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## **Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO)**

Caroline Wall 1 Hua Xiang 2 Ben Palmer 2 Elizabeth Chalmers 3 Pratima Chowdary 4 Peter W. Collins 5 Simon Fletcher 6 Georgina W. Hall 6 Daniel P. Hart 7 Mary Mathias 8 Paul Sartain 9 Susan Shapiro 6 David Stephensen 10 Kate Talks 11 Charles R.M. Hay 1,2 the UK Haemophilia Centre Doctors' Organisation (UKHCDO)

- 1- Manchester Royal Infirmary, Manchester, UK
- 2- National Haemophilia Database, Manchester, UK
- 3- Royal Hospital for Children, Glasgow, UK
- 4- Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK
- 5- School of Medicine, Cardiff University, Cardiff, UK
- 6- Oxford University Hospitals, Oxford, UK
- 7- The Royal London Hospital, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
- 8- Great Ormond Street Hospital, London, UK
- 9- Patient Representative, The Haemophilia Society, UK
- 10- Kent and Canterbury Hospitals, Canterbury, UK
- 11- Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK

Correspondence Charles R.M. Hay, University Department of Haematology, 3<sup>rd</sup> Floor  
Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. Email:  
[Charles.Hay@mft.nhs.uk](mailto:Charles.Hay@mft.nhs.uk)

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## Abstract

**Introduction:** The UK National Haemophilia Database (NHD) collects data from all UK persons with haemophilia A with inhibitors (PwHA-I). It is well-placed to investigate patient selection, clinical outcomes, drug safety and other issues not addressed in clinical trials of emicizumab.

**Aims:** To determine safety, bleeding outcomes and early effects on joint health of emicizumab prophylaxis in a large, unselected cohort using national registry and patient reported Haemtrack (HT) data between 01 January 2018 and 30 September 2021.

**Methods:** Prospectively collected bleeding outcomes were analysed in people with  $\geq 6$  months emicizumab HT data and compared with previous treatment if available. Change in paired Haemophilia Joint Health Scores (HJHS) were analysed in a subgroup. Adverse events (AEs) reports were collected and adjudicated centrally.

**Results:** This analysis includes 117 PwHA-I. Mean annualised bleeding rate (ABR) was .32 (95%CI, .18;.39) over a median 42 months treatment with emicizumab. Within person comparison ( $n=74$ ) demonstrated an 89% reduction in ABR after switching to emicizumab and an increase in zero treated bleed rate from 45 to 88% ( $p<.01$ ). In a subgroup of 37 people, total HJHS improved in 36%, remained stable in 46% and deteriorated in 18%, with a median (IQR) within -person change of  $-2.0$  ( $-9,1.5$ ) ( $p=.04$ ). Three arterial thrombotic events were reported, two possibly drugrelated. Other AEs were generally non severe and usually limited to early treatment, included cutaneous reactions (3.6%), headaches (1.4%), nausea (2.8%) and arthralgia (1.4%). **Conclusions:** Emicizumab prophylaxis associated with sustained low bleeding rates and was generally well tolerated in people with haemophilia A and inhibitors.

## 1 INTRODUCTION

Regular prophylaxis with factor VIII (FVIII) concentrate is used to reduce bleeding and prevent haemarthroses in people with severe haemophilia A (SHA) and a severe bleeding phenotype.<sup>1–4</sup> The development of FVIII neutralising inhibitors occurs in up to 30% of people with SHA, influenced by both genetic and environmental risk factors.<sup>5,6</sup> Inhibitors render prophylaxis with FVIII ineffective, resulting in increased morbidity and mortality.<sup>7</sup> Inhibitors also occur in approximately 5% of people with non severe haemophilia A, commonly resulting in a deterioration in the bleeding phenotype.<sup>8</sup>

The standard approach in the UK has been to attempt inhibitor elimination using immune tolerance induction (ITI) and to treat or prevent bleeding using the bypassing agents (BPA) activated prothrombin complex concentrate (aPCC) (FEIBA, Takeda, Vienna) and rFVIIa (Novoseven, Novo Nordisk, Denmark), or FVIII, if responsive. ITI is costly and may be demanding for the individual and their family but is successful in 70%–80% of people.<sup>9,10</sup> The management of bleeding in those with active inhibitors has until recently been difficult. Bypass therapy agents are only partially effective.<sup>11–16</sup> Both agents, particularly rFVIIa, have short half lives which are not ideal for prophylaxis.<sup>17,18</sup> Venous and arterial thrombotic events have also been described in relation to both products.<sup>19</sup>

