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Real-World Unmet Needs of Patients With Haemophilia A and Haemophilia B With or Without Inhibitors: End-of-Study Results From the explorer6 Non-Interventional Study

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ABSTRACT

Introduction: Haemophilia is associated with high disease and treatment burdens. Prospective evaluation of data from patients with haemophilia helps understand and define unmet needs, optimise treatment and improve healthcare outcomes.

Aim: To present end-of-study data from explorer6 (NCT03741881), a prospective, non-interventional study across multiple countries in patients with haemophilia (haemophilia A or B without [HA or HB] or with inhibitors [HAwI or HBwI]).

Methods: Patients ≥12 years old with severe HA, severe/moderate HB or HAwI/HBwI of any severity were treated according to the local standard of care (SoC). The number of bleeding episodes from enrolment up to a maximum of 115 weeks, physical activity based on data collected by a wrist-worn physical activity tracker, target joints and Haemophilia Joint Health Score (HJHS) measurements were assessed.

Results: A total of 231 patients across 33 countries were enrolled. The mean annualised bleeding rate (ABR) (standard deviation) for treated bleeding episodes was investigated for patients receiving prophylaxis (HA: 4.7 [5.9]; HB: 2.2 [3.0]; HAwI: 10.3 [8.5]; HBwI: 12.4 [14.1]) and those receiving on-demand (OnD) treatment (HA: 21.5 [17.7]; HB: 10.5 [8.6]; HAwI: 15.2 [14.8]; HBwI:

9.3 [13.3]). Physical activity levels were lowest among patients with HBwI. Target joints were similar among haemophilia types and treatments. Overall, mean and median HJHS total scores were lower for patients receiving prophylaxis compared with OnD treatment.

Conclusion: The explorer6 study assessed a large haemophilia patient population in a real-world setting across 33 countries. The results indicate that an unmet need remains among patients receiving OnD treatment and those with inhibitors.

Trial Registration: ClinicalTrials.gov identifier: NCT03741881

1 | Introduction

Haemophilia, a congenital bleeding disorder caused by coagulation factor VIII (FVIII) or factor IX (FIX) deficiency (in haemophilia A [HA] and haemophilia B [HB], respectively), is commonly associated with musculoskeletal damage caused by repeated bleeding episodes in the joints and muscles [1]. The haemophilia burden of disease is associated with compromised joint health, joint pain, reduced physical activity and reduced health-related quality of life (HRQoL) [2, 3].

Haemophilia treatments aim to prevent bleeding episodes and long-term joint damage [4], and several novel therapies have been developed (e.g., extended half-life recombinant FVIII/FIX concentrates, non-factor-replacement therapies and gene therapy) [5–7]. However, haemophilia treatments may also contribute to the burden of disease [8]. Coagulation factor replacement therapy can require multiple weekly intravenous injections that may lead to a significant treatment burden due to injection pain, time-consuming administration and venous access challenges, which are common [8, 9]. A further complication in haemophilia management is the development of antibodies (inhibitors) that neutralise exogenous FVIII or FIX, thus rendering treatments less effective [10, 11]. Patients with inhibitors have limited treatment options, a resultant higher disease burden and reduced HRQoL [12].

Prophylaxis (PPX) with coagulation factors has been shown to be superior to episodic treatment in reducing bleeding tendencies and long-term complications and is recommended by current guidelines as the standard of care (SoC) for patients with severe haemophilia [13]. Recently, clinical trials have demonstrated that non-factor products are able to provide similar or improved protection from bleeding [14–16].

However, many patients still receive on-demand (OnD) treatment due to factors such as healthcare economics and socio-economic considerations [17].

Given the disease burden associated with haemophilia, the lack of effective treatment options for HBwI and the need for non-intravenous prophylaxis alternatives for HB, unmet needs persist in terms of effective disease management. Evaluating real-world data from patients with haemophilia would better define existing unmet needs and could assist in improving healthcare outcomes.

The prospective, non-interventional explorer6 study collected real-world data across multiple countries among patients with HA or HB with and without inhibitors. Historical haemophilia and baseline characteristics of patients enrolled in explorer6 (e.g., treatment history, bleeding history, details on sports activities and patient-reported-outcomes [PROs], including 36-item Short Form Health Survey [SF-36v2] results and Haemophilia Treatment Experience Measure [Hemo-TEM] results) have been reported previously [18]. Here, we present end-of-study data from explorer6, focusing on bleeding episodes, physical activity and joint health, including target joint assessment in routine clinical practice.

