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ORIGINAL ARTICLE

# The efficacy of the entire-vial dosing of emicizumab: Real-world evidence on plasma concentrations, bleeds, and drug waste

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## Abstract

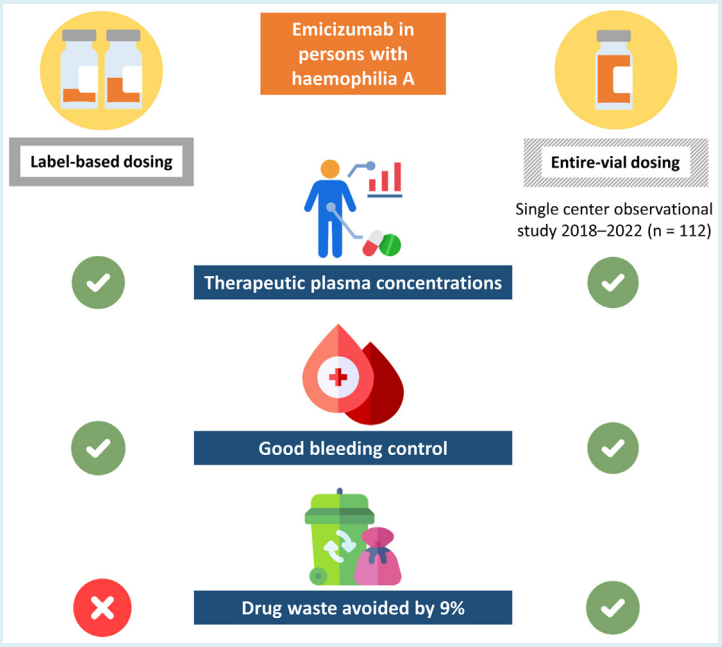
**Background:** Prophylaxis with emicizumab provides effective bleeding protection in persons with hemophilia A (PwHA) but pressures healthcare budgets. The body weight–adjusted dosing at 7-, 14-, or 28-day intervals, according to the label, often mismatches the vial content. Entire-vial dosing resulted in therapeutic concentrations according to pharmacokinetic simulations and was introduced to avoid waste.

**Objectives:** The objective of this study was to evaluate the efficacy of entire-vial dosing of emicizumab by investigating real-world evidence of plasma concentrations, bleeds, and drug waste.

**Methods:** This is a single-center, observational study with PwHA receiving emicizumab in mg/kg doses according to label but dosing interval extrapolated to the nearest vial size. Patient characteristics and bleeds were compared 1 year before starting emicizumab and during emicizumab until January 2022. Concentrations were assessed at weeks 4, 12, and annually. The mean (95% CI) annualized bleed rates were compared by using negative binomial regression. Drug waste between label-based dosing and entire-vial dosing was compared.

**Results:** A total of 112 individuals (94% severe phenotype and 9% positive FVIII inhibitors) were followed for a median of 56 weeks (interquartile range [IQR] 52-68) before and 51 weeks (IQR 29-75) after starting emicizumab. The median emicizumab dose was 5.9 (IQR 5.5-6.2) mg/kg/4 wk with median concentrations of 63 (IQR 51-80) μg/mL. The annualized bleed rate of treated bleeds before emicizumab was 3.6 (95% CI 2.9-4.4) and was 0.8 (95% CI 0.6-1.1) during emicizumab ($P < .001$). Drug waste was reduced by 9%.

**Conclusion:** The entire-vial dosing of emicizumab is an attractive treatment option for PwHA leading to therapeutic plasma concentrations, good bleeding control, and drug waste avoidance.




**KEYWORDS**
emicizumab, entire-vial dosing, hemophilia A, observational study, real-world evidence

**Essentials**

- Emicizumab was dosed with entire vials at varying intervals (7-28 days) in 112 persons.
- Therapeutic concentrations and good bleeding control were seen in 96 person-years on emicizumab.
- Entire-vial dosing avoided 9% of drug waste per individual, which was ~260 mg per adult per year.

## 1 | INTRODUCTION

Emicizumab (Hemlibra) prophylaxis provides effective bleeding prevention in persons with hemophilia A (PwHA) [1]. This humanized, bispecific FVIII-mimicking antibody was approved by the European and US regulatory authorities for PwHA with and without factor VIII (FVIII) inhibitors in 2018. The advantages of using emicizumab over the traditional FVIII concentrates are subcutaneous administration instead of intravenous administration, longer dosing intervals with continuous bleeding protection, and no interference with FVIII inhibitors [2]. Emicizumab reduces the treatment burden for PwHA on prophylaxis, especially for those with FVIII inhibitors on bypassing agents (BPAs) or with difficult venous access, and may enhance treatment adherence. Although many PwHA are candidates for emicizumab therapy, access to this therapy is limited owing to the financial impact on healthcare budget of hospitals [3–5].