The introduction of the bispecific, monoclonal antibody emicizumab (Hemlibra, Roche, Switzerland) has changed the therapeutic approach to inhibitor management significantly. This partial FVIII mimetic bridges FIXa and its substrate FX, facilitating the activation of FX without the requirement for thrombin.<sup>20,21</sup> In the pivotal clinical trials, emicizumab was associated with a significant reduction in bleeding events when compared with on-demand

or prophylactic by passagent therapy.<sup>22,23</sup> Thrombotic microangiopathy and thrombosis were reported in association with the coprescription of a PCC in HAVEN1, resulting in a recommendation to avoid, or limit, concomitant use of a PCC with emicizumab.<sup>24</sup> Emicizumab was otherwise generally well-tolerated with a side effect profile typical of humanised monoclonal antibodies. <sup>22,23,25,26,27</sup>

The National Haemophilia Database (NHD) monitors and reports the use, safety and efficacy of all products in the UK through a centralised collection of haemophilia centre derived and patient reported outcome (PRO) data. This provides an opportunity to analyse real world emicizumab outcomes.<sup>28</sup> Real world evidence provides valuable information on the safety and efficacy of new agents outside the clinical trial setting.<sup>29,30</sup> The objectives of this study are to describe the patient selection and utilisation of emicizumabin PwHA-I, to determine the efficacy in a relatively unselected cohort, provide additional long term safety data and contribute to the understanding of issues not addressed in the original licensing trials.

## **2 METHODS AND MATERIALS**

### **2.1 Study design and data collection**

This national post-marketing study was designed to assess real world safety and efficacy of emicizumab prophylaxis in Pw HA-I and at least 6 months data, between 01 January 2018 and 30 September 2021. Emicizumab was prescribed at the discretion of the local clinical teams. The NHD is a centralised UK database designed to collect data on the diagnosis, management, and complications of all UK people with bleeding disorders. Baseline diagnostic and demographic details are collected and combined with quarterly updates including weight, inhibitor status and the treatment issued by haemophilia centres. Individual treatments and bleed data (chronological details, treatment indication, product type and dose used) are derived from the Haemtrack (HT) electronic home therapy diary. HT therefore only records prophylaxis and treated bleeds; and not 'untreated bleeds'. Details of these systems and data validation steps have previously been described (Hay et al.<sup>28</sup>).

A minimum of 6 months HT treatment data was considered necessary to assess bleeding outcomes. A subgroup with greater than 6 months HT therapy data immediately prior to emicizumab underwent additional within person analysis. By using each person as their own control, the effect of potential confounders is minimised.

The cohort of people not prescribed emicizumab ('non-switchers') during the study period is described, not for the purpose of comparison with switchers, but to provide insight into factors potentially influencing treatment choice.

Annual assessment of joint health using the Haemophilia Joint Health Score (HJHS) version 2.1 is recommended and data collected centrally. <sup>31</sup> Higher scores are associated with poorer joint health. Participants with a HJHS within the 2 years prior to starting emicizumab (T0) and a paired score at least 3 months (T1) after starting emicizumab were included. A change in total joint score of  $\geq 4$  was considered clinically meaningful. <sup>32</sup>

Adverse events (AEs) are reported electronically to the NHD and are investigated and evaluated by the Adverse Events Panel of the UKHCDO. All AEs are reported monthly to the manufacturer and regulators.

## **2.2 Study objectives and outcome measures**

The primary outcome measure of efficacy is the annualised treated bleed rate (ABR). Secondary end points include annualised joint bleed rates (AJBR), annualised spontaneous bleed rates (ASBR), proportion of people with zero treated bleeds and change in total HJHS. The primary safety objectives were to evaluate the frequency of venous and arterial thrombosis, including thrombotic microangiopathy (clinically manifested and/or laboratory diagnosed). Neutralising anti-drug antibodies were tested for only if suspected on clinical or laboratory grounds. Secondary safety outcomes included other AEs.