2 | Methods

2.1 | Study Design

The explorer6 prospective, non-interventional study collected real-world data on patients with HA or HB with and without inhibitors. Patients were offered screening for eligibility to participate in subsequent concizumab Phase 3 interventional trials following the explorer6 study. Data collected as part of explorer6 were intended to be used for non-inhibitor within-patient comparisons with data obtained during subsequent concizumab clinical trials. During the explorer6 study, each patient was treated according to local SoC at the discretion of the treating physician in their respective country between December 2018 and October 2021. Treatment regimens were classified as OnD treatment of bleeding episodes or PPX treatment with coagulation factor replacement therapy or bypassing agents. The duration of maximum 115 weeks for data collection on bleeding episodes was chosen to ensure that data from an observation period of at least 24 weeks were obtained for patients with HA or HB receiving PPX treatment who proceeded to the explorer8 (NCT04082429) trial. The observation period for the physical activity tracker (see *Data collection and analysis*) was 3–12 weeks from the first visit and was considered sufficient to obtain reliable data.

2.2 | Inclusion and Exclusion Criteria

Male patients ≥12 years of age were included if they had severe congenital HA (FVIII activity <1%), severe/moderate congenital HB (FIX activity ≤2%) or HAwI/HBwI of any severity (≥0.6 Bethesda unit [BU]). Inclusion and exclusion criteria were previously reported [18] and are presented in Table S1.

2.3 | Objectives and Assessments

The primary objective was to investigate the number of bleeding episodes from enrolment up to a maximum of 115 weeks during

TABLE 1 | Baseline characteristics and haemophilia severity at end of study in the explorer6 non-interventional study.

	Haemophilia A without inhibitors		Haemophilia B without inhibitors		Haemophilia A with inhibitors		Haemophilia B with inhibitors	
Treatment regimen	**OnD**	**PPX**	**OnD**	**PPX**	**OnD**	**PPX**	**OnD**	**PPX**
Number of patients								
Number of patients screened	19	56	19	53	35	18	14	17
Number of patients enrolled	19	56	19	53	35	18	14	17
Number of patients withdrawn, *N* (%)	0 (0.0)	5 (8.9)	0 (0.0)	4 (7.5)	1 (2.9)	3 (16.7)	0 (0.0)	0 (0.0)
Number of patients completing study, *N* (%)	19 (100.0)	51 (91.1)	19 (100.0)	49 (92.5)	34 (97.1)	15 (83.3)	14 (100.0)	17 (100.0)
Age at screening (years)								
Mean (SD)	35.3 (13.1)	31.2 (15.4)	32.3 (16.4)	29.5 (14.2)	29.4 (16.3)	30.1 (17.3)	26.6 (13.5)	26.1 (17.5)
Median (Q_1; Q_3)	36.0 (28.0; 44.0)	32.0 (15.0; 43.5)	26.0 (23.0; 48.0)	27.0 (17.0; 38.0)	25.0 (15.0; 42.0)	28.0 (15.0; 40.0)	23.0 (14.0; 38.0)	17.0 (14.0; 37.0)
Race, *N* (%)								
American Indian or Alaska Native	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.9)	1 (5.6)	0 (0.0)	0 (0.0)
Asian	5 (26.3)	14 (25.0)	7 (36.8)	5 (9.4)	8 (22.9)	1 (5.6)	6 (42.9)	5 (29.4)
Black or African American	3 (15.8)	3 (5.4)	1 (5.3)	1 (1.9)	4 (11.4)	1 (5.6)	1 (7.1)	0 (0.0)
White	9 (47.4)	39 (69.6)	9 (47.4)	43 (81.1)	21 (60.0)	15 (83.3)	4 (28.6)	9 (52.9)
Other	0 (0.0)	0 (0.0)	1 (5.3)	2 (3.8)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)
Not reported	1 (5.3)	0 (0.0)	1 (5.3)	1 (1.9)	1 (2.9)	0 (0.0)	2 (14.3)	3 (17.6)
Severity								
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	0 (0.0)	1 (5.3)	3 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	19 (100.0)	56 (100.0)	18 (94.7)	50 (94.3)	35 (100.0)	17 (94.4)	14 (100.0)	17 (100.0)

Abbreviations: *N*, number of patients; OnD, on-demand treatment; PPX, prophylaxis treatment; Q_1, first quartile; Q_3, third quartile; SD, standard deviation.

routine clinical treatment practice in patients with HA/HB, with and without inhibitors. Exploratory objectives and endpoints included physical activity and the number of treated spontaneous bleeding episodes, treated traumatic bleeding episodes and treated joint bleeding episodes from enrolment up to a maximum of 115 weeks. Further investigations included target joint assessment and Haemophilia Joint Health Score (HJHS) measurements [19–22], which were entered into the patient's electronic case report form (eCRF), if available. Target joints were defined as a single joint with ≥3 spontaneous bleeding episodes in any consecutive 6-month period [23].

