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ORIGINAL ARTICLE
Clinical haemophilia

Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry

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Abstract

Introduction: Despite the rapid uptake of emicizumab in the paediatric haemophilia A (HA) population, real-world data on the safety and efficacy is limited.

Aim: To report on bleeding and safety in paediatric patients receiving emicizumab prophylaxis.

Methods: Data were extracted from the multicentre prospective observational Ped-Net Registry (NCT02979119). Children with haemophilia A, and ≥50 FVIII exposures or inhibitors present receiving emicizumab maintenance therapy were analysed. Data were summarized as medians with interquartile range (IQR, P25–P75). Mean (95% confidence interval (CI)), annualized (joint) bleeding rate (A(J)BR) during emicizumab and ≤2 years before emicizumab prophylaxis were modelled and compared using negative binomial regression.

Results: Total of 177 patients started emicizumab at median 8.6 years (IQR 4.8–13.1), most had no FVIII inhibitors (64%). Follow up before emicizumab was median: 1.68 years (IQR: 1.24–1.90) and during emicizumab: 1.32 years (IQR: .94–2.11).

In patients without inhibitors, mean ABR reduced after starting emicizumab from 2.41 (CI 1.98–2.95) to 1.11 (CI .90–1.36, $p < .001$), while AJBR reduced from .74 (CI .56–.98) to .31 (CI .21–.46, $p < .001$). Concordantly, in patients with inhibitors, mean

ABR reduced from 5.08 (CI 4.08–6.38) to .75 (CI .56–1.01, $p < .001$), while AJBR reduced from 1.90 (CI 1.42–2.58) to .34 (CI .21–.56, $p < .001$). Five emicizumab-related adverse events were reported (3% of the cohort), including one patient with antidrug antibodies.

Conclusion: This study showed improved bleeding control compared to previous treatment and a favourable safety profile during emicizumab therapy in paediatric haemophilia A patients.

KEYWORDS

emicizumab, haemophilia A, haemorrhage, observational study, paediatrics

1 | INTRODUCTION

Haemophilia A (HA) is a genetic X-linked bleeding disorder characterized by repeated bleeding, especially in joints.[1] The cornerstone of treatment in patients with severe haemophilia A (SHA) is administration of intravenous coagulation factor concentrate (CFC) to treat bleeds and as prophylactic replacement therapy (prophylaxis) to prevent bleeding and subsequent arthropathy. Although bleeding rates are significantly reduced by CFC prophylaxis, the frequent venous access required is often challenging, especially in young children.[1,2] Moreover, approximately 30% of SHA patients develop anti-FVIII antibodies (inhibitors) that interfere with CFC treatment, and result in the need for treatment with costly bypassing agents (BPA) which are difficult to monitor and less effective than CFC treatment.[1] Eradication of inhibitors requires intensive immune tolerance induction (ITI), and is successful in ~66% only.[1]

In 2018, emicizumab was licensed as the first nonreplacement therapy in Europe. This humanized bispecific antibody connects factor IXa and factor X, thus enabling activation of FX and subsequent thrombin generation.[3] In contrast to CFCs, emicizumab is administered subcutaneously and has a long half-life, making it especially attractive for prophylaxis in (young) children.[2] The first HAVEN studies showed emicizumab treatment to be safe and effective in adults and adolescents with SHA, with and without FVIII inhibitors.[3–5] However, data on the paediatric population are limited to 88 children (aged 1–15 yrs) with inhibitors in the HAVEN 2 study,[6] 54 infants under 12 months without inhibitors in the HAVEN 7 study and three single-centre studies.[7–10] Other single centre studies reported on mixed cohorts without separately presenting their paediatric data.[11–13]

Today, emicizumab prophylaxis is becoming more widely used in paediatric HA patients with inhibitors and its use in patients without inhibitors is expanding.[2,14] However, there is a paucity of data regarding the bleeding control and safety of emicizumab prophylaxis in previously untreated patients. Furthermore, many questions remain regarding establishing or maintaining tolerance to FVIII on emicizumab prophylaxis.[15,16]

A large multicentre international prospective paediatric observational cohort study such as the PedNet registry, provides a unique opportunity to generate timely real-world data on emicizumab prophylaxis.[17] This study aims to evaluate bleeding control, safety and CFC consumption of emicizumab compared to FVIII and/or CFC prophylaxis in paediatric HA patients in the PedNet registry.