## **2.3 Statistics**

Descriptive statistics (median, interquartile ranges and arithmetic range) are used to summarise baseline demographics and bleeding outcomes. Bleeding outcomes are also reported using a negative binomial regression model to allow for different length of follow up and to facilitate comparison with clinical trial data. Within-person comparison of ABR, AJBR and HJHS were analysed using Wilcoxon matched pairs signed rank test and zero treated bleed rates were calculated using the X2 McNemartest. Zero treated bleed rates are reported over matched time frames to avoid misinterpreting favourable outcomes with shorter follow-up. Stata Statistical Software release 11 (StataCorp, TX) and R StudioTeam2020 (RStudio, MA) were used to perform analyses on NHD and HT datasets, respectively.

## **2.4 Study conduct**

Observational research conducted by the data base is permitted by ethical approval granted by the NHS Health Research Authority NorthWest–Haydock Research Ethics Committee (RECref19/NW/0009; IRASprojectID:252831).

# **3 RESULTS**

## **3.1 Study population**

In total, 264 people with haemophilia A and an active inhibitor were registered, of whom 138 (52%) were treated with emicizumab (Figure 1). Of the 117 with  $\geq 6$  months HT data, median age 22 years, 106 had severe haemophilia and 11 had non-severe disease. Four children (3.4%) were under 2 years old.

During the study period 126 people were not treated with emicizumab and  $\geq 6$  months HT data was available in 54. Their median age was 4 years (14 (25.9%) aged under 2 years); 47 with severe and 7 with non-severe haemophilia. Bleeding outcomes and treatments used for this group are supplied to provide a complete overview of the UK inhibitor cohort and describe variables which may have influenced treatment choice (Table 2). Product use pre emicizumab (for switchers) and in non-switchers is shown in Figure 2.

## **3.2 Emicizumab treated cohort ('switchers')**

An efficacy analysis was conducted in 117/138 (84.7%) people who switched to emicizumab band had at least 6 months HT data (Table 1). After loading, emicizumab was administered weekly to 48.7% (QW) and every 2 weeks to 49.6% (Q2W). Four weekly dosing (Q4W) was used by 1.7%. Regimens changed in 40 people, largely between QW and Q2W dosing.

The overall mean annualised bleeding rate (ABR) on emicizumab, calculated using a negative binomial model, was .32 (95% CI, .18 to .58). Spontaneous bleeds and joint bleeds occurred infrequently, at a rate of .16 (.06, .39) and .22 (.11, .42), respectively. During the study period 104 (89%) of emicizumab treated individuals did not report bleeding. Children <12 years old reported zero - treated bleeds in 39/40 (98%) (Table 1).

### 3.3 Within-person analysis

Bleeding outcomes before and after starting emicizumab were compared in the cohort of 74 individuals with  $\geq 6$  months pre- and post-switch HT data and summarised in Table 2. The model-based ABR was 4.97 (95% CI, 3.16 to 7.82) with prior treatment compared with .50 (95% CI, .26 to .97) with emicizumab, an 89% reduction in ABR ( $p < .001$ ). The use of emicizumab was also associated with significant reduction in AJBR and ASBR (Table 2).

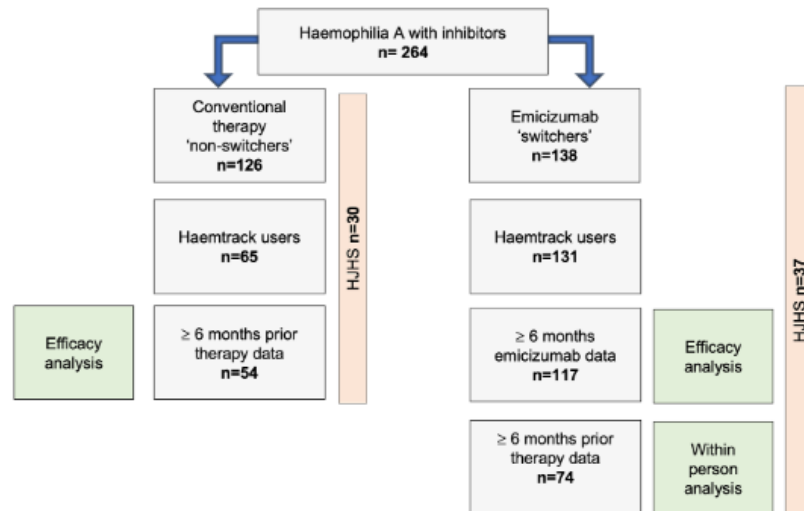
The proportion of people reporting no treated bleeds increased from 45% to 88% over a matched 52-week duration of follow-up ( $p < .001$ ). Target joints conforming to the ISTH definition were uncommon, being reported in six joints in five people at baseline. 33 One occurred in a child aged twelve and the remainder in adults. Of these 5/6 (83%) resolved after starting emicizumab.