2.4 | Data Collection and Analysis

Information on bleeding episodes and treatment of bleeds was recorded in a patient eDiary. Physical activity data were collected by a wrist-worn physical activity tracker, and subsequent data were recorded in the patient eCRF. A water-resistant ActiGraph CentrePoint Insight Watch (CPW01) [24–27] was worn on the non-dominant wrist, and triaxial activity data were recorded at a frequency of 32 Hz. Light, moderate and vigorous activities were recorded. Moderate to vigorous physical activity was calculated as the sum of moderate and vigorous activity. Patients or caretakers connected the physical activity tracker via a universal serial bus cable to the CentrePoint Data Hub to synchronise data to the online CentrePoint account whilst charging the device. The remaining unsynchronised data were collected and compliance was assessed at each patient visit.

All statistics are descriptive and exploratory. The sample size evaluation was based on simulated data for the bleeding rate including a 95% confidence interval. Results are presented according to treatment regimen (PPX or OnD), haemophilia type (HA

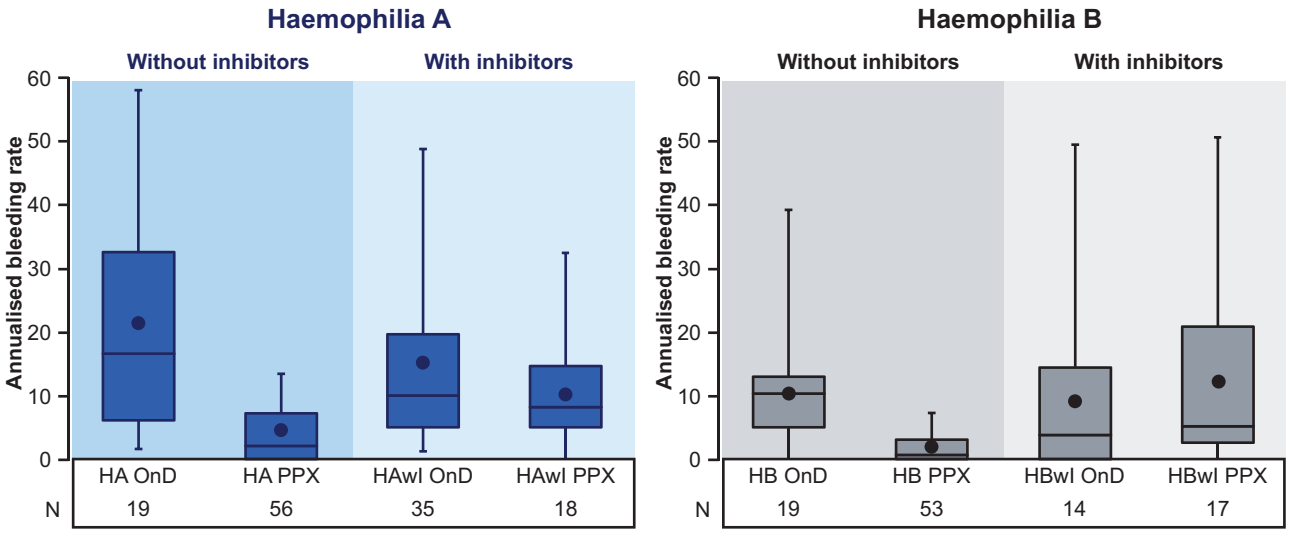

FIGURE 1 | Annualised bleeding rate—treated bleeding episodes at end of study in the explorer6 non-interventional study. Black horizontal lines represent median ABRs, the filled circles represent mean ABRs, boxes represent the first/third quartile, and error bars represent 5th and 95th percentiles. ABR, annualised bleeding rate; HA, haemophilia A; HAwI, haemophilia A with inhibitors; HB, haemophilia B; HBwI, haemophilia B with inhibitors; N, number of patients; OnD, on-demand treatment; PPX, prophylaxis treatment.

or HB) and inhibitor status (yes/no) at the end of study. No comparative analyses between subgroups were performed in this observational study.

