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DosEmi study protocol: a phase IV, multicentre, open-label, crossover study to evaluate non-inferiority of pharmacokinetic-guided reduced dosing compared with conventional dosing of emicizumab in people with haemophilia A

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ABSTRACT

Introduction Emicizumab effectively prevents bleeding in people with haemophilia A (PwHA), but is a burden for national healthcare budgets and consequently may limit access. According to the drug label, dosing of emicizumab is based on body weight with fixed intervals of 7, 14 or 28 days, which leads to mean plasma concentrations of 55 µg/mL (SD 15 µg/mL). However, a moderate variability of concentrations and a minimal effective concentration of 30 µg/mL have been suggested in studies. Therefore, a dose of emicizumab that targets a trough concentration of 30 µg/mL is hypothesised to be equally effective as conventional dosing in the prevention of bleeding.

Methods and analysis We designed a phase IV, multicentre, open-label, crossover study to evaluate non-inferiority of bleed control of ≥6 months on conventional dosing in comparison to ≥6 months on dose intervention. This dose intervention consists of reducing the dose of emicizumab to target a trough concentrations of 30 µg/mL using individual pharmacokinetic (PK) parameters. Ninety-five PwHA aged >1 years who received conventional dosing of emicizumab for ≥12 months with good bleeding control during the last 6 months will be recruited from all Dutch haemophilia treatment centres. The study is powered to detect a clinically relevant decrease (risk difference) of 15% in the proportion of patients without treated bleeds during follow-up. Secondary endpoints are spontaneous joint or muscle bleeds, and annualised treated bleeding rates (using negative binomial regression). Cost-effectivity between conventional dosing and individualised PK-guided dosing of emicizumab will be compared.

Ethics and dissemination The DosEmi study was approved by the Medical Ethics Review Committee NedMec of the University Medical Center of Utrecht, The Netherlands. Study results will be communicated through publications in international scientific journals and presentations at (inter)national conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The DosEmi study is an investigator-driven, phase IV, open-label, crossover study including people with haemophilia A from all haemophilia centres in The Netherlands.

⇒ The study provides a unique opportunity to evaluate alternative emicizumab dosing strategies in a safe and well-controlled clinical setting.

⇒ Participation in the DosEmi study is expected to reduce the pain associated with emicizumab injections.

⇒ Sample size is relatively large for a rare disorder, requiring a labour-intensive multicentre design.

⇒ Potential participants may be reluctant to reduce dosing of effective treatment due to perceived risk of bleeds

INTRODUCTION

People with haemophilia A (PwHA) have a deficiency of coagulation factor VIII (FVIII) and present with spontaneous or provoked bleeds, predominantly into major joints leading to painful and chronic arthropathy.[1 2] The cornerstone in the management of haemophilia A is still self-administration of FVIII concentrates by intravenous injections.[3] These injections are two to seven times weekly to prevent bleeds (prophylaxis), or at the time of bleeding (on demand) when

prophylaxis is unavailable. Prophylaxis with FVIII concentrates has effectively reduced the number of treated bleeds from an annual mean of 20–30 to 1–4.[4–7] Additionally, anti-FVIII antibodies (known as inhibitors) render therapy with FVIII concentrates ineffective and develop in 30% of PwHA, who then require alternative, suboptimal therapies.[8]

The first globally approved non-factor therapy is the bispecific, FVIII-mimicking antibody, emicizumab (Hemlibra).[9] Emicizumab became available to PwHA with severe haemophilia A in the Netherlands in July 2020. This novel drug promotes effective haemostasis, regardless of inhibitor status, achieving complete eradication of treated bleeds in around 80% of PwHA (n=374) during the second 24-week interval of treatment.[10] More benefits of emicizumab are the subcutaneous and less frequent injections every 1, 2 or 4 weeks. Reported side effects are thrombotic microangiopathy or thrombotic events when concomitantly using activated prothrombin complex concentrates in doses over 100 IU/kg/day, which have not been observed since a change in guidelines for treatment of breakthrough bleeding.[10] Remaining side effects are the development of neutralising or clearing anti-drug antibodies (ADA) against emicizumab (<1%) and injection-site reactions.[10 11] Although many PwHA are candidates for prophylaxis with emicizumab, global access is limited due to the financial impact on healthcare budgets.