Emicizumab is available as injection vials for single use in 4 different vial sizes: 30 mg/1.0 mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/1.0 mL [6]. The maintenance dosage regimens, according to the drug label, are 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks (ie, the dose per administration varies with body weight, but the dosing intervals are fixed). Given an individual's weight, the dose is unlikely to exactly match the content of the vial size suggested by the online Hemlibra calculator that is provided by the manufacturer, which often forces the prescribers to either overdose or discard the unused remainder of a vial. This introduces the risk of administration errors and leads to expensive drug waste, which are 2 topics of concern in the hemophilia community and society in general [7].

Entire-vial–based dosing could be used to tackle these 2 issues. While maintaining the mg/kg dose according to the registered label, the prescriber could extrapolate the dosing interval to the nearest vial size. For example, a PwHA with a body weight of 13 kg who receives 39 mg every 14 days according to the drug label (discarding 21 mg of a 60 mg/0.4 mL vial) could instead be given 60 mg every 21 days according to the entire-vial dosing. Until now, no studies on the efficacy outcomes of entire-vial dosing for PwHA in daily clinical practice were reported. Entire-vial dosing can be justified by the long elimination half-life of emicizumab (ie, ~30 days), and the linear relationship across the 3 available dosing regimens suggests that alternative dosing combinations will result in similar plasma concentrations [7]. Furthermore, entire-vial dosing has been suggested to result in

therapeutic plasma concentrations (~55 μg/mL) in 2 reports on pharmacokinetic modeling simulations [8,9]. Therefore, we introduced entire-vial dosing to PwHA who receive emicizumab therapy in our clinic. The objective was to evaluate the efficacy of the entire-vial dosing of emicizumab by investigating real-world evidence of the plasma concentrations, bleeds, and drug waste.

## 2 | MATERIALS AND METHODS

### 2.1 | Design and setting

This single-center, retrospective observational study on prospectively registered data was conducted at the Van Creveldkliniek, University Medical Center in Utrecht, The Netherlands. All PwHA (adults and children) who started emicizumab between July 2018 and January 26, 2022 were eligible. The inclusion criteria were a diagnosis of congenital hemophilia A, at least 1 plasma emicizumab concentration measurement available, and no objection against the usage of clinical data for research in the electronic health record.

The PwHA were switched from prophylaxis or on-demand therapy with either FVIII concentrates (standard half-life [SHL] or extended half-life [EHL]) or BPAs (ie, recombinant activated factor VII or activated prothrombin concentrate complex) to emicizumab therapy during a regular medical visit. All PwHA received emicizumab loading doses of 3 mg/kg per week for 4 consecutive weeks according to the drug label. Subsequently, the maintenance dose (≥28 days after the first loading dose) was an equivalent of the registered dose of 6 mg/kg/4 wk, but with varying dosing intervals that were rounded to the highest frequency and the nearest vial size [8,9]. These dosing intervals ranged between 7 and 28 days and were based on shared decision making between the PwHA and their own treating clinician. Previous prophylaxis was continued for 1 week during the emicizumab loading phase, except for individuals with inhibitors or frequent bleeding, who then continued their regular prophylaxis for 2 weeks after starting emicizumab. The PwHA were instructed to contact the center in the case of suspected bleeds. Bleeding episodes were treated with regular doses of FVIII or recombinant activated factor VII. This study was evaluated and approved by the Medical Ethics Review Board of UMC Utrecht with study number 21/825. Individual informed consent was waived.

### 2.2 | Variable and outcome analyses

The data sources were health diaries, telephone calls to attending clinicians, and clinical visits. The data on outcomes and variables were prospectively registered in the electronic health records and extracted by performing retrospective chart reviews. The data were collected preferably at 1 year (but at least 12 weeks) before starting with emicizumab therapy until the study's end date of January 26, 2022 (see Figure 1 for a schematic study timeline per individual).

#### 2.2.1 | Baseline characteristics

The following baseline characteristics were collected: hemophilia A severity, FVIII inhibitor status, age, weight, body mass index (BMI), previous factor-replacement regimen, and emicizumab regimen. The hemophilia severity was classified on endogenous FVIII activity as severe (<1%), moderate (1%-5%), or mild (>5%-40%) [10]. The FVIII inhibitor status was classified as present if the inhibitor titre at baseline was ≥0.3 Bethesda units/mL. All maintenance doses of emicizumab were converted to a 4-week dosing frequency for comparison (ie, each mg/kg dose was divided by the dosing interval and multiplied by 28 days).