3 | Results

3.1 | Patients

The explorer6 study enrolled a total of 231 patients from 109 clinical centres across 33 countries (Figure S1). Most (97.8%) patients had severe haemophilia; five patients had mild to moderate haemophilia (HAwI: 1; HB: 4). Patients were divided into subgroups according to the treatment regimen, haemophilia type and inhibitor status at the end of the study. There were 138 patients in the HA/HB without inhibitors (HA: 70; HB: 68) and 80 in the HA/HB with inhibitors subgroups (HAwI: 49; HBwI: 31) who completed the study. Baseline characteristics and demographics were reported previously [18], and relevant data are displayed according to the overall status (treatment regimen, haemophilia type and inhibitor status) at the end of the study in Table 1. Patients who discontinued treatment withdrew from the study themselves (HA: 1; HAwI: 2), by the parent or legally acceptable representative (HA: 1; HB: 2; HAwI: 2), were lost to follow-up (HB: 1), or discontinued at the discretion of the investigator (HA: 3; HB: 1; HAwI: 1). No deaths were reported.

3.2 | Annualised Bleeding Rate (ABRs)

Mean and median ABRs for treated bleeding episodes are presented in Figure 1. The mean ABRs (standard deviation) for treated bleeding episodes were reported for OnD treatment (HA: 21.5 [17.7]; HB: 10.5 [8.6]; HAwI: 15.2 [14.8]; HBwI: 9.3 [13.3]) and for PPX (HA: 4.7 [5.9]; HB: 2.2 [3.0]; HAwI: 10.3 [8.5]; HBwI: 12.4 [14.1]). ABRs for treated spontaneous bleeding episodes, treated traumatic bleeding episodes, treated joint bleeding episodes and treated target joint bleeding episodes are shown in Table 2.

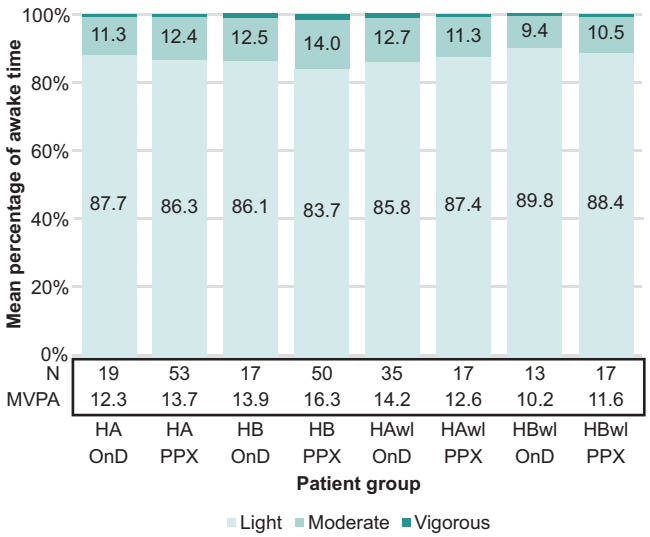

FIGURE 2 | Physical activity levels at the end of the study in the explorer6 non-interventional study as measured via the physical activity tracker. HA, haemophilia A; HAwI, haemophilia A with inhibitors; HB, haemophilia B; HBwI, haemophilia B with inhibitors; MVPA, moderate to vigorous physical activity; N, number of patients; OnD, on-demand treatment; PPX, prophylaxis treatment.

3.3 | Physical Activity Levels

Physical activity levels (light, moderate and vigorous) were collected for 221 (95.7%) patients as mean percentage of awake time through the physical activity tracker (Figure 2). Overall, 83.7%–89.8% of light physical activity and 10.2%–16.3% of moderate to vigorous physical activity were measured as mean percentage

TABLE 2 | Annualised bleeding rate for treated bleeding episodes at end of study in the explorer6 non-interventional study.