Emicizumab was approved with a loading dose of 3 mg/kg/week for 4 weeks and a maintenance dose of 1.5 mg/kg/week, 3 mg/kg/2 weeks or 6 mg/kg/4 weeks.[12] These dosing regimens were simulated in a pharmacometric approach, instead of a traditional dose-finding study, targeting a trough concentration (C_{trough}) of 45 μg/mL.[13] Dosing according to drug label leads to mean concentrations of 55 μg/mL with moderate variability of 66% of observations between 40 and 70 μg/mL.[12 14] Additional real-world evidence from the Netherlands demonstrated that entire-vial dosing led to even higher concentrations of 63 μg/mL with 81% of PwHA having concentrations >40 μg/mL.[15] In the meantime, the long-term bleed data from the phase III and IV studies were included in pharmacokinetic (PK) and pharmacodynamic (PD) modelling studies, and the minimal effective C_{trough} was suggested at 30 μg/mL.[14 16–18] Although this new target is substantially lower than the previous target, the dosing regimens in the drug label were not altered.

Concomitantly, reduced dosing of emicizumab, by 20–96%, without treated bleeds has been reported.[19] Consequently, we hypothesised that reducing the dose of emicizumab to target a C_{trough} of 30 μg/mL using individual PK is equally effective in the prevention of bleeding as conventional dosing. We designed the DosEmi study to investigate this hypothesis in a large cohort of adult and paediatric PwHA. Additional benefits from this intervention are less frequent injections or lower injection volumes. This is especially beneficial for children, as 66% used a local anaesthetic prior to injection to prevent pain at the injection site.[15] The DosEmi study will be conducted with intensive clinical and laboratory monitoring and is expected to result in significant healthcare savings and improved cost-effectiveness without loss of bleeding control. In this report, we publish the study protocol of the DosEmi study.

METHODS AND ANALYSIS
Primary objective
The primary objective of the DosEmi study is to determine whether individualised PK-guided dosing of emicizumab targeting a C_{trough} of 30 μg/mL is non-inferior to conventional dosing of emicizumab in the prevention of treated bleeds in people with congenital haemophilia A.

Eligibility
A participant must meet the following inclusion criteria: confirmed diagnosis of congenital haemophilia A with a baseline FVIII activity of <6 IU/mL (men), aged >1 year, receiving conventional dosing of emicizumab dosed according to label (±6 mg/kg per 4 weeks, rounded to entire vials) at one to four weekly intervals for a duration of ≥12 months prior to inclusion and demonstrating good bleeding control defined as (1) no spontaneous joint/muscle bleeds in the previous 6 months, and (2) a maximum of two treated (traumatic) bleeds in the previous 6 months.

Study design and setting
The DosEmi study is a multicentre, prospective, open-label, crossover study. It was designed as a non-inferiority study that was powered to detect a clinically relevant decrease of 15% (risk difference) in the proportion of patients without treated bleeds during follow-up (see Sample size). The non-inferiority margin is based on long-term bleed outcomes and clinical discussions with haemophilia physicians and patient representatives across the Netherlands.[10 15] The crossover intervention was chosen to account for potential imbalanced baseline characteristics, which might occur at treatment start (eg, different joint health), and to ensure comparability in an open-label setting.[20]

A schematic summary of the study design is shown in figure 1 and in more detail in online supplemental figure 1. The different phases depicted are a retrospective Clinical Phase, and a total prospective study duration of 18 months, which includes 6 months of bleeding assessment on conventional dosing, 6 months of PK-guided dosing and 6 months of dose continuation. The first participant was enrolled in September 2022 and total inclusions with sufficient follow-up time are expected to be reached in 2026.