#### 2.2.2 | Plasma concentrations of emicizumab

According to the local protocol, plasma samples for emicizumab concentration measurements were usually assessed before the 4$^{th}$ loading dose (ie, after receiving 3 loading doses), at 3 and 12 months after starting emicizumab and at least once a year thereafter. All concentrations were combined with monitoring of complete blood count and renal function.

A (cross-)validated liquid-chromatography tandem mass spectrometry method was used to quantify the concentration of emicizumab in human plasma [11,12]. The plasma concentration-time curve was fitted

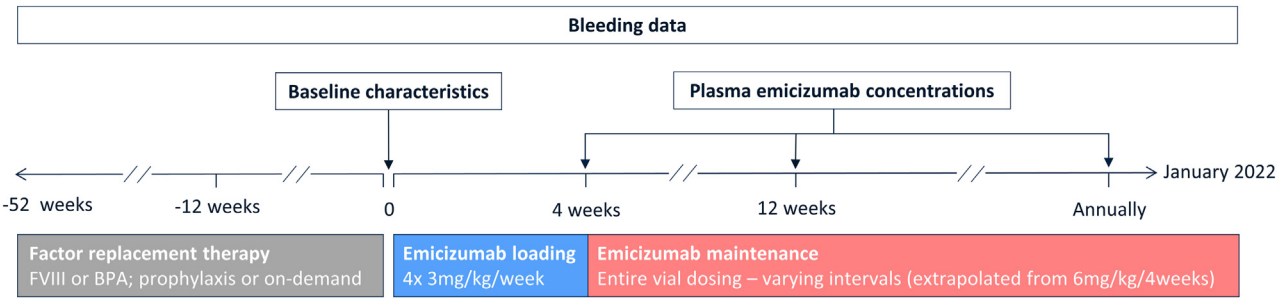



**FIGURE 1** Schematic study timeline per individual. BPA, bypassing agent; FVIII, factor VIII.

by using a weighted nonlinear least squares regression with a 1-phase association model, and the fit was presented with 90% prediction bands of points. The between- and within-individual variabilities of plasma emicizumab concentrations during the maintenance phase (defined from ≥28 days) were expressed as the percentage coefficient of variation, which was calculated as (SD/mean) × 100%. The within-individual variability was calculated for both ≥2 and ≥3 concentrations per individual without dose changes during the studied period.

### 2.2.3 | Bleeds

The PwHA were monitored closely over time, and it was mandatory to contact a 24/7-available attending clinician at any suspicion of bleeding. During those calls or visits, the need for FVIII/BPA treatment was evaluated, and all cases of suspected joint or muscle bleeds were evaluated at the clinic. Adverse events (eg, thrombotic) were documented in patient files as well. Bleeding events were defined according to the definitions of the International Society on Thrombosis and Haemostasis as pain and/or swelling, and only bleeds treated with additional FVIII/BPAs were considered in this study [13]. Bleeds were classified as all, joint and/or muscle bleeds. The mean annualized bleeding rate (ABR) and the mean annualized joint bleeding rate (AJBR) with 95% CI were modeled by using a negative binomial regression with a log link to account for variations in follow-up times and the skewness of bleeding data. The ABRs before and during emicizumab therapy were compared by using this regression model.

The proportions of PwHA with 0 bleeds, 1 to 3 bleeds, and >3 bleeds during the 24-week intervals of 0 to 24, 25 to 48, 49 to 72, and 73 to 96 weeks after starting emicizumab were estimated to enable a comparison with the data from the HAVEN studies [1]. The individuals were only included in a 24-week interval if they completed the entire interval.

### 2.2.4 | Drug waste

The drug waste (ie, the difference between the prescribed dose and the dispensed drug in the vial[s]) was calculated by subtracting the label-based dose from the vial size suggestion, which were both obtained by entering every individual's body weight in the Hemlibra Dosing Calculator (http://www.hemlibra-hcp.com/dosing-administration/dosing-calculator). This drug waste was expressed as a proportion or was calculated as waste during follow-up or as annualized waste. For individuals with a maintenance-dosing interval of 21 days, the mean of the label-based doses at 14- and 28-day intervals was used. The closest label-based interval was taken for other alternative intervals.