	Haemophilia A without inhibitors		Haemophilia B without inhibitors		Haemophilia A with inhibitors		Haemophilia B with inhibitors	
Treatment regimen	**OnD**	**PPX**	**OnD**	**PPX**	**OnD**	**PPX**	**OnD**	**PPX**
Number of patients	19	56	19	53	35	18	14	17
Treated bleeding episodes								
Number of treated bleeding episodes	**487**	**209**	**299**	**134**	**372**	**166**	**59**	**136**
Median ABR (Q_1; Q_3)	**16.7 (6.2; 32.7)**	**2.2 (0.2; 7.3)**	**10.5 (5.1; 13.2)**	**0.9 (0.0; 3.4)**	**10.1 (5.2; 19.7)**	**8.3 (5.1; 14.8)**	**4.1 (0.0; 14.6)**	**5.5 (2.8; 21.0)**
Mean ABR (SD)	**21.5 (17.7)**	**4.7 (5.9)**	**10.5 (8.6)**	**2.2 (3.0)**	**15.2 (14.8)**	**10.3 (8.5)**	**9.3 (13.3)**	**12.4 (14.1)**
Treated spontaneous bleeding episodes								
Number of treated spontaneous bleeding episodes	341	114	230	76	261	109	43	102
Median ABR (Q_1; Q_3)	5.9 (2.8; 29.3)	1.3 (0.0; 3.6)	7.1 (1.7; 10.0)	0.0 (0.0; 1.8)	7.5 (3.1; 12.2)	6.0 (2.7; 11.1)	2.8 (0.0; 11.2)	4.5 (0.0; 15.1)
Mean ABR (SD)	15.9 (16.9)	2.9 (5.3)	7.7 (8.3)	1.3 (2.2)	10.2 (10.7)	7.0 (6.2)	6.4 (7.7)	9.0 (10.8)
Treated traumatic bleeding episodes								
Number of treated traumatic bleeding episodes	146	93	69	58	110	56	16	34
Median ABR (Q_1; Q_3)	3.4 (1.7; 7.0)	0.0 (0.0; 3.3)	1.7 (0.0; 2.7)	0.0 (0.0; 1.7)	1.6 (0.0; 8.3)	3.3 (0.0; 4.8)	0.0 (0.0; 2.5)	2.1 (0.0; 4.3)
Mean ABR (SD)	5.6 (5.9)	1.8 (2.5)	2.8 (3.8)	0.9 (1.5)	5.0 (7.6)	3.3 (2.9)	2.9 (7.0)	3.4 (4.9)
Treated joint bleeding episodes								
Number of treated joint bleeding episodes	415	151	292	93	266	143	48	101
Median ABR (Q_1; Q_3)	12.5 (5.0; 31.9)	1.6 (0.0; 5.4)	8.9 (1.7; 12.7)	0 (0.0; 1.9)	7.5 (1.8; 17.2)	5.9 (3.6; 10.5)	1.2 (0.0; 12.9)	4.5 (1.4; 11.3)
Mean ABR (SD)	18.7 (15.6)	3.0 (3.4)	9.5 (10.6)	1.7 (2.5)	11.0 (11.8)	8.3 (8.2)	7.4 (11.9)	9.2 (10.7)
Treated target joint bleeding episodes								
Number of treated target joint bleeding episodes	189	43	141	32	76	40	15	12
Median ABR (Q_1; Q_3)	3.5 (0.0; 14.8)	0.0 (0.0; 0.0)	1.9 (0.0; 6.1)	0.0 (0.0; 0.0)	0.0 (0.0; 3.1)	0.3 (0.0; 5.1)	0.0 (0.0; 0.0)	0.0 (0.0; 2.8)
Mean ABR (SD)	9.4 (14.1)	0.7 (1.9)	4.5 (8.3)	0.4 (1.2)	3.7 (8.3)	3.4 (5.5)	1.2 (2.8)	1.7 (3.0)

Abbreviations: ABR, annualised bleeding rate; OnD, on-demand treatment; PPX, prophylaxis treatment; Q_1, first quartile; Q_3, third quartile; SD, standard deviation.

of awake time. The percentage of moderate to vigorous physical activity were reported for adults receiving OnD treatment (HA: 11.3; HB: 12.2; HAwI: 13.7; HBwI: 10.0) or PPX (HA: 11.7; HB: 15.5; HAwI: 10.9; HBwI: 11.2) and adolescents receiving OnD treatment (HA, 17.8; HB: 21.9; HAwI: 15.2; HBwI: 10.4) or PPX (HA: 17.6; HB: 18.2; HAwI: 15.7; HBwI: 12.0) (Figure S2). Albeit the number of patients for some treatment groups are very small when divided by age.