The study is investigator-driven with the UMC Utrecht as study sponsor. The UMC Utrecht acts as coordinating centre and participants will be recruited from all Dutch haemophilia treatment centres, which are located in Amsterdam, Den Haag, Groningen, Leiden, Maastricht,
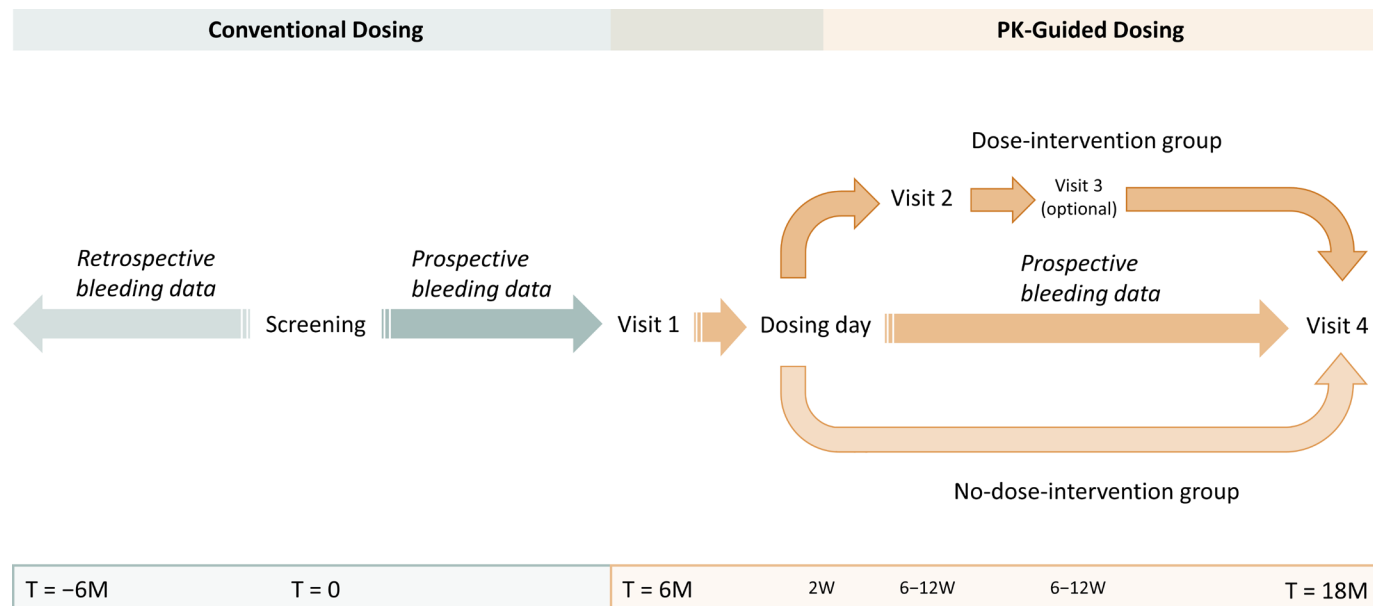
Figure 1 DosEmi study design. M, months; PK, pharmacokinetic; W, weeks.

Rotterdam, Utrecht, Nijmegen and Eindhoven. All sites were involved in the design of the study and have personnel with the expertise to assess bleeds, examine joint health, assist in questionnaires and perform clinical and laboratory monitoring. Day-to-day activities of the study are performed by the principal investigator (study supervision and medical responsibility), study coordinator (trial registration, coordinates study visits, annual safety reports), study physicians (identify potential participants, obtain informed consent, ensure follow-up according to protocol) and data manager (supports in data capture, safeguards quality of data). The study team of the coordinating centre meets weekly. A multidisciplinary study steering committee has been installed, consisting of (but not limited to) haemophilia clinicians, pharmacists, representative from the Dutch Haemophilia Patients Organisation and the SYMPHONY consortium for valued based healthcare support and PK guidance.[21] Study monitoring will be performed by a professional contract research organisation (Julius Clinical, Zeist, the Netherlands). The monitoring plan is available on request. Furthermore, the Board of Dutch Haemophilia Treaters (NVHB) and the Steering Committee will act as Scientific Advisory Committee and periodically review study results and safety data. Unblinding and randomisation procedures are not applicable due to the type of intervention, self-treatment and the crossover design of the study.