2 | METHODS

2.1 | The PedNet registry

The PedNet Registry is a prospective, observational multicentre study collecting data from 33 haemophilia treatment centres in 19 countries. The registry includes patients with factor VIII (FVIII) or factor IX (FIX) activities ≤25% who are treated at participating haemophilia treatment centres, listed in Supplemental. This registry prospectively collects data on treatment and side effects in electronic case report forms according to a specific protocol (https://www.pednet.eu; Clin.gov.trial-NCT02979119). Data collected include all details on the first 50 exposures to clotting factor concentrate, followed by annual collection of bleeding, surgery, prophylaxis and CFC consumption, as well as all inhibitor test results.[17]

Ethical approval was obtained from local or national ethical review boards, and written informed consent was obtained from the parents/guardians of all participants.

3 | PATIENT SELECTION AND FOLLOW UP

This study included patients with congenital haemophilia A with and without inhibitors extracted from the PedNet registry on 1 January 2022. Inclusion criteria were: presence of an inhibitor against FVIII, or ≥50 exposure days (EDs) of before emicizumab, and had ≥4 weeks of emicizumab maintenance therapy. Patients with concomitant coagulopathy were excluded.

Data were collected for up to two years before the initiation of emicizumab therapy and until January 2022 or first negative inhibitor titter. Data collected included all treated- and life-threatening bleeds, previous CFC therapy, inhibitor status and history of immune tolerance

induction. Emicizumab specific data included inhibitor status at start of emicizumab, dose of emicizumab received, any drug related (serious) adverse events, including injection-site reactions, thromboembolic events, and antidrug antibodies.

3.1 | Clinical data

According to the PedNet protocol, only treated bleeds were considered, with location defined as joint or nonjoint.[17] Life-threatening bleeds were defined as any potentially life-or limb-threatening bleed according to the treating physician, including intracranial bleeds. The cause of bleeding (e.g., traumatic or spontaneous) was not registered.[17]

Inhibitor testing was performed at least every 5th ED during the first 20 EDs and at least quarterly until 50 EDs. Inhibitors were defined as ≥2 consecutive positive inhibitor tests with reduced recovery.[18]

As many centres start FVIII prophylaxis with once weekly infusions, the start of prophylaxis was defined as infusion of CFCs at regular intervals, in the absence of bleeding, at least three times within 15 days for at least two consecutive months.[19]

In inhibitor patients, ITI was defined as any regular FVIII infusion schedule given ≥3x/week and at a dose ≥45 IU/kg/infusion for ≥4 weeks.[20] BPA prophylaxis was defined as infusions ≥2x/week (for ≥3 months) with either recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). All other therapies were classified as on-demand therapy.

Testing for ADAs against emicizumab was done indirectly (by APTT and/or emicizumab levels) in most centers.[18] During emicizumab prophylaxis, FVIII inhibitor testing was performed at least annually or after exposure to FVIII. Patients were receiving emicizumab dosing according to the label (i.e., 6 mg/kg/4wks, with varying intervals).

3.2 | Outcomes

Primary endpoint was annualized bleeding rate (ABR) before emicizumab therapy versus during emicizumab therapy.

Secondary endpoints were annualized joint bleed rate (AJBR) and life-threatening bleeds. In addition, changes in A(J)BR were compared according to subgroups of age (preschool < 7 yrs, school: 7−12 years, and teenagers: ≥13 years), haemophilia A severity, and therapy before emicizumab.

For evaluation of safety, all the adverse events reported during emicizumab therapy were recorded.

To evaluate changes in treatment, the number of intravenous and/or subcutaneous injections before and during emicizumab prophylaxis were compared. The annual number of injections was calculated by adding the prophylaxis regimen to the number of injections related to bleeding.

Annualized consumption rate of CFCs (IU/kg/yr), BPA (mg/kg/yr) or emicizumab (mg/kg/yr) before and during emicizumab prophylaxis were compared before and after initiation of emicizumab prophylaxis.

3.3 | Statistical analysis

Patient characteristics were summarized as numbers (%) and medians with IQR (P25−P75). To enable adjustment for variation in available follow-up while taking into account the skewed distribution of the data mean ABR and AJBR were modelled with their 95% confidence interval (CI) by negative binomial regression modelling.[21]

The consumption rate of CFCs and number of intravenous and/or subcutaneous injections were compared before and during emicizumab using the nonparametric Wilcoxon signed-rank test. Statistical analyses were performed with R Studio (version R4.3.1, R Core Team) and SPSS (version 26; IBM Corp.). Two-tailed p-values of less than.05 were considered statistically significant.