3.4 | Joint Assessments

3.4.1 | Target Joints

A total of 121 (52.4%) patients reported target joints at the last target joint assessment. Target joints were mostly reported in the knee (54.5%), elbow (50.4%) and ankle (37.2%), with some also reported in the hip, shoulder and toe (Figure 3). The mean

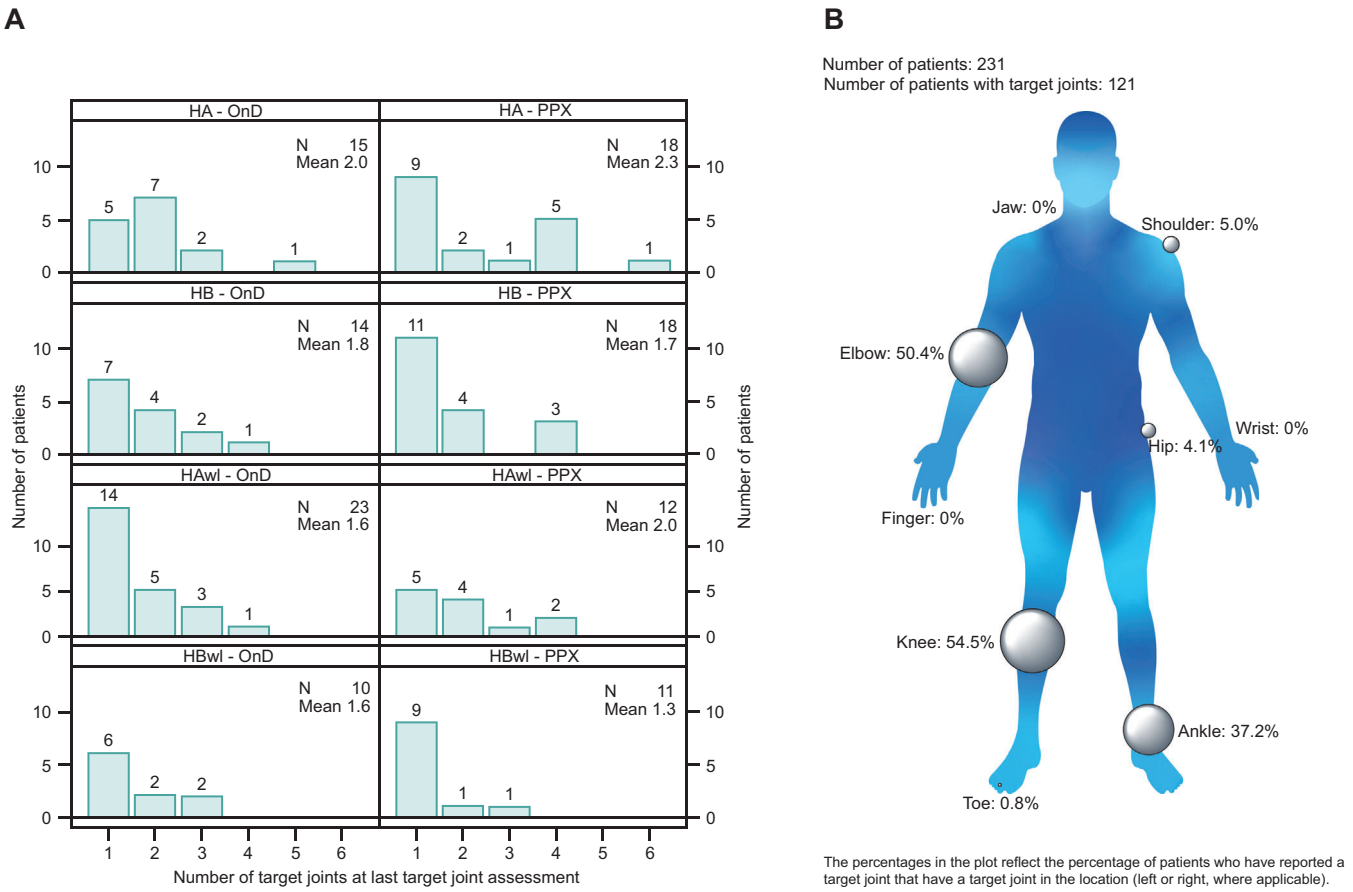

FIGURE 3 | Target joint assessment at end of study in the explorer6 non-interventional study (a) last target joint assessment during the observation period and (b) location of target joints according to last target joint assessment during the observation period. Joints assessed, and target joints reported at the end of study in the explorer6 are shown. HA, haemophilia A; HAwI, haemophilia A with inhibitors; HB, haemophilia B; HBwI, haemophilia B with inhibitors; N, number of patients with target joints; OnD, on-demand treatment; PPX, prophylaxis treatment.

number of target joints per patient at the last assessment ranged between 1.3 and 2.3 for all patient groups.

3.4.2 | HJHS

Mean and median HJHS total scores were available for 130 (56.3%) patients and are presented according to haemophilia type, inhibitor status and treatment regimen (Figure 4). A lower HJHS total score would indicate better joint health [19, 20]. Overall, for HA, HB and HAwI, numerically lower mean and median HJHS total scores were reported for patients receiving PPX compared with OnD treatment. Similar mean and numerically lower median HJHS total scores were reported for HBwI for PPX versus OnD treatment.

