$; 40.0%) and increased contact with the HCP ($n = 5$; 25.0%; Figure 1A).

For the subgroup of patients impacted by other factors than HJHS/HEAD-US ($n = 19$), management changes included change to physical therapy regimen ($n = 7$; 36.8%), change in contact with the HCP ($n = 7$; 36.8%) and change in prescribed anti-inflammatory or pain medication ($n = 2$; 10.5%; Figure 1B).

3.5 | Joint Health

In the FAS, both the mean HJHS total joint score (range 0–120) and mean HEAD-US total score (range 0–48) decreased from baseline to 12 months (Figure 2). However, comparisons over time were limited as some patients did not have available data at 12 months. Joint health scores according to treatment management changes (Yes/No) are presented in Figure S1.

One patient with haemophilia management changes impacted by HJHS/HEAD-US developed a new target joint, recorded at 12 months. Further details are presented in the Supplementary Results.

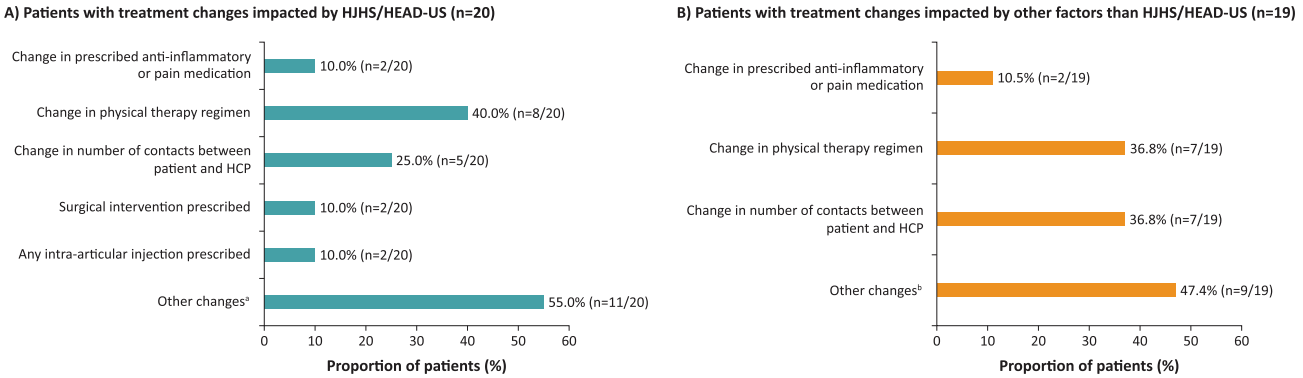

FIGURE 1 | Haemophilia management changes other than FVIII treatment. Some patients experienced multiple treatment changes. [a]Other changes include chiropodist orthopaedic insoles, radiography, rheumatology consultation, ankle x-ray prescription, co-occurring treatment, MRI prescription, proposed corticoids and a discussion to change from prophylactic to non-replacement therapy. [b]Other changes include rheumatologist consultation, decreased sports activity, increased prophylaxis, prescribed physiotherapy, stimulation physical activity, MRI, radiography and treatment change to non-factor replacement therapy. FVIII, factor VIII; HCP, healthcare professional; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound, HJHS, Haemophilia Joint Health Score.

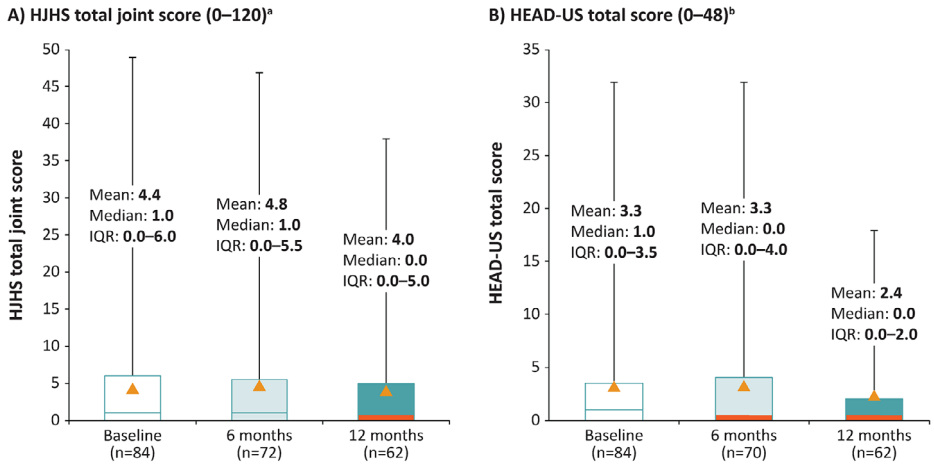

FIGURE 2 | HJHS and HEAD-US joint health scores from baseline to 12 months. Figures show mean (triangle), median (line splitting the box), IQR (box boundaries) and maximum/minimum values (whiskers); thick red lines indicate equal medians/quartiles. [a]Missing data for n = 2 at baseline, n = 5 at 6 months and n = 6 at 12 months. [b]Missing data for n = 2 at baseline, n = 7 at 6 months and n = 6 at 12 months. HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound; HJHS, Haemophilia Joint Health Score; IQR, interquartile range.