4 | RESULTS

4.1 | Baseline characteristics

Patient selection is shown in Figure 1. A total of 177 patients from 29 haemophilia treatment centres were included. Sixty-seven patients were excluded for having <50 ED on CFC before starting emicizumab therapy or receiving emicizumab therapy for less than 4 weeks (n = 8).

Patient and treatment characteristics are shown in Table 1. The median age at start of emicizumab therapy was 8.6 years (IQR: 4.8–13.1, range: 1.0–17.9). The median follow-up before emicizumab therapy was 1.68 (IQR: 1.24–1.90) years and during emicizumab therapy was 1.32 years (IQR: .94–2.11), resulting in 288 patient-years before emicizumab therapy and 280 patient-years during emicizumab therapy.

The majority (95%) of patients had severe HA. At start of emicizumab therapy, 52% never had FVIII inhibitors, 12% were tolerized, whereas 36% had active inhibitors. Overall, patients with FVIII inhibitors started emicizumab earlier: at a median of 7.8 years (IQR: 4.0–11.9) compared to a median of 9.4 years (IQR: 5.1–13.3) in patients without FVIII inhibitors, resulting in a longer follow-up on emicizumab of median of 2.18 years (IQR: 1.16–3.0) for those with- and median 1.07 years (IQR: .74–1.52) for those without inhibitors present.

4.2 | Bleeding control

As shown in Figure 2, bleeding rates were significantly reduced during emicizumab prophylaxis.

Before emicizumab therapy, patients with FVIII inhibitors showed more frequent overall bleeding compared to patients without FVIII inhibitors (mean ABR 5.08 vs. 2.41/year; incidence rate ratio (IRR): 2.10 (CI: 1.56–2.84), p < .001), as well as joint bleeding (mean ABR 1.90 vs.74/year; IRR 2.58 (CI: 1.71–3.90), p < .001). Tolerized patients had similar bleeding rates to those who never had inhibitors.

During emicizumab therapy, patients with FVIII inhibitors showed a lower overall bleeding compared to patients without FVIII inhibitors (mean ABR.75 vs. 1.11/year; IRR.66 (CI: .46–.93), p < .016), but the
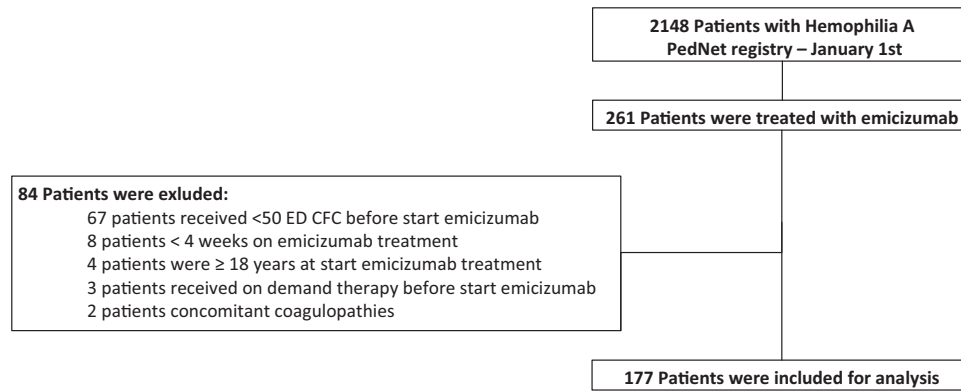
FIGURE 1 Overview patient selection on 1 January 2022.

TABLE 1 Patient and treatment characteristics at start of emicizumab.

Baseline characteristics	Children (N = 177)
Age start emicizumab therapy (years)	8.6 (4.8–13.1)
<2 years	8 (4.5)
Follow-up (years)	
Before emicizumab therapy*	1.68 (.97–1.82)
During emicizumab therapy	1.32 (.94–2.11)
Haemophilia severity—no. (%)	
Severe	168 (95)
Moderate	7 (4)
Mild	2 (1)
Inhibitor history—no (%)	
No inhibitor history	91 (52)
Tolerized patients	22 (12)
Inhibitor present at start of emicizumab	64 (36)
Therapy prior to emicizumab—no. (%)	
Patients without FVIII inhibitors	
Prophylaxis FVIII	
Recombinant FVIII	34 (30)
Plasma derived FVIII	11 (10)
Long acting FVIII	68 (60)
Patients with FVIII inhibitors	
ITI	26 (41)
Prophylaxis BPA	31 (48)
Prophylaxis FVIII	7 (11)

Results are presented as number (%) or median (P25–P75).