4 | Discussion

The explorer6 non-interventional study collected real-world data in patients with HA or HB with and without inhibitors across 33 countries. Given the lower prevalence of HB [28, 29] and even more so of HBwI [10, 29, 30], explorer6 included a large HBwI population (31 patients, 13.4%) as part of a real-world study.

Overall, ABRs for number of treated bleeding episodes were within expected ranges. The observed ABRs were slightly higher than expected for HA receiving PPX, and the observed ABRs were slightly lower than expected for HB receiving OnD treatment. When comparing the ABRs by treatment regimen, numerically lower mean and median ABRs were observed for patients with HA, HB or HAwI receiving PPX versus those receiving OnD treatment. The median ABR was higher for PPX than for OnD for HBwI (5.5 vs. 4.1, respectively), which was unexpected. When comparing the ABRs by haemophilia subtype, numerically lower ABRs were observed among patients with HA or HB receiving PPX versus HAwI or HBwI, respectively. These data indicate that an unmet need remains among patients receiving OnD treatment, especially in patients with inhibitors, irrespective of the treatment regimen.

The World Federation of Haemophilia encourages physical activity by haemophilia patients, as this has been shown to improve long-term joint, bone and muscle health and promote physical fitness and normal neuromuscular development [13, 31]. However, participation in these activities may be accompanied by the risk of traumatic bleeding and joint pain, leading to a reduction in levels of physical activity [2, 3, 32]. Given that patients with haemophilia often experience joint pain and engage in reduced levels of physical activity [2, 3], it is, therefore,

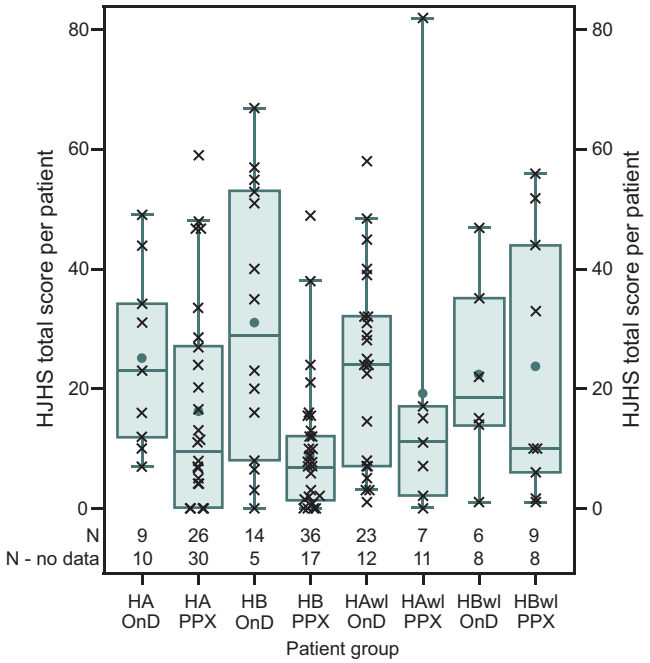

FIGURE 4 | Haemophilia Joint Health Score (HJHS) total scores at end of study in the explorer6 non-interventional study. The filled circles represent mean HJHS total scores, the top/bottom of the box outline is the first/third quartile, the green horizontal lines represent median HJHS total scores, and error bars represent 5th and 95th percentiles. The x symbols represent the individual values that are summarised in the box plot. The 'N–no data' row shows the number of patients with no HJHS data. HA, haemophilia A; HAwI, haemophilia A with inhibitors; HB, haemophilia B; HBwI, haemophilia B with inhibitors; HJHS, Haemophilia Joint Health Score; N, number of patients; OnD, on-demand treatment; PPX, prophylaxis treatment.

expected that most patients would engage in light physical activity and most patients would likely refrain from performing moderate or vigorous physical activity. Patients were asked to report on sports activities at baseline in explorer6 [18]. Analysis of explorer6 data at baseline indicated that approximately two-thirds of patients without inhibitors treated with a PPX regimen reported engaging in sports activities during the month prior to screening, whilst in contrast, patients with inhibitors treated OnD reported the least participation in sports activities [18]. To assess physical activity, measurements via a physical activity tracker were collected during the explorer6 study. Overall, similar levels of physical activity were measured via the tracker for PPX versus OnD patients within each patient group. Across all patients, the measured physical activity levels were the lowest among patients with HBwI.