The median (IQR) age of people who continued to bleed whilst using emicizumab prophylaxis was 42 (25; 51) years ( $n=17$ ). The model based ABR with conventional treatment in this cohort was 5.89 (4.15; 17.33) (95% CI, 7.51 to 19.8) and 1.12 (.63; 2.05) (95% CI, 1.34 to 3.98) with emicizumab. Most bleeds (91/114) were treated with one or two doses of rFVIIa at a mean dose of 63 (95% CI, 58 to 69) mcg/kg. Four people used rFVIII at a mean dose of 40 (95% CI, 39 to 41) IU/kg. There were no reports of co-prescription of a PCC and emicizumab.

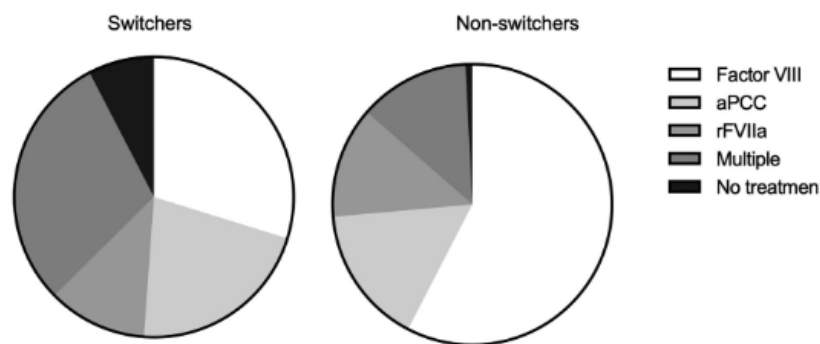
### 3.4 Haemophilia Joint Health Scores

Thirty-seven switchers with paired joint health scores were identified and are summarised in Table 3 and Figures 3 and 4. Increase in age was associated with higher total HJHS score ( $p < .0001$ ). The base line total HJHS was median (IQR) 16 (4; 34). This improved in 39%, remained stable in 36% and deteriorated in 25% or remained over median 25 months follow-up after starting emicizumab (Figure 4). The within person change in total HJHS was statistically significant but did not meet the magnitude for clinical significance.

Data for 30 non-switchers with paired HJHS were also available (Table 3). The median (IQR) baseline total joint health score in this cohort was 4 (0; 13) and remained stable over the 25 month period of observation.



**FIGURE 1** Consort diagram. At least 6 months Haemtrack (HT) data are required for inclusion in bleeding outcome analyses. Haemophilia joint health score (HJHS) data is independent of HT use.



**FIGURE 2** Product use in non-switchers and in switchers prior to emicizumab. Data are derived from quarterly product issue updates submitted by haemophilia centres to the National Haemophilia Database (NHD). The proportion of non-switchers using factor VIII is significantly higher than in those who switch to emicizumab whilst multiple product use is more frequent in switchers.

### 3.5 Safety

Twenty-four drug-related AEs were reported in 13/114 (11.4%) individuals treated with emicizumab. No reports of microangiopathy, loss of efficacy or neutralising antidrug antibodies were reported during the study period.

### 3.6 Serious adverse events (SAEs)

Two deaths were reported in emicizumab-treated individuals during the study period. A 51-year-old male died from multi-organ failure after fulminant viral infection (pre COVID-19). The death was not considered causally related to emicizumab. The second death occurred in a 27-year-old male after a delayed presentation with massive intra-abdominal bleeding, hypovolaemic shock and cardiac arrest. This was accompanied by severe secondary disseminated intravascular coagulation. The individual was given rFVIIa and not treated with FEIBA. Emicizumab levels of 24.8 mcg/mL were recorded 3 weeks before admission. The event was considered possibly related to emicizumab.