AJBR were similar (mean AJBR .34 vs. .31/year, IRR: 1.02 (CI: .55–1.88, $p = .957$).

Consequently, ABR reduction was most pronounced in patients with inhibitors, for whom ABR was reduced from 5.08 (CI: 4.08–6.38) to .75

(CI: .56–1.01, IRR: .15 (CI: .10–.21), $p < .001$), while AJBR was reduced from 1.90 (CI: 1.42–2.58) to .34 (CI: .21–.56, IRR:.17 (CI: .10–.28), $p < .001$). Those without FVIII inhibitors showed a less pronounced but significant reduction in mean ABR after starting emicizumab: from 2.41 (CI: 1.98–2.95) to 1.11 (CI: .90–1.36, IRR: .47 (CI: .35–.63), $p < .001$), while AJBR reduced from .74 (CI: .56–.98) to .31 (CI: .21–.46, IRR: .43 (CI: .26–.69, $p < .001$).

Details of overall mean ABR and AJBR before and during emicizumab therapy according to inhibitor status, age, severity and FVIII concentrate type are shown in Table S1.

## 4.3 | Concomitant therapy during emicizumab therapy

During emicizumab therapy, 8/64 inhibitor patients continued ITI treatment for a median duration of 50 weeks (IQR 28–81). Inhibitor patients who received concomitant ITI showed a trend towards lower bleeding rates to those who received emicizumab only (mean ABR .32 vs. .84/year, IRR: .39 (CI: .14–.98), $p = .052$).

Furthermore, 3/113 noninhibitors patients continued FVIII prophylaxis for a median of five weeks (range: 5–29). The ABR was similar between patients with and without continued FVIII prophylaxis (mean ABR .32 vs. .93, IRR 1.64 (CI: .51–4.95), $p = .384$).

4.4 | Life-threatening bleeds

Before emicizumab therapy, 10 life-threatening bleeds (six intracranial bleeds, three iliopsoas bleeds, and one severe throat bleed) were reported in seven patients, including three without FVIII inhibitors on prophylaxis, and four with FVIII inhibitors. Most (3/4) inhibitor patients were receiving ITI treatment and one received only BPA prophylaxis.

During emicizumab therapy, no life-threatening bleed was reported.
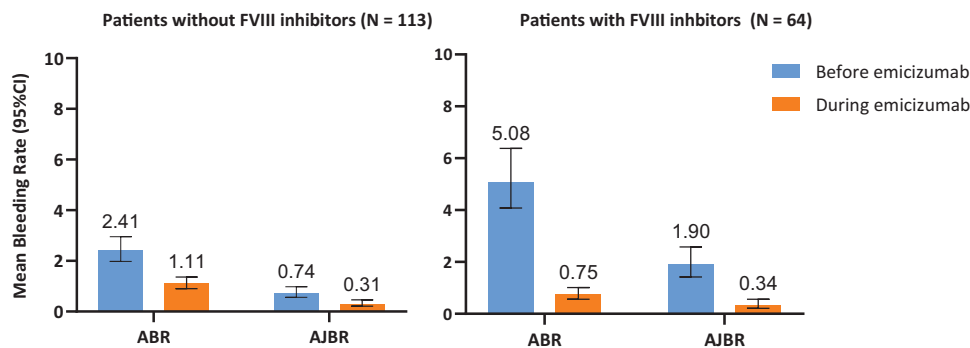
FIGURE 2 Mean annualized (joint) bleeding rate and 95 CI, before and during emicizumab in patients with and without FVIII inhibitors present.

4.5 | Safety

Five drug-related adverse events were reported during emicizumab therapy in eight patients (3% of cohort). One patient developed non-neutralizing antidrug antibodies, detected during routine testing of emicizumab levels.[22] While the aPTT remained in normal ranges, suspicion for an ADA was raised due to lower emicizumab levels (despite compliance) and recurrent bleeding episodes. Additional laboratory analyses confirmed anti-FIXa and anti-FX antiemicizumab antibodies at low levels. Although bleeding control was maintained, the patient opted to revert back to FVIII prophylaxis and discontinued emicizumab after seven months.[22]

In addition, four patients reported injection site reactions after administration of emicizumab.