Target joints were mostly reported in the ankle, elbow and knee, with the mean number of target joints per patient at the last assessment ranging between 1.3 and 2.3, irrespective of haemophilia type or inhibitor status. Overall, mean and median HJHS total scores were lower for patients receiving PPX compared with OnD treatment. Mean HJHS were similar in HBwI patients irrespective of their treatment regimen (OnD vs. PPX). This may indicate the contribution of PPX treatment on improved joint health and highlight the unmet need for more effective treatment for HBwI.

explorer6 may have been susceptible to limitations typically seen with non-interventional studies, such as selection bias, which were previously discussed in detail [18]. Patient enrolment in subsequent concizumab clinical trials (NCT04083781; NCT04082429) may have affected participation in the study. Patients on emicizumab PPX were excluded, therefore, the results presented are only applicable to those treated with factor replacement and bypassing agents. Variation in local SoC treatment could contribute to variation in the descriptive analysis. All subgroups within explorer6 were subject to the same limitations across 33 countries.

It is evident that unmet needs, in particular the management of bleeding episodes, joint health and physical activity, remain for patients receiving OnD treatment and patients with inhibitors, and these are even more substantial for those with HBwI for whom no efficacious PPX treatment regimen is available. These unmet needs emphasize the necessity of new therapeutic options to improve haemophilia management. In understanding and better defining these unmet needs, health outcomes can be improved.

Author Contributions

All authors contributed to the conceptualisation, investigation, analysis and interpretation of data. All authors contributed to the writing, reviewed the manuscript critically for important intellectual content, and approved the final version of the manuscript.

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Ethics Statement

The explorer6 study was approved according to local regulations by the appropriate independent ethics committees or institutional review boards and was conducted in accordance with the principles of the Declaration of Helsinki. All participating sites obtained approval from their relevant local Ethics Committee or Institutional Review Board. Written informed consent was obtained from all patients (or from the patient's legal guardian) before any study-related activities. The reporting of this study conforms to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement [33].

Consent

All patients provided prior consent to partake in this study.

Conflicts of Interest

A.P.W. has received research funding form Octapharma, and has been a consultant or participated in advisory boards for the following companies: Bayer, BioMarin, CSL Behring, Genetech, HEMA biologics, Novo Nordisk, Pfizer, Sanofi, Star Therapeutics and Takeda over the last 36 months. **A.A**. has received travel grants and participated in advisory board meetings for Novo Nordisk, and received funding support for investigator initiated trials/studies by Novo Nordisk and Roche. **R.D.O**. has received speaker fees or honoraria and participated in advisory board meetings for the following companies: Takeda, BioMarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Roche/Chugai, Sobi/Sanofi,

UniQure and Spark. **H.E**. has acted as a paid consultant, has received payment for presentations and chair activities, and has received travel grants and accommodation for scientific meetings from Novo Nordisk. He has received speaker fees or honoraria and participated in advisory board meetings for the following companies: Bayer Vital, BioMarin, CSL Behring, Novo Nordisk, Pfizer and Roche. **K.H**. has received speaker fees from Novo Nordisk, Sobi and Roche. **F.J.L.J**. has received speaker fees, research funding and participated in advisory board meetings for the following companies: Amgen, Bayer, CSL Behring, Novo Nordisk, Sobi, Octapharma, Pfizer, Takeda, Rovi and Novartis. **K.N**. has received grants, personal fees and non-financial support from Chugai Pharmaceuticals and Sysmex, personal fees from Roche and Pfizer, and grants and personal fees from the following companies: Takeda, Sanofi, CSL Behring, KM Biologics, Novo Nordisk, Bayer and Fujimoto Pharmaceuticals. **J.W**. has received speaker fees, research funding and participated in advisory board meetings for the following companies: Alnylam, Amgen, AstraZeneca, Bayer, CSL Behring, LFB, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Siemens, Sobi, Takeda and Werfen. **B.Z**. has received research funding from Pfizer and Takeda, and consulted and participated in advisory board meetings for the following companies: CSL Behring, Novo Nordisk, Sanofi and Genveon. **G.C**. has received speaker fees or participated in advisory board meetings for the following companies: BioMarin, CSL Behring, LFB, Novo Nordisk, Pfizer, Roche, Sobi and Takeda. **C.B**., **C.J.L**. and **C.S**. have no conflict of interest to declare. **R.B.F**. and **C.M.M.T**. are employees of Novo Nordisk A/S, Søborg, Denmark. This project was initiated and funded by Novo Nordisk A/S.

Data Availability Statement

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

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Supporting Information

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