Patient and public involvement

A representative from the Dutch Haemophilia Patients' Organisation (NVHP) has been involved in grant applications, study design and protocol drafting. As a member of the multidisciplinary study steering committee, he will be a full author on any publications originating from this project. This study is supported by the Dutch federation of academic hospitals.

Intervention

The following will be compared within each participant:
► Comparator: 6 months of conventional dosing of emicizumab (ie, 6 mg/kg per 4 weeks at individualised one to four weekly intervals).
► Intervention: 12 months of individualised PK-guided dosing of emicizumab to achieve a target C_{trough} of 30 µg/mL (range 25–35 µg/mL).

The research pharmacists of the SYMPHONY consortium will provide a PK-guided dose advice based on a maximum a posteriori (MAP) Bayesian analysis of the individual observed concentration using an online platform https://opticlot.nl.[21 22] MAP Bayesian will be performed using NONMEM software (V.7.4.1, Icon Development Solutions, Gaithersburg, Maryland, USA). Population PK parameters will be used as reported by Retout et al.[18] The patient variables (ie, body weight, height, age and serum albumin) will be included in the PK simulations. A dose advice consists of: a lag-time period providing a restart date for new dosing, a dose in entire vials and a dosing interval. The research pharmacists will also provide a window for the next C_{trough} measurement, to check if the target C_{trough} is reached following the intervention. In general, this will be done after one or two half-lives (i.e. 30–60 days) based on the C_{trough}. Both a target C_{trough} between 25 and 35 µg/mL, as well as a varying dosing interval between 7 and 42 days, are allowed to enable use of entire vials only. The maximum dose-reduction at each step will be 50%, and doses will be increased if the new $C_{troughs}$ is less than 25 µg/mL. The target C_{trough} between 25 and 35 µg/mL reflects the target for the PK model; while during the dose intervention, C_{trough} between 25 and 39 µg/mL in individual participants will be accepted. The

dose advice also takes individual preference in dosing interval and maximum injection volume of 2 mL/dose into account.

Outcomes
Primary outcome
The proportion of patients without treated bleeds during 6 months on conventional dosing (comparator) compared with 6 months on individual PK-guided dosing (intervention).

Secondary outcomes
The secondary outcomes on bleeds are:
► The proportion of patients without treated bleeds in the follow-up periods of 12 months on conventional dosing in comparison to 12 months on individual PK-guided dosing.
► The proportion of patients without spontaneous joint or muscle bleeds in the periods of 6 and 12 months on conventional dosing in comparison to the 6 and 12 months on individual PK-guided dosing, respectively.
► Annualised bleed rates of treated bleeds, including joint bleeds and sports induced bleeds in the periods of 6 and 12 months on conventional dosing in comparison to the 6 and 12 months on individual PK-guided dosing, respectively.

Other secondary outcomes are: Health-related quality of life (HR-QoL), maintenance of stable joint health and sports participation will be compared before and after the dose intervention, reduced pain due to emicizumab injections, the performance of the population PK model, the cost-effectiveness, thrombin generation parameters as PD biomarkers for emicizumab treatment efficacy.

Assessments
The study design is shown in figure 1, online supplemental figure 1 and the schedule of all assessments over time is presented in online supplemental table 1. If inclusion criteria are met and informed consent is signed, the retrospective data on bleeds during the 6 months prior to inclusion will be collected (Clinical Phase (non-study, used for inclusion criterion)). On inclusion in the DosEmi study, participants will be monitored for a period of 6 months to prospectively assess bleeds (Bleeding Assessment Phase). During the following phase, participants are categorised into the 'Dose Intervention Group' when plasma emicizumab concentrations at visit 1 are ≥40 μg/mL, or the 'No Dose Intervention Group' when emicizumab plasma levels are <40 μg/mL.

The Dose Intervention Group undergoes individualised PK-guided dosing of emicizumab at 2–3 weeks after Visit 1 (Dosing Day). The emicizumab concentration is checked again on Visit 2, and if the target concentration was not reached the (optional) Visit 3 is planned to check emicizumab concentration after the second dose adjustment. Participants will be followed for 6 months after Visit 1 (PK-guided Dosing Phase), after which the participants continue with their PK-guided dosing regimen for

another 6 months (Dose Continuation Phase). Thus, a total of 12 prospective months of follow-up on PK-guided dosing regimen per participants are obtained.