Additional secondary endpoint results (PRO for pain, ABR, pain and inflammation concomitant medication use and PRO for functional ability) can be found in the Supplementary Results.

3.6 | Safety

Of the patients treated with rFVIIIFc, one paediatric male patient with moderate haemophilia at enrolment experienced a serious AE (low-titre FVIII inhibitor; 0.9 Bethesda Unit [BU/mL]) and therefore stopped rFVIIIFc treatment and discontinued the study. The event was considered resolved with a negative titre (<0.6 BU/mL) at a later timepoint. No other serious AEs or non-serious AEs leading to permanent rFVIIIFc treatment discontinuation were reported in the study.

4 | Discussion

Final data from the large, multicentre A-MOVE study in France indicated that systematic joint assessments, through functional/physical examination and ultrasound (across ankles, knees and elbows), may impact treatment management decisions in persons with haemophilia A. Findings indicate that regular monitoring of joint health in general practice may lead to haemophilia management change.

Although the World Federation of Hemophilia (WFH) recommends annual assessment and documentation of musculoskeletal and overall health of patients [3], imaging tools were not routinely used in clinical practice in many places during this study. To our knowledge, this is the first study of its kind to prospectively evaluate the impact of systematic joint examination (functional and structural) in France.

Over the 12-month evaluation period in A-MOVE, almost a quarter of patients (24.4%) had an impact on their haemophilia management due to HEAD-US or HJHS findings. The most frequent changes were to the dose and dosing frequency of FVIII replacement therapy (no FVIII product changes), prescribed physiotherapy and contact with HCPs. Comparatively, few

patients experienced changes to prescribed anti-inflammatory or pain medication or had changes to prescribed surgical interventions or any intra-articular injections. Approximately a third of patients (33.7%) had haemophilia management decisions impacted by factors other than HJHS/HEAD-US, such as general physical examination findings on extremities and joints, bleeding episodes, physical activity levels, change in body weight and FVIII activity level.

More patients had changes to their haemophilia management due to HEAD-US findings ($n = 20$) compared to HJHS ($n = 11$). This finding is expected, given the higher sensitivity of ultrasound methods such as HEAD-US, which can diagnose early joint abnormalities and may help clinicians decide whether to adjust individual treatment management earlier [3]. Moreover, at baseline, more patients had already recorded an impact of HEAD-US on their haemophilia management compared to HJHS.

It is known that prophylaxis is most efficient when started at an early age and before the first joint bleed. Therefore, early detection and diagnosis of joint abnormalities may be critical for preserving joint function [2, 10]. Previous studies report that HJHS shows strong convergent and discriminant construct validity in the detection of arthropathy [11]. Physical examination scales such as the HJHS, although successfully able to assess joint outcomes, are known to have lower sensitivity compared with imaging techniques [12]. Several studies have reported weak or no correlation between bleeding outcomes and HJHS, with asymptomatic and subclinical bleeds not being identified by physical examinations alone [12]. Meanwhile, previous studies suggest that HEAD-US can detect joint abnormalities with greater sensitivity compared with HJHS [11–13].

Overall, in A-MOVE, patients (most treated with rFVIIIFc) showed good responses during the study follow-up in terms of joint scores and secondary endpoints such as bleeding rates, pain outcomes and use of anti-inflammatory and anti-pain medication. These findings are in line with previous studies of patients treated with rFVIIIFc for up to 12 months, which demonstrated low joint bleeding rates and well-preserved joint status [14, 15]. The lack of impact of either joint health assessments or other factors on treatment management decisions in approximately half of patients (48.8%) could suggest adequate management of haemophilia symptoms in these patients; however, a greater proportion of joint bleeds and target joints were reported in this group at baseline. Although beyond the scope of the present study, further investigation into the treatment of these patients could provide more detailed answers in this population.

This large, multicentre, prospective study, which included patients of all disease severities, had several strengths. A-MOVE is the first study assessing the impact of joint assessment with ultrasound on treatment decision-making in haemophilia care. Further, the broad inclusion criteria allowed a large representation of the haemophilia A population.

