# Pharmacokinetic-guided dosing of emicizumab in congenital haemophilia A patients - The DosEmi study

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This study has been transitioned to CTIS with ID 2024-515528-35-00 check the CTIS register for the current data. Primary objectiveTo determine whether individualized pharmacokinetic (PK)-guided dosing of emicizumab is non-inferior to conventional...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Blood and lymphatic system disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56007

**Source**
ToetsingOnline

**Brief title**
DosEmi study

### Condition

- Blood and lymphatic system disorders congenital

**Synonym**
Bleeding disorder, FVIII deficiency

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Emicizumab, Haemophilia A, Pharmacokinetic-guided dosing

## Outcome measures

### Primary outcome

The primary outcome parameter is bleeding, defined as:

1) Proportion of patients without treated bleeds (6 months Bleeding Assessment Phase versus 6 months PK-Guided Dosing Phase).

### Secondary outcome

The secondary outcome are defined as:

1. Proportion of patients without treated bleeds (12 months Clinical Phase+Bleeding Assessment Phase versus 12 months PK-guided Dosing Phase+Dose Continuation Phase)

2. Proportion of patients with spontaneous joint- or muscle bleeds (6 months Bleeding Assessment Phase versus 6 months PK-Guided Dosing Phase).

3. Proportion of patients with spontaneous joint- or muscle bleeds (12 months Clinical Phase+Bleeding Assessment Phase versus 12 months PK-guided Dosing Phase+Dose Continuation Phase).

4. Annualized bleeding rate (ABR) of treated bleeds, including joint bleeds and sports induced bleeds ((6 months Bleeding Assessment Phase versus 6 months PK-Guided Dosing Phase).

5. Annualized bleeding rate (ABR) of treated bleeds, including joint bleeds and sports induced bleeds (6 months retrospective + 6 months prospective data (Clinical Phase+Bleeding Assessment Phase) versus 12 months prospective data of PK guided dosing (PK-guided Dosing Phase+Dose Continuation Phase).

6. Cost-effectiveness between 6 months of conventional dosing (Bleeding Assessment Phase) and 6 months of individualized PK-guided dosing of emicizumab (PK-Guided Dosing Phase):

7 Direct and indirect medical costs:

7.1 Direct medical costs are predominantly determined by consumption of emicizumab, additional FVIII, and/or bypassing agents, extracted from the hospital*s pharmacy records. These data are highly reliable, as this medication is exclusively distributed by haemophilia treatment centers.

7.2 Indirect medical costs: are number of (emergency) hospital visits, bleeding related hospital admissions and/or unscheduled surgeries, and days lost from work/school (for patients and/or caregivers).

8. Predictive performance of the MAP Bayesian procedure used for the dose adaptation procedure, defined as % of patients within ±20% of within the target level of 20-39 µg/mL of emicizumab. All emicizumab plasma levels will be determined in the laboratory of the University Medical Center Utrecht using a specifically developed LC-MS/MS.

9. Joint status as measured by physical examination (Haemophilia Joint Health Score; HJHS), ultrasound (if available, according to the HEAD US score) and biomarkers of bone and cartilage turnover.

10. Health related quality of life will be assessed with EQ5D(Y) (5 questions), and PROMIS instruments (Physical Function/mobility and Pain Interference short forms) (8 questions each).

11. Assessment of pain during emicizumab administration by Visual Analogue Scale (VAS).

12. Sports participation (type, duration, frequency) will be assessed with

Modifiable Activities Questionnaire (MAQ).

13. Plasma coagulation potential will be measured with thrombin generation

tests as a potential read-out for pharmacodynamics.

14. Assessment of the cumulative number of sc. and/or iv. Injections related to

coagulation correction.

# Study description

**Background summary**

Haemophilia A is a coagulation disorder that is caused by a reduced or malfunctioning of coagulation factor FVIII. Patients with severe haemophilia suffer from spontaneous or trauma induced bleeds, mainly targeted in joints and muscles. In life-time, this can result in development of invalidating arthropathy, reduced quality of life, increased risk for brain hemorrhages and early death.

Clinical management of haemophilia therefore is focussed on prevention of bleeds and thereby preventing the development of arthropathy. For many decades, patients have been treated with intravenous administration of FVIII concetrates in order to prevent bleeds (prophylaxis) or incendentally (on demand). Prophylactic treatment with FVIII concetrates has been shown to be very effective in prevention of bleeds. However administration may be very burdensome for patients or his parents. Since it encounters intravenous administration for 2-6 times per week. Therapy is usually start at young age, when children start crawling.

Emicizumab is the first commercially available non-factor replacing product that can be administered subcutaneously. It is a recombinant, humanized, bi-specific monoclonal antibody that restores function of missing activiated FVIII by bridiging activated FIX and FX to facilitate effective hemostasis in patients with haemophilia A. Due to long half-life properties of emicizumab of 30 days, admistration intervals can be expanded.

The standard dose of pharmaceutical company Roche is based on body weight and results in Ctrough levels of 50µg/mL. This does not take in account the inter-individual differences. Based on the results of the phase I-III studies,PK/PD studies and our own experience the current dose seems

unecessarily high. Our model showed that Ctrough levels of 30µg/mL may be equally effective but less costly in prevention of bleeds compared to conventional dosing. We expect that individualized pharmacokinetic-based dosing of emicizumab with intensive monitoring of both clinical and laboratory parameters, will lead to significant reduction of healthcare cost and improve cost-effectiveness, without posing patients at risk of developing bleeds

## Study objective

This study has been transitioned to CTIS with ID 2024-515528-35-00 check the CTIS register for the current data.

Primary objective
To determine whether individualized pharmacokinetic (PK)-guided dosing of emicizumab is non-inferior to conventional dosing of emicizumab in the - proportion of patients