The Non-Intervention Group includes two groups for observational data collection. Participants with an emicizumab plasma concentration 25–39 μg/mL at Visit 1 will continue on their current dose regimen and will be followed according to the same assessment schedule as the Intervention Group, except for Visit 2. These participants will be followed for 12 months in total to collect additional data on bleeding according to emicizumab concentrations. Participants with emicizumab C_{trough} concentrations <25 μg/mL at Visit 1 will be monitored closely by their treating physician, and may receive increased emicizumab dosing at the discretion of their treating physician. Since treatment of these PwHA (emicizumab C_{trough} <25 μg/mL) is outside the scope of this study (ie, dose reduction intervention), these PwHA will not perform Visit 2 through Visit 4. However, to follow-up on safety, we will continue to collect available selective safety data, such as bleed assessment and the presence of ADA, for these PwHA for a period of 12 months.

The study is designed with two age-based cohorts consisting of participants aged ≥16 years (Cohort 1) and aged <16 years (Cohort 2). After a total of 25 participants from Cohort 1 have completed 6 months of follow-up on PK-guided dosing, data on bleeding will be analysed and the power calculation will be repeated to provide a more precise estimate of the number of participants required for the study. Data of this interim analysis will be reviewed by the Scientific Advisory Committee (NVHB and Steering Committee). Enrolment of paediatric participants of Cohort 2 can start if bleed control in these 25 participants of Cohort 1 participants is good according to definitions in the inclusion criteria, combined with a maximum of one additional bleed in 6 months.

Discontinuation of study
Criteria for discontinuation are withdrawal of consent (at any time for any reason), development of a medical condition that precludes participation and/or is associated with increased bleeding risk (eg, other bleeding disorders), formation of neutralising or clearing ADA against emicizumab, occurrence of a spontaneous joint or muscle bleed or >2 treated bleeds during 6 months as determined by the investigator or haemophilia treating physician, persistent non-adherence to protocol requirements or loss to follow-up. Withdrawn participants during the Bleeding Assessment Phase may be replaced to reach the required sample size. All efforts will be made to complete and report the protocol-defined study observations up to the time of the participant's withdrawal as completely as possible. No further data will be collected after the moment of withdrawal, except for withdrawal due to ADAs after which selective safety data will be collected, and discontinuation of emicizumab treatment, after which one last contact moment will be arranged.

Participant recruitment and retention

As haemophilia is a lifelong condition, PwHA remains in care at their haemophilia treatment centres. Recruitment is based on both information provided in ongoing conversations with their haemophilia treating team and information provided by the patient society (NVHP) which is represented in the Steering Committee. No specific measures for patient retention during follow-up are in place.

Sample size

The power calculations are based on the ability to detect a clinically relevant difference between the groups before and after the dose intervention in the proportion of participants without treated bleeding. The treatment centres and study group reached consensus on an expected response of 80% without treated bleeds in both groups before and after dose intervention and a non-inferiority margin of 15% (ie, risk difference).[10] A required inclusion of 88 participants results from sample size calculations with settings of a non-inferiority test, crossover design, binary data, 80% power, one-sided alpha 0.05, non-inferiority margin 0.15 and expected response in both groups 0.8 https://app.sampsize.org.uk. To account for possible drop-out, we will aim for inclusion of 95 participants. The power calculation will be repeated after the first 25 participants have completed 6 months of follow-up after the dose intervention.

Recruitment

Potential participants, who meet the inclusion criteria, will be informed about the DosEmi study by their treating physician. To allow sufficient time for consideration, the informed consent procedure will be executed after a minimum of 1 weeks' delay of the formal invitation and opportunity to ask questions regarding the Informed Consent.