## 2.3 | Statistical methods

The continuous variables were presented as means with SDs if they were normally distributed or as medians with interquartile ranges (IQRs) and categorical variables were presented as individual counts with percentages. The last emicizumab concentration that was observed for each individual during maintenance therapy (steady state condition), and the ABRs were compared across subgroups by using nonparametric tests and multivariable regressions, respectively. Subgroups included age categories (adults/adolescents [≥12 years] vs children [<12 years]), dosing interval categories (label-based [7, 14, 28 days] vs alternative dosing intervals), BMI categories (BMI <18 versus 18-25 vs >25 kg/m$^2$), FVIII inhibitor status at baseline (present vs absent), and adherence categories (adherent vs nonadherent). For this last category, the individuals who self-reported skipping injections of emicizumab repeatedly were defined as nonadherent. When self-reported, nonadherence was quantitated by comparing the pharmacy expenditure records with a prescribed dose [14]. In addition, the ABRs and AJBRs were compared across the subgroups of concentrations (<40 vs 40-80 vs >80 μg/mL). These concentration subgroups were based on the mean ± SD of 6 mg/kg every 4 weeks (highest peak-trough fluctuation), as stated in the drug label [6].

Two-tailed *P* values of less than 0.05 were considered statistically significant. Statistical analyses were performed by using IBM SPSS Statistics (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. IBM Corp), and graphics were made by using GraphPad Prism (GraphPad Software LLC, Version 8.3.0).

# 3 | RESULTS

## 3.1 | Baseline characteristics

A total of 115 individuals treated with emicizumab were studied from July 2018 to January 2022. Three individuals were excluded, including 1 individual with type III von Willebrand disease and 2 individuals with acquired hemophilia A. The baseline characteristics are presented in Table 1; 112 PwHA were included in the studied cohort. Most of these PwHA (94%) had severe hemophilia A, 10 (9%) had FVIII inhibitors at baseline, and the median age was 24 (IQR 10-49) years.

The cohort consisted of 80 adults/adolescents and 32 children; baseline characteristics according to the age subgroup are presented in Supplementary Table 1. Ten children started emicizumab therapy before the age of 3 years, including 5 previously untreated patients (PUPs), who started with emicizumab prophylaxis before FVIII exposure.

The median follow-up time before starting emicizumab was 56 weeks (IQR 52-68 and range 12-166) per individual. The individuals had a follow-up time of at least 1 year, except for 4 children who were less than a year old, who had 12 to 15 weeks, 1 3-year-old child with 36 weeks, and 1 adolescent (age 14) with 47 weeks of follow-up time. Most PwHA (*n* = 97, 87%) were on FVIII prophylaxis before starting emicizumab therapy. The median prophylactic dose of the FVIII-SHL products was 44 units/kg/wk and was higher for the FVIII-EHL products at 60 units/kg/wk. Most of the adults received FVIII-SHL prophylaxis, whereas most of the children received FVIII-EHL prophylaxis; 5 were PUPs, as demonstrated in Supplementary Table 1.

**TABLE 1** Baseline characteristics ($n$ = 112).

| Baseline characteristic | Median (IQR) or $n$ (%) |
|---|---|
| Hemophilia A severity, $n$ (%) | |
| Severe | 105 (94%) |
| Moderate | 5 (4%) |
| Mild | 2 (2%) |
| FVIII inhibitor present, $n$ (%) | 10 (9%) |
| Age (y), median (IQR) | 24 (10-49) |
| Body weight (kg), median (IQR) | 70 (34-89) |
| BMI (kg/m$^2$), median (IQR) | 24 (17-27) |
| Previous therapy, $n$ (%) | |
| PwHA without inhibitors | |
| FVIII-SHL prophylaxis | 50 (45%) |
| FVIII-EHL prophylaxis | 47 (42%) |
| FVIII-SHL and -EHL on demand | 5 (4%) |
| PwHA with inhibitors | |
| rFVIIa prophylaxis | 1 (1%) |
| aPCC prophylaxis | 2 (2%) |
| rFVIIa and aPCC on demand | 2 (2%) |
| Previously untreated persons | 5 (4%) |

aPCC, activated prothrombin complex concentrate; BMI, body mass index; EHL, extended half-life; FVIII, factor VIII; IQR, interquartile range; PwHA, persons with hemophilia A; SHL, standard half-life; rFVIIa, recombinant, activated factor VII.

### 3.1.1 | Emicizumab therapy

The reasons for switching from the previous treatment to emicizumab were breakthrough bleeds/ineffectiveness ($n$ = 34, 30%), difficult venous access ($n$ = 34, 30%), user-friendliness/individual preference ($n$ = 17, 15%), nonadherence ($n$ = 12, 11%), or FVIII-inhibitor development ($n$ = 10, 9%), additionally, 5 individuals (4%) were PUPs. The reasons to start emicizumab according to the age subgroup are represented in Supplementary Table 2.