Thrombosis was regarded as an event of special interest. A cardiovascular risk profile was completed for 86/114 people who were prescribed emicizumab during the study period. Of these, 7 (8.1%) were reported to have hypertension, four (4.7%) ischaemic heart disease, one (1.2%) diabetes and one (1.2%) prior ischaemic stroke. Three thrombotic events were recorded during the study, two considered Possibly related to emicizumab and not associated with concomitant use of BPA

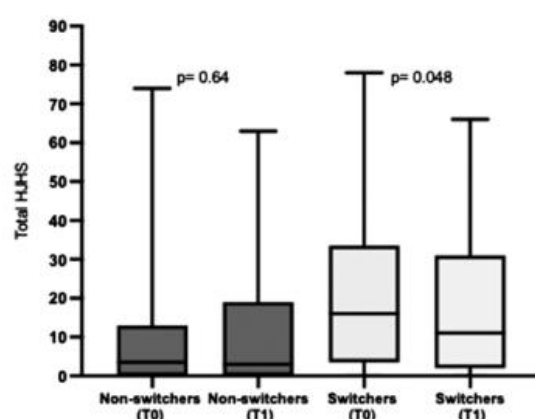
**TABLE 1** Efficacy analysis. Bleeding outcomes in people treated with emicizumab ('switchers') or continuing conventional treatment (non-switchers') and at least 6 months Haemtrack data are shown

	Switchers				Non-switchers
Age range	<12	12–18	>18	All	All
	n = 40	n = 12	n = 65	n = 117	n = 54
Age	5 (3; 8)	13 (13; 14)	45 (27; 58)	22 (8; 43)	4 (1; 12)
median (IQR) [range]	-	-	-	[0–79]	[0–57]
Follow-up weeks median (IQR)	161 (154; 191)	191 (175; 194)	164 (103; 194)	168 (125; 194)	190 (146; 247)
<b>ABR</b>					
Median (IQR)	.00 (.00; .00)	.00 (.00; .16)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .22)
range	[.00, 1.24]	[.00, 4.82]	[.00, 15.4]	[.00, 15.4]	[.00, 3.30]
mean (95% CI)	.04 (.00, .21)	.54 (.13, 2.27)	.37 (.18, .79)	.32 (.18, .58)	.30 (.18, .53)
<b>ASBR</b>					
median (IQR)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)
range	[.00, .00]	[.00, .73]	[.00, 11.7]	[.00, 11.7]	[.00, 3.30]
mean (95% CI)	– (-, -) <sup>a</sup>	.11 (.02, .62)	.23 (.08, .65)	.16 (.06, .39)	.09 (.04, .25)
<b>AJBR</b>					
median (IQR)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)	.00 (.00; .00)
range	[.00, .37]	[.00, 1.61]	[.00, 12.5]	[.00, 12.5]	[.00, 2.89]
mean (95% CI)	.01 (.00, .31)	.22 (.06, .90)	.32 (.15, .68)	.22 (.11, .42)	.15 (.07, .31)
Zero treated bleed rate <sup>b</sup>	39 (98%)	9 (75%)	56 (86%)	104 (89%)	34 (63%)

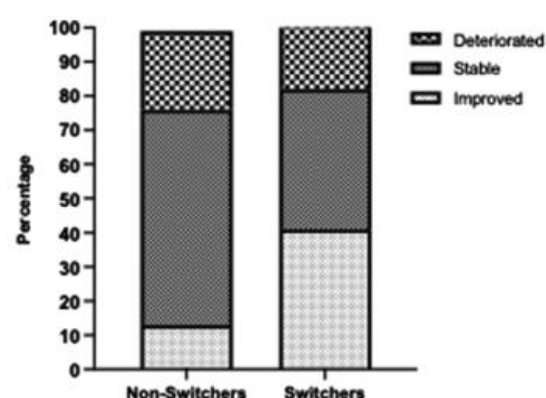
Abbreviations: ABR, annualised bleed rate; ASBR, annualised spontaneous bleed rate; AJBR, annualised joint bleed rate.

<sup>a</sup>Model based ASBR and 95% CI were not estimable because too few events had occurred over the efficacy people to calculate values using the negative binomial regression model.

<sup>b</sup>Matched over 52 weeks.



**FIGURE 3** Box and whisker plot. Change in total Haemophilia Joint Health Score (HJHS) between baseline (T0) and median 25 months follow up (T1), calculated by Wilcoxon matched pairs signed rank test.



**FIGURE 4** Change in total Haemophilia Joint Health Score (HJHS) over a median 25 months follow up. A change in total HJHS of  $\geq 4$  defines clinical significance.