Data collection and management

All study data will be entered in the Good Clinical Practice (GCP) compliant electronic Case Report Form (eCRF) system Castor.[23] The medical data will be collected during study visits and monthly contact. The primary source for medical data is the electronic medical record system of the hospitals. Blood samples for routine checks will be measured locally at the laboratories of the hospitals. The blood samples for emicizumab concentration and thrombin generation will be measured centrally in the UMC Utrecht by ISO-certified laboratories. The emicizumab concentration will be measured using a validated liquid-chromatography tandem mass spectrometry method.[24 25] Plasma coagulation potential will be measured using thrombin generation tests as a potential read-out for pharmacodynamics. Joint status will be measured by physical examination (Haemophilia Joint Health Score),[26–28] ultrasound (if available, according to the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD US) score).[29] HR-QoL will be assessed with EQ5D(Y)-3L,[30–32] and PROMIS (Patient-Reported Outcomes Measurement Information System) instruments (Physical Function/mobility and Pain Interference short forms).[33–35]

Assessment of pain during emicizumab administration will be scored with the Visual Analogue Scale. Sports participation (type, duration, frequency) will be assessed with Modifiable Activities Questionnaire.[36 37] These QoL-questionnaires (ie, total of 34 questions per visit) will be sent out electronically via Castor.

A data management plan is generated to describe data collection, handling, storage and back-up, analysis, archiving and sharing. Participants will be assigned a unique study number, stored according to GCP requirements. All data will be reported at group level. As the data is privacy-sensitive, we publish the descriptive metadata, as soon as legally and ethically possible, in the data repository with a description of how a data request can be made (by sending an email to the corresponding author). In the event that peers like to reuse our data this can only be granted if the research question is in line with the original informed consent signed by the study participants. Every application therefore will be screened on this requirement. If granted, a data usage agreement is signed by the receiving party.

Statistical methods

All analyses will be performed by within-patient comparisons using paired tests. All participants receiving dose reduction will be included in the statistical analyses, merging data of Cohort 1 and Cohort 2. Primary and secondary outcomes on proportion of bleeds will be analysed with McNemar test one-sided p value threshold 0.05. The treated annualized (joint) bleeding rates (mean and 95% CIs) will be modelled with negative binomial regression.

Data from withdrawn participants with at least one concentration sample available can be included in the analysis. Treatment adherence will be assessed by the percentage of vials distributed by the hospital pharmacy versus prescribed by physician. The percentage of vials taken will be calculated as: $100 \times$ (total number of vials administered) / (total number of vials prescribed). The percentage of vials taken will be summarised descriptively as quantitative variables. The number and percentage of participants whose treatment compliance is <80% or ≥80% will be summarised. Available data of non-adherent participants will be included in the analysis of bleeding according to emicizumab concentration. Missing data on emicizumab concentrations or bleeding will not be imputed nor analysed.

Safety

The collection of adverse events (AEs) will be limited to AEs of special interest (AESI). The AESIs include bleeds (ie, trauma-related or spontaneous), haemophilia-related events (such as inhibitor development or pain), thromboembolic events (arterial, venous, catheter related and thrombotic microangiopathy) and development of neutralising ADAs. Recording of serious AEs (SAEs) will be restricted to SAEs of special interest (SAESI) as well. The SAESI will be immediately reported to the coordinating investigator and announced to the Medical Ethics Review Committee of the UMC Utrecht.

ETHICS AND DISSEMINATION

The protocol of the DosEmi Study was approved by the MERC NedMec of the UMC Utrecht (local study registration number NL81112.041.22) in July 2022. Approval by the local MERCs of participating centres is requested/pending. All substantial amendments to the protocol will be notified to the MERC and competent authority. Non-substantial amendments will be recorded and filed by the coordinating investigator. All participants or their guardians will be asked to provide written informed consent to participate in the study. All study procedures will be performed in accordance with the ethical standards of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO).

Results from this study will be analysed and submitted for publication in peer-reviewed international scientific journals and presented at scientific meetings. The coordinating investigator will initiate these scientific activities. There are no restrictions regarding the public disclosure and publication of the research data. The study was registered in the public trial registries of EUDRACT (included in the WHO registry and accepted by all major international medical journals) and the competent authority, prior to inclusion of the first participant.