The median follow-up time during emicizumab therapy was 51 (IQR 29-75 and range 1-190) weeks. The median dose of emicizumab at the initiation of the maintenance phase was 5.9 (IQR 5.5-6.2) mg/kg/4 wk with dosing intervals ranging from 7 to 28 days, as demonstrated in Figure 2. Although most adult/adolescent PwHA ($n$ = 74) were treated with the registered dosing intervals of 7 or 14 days with entire-vial dosing, most children ($n$ = 17) had alternative dosing intervals, usually 21 days ($n$ = 12, 38%). Six adolescents self-reported nonadherence to emicizumab treatment; their median age was 17 years (IQR 15-20 and range 13-24). Their emicizumab consumption was only 53% (range 31%-81%) of the prescribed amount.

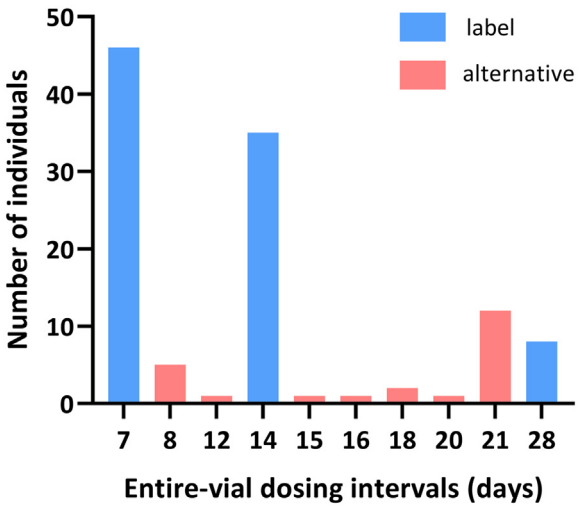



**FIGURE 2** The number of individuals per entire-vial dosing interval of the initial maintenance dose of emicizumab ($n$ = 112).

## 3.2 | Plasma concentrations of emicizumab

A total of 264 plasma concentrations of emicizumab during the loading phase ($n$ = 90) and the maintenance phase ($n$ = 174) were available. These emicizumab concentrations according to the time after the first injection with emicizumab are presented in Figure 3. The concentrations from the 6 (self-reported) nonadherent individuals (red squares) were comparable with those from the adherent individuals (blue points) during the loading phase, but their concentrations declined during the maintenance phase. In only the adherent individuals (88 of 106 had a concentration during maintenance phase available), the between-individual variability (percentage coefficient of variation) increased with time and was 38%, whereas the within-individual variability was 15% for individuals with at least 2 concentrations ($n$ = 42) and was 22% for individuals with at least 3 concentrations ($n$ = 15).

The subgroup analyses on the last observed concentration per individual in the maintenance phase demonstrated a significant difference in the adherence subgroups: nonadherent individuals ($n$ = 6) had a median concentration of 18 (IQR 8-30) μg/mL, whereas adherent individuals ($n$ = 88) had a median concentration of 63 (IQR 51-80) μg/mL ($P$ < .001), which included 8 individuals (9%) with last concentrations of <40 μg/mL. Therefore, the concentrations from nonadherent individuals were excluded from further analyses of the age, dosing interval, and BMI subgroups. The adults/adolescents had median concentrations of 69 (IQR 51-87) μg/mL, whereas the children had median concentrations of 58 (IQR 51-66) μg/mL ($P$ = .017). The concentrations were similar across the dosing interval and BMI subgroups, as presented in Supplementary Table 3.