No inhibitor recurrence was observed in the 22 tolerized patients after a median of 1.2 years (range: .3–2.7) on emicizumab therapy. Finally, no TMA or thromboembolic events were reported.

4.6 | Changes in number of injections and CFC consumption

Following the start of emicizumab prophylaxis, the number of injections and CFC consumption were significantly reduced in both patients with and without FVIII inhibitors, Table 2.

Before emicizumab, almost half (48%. 31/64) of inhibitor patients received BPA prophylaxis and 41% (26/64) received ITI, requiring a median of 364 injections/year. After starting emicizumab, the injection rate was significantly reduced to 52/yr $p < .001$) and FVIII consumption was reduced by 97.6%, from 22218 IU/kg/yr to 546 IU/kg/yr ($p < .001$), while consumption of rFVIIa was significantly reduced by 94.8%, from.57 mg/kg/yr to.03 mg/kg/yr ($p < .001$).

Most patients without FVIII inhibitors (60%, 68/113) were receiving long acting FVIII prophylaxis before emicizumab, at a median of 129 injections/year. On emicizumab prophylaxis, the number of injections was reduced to 35/yr ($p < .001$) and CFC consumption was reduced by 97.6%, from median 4847 IU/kg/yr to 116 IU/kg/yr ($p < .001$).

TABLE 2 Injection rate and CFC consumption in both patients with and without FVIII inhibitors.

	Before emicizumab	During emicizumab	p-value
Patients without FVIII inhibitors (n = 113)			
Injection rate			
No. of injections /yr	129 (104–170)	35 (28–52)	<.001
Annualized CFC consumption			
FVIII consumption (IU/kg/yr)	4847 (3333–6532)	116 (90–370)	<.001
Emicizumab consumption (mg/kg/yr)	NA	77 (68–78)	NA
Patients with FVIII inhibitors (n = 64)			
Injection rate			
No. of injections /yr	364 (186–448)	52 (44–54)	<.001
Annualized CFC consumption			
rFVIIa consumption (mg/kg/yr)	.57 (.09–3.05)	.03 (0–.18)	<.001
aPCC consumption (IU/kg/yr)	12668 (4366–21539)	NA	NA
FVIII consumption (IU/kg/yr)	22218 (8306–44209)	546 (137–3451)	<.001
Emicizumab consumption (mg/kg/yr)	NA	77 (72–79)	NA

Results presented as median (P25–P75). NA = not applicable.

5 | DISCUSSION

5.1 | Main findings

With 177 patients, the current study reports on the largest paediatric cohort treated on emicizumab with prospectively collected data including 280 patient-years of emicizumab therapy. Emicizumab prophylaxis resulted in an improved bleeding control for both patients with- (IRR: .15 (CI: .10–.21), $p < .001$) and without FVIII inhibitors present (IRR: .47 (CI: .35–.63), $p < .001$). Concomitantly, the number of injections was significantly reduced in both groups: from 364 to 52/yr in inhibitor patients, and from 129 to 35/yr in those without inhibitors, use of CFC was reduced by 97.6% in both groups, and use of rFVIIa in inhibitor patients was reduced by 94.8%. Median emicizumab consumption was 77 mg/kg/yr in both groups.

5.2 | Strengths and limitations

The strengths of our study include the large international unselected prospective paediatric cohort, with standardized and externally monitored data collection. Calculation of A(J)BRs was done using state of the art negative binomial regression techniques, allowing for variation in follow up as well as direct comparison to HAVEN studies.[3,4,6,10]

External validity was enhanced by the inclusion of patients of all ages and varying inhibitor status from different countries with varying treatment protocols.

Limitations are inherent to the PedNet study design: proportions of patients without bleeding could not reliably be calculated for 6 month-periods as data are collected annually after 50 EDs, nor was the cause of bleeding collected. Collection of drug-related adverse events only started in 2019 with the introduction of emicizumab. This may have led to underestimation of adverse events related to emicizumab use. On the other hand, participating centres were extra vigilant regarding adverse events associated with emicizumab, the reduction of bleeding during emicizumab therapy in patients without FVIII inhibitors may have been overestimated, as those with a poor bleeding control on FVIII prophylaxis may have been switched first to emicizumab.