DISCUSSION

Individualised dosing of emicizumab based on a target C_{trough} of 30 µg/mL is hypothesised to be equally as effective in the prevention of bleeds as conventional dosing. Besides the benefits for participants (ie, less frequent injections and/or with lower volume), this PK-guided dosing is expected to result in significant healthcare savings and improved cost-effectiveness without loss of bleeding control. The DosEmi Study has enrolled its first participant in September 2022.

Our study is supported by several reports on reduced dosing of emicizumab without loss of efficacy. Reported first was a case of a boy in whom higher emicizumab concentrations of ~90 µg/mL were associated with more episodes of pain in muscles and joints.[38] The dose was reduced to result in emicizumab concentrations of ~24 µg/mL, after which the pain resolved and no bleeds occurred during the following 6 months. Subsequently, emicizumab was given in lower doses in 11 PwHA from Finland and 6 PwHA from Thailand without loss of efficacy.[19 39] Additionally, real-world evidence from our centre demonstrated similar bleed rates across the concentration subgroups of <40 µg/mL (n=13), 40–80 µg/mL (n=59) and >80 µg/mL (n=22).[15] We assume that, in clinical practice, many others dose emicizumab in a reduced form without publishing the results, especially as global access is limited.[40]

There are limitations and strengths to the DosEmi Study. The sample size is relatively large for a rare disorder, requiring a labour-intensive multicentre design. Furthermore, recruitment of paediatric participants may be difficult[41] and potential participants may be reluctant to reduce dosing of an effective treatment. Nevertheless, the study provides a unique opportunity to evaluate alternative dosing strategies in a safe and well-controlled clinical setting. Additionally, the opportunity for patients (especially children) to receive fewer painful emicizumab injections is provided. This study can eventually provide meaningful conclusions that benefit the global application of reduced dosing.

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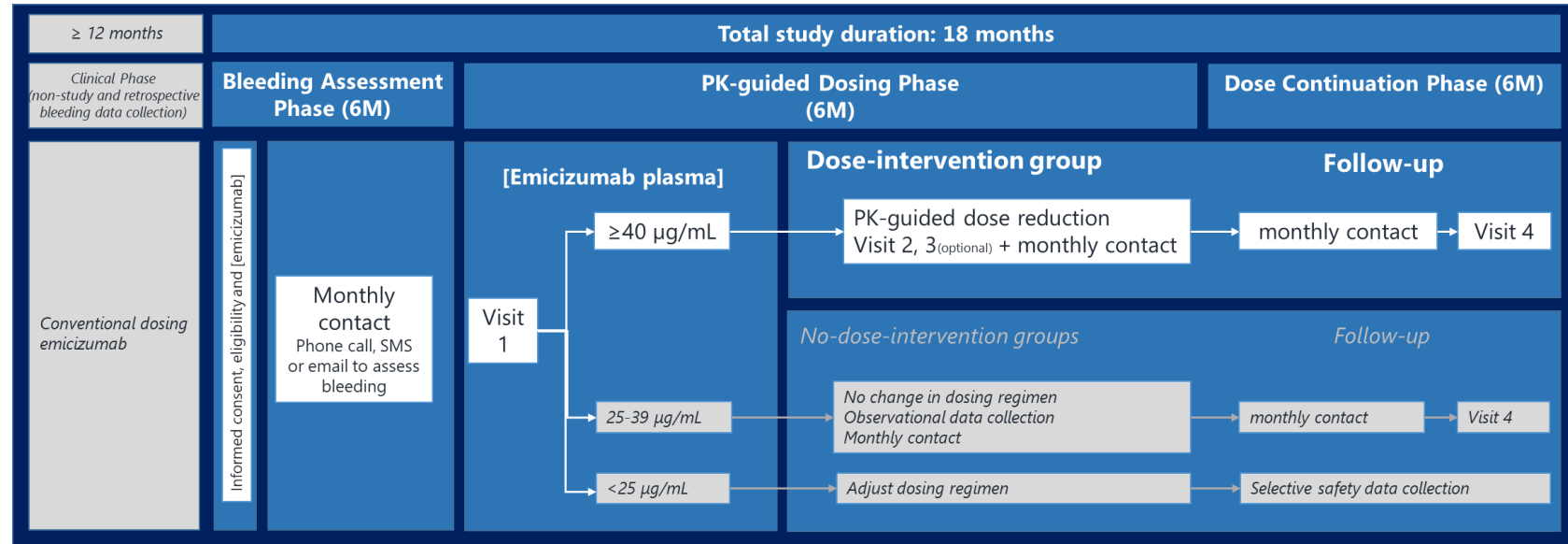
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SUPPLEMENTARY