The potential patient selection bias is an inherent limitation of this observational study. Only patients with haemophilia A were included, with no data reported for patients with haemophilia B. Furthermore, the choice of participating centres and the tendency of more severely treated patients requiring treatment management than patients with less severe haemophilia could pose further selection bias. The number of patients in each severity group was relatively low, therefore conclusive recommendations and comparisons relating to the severity of haemophilia cannot be made. Additionally, comparisons of PROs (including bleeding and pain outcomes) over time were limited as some patients had no available data at 12 months (79% of patients [$n = 68/86$] had available data). The exclusion of patients treated with non-factor therapies further limits the comparisons of the results to wider treatment management strategies.

5 | Conclusions

Final data from the A-MOVE study show that systematic joint assessments, through functional/physical examination and ultrasound, may impact treatment management decisions in persons with haemophilia A. Regular monitoring of joint health using HEAD-US and HJHS could help physicians decide whether to adjust individual treatment management earlier. Overall, these results highlight the importance of joint assessments in persons with haemophilia.

Author Contributions

Substantial contributions to study conception and design: N.D., V.B., J.B.V., R.J., A.L., B.P.P., S.M.C., B.F., L.F., S.J.J., H.C., M.A., M.F., C.G., M.Z., O.M. and Y.R. Substantial contributions to analysis and interpretation of the data: N.D., V.B., J.B.V., R.J., A.L., B.P.P., S.M.C., B.F., L.F., S.J.J., H.C., M.A., M.F., C.G., M.Z., O.M. and Y.R. Drafting the article or revising it critically for important intellectual content: N.D., V.B., J.B.V., R.J., A.L., B.P.P., S.M.C., B.F., L.F., S.J.J., H.C., M.A., M.F., C.G., M.Z., O.M. and Y.R. Final approval of the version of the article to be published: N.D., V.B., J.B.V., R.J., A.L., B.P.P., S.M.C., B.F., L.F., S.J.J., H.C., M.A., M.F., C.G., M.Z., O.M. and Y.R.

Acknowledgements

The authors thank the patients, the investigators and their teams who took part in this study. The authors acknowledge Daniela Bruni, PharmD PhD, from Sobi, for publication coordination and Sana Yaar, PhD, and Riddhi Naik, MSci, from Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction. This study was funded by Sobi. Sobi and Sanofi reviewed and provided feedback on this manuscript. Some data in this manuscript have previously been presented at the International Society on Thrombosis and Haemostasis (ISTH) 2023 Congress, Montreal, Canada, 24–28 June 2023 and World Federation of Hemophilia (WFH) 2023 Comprehensive Care Summit, Buenos Aires, Argentina, 10–12 May 2023.

Ethics Statement

A-MOVE study protocol was approved by institutional review boards and/or ethics committees at participating institutions. Patients/their guardians provided written informed consent prior to participation; if appropriate, adolescent/paediatric patients also provided assent. A-MOVE was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and ethical principles that comply with the Declaration of Helsinki and is registered with ClinicalTrials.gov (NCT04133883).

Conflicts of Interest

Nicolas Drillaud: Research grants from Novo Nordisk; speaker/honoraria for Octapharma, Roche Chugaï and Sobi. Virginie Barbay: Speaker/honoraria for LFB; consulting fees from Sobi; grant/research support from CSL Behring. Jean Baptiste Valentin: Consultant for Sobi, has received hospitality from Octapharma, Roche and CSL Behring. Romain Jailler: Research grants from Sobi. Aurélien Lebreton: Grant/research support from CSL Behring, Novo Nordisk, Octapharma and Sobi; consultant for Bayer, LFB, Octapharma, Pfizer, Roche and Sobi. Brigitte Pan-Petesch: Consultant for BioMarin, CSL Berhing, Novo Nordisk, Roche/Chugai, Sobi and Takeda. Sabine Marie Castet: Consultant (advisory board honoraria or invitation as speaker in symposia) for CSL Behring, LFB, Novo Nordisk, Roche, Sobi and Takeda. Birgit Frotscher: Consultant for BioMarin, CSL Behring, Novo Nordisk, Sobi and Takeda. Laurent Frenzel: Consulting fees are from CSL Behring, Pfizer, Roche and Sobi. Sandrine Jousse-Joulin: No conflicts of interest to declare. Hervé Chambost: Consulting fees from BioMarin, CSL Behring, Pfizer, Roche Chugai and Sobi; payment/honoraria for lectures/speakers bureau from BioMarin, CSL, Roche Chugai and Sobi; payment for expert testimony from BioMarin; support for attending meetings from BioMarin, Novo Nordisk, Roche and Sobi. Mikaela Alenäs: Contractor for Sobi; consultant for Aixial Group. Markus Fusser, Corinne Gandossi, Meriem Zidi, Oussama Mahdout: Employees and/or shareholders of Sobi. Yohann Repessé: Grant/research support from CSL Behring and Octapharma; consultant for (scientific advisory board honoraria) LFB, Roche and Sobi.