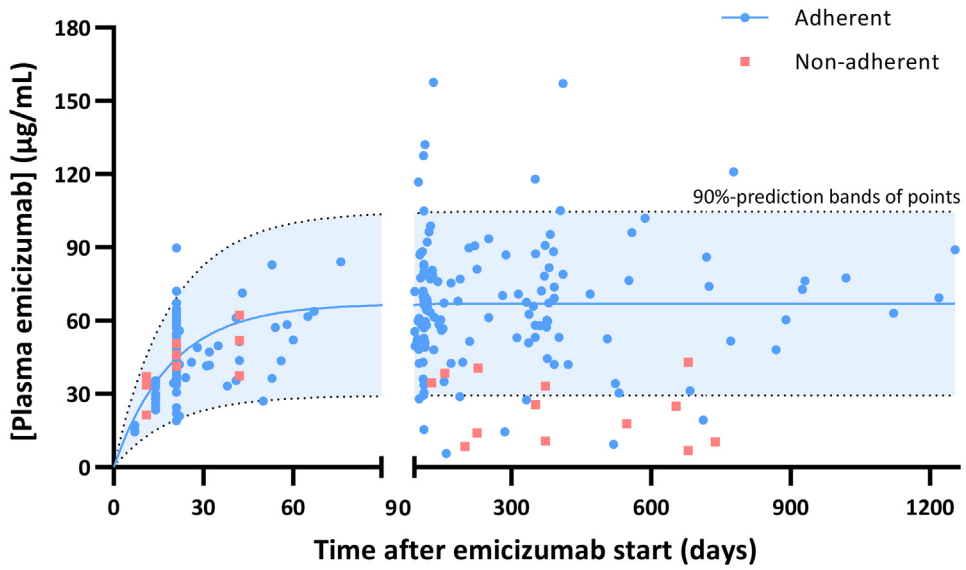



**FIGURE 3** Plasma concentrations of emicizumab according to the time since starting emicizumab with adherence.

## 3.3 | Bleeds

The data on treated bleeds with an overall follow-up in of 131 person-years before and 96 person-years during the emicizumab therapy are summarized in Table 2. The total number of treated bleeds observed decreased from 442 before to 74 during the emicizumab therapy, with a concomitant significant reduction of ABRs from 3.6 (95% CI 2.9-4.4) to 0.8 (95% CI 0.6-1.1) ($P < .001$). The number of treated joint bleeds decreased from 271 before to 34 during the emicizumab therapy, with a concomitant significant reduction of AJBRs from 2.2 (95% CI 1.7-2.7) to 0.4 (95% CI 0.2-0.6) ($P < .001$). The number of treated muscle bleeds decreased from 72 before to 13 during the emicizumab therapy. As presented in Table 2, the bleed rates before emicizumab were higher in adults/adolescents than in children. Concomitantly, the reduction in bleed rates after switching to emicizumab therapy appeared more pronounced in adults (ABR, 80%; AJBR, 86%) than in children (ABR, 70% AJBR, 50%).

To allow comparison with previous reports, the proportion of individuals without (joint) bleeds during emicizumab were calculated in 24-week intervals. A total of 78 PwHA had a follow-up time of ≥24 weeks after starting emicizumab therapy (ie, the first 24-week interval), of which the proportion without any bleeds was 73.1%; the proportion with 1 to 3 bleeds was 24.4%, and the proportion with >3 bleeds was 2.6% (Supplementary Figure). Ten of the total 32 bleeds (31%) in the first 24-week interval occurred during the loading phase. Only 2 individuals had >3 bleeds during this first 24-week interval: the first 1 had 5 bleeds during the loading phase and 1 during the maintenance phase, and the second individual had 4 bleeds during the maintenance phase. The 0-bleed proportion of all individuals was 75.0%, 73.3%, and 80.0%, respectively, in the consecutive 24-week

**TABLE 2** Bleeds before and during emicizumab therapy ($n$ = 112) according to age subgroups.

| | All ($n$ = 112) | | Adults/adolescents ($n$ = 80) | | Children ($n$ = 32) | |
|---|---|---|---|---|---|---|
| | Before | During | Before | During | Before | During |
| Total follow-up (person-y) | 131 | 96 | 81 | 67 | 37 | 29 |
| Follow-up (wk), median (IQR) | 56 (52-68) | 39 (19-58) | 53 (52-64) | 37 (17-56) | 67 (53-77) | 50 (29-63) |
| Total number of bleeds | 442 | 74 | 360 | 55 | 82 | 19 |
| ABR, mean (95% CI) | 3.6 (2.9-4.4) | 0.8 (0.6-1.1) | 4.0 (3.2-5.3) | 0.8 (0.6-1.2) | 2.3 (1.5-3.5) | 0.7 (0.4-1.2) |
| Total number of joint bleeds | 271 | 34 | 257 | 29 | 14 | 5 |
| AJBR, mean (95% CI) | 2.2 (1.8-2.8) | 0.4 (0.2-0.6) | 2.9 (2.3-3.9) | 0.4 (0.3-0.7) | 0.4 (0.2-0.7) | 0.2 (0.1-0.5) |
| Total number of muscle bleeds | 72 | 13 | 57 | 11 | 15 | 2 |

Only treated bleeds were considered.

ABR, annualized bleed rate; AJBR, annualized joint bleed rate; IQR, interquartile range.