### **3.6.1 Thrombotic event 1**

A 32-year-old with a history of hypertension, diabetes and smoking presented with chest pain and non-specific ECG changes. This event occurred within 24 h of the third loading dose of emicizumab. CT angiography was normal but subsequent MRI scanning showed a small subendocardial infarct. Emicizumab was discontinued. The event was considered definitely drug-related (grade 3 severity).

### **3.6.2 Thrombotic event 2**

Occurred in a 78-year-old man with a history of symptomatic ischaemic heart disease including myocardial infarction. He had a non-ST-elevation myocardial infarction (NSTEMI) in the context of a portacath infection after his first dose of emicizumab. Emicizumab has continued for more than 2 years since without recurrence. This event was considered possibly related to emicizumab (grade 3 severity).

### **3.6.3 Thrombotic event 3**

A 53-year old smoker with long standing abdominal pain was found to have chronic superior mesenteric artery stenosis with thrombosis on CT scanning. He had been using emicizumab for 18 months and continues to use it. The age of the thrombus could not be determined. This was considered possibly drug related (grade 2 severity).

### **3.7 Adverse events (AEs)**

Twelve cutaneous reactions related to emicizumab were reported in 5 (3.6%) people. In three individuals these were self-limiting grade one severity injection site reactions occurring during the loading phase of treatment. Emicizumab was discontinued in one person because of an increasingly severe, recurrent widespread rash. Only one cutaneous reaction (urticaria), possibly related to emicizumab, developed outside the loading period (at 40 weeks). Recurrent headaches, temporally related to emicizumab administration, were reported in 2 (1.4%) people. Other reported AEs included grade one nausea and anorexia in four individuals (2.9%) and small joint arthralgia in two (1.4%). Single reports of tibial osteonecrosis, ureteric calculi and transient proteinuria were noted but with uncertain relationship to emicizumab therapy.

**TABLE 3** Sub-group analysis of individuals with paired Haemophilia Joint Health Scores (HJHS) at baseline (T0) and repeated at ≥3-month interval (T1). Demographics, bleeding outcomes during the study period and change in total HJHS are reported for emicizumab treated 'switchers' and people continuing on conventional therapy (non-switchers)

	Non-switchers (n = 30)		Switchers (n = 37)	
<b>Severity</b>				
Severe	18		34	
Moderate	11		3	
Mild	1		0	
<b>Age at baseline</b>	16 (8;37) [2, 83]		16 (10, 34) [10, 72]	
<18 (n)	17 (58.6%)		19 (51.4%)	
≥ 18 (n)	12 (41.4%)		18 (48.6%)	
<b>Interval (months) med (IQR).</b>	25 (18, 37)		25 (13;32)	
[range]	[10, 51]		[4, 45]	
<b>ABR med (IQR)</b>	.23 (.06, .50)		.00 (.00, .00)	
<b>Total HJHS</b>	T0	T1	T0	T1
median (IQR)	4 (0, 13)	3 (0, 19)	16 (4, 34)	11 (2, 31)
[range]	[0, 74]	[0, 63]	[0, 78]	[0, 66]
	$p = .64$		$p = .04$	
<b>Within person change in total HJHS<sup>c</sup></b>				
Median (IQR)	0 (-2, 3.3)		-2 (-9, 1.5)	
[Range]	[-22, 19]		[-32, 15]	

<sup>a</sup>(non-switchers) 8/30 have Haemtrack data. <sup>b</sup>(switchers) 36/37 have Haemtrack data.

<sup>c</sup>Within person change in total Haemophilia Joint Health Score calculated by two tailed Wilcoxon matched pairs signed rank test.

## 4 DISCUSSION

A clinically and statistically significant reduction in bleeding events relative to prior treatment was observed in this national post marketing study of emicizumab. An 89% overall reduction in ABR was observed after starting emicizumab ( $p < .001$ ) and the proportion reporting no treated bleeds increased from 45 to 88%. Those who continued to bleed were generally older and tended to have higher bleeding rates on conventional therapy. Nonetheless, this subgroup reported a median (IQR) within person reduction of 3.7 (3.0;13.3) bleeds per year.

This study is representative of real world practice. The HAVEN trial subjects tended to have a severe bleeding phenotype and high (>70%) incidence of target joints prior to study entry. 22,23,25 In our study, comparison between those changed to emicizumab with those who remained on conventional inhibitor therapy showed that those chosen to change were significantly older, had a higher pre-switch ABR and were more likely to use bypass therapy prior to starting emicizumab. Overall, the UK cohort had a far lower ABR and incidence of target joints prior to changing to emicizumab than the subjects reported in the HAVEN studies.