Supplementary Figure 1. DosEmi study design in detail

Supplemental material

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Supplementary Table 1. Schedule of Assessments

Visit	Clinical Phase (6M) N/A	Bleed Assessment Phase (6M) Screening	Monthly contact[a]	PK-guided Dosing Phase (6M) Visit 1	Dosing Day (phone call)	Visit 2[b]	Visit 3[c] Optional	Monthly contact[a]	Dose Continuation Phase (6M) Visit 4	Selective Safety Data Collection[d]
Timing relative to Visit 1	-12M	-7M to -6M	-5, -4, -3, -2, -1M	NA	+ 2-3 weeks	+ 6-12 weeks	+6-12 weeks	Monthly if no site visit	12 ±1 months	Up to +12 months
Procedures										
Informed consent		X								
Assessment of eligibility		X		X						
Demographics				X						
Weight				X					X	
Height				X					X	
Medical history				X						
Concomitant medication				X						
Bleeding assessment - Medical chart - VastePrik/HemoNED	X retrospective	X	X		X	X	X	X	X	X
Emicizumab parameters — Serum albumin				X routine						
Emicizumab parameters — Emicizumab plasma concentration[e]				X		X	X		X	
Emicizumab parameters — Anti-drug antibodies							If conc < expected		If conc < expected	
Coagulation potential/ thrombin generation				X		X	X		X	

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Visit	Clinical Phase (6M)	Bleed Assessment Phase (6M)		PK-guided Dosing Phase (6M)					Dose Continuation Phase (6M)	
	N/A	Screening	Monthly contact[a]	Visit 1	Dosing Day (phone call)	Visit 2[b]	Visit 3[c] Optional	Monthly contact[a]	Visit 4	Selective Safety Data Collection[d]
Timing relative to Visit 1	-12M	-7M to -6M	-5, -4, -3, -2, -1M	NA	+ 2-3 weeks	+ 6-12 weeks	+6-12 weeks	Monthly if no site visit	12 ±1 months	Up to +12 months
HR-QoL questionnaires - EQ5D(-Y) - PROMIS Pain Interference-SF - PROMIS Physical Function/Mobility- SF Sports participation MAQ - Administration pain (VAS)				X		X			X	
Biomarkers joint, cartilage and inflammation[f] - Urine & Blood				X		X (or Visit 1)			X	
Joint health HJHS				X		X (or Visit 1)			X	
Joint health ultrasound (Head US)[g]				X		X (or Visit 1)			X	

SUPPLEMENTARY

[a]Monthly contact by phone call, SMS or email depending on subjects' preference. In addition to information on bleeds and (sports related trauma, data will be collected on number of (emergency) hospital visits, bleeding related hospital admissions and/or unscheduled surgeries, and days lost from work/school (for patients and/or caregivers).

[b]Timing of blood withdrawal is determined based on advice of the research pharmacist. See section 3.6 for more information.

[c]Optional visit. Only applicable if emicizumab plasma target concentrations of 25-39 μg/mL was not reached at Visit 2.

[d]Selective Safety Data Collection will only be performed for subjects with low emicizumab C_{trough} levels (<25μg/mL), who will continue dose increase in a clinical setting according to local protocol (outside this study). Only available data will be collected so no scheduled study visits will be performed.

[e]Emicizumab plasma concentrations of the subjects at all participating sites will be measured at the UMC Utrecht.

[f]Urine and blood sampling for biomarkers to be performed at the same day as HJHS and HEAD US – if applicable (see g)

[g]Only applicable if Head US is available at the participating site. To be performed at same day as HJHS and biomarker sampling.