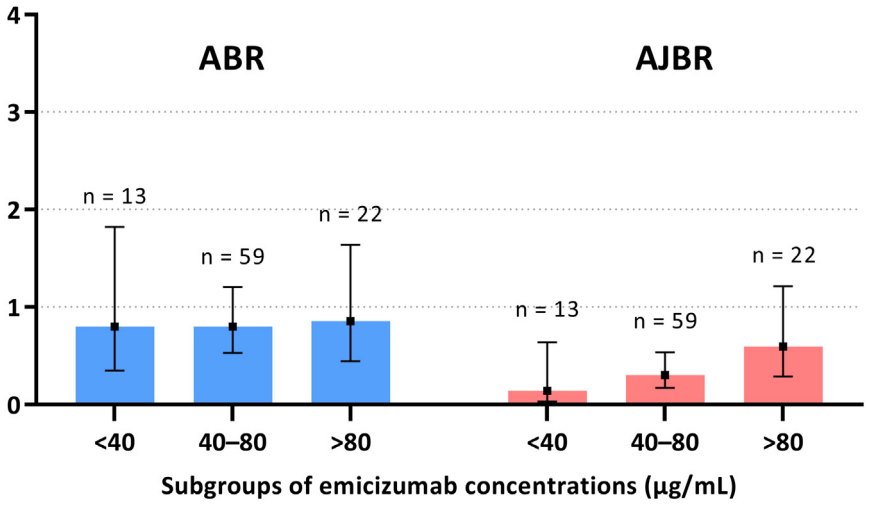



**FIGURE 4** The mean annualized bleed rates (ABRs) and annualized joint bleed rates (AJBRs) (95% CI) of only treated bleeds across the subgroups of the plasma concentration of emicizumab.

intervals. After the first 24-week interval, the proportion with >3 bleeds remained at 0% for all the consecutive 24-week intervals.

Owing to pain experienced during infusion of emicizumab, most children (*n* = 21, 66%) used a local anesthetic cream (EMLA) before the injection. Except for local pain, no adverse events of changes in the complete blood count and the renal function nor thromboses or losses of response were observed.

As presented in Figure 4, bleed rates (*P* = .997 and .863) and joint bleed rates (*P* = .354 and .148) were similar across the concentration subgroups of <40, 4 to 80, and >80 µg/mL. In addition, similar bleed rates were observed across the adherence, age, dosing interval, BMI, and FVIII inhibitors subgroups, which are presented in Supplementary Table 3.

### 3.4 | Drug waste

Compared with label-based dosing, the total drug waste avoided was 28,533 mg of emicizumab in the period studied, corresponding to a mean annualized drug waste of ∼260 mg per adult/adolescent or ∼200 mg per child. The mean relative drug waste was 9% per individual with a minimum of 0% and a maximum of 40%. The 18 individuals with a drug waste of ≥15% had a median body weight of 16 (13-23) kg and a median age of 4 years (IQR 2-7). These individuals (*n* = 8) were mostly prescribed dosing intervals of 21 days for entire-vial dosing.

## 4 | DISCUSSION

We demonstrated the efficacy of entire-vial dosing of emicizumab in 112 PwHA during 96 person-years. Real-world evidence demonstrated therapeutic plasma concentrations and good bleeding control. The drug waste was reduced by 9% after introduction of entire-vial dosing in our clinic, which was equal to a mean annualized drug waste of ∼260 mg per adult per year.

When emicizumab is dosed with 6 mg/kg every 4 weeks according to the drug label, the mean trough concentration is 38 µg/mL, midway 54 µg/mL, and peak 67 µg/mL, whereas weekly dosing intervals result in almost constant concentrations varying between 51 and 55 µg/mL [6]. Owing to the retrospective study design, the concentrations could not be classified as trough, midway, or peak concentrations. Nevertheless, the observed median concentration was 63 µg/mL and was 69 µg/mL in adults/adolescents, which indicates higher concentrations in this study than in the drug label [6]. Possibly entire vial dosing may have resulted in higher concentrations owing to the overfilling of vials. Indeed, regulators have recommended overfilling vials of liquid drug products because it may be difficult or impossible to remove 100% of the content from a vial. Regulators are concerned that manufacturers overfill vials without appropriate justification, which is not clear or made public for emicizumab vials [15]. Thus, the entire-vial dosing may have led to the administration of overfilled vials in our cohort, explaining the higher concentrations achieved in comparison to concentrations from the registration studies, and we recommend to measure a concentration when applying the entire-vial dosing strategy.

The within-individual variability observed (15% and 22%) is in line with previous studies [16] and may have originated from the undefined sampling times (trough-peak fluctuations) or/and (not reported) adherence issues. Based on clinical observation and emicizumab concentrations, the presence of anti-drug antibodies (ADAs) against emicizumab was not suspected in our cohort. This is in concordance with the low reported immunogenicity risk [17] and the current guidelines recommending emicizumab's concentration measurement in the absence of ADA-detection assays [18].

The bleed rates were reduced substantially before and during the emicizumab therapy and were more reduced in adults/adolescents than in children due to baseline imbalances (Supplementary Table 1).

Most children (*n* = 21, 66%) used a local anesthetic cream (EMLA) before the injection, which has not been reported in existing

literature. Except for local pain, there were no documented side effects: no cases of a declining pharmacokinetic profile or suspected ADAs, sudden or gradual loss of response, or thrombosis/thrombotic microangiopathy were reported at our center.