However, at 2.41/yr (CI: 1.98–2.95) the mean ABR on FVIII prophylaxis observed was similar to the paediatric data reported by Young[23] (mean ABR 2.34, SD 4.27) and Konkle[24] (mean ABR 2.0, CI: 1.0–4.0).[23,24] Moreover, other reports, including the HAVEN studies, are likely to suffer from similar selection, as patients with poor bleeding control are likely to participate first.[3,4,6–8,13,25]

5.3 | Comparison with previous research—bleeding control on emicizumab

In comparison with HAVEN 2 ($n = 88$, inhibitor positive, median 7 years) the 64 inhibitor patients (median 7.8 years) in PedNet showed a significantly higher ABR (PedNet.75/yr (CI: .56–1.01) vs. HAVEN 2.30/yr (CI: .17–.50) and a trend towards a higher AJBR of .34/yr (CI: .21–.56) vs. .2/yr (CI: .01–.29).[6]

The recently published HAVEN 7 study has reported on 55 patients aged 4 months at start of emicizumab and followed for 2 years, reported a much lower mean ABR of .4 (CI: .30–.63), all traumatic, but these children are likely much less physically active than those at school age participating in sports.[10] Two large single centre cohort studies in Europe have reported good bleeding control in adults and children on emicizumab. First, the Israeli cohort, including 58 children, 40% inhibitors, with a median age of 6 years, reported a higher ABR at a median of 4.0 treated bleeds/year (P25–P75 1.75–7.25).[13] We have no explanation for this discrepancy. Second, the Dutch cohort including 32 children, 13% inhibitors, with a median age of 4 years, reported a comparable mean ABR of.7 (CI: .4–1.2).[25]

5.4 | Comparison with previous research-side effects

The incidence of neutralizing antibodies in the present cohort of.4% is consistent with the previously reported ADA incidence of <1% of patients from previous HAVEN and STASEY trials.[26,27] However, as not all centres routinely measured emicizumab levels or may have tested irregularly, the incidence of ADA may have been underestimated in our study.

Furthermore, we reported injection site reactions after administration of emicizumab in only 2%, which is lower than reported in previous studies, and may have been underestimated in our study.

The absence of thrombo-embolic events or TMA is in accordance with the age category and avoidance of concomitant aPCC treatment.

5.5 | Comparison with previous research—consumption

Although the present study could not consider treatment costs due to the heterogenicity of pricing for both CFC and emicizumab across the participating countries, the present data gives an indication of changes in consumption that may be used for economic analyses.

Among two mixed cohort studies reporting on CFC consumption pre- and post switch including paediatric patients without inhibitors, the study of Batt et al was most comparable to our cohort.[28,29] They performed a retrospective cost-analysis study using insurance records data, comparing 112 patients without FVIII inhibitors (40% <18 years) with a mean follow-up time of 2.5 years before emicizumab and 1.1 years during emicizumab.[28]

The median FVIII consumption before emicizumab was 70 IU/kg/week (IQR: 56–98), which is comparable to the mean FVIII consumption of 90 IU/kg/week (IQR: 64–126) in patients without FVIII inhibitors in our study. However, a major limitation of the study was the fact that the database was using insurance records used, lacking information about specific patient characteristics (e.g., frequency of emicizumab injections).

5.6 | Clinical implications and future research

The present study confirms the clinical efficacy of emicizumab prophylaxis, but does not provide definitive proof that emicizumab prophylaxis is superior to FVIII prophylaxis, since patients switching early may have introduced selection bias and factors such as (non)adherence and high-risk activities were not included.

However, the current cohort includes a heterogeneous group of patients (29 haemophilia centres) than published in phase 3 or single-centre studies. Although prophylaxis with emicizumab is safe and highly effective in preventing bleeds in HA patients with and without FVIII inhibitors, there are remaining questions on its use in young children, the need for concomitant FVIII administration to prevent inhibitor development in patients starting < 50 EDs to FVIII, and the risk of inhibitor recurrence in tolerized patients. We plan to monitor and study these issues closely in the coming years.

6 | CONCLUSION

In conclusion, our data confirms the safety of emicizumab prophylaxis and suggests improved bleeding control among prospectively followed paediatric patients in a large real-world cohort of children with HA.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the registry of the PedNet Haemophilia Research Foundation. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the PedNet Haemophilia Research Foundation (https://www.pednet.eu).

ETHICS STATEMENT
Ethical approval and informed consent were obtained according to the regulations in each participating centre for the PedNet registry.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.