Data Availability Statement

Sobi is committed to responsible and ethical sharing of data at the participant level and summary data for medicines and indications approved by EMA and/or FDA, while protecting individual participant integrity and compliance with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity and commitment to publication of the results. To request access to study data, a data sharing request form (available at www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at: https://www.sobi.com/en/policies.

References

1. B. Samuelson Bannow, M. Recht, C. Negrier, et al., "Factor VIII: Long-Established Role in Haemophilia A and Emerging Evidence Beyond Haemostasis," *Blood Reviews* 35 (2019): 43–50.

2. J. Oldenburg, "Optimal Treatment Strategies for Hemophilia: Achievements and Limitations of Current Prophylactic Regimens," *Blood* 125 (2015): 2038–2044.

3. A. Srivastava, E. Santagostino, A. Dougall, et al., "WFH Guidelines for the Management of Hemophilia, 3rd Edition," *Haemophilia* 26, no. Suppl 6 (2020): 1–158.

4. E. B. Karin Knobe, "Haemophilia and Joint Disease: Pathophysiology, Evaluation, and Management," *Journal of Comorbidity* 1 (2011): 51–59.

5. J. Hmida, T. Hilberg, P. Ransmann, et al., "Most Subjectively Affected Joints in Patients With Haemophilia—What Has Changed After 20 Years in Germany?" *Haemophilia* 28 (2022): 663–670.

6. P. Hilliard, S. Funk, N. Zourikian, et al., "Hemophilia Joint Health Score Reliability Study," *Haemophilia* 12 (2006): 518–525.

7. M. Franchini, G. Marano, I. Pati, et al., "Emicizumab for the Treatment of Haemophilia A: A Narrative Review," *Blood Transfusion* 17 (2019): 223–228.

8. C. Martinoli, O. Della Casa Alberighi, G. Di Minno, et al., "Development and Definition of a Simplified Scanning Procedure and Scoring Method for Haemophilia Early Arthropathy Detection With Ultrasound (HEAD-US)," *Thrombosis and Haemostasis* 109 (2013): 1170–1179.

9. H. De la Corte-Rodriguez, E. C. Rodriguez-Merchan, M. T. Alvarez-Roman, et al., "HJHS 2.1 and HEAD-US Assessment in the Hemophilic Joints: How Do Their Findings Compare?," *Blood Coagulation & Fibrinolysis* 31 (2020): 387–392.

10. A. Nijdam, W. Foppen, Y. T. van der Schouw, et al., "Long-Term Effects of Joint Bleeding Before Starting Prophylaxis in Severe Haemophilia," *Haemophilia* 22 (2016): 852–858.

11. J. St-Louis, A. Abad, S. Funk, et al., "The Hemophilia Joint Health Score Version 2.1 Validation in Adult Patients Study: A Multicenter International Study," *Research and Practice in Thrombosis and Haemostasis* 6 (2022): e12690.

12. R. Gooding, J. Thachil, J. Alamelu, J. Motwani, and P. Chowdary, "Asymptomatic Joint Bleeding and Joint Health in Hemophilia: A Review of Variables, Methods, and Biomarkers," *Journal of Blood Medicine* 12 (2021): 209–220.

13. D. Plut, B. F. Kotnik, I. P. Zupan, et al., "Diagnostic Accuracy of Haemophilia Early Arthropathy Detection With Ultrasound (HEAD-US): A Comparative Magnetic Resonance Imaging (MRI) Study," *Radiology and Oncology* 53 (2019): 178–186.

14. C. Altisent, M. Martorell, A. Crespo, et al., "Early Prophylaxis in Children With Severe Haemophilia A: Clinical and Ultrasound Imaging Outcomes," *Haemophilia* 22 (2016): 218–224.

15. B. A. Konkle, J. Oldenburg, J. Pasi, et al., "Prophylaxis With a Recombinant Factor VIII Fc in Hemophilia A: Long-Term Follow-Up on Joint Health, Efficacy, and Safety From Phase 3 Studies in Children and Adults," *Research and Practice in Thrombosis and Haemostasis* 7 (2023): 102180.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.