In several European countries, the drug waste of emicizumab accounted for 6% of its total cost for adolescents/adults and 26% for children [4]. The costs of emicizumab originate from the exorbitant acquisition costs/list pricing costs that are based on separate deals that countries have with the manufacturer, which is why even low drug waste has a considerable financial impact. We demonstrated 9% drug waste in this study, which is in line with previous studies that reported 8.4% for emicizumab and 7% to 9% for comparable drugs [19,20]. Furthermore, the 9% drug waste that was observed during this study was calculated based on the manufacturer's calculator and is probably higher in clinical practice, especially because the manufacturer prohibits combining 2 different strengths in 1 injection syringe, which often leads to a suggestion of at least 2 injections instead of 1 injection. Because this is very inconvenient for the recipient, the manufacturer's instructions are probably not adhered to in daily practice, which would implicate that larger vial sizes are used and even more of the drug is wasted, as has been suggested before [4].

Almost all self-reported nonadherent PwHA were teenagers. The injection avoidance might result from a combination of factors, including independence, risky behavior at that age, and painful experiences that might be linked to the high drug viscosity and/or to a lack of adipose tissue in male teenagers. Injection pain seemed an important issue because children had a low BMI and 66% used EMLA before injection [15]. The manufacturer's prohibition to combine 2 different strengths in 1 injection syringe, even when the maximum volume for subcutaneous administration (2 mL) is not exceeded, is pointless from a pharmacological perspective and leads to more painful injections per dose, and further reduces the user-friendliness of emicizumab. Fortunately, the forgiveness of poor adherence is higher for emicizumab than for factor replacement therapy because of the drug's long half-life and the high exposure that comes from label-based dosing. The absence of bleeding on emicizumab might encourage the PwHA to adopt new behaviors that may increase their risk profiles and potentially later lead to more trauma-related bleeds. Treating clinicians should be aware of this potentially changing profile and inquire about the individual's pain experience to assist with adequate treatment adherence.

The limitations of this study are typical to those of most retrospective observational studies, although prospectively registered data were used. For instance, ethnicity was not available as determinant in analysis. A limitation might be that the bleed rates we calculated during emicizumab in this study were overestimated. Selection bias might have been introduced because the need to start emicizumab prophylaxis quickly could have been higher in PwHA with insufficient bleeding control on previous therapy, which could have led to more bleeds for the early switchers in comparison to the later switchers. To overcome this effect, state-of-the-art bleed modeling was performed by using a negative binomial regression to account for some of the channeling effects (skewness of bleed data) [21], although the long-term data will be more accurate on bleeds during emicizumab. Furthermore, the bleed rates might have been overestimated because some PwHA experience pain and start episodic treatment immediately without an actual bleed occurring [22], and not all of the bleeds were verified by a clinician or were confirmed by imaging. Nevertheless, all the included bleeds were treated with FVIII/BPAs. This is relevant from a financial perspective, regardless of whether the bleed occurred. Therefore, this study does reflect the real-world setting after emicizumab's market entry.

For future research, we recommend investigating the role of the cost-efficient monitoring of emicizumab. First, the effectiveness plateau was set at >30 μg/mL, whereas most of the PwHA in this study (81%) had a concentrations of >40 μg/mL. Second, similar bleed rates were demonstrated in this study across the concentration subgroups of <40, 40 to 80, and >80 μg/mL. These 2 study findings suggest a highly variable dose–response relationship. When considered in this context, entire-vial dosing seems noncontroversial, and a more liberal dose range might be considered to allow whole-weekly intervals, without the need for monitoring emicizumab concentrations. Furthermore, these 2 study findings support dosing lower than 6 mg/kg/4 wk (or an equivalent mg/kg with shorter intervals) in a substantial proportion of PwHA. An intervention study is needed to confirm this hypothesis.

In conclusion, we evaluated the efficacy of entire-vial dosing of emicizumab in a large Dutch cohort of PwHA and observed therapeutic plasma emicizumab concentrations, good bleeding control, and a 9% reduction of drug waste. This real-world evidence supports entire-vial dosing as an attractive and practical option for clinicians who treat PwHA with emicizumab therapy.

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## AUTHOR CONTRIBUTIONS

All authors designed the study. A.A.M.T.D. and K.v.d.Z. collected data and performed data analyses, which K.F. critically reviewed. A.A.M.T.D. wrote the manuscript, which all authors critically revised and reviewed.

## RELATIONSHIP DISCLOSURE

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## SUPPLEMENTARY MATERIAL

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