Bleeding outcomes observed in UK clinical practice were comparable to those reported from the HAVEN studies, although a higher proportion of the UK cohort reported no treated bleeds. This probably reflects differences in cohort disposition. In other smaller real-world studies, zero treated bleed rates varied between 44% and 95%. 34–37 These studies may not be directly comparable due to differences in sample size, proportion of paediatric subjects and duration of follow-up.

It is important to note that, in contrast to the HAVEN studies, only treated bleeds were recorded, because untreated bleeds are subject to a high degree of diagnostic uncertainty. The threshold for precautionary treatment of minor trauma or equivocal bleeding episodes

whilst using emicizumab prophylaxis may differ from those using factor VIII prophylaxis. 24 This may contribute to the observed reduction in bleed rate after changing from factor VIII to emicizumab prophylaxis. However, this study utilised within-person comparisons, using the individual as their own control, which minimises such reporting bias.

There are limited data on the effect of emicizumab on joint health. Callaghan et al reported resolution in around 95% of target joints in a pooled analysis of the HAVEN studies 25. Target joints were relatively uncommon in our cohort, but 87% resolved. In the HJHS sub-analysis, people who continued conventional treatment generally had better joint health and a milder bleeding phenotype than those who changed to emicizumab, despite similar ages within the subgroups. Change in total HJHS after switching to emicizumab varied between individuals. Some demonstrated a marked improvement in total HJHS, reflected by a reduction in the group median total HJHS from 16 (4,34) to 11 (2;31),  $p=.04$ . However, the within person change in total HJHS was not clinically significant. 32 Preventing bleeding, either using factor concentrates or non -factor replacement, may halt or slow the progression of arthropathy. This study provides some evidence to this effect; however, the number of subjects is small and follow-up may be inadequate. The COVID-19 pandemic limited the number attendances for joint health assessment.

Inhibitor eradication remains the recommended approach in the UK to restore normal FVIII pharmacokinetics. 39–41 There is a clinical and economic justification for using emicizumab to prevent bleeding during ITI, 10, 39, 42a position endorsed by the UK Haemophilia Doctors' Organisation (UKHCDO). 41 Further data from clinical trials and post-marketing studies are required to further to guide future practice. 43–47

Emicizumab was well tolerated and almost all side effects occurring in the first 3 months of treatment. Cutaneous reactions, mostly local injection site reactions, were the most commonly observed AE (4.4%), although at a lower frequency than reported in the HAVEN series (22%). 25, 48 Most reactions (83.3%) occurred during the loading phase of treatment. AEs leading to cessation of treatment occurred in two (1.3%). Four serious AEs were deemed possibly or definitely related to treatment, three thrombotic. It is unclear if thrombosis may be a drug-specific effect but pre-existing cardiovascular risk factors were reported in each case of thrombosis. Notably, one person who developed a subendocardial infarct, deemed related to emicizumab, was young and had normal coronary arteries on CT angiography. Haemophilia A confers an increase in cardiovascular mortality although atherosclerosis develops as it does in the non-haemophilic population. 49, 50, 51 As haemophilia treatments evolve, the haemostatic balance shifts and the haemophilia population ages, it is perhaps increasingly important to actively monitor and modify cardiovascular risk factors. The limitations of this study are typical of observational studies but have been mitigated where possible. The potential impact of inter-personal inconsistency in bleed diagnosis has been addressed using within person analysis: each individual acting as their own control. A robust, median 3.2-year follow up minimises the risk of inferring incorrect assumptions due to regression towards the mean. There is an unavoidable risk of selection bias, with a paucity of data from people not using HT regularly. The study is representative of UK clinical practice.

In conclusion, this study complements and supports clinical trial data in demonstrating sustained low bleeding rates over a considerable duration of follow up. There is a signal that the reduction in bleed following the change to emicizumab prophylaxis, may be associated

with preservation or improvement in joint health. A longer period of follow-up will be needed to confirm this. Whilst generally well tolerated, ongoing pharmacovigilance is required. This should occur in a standardised framework of mortality and morbidity reporting across all treatment modalities.<sup>50,51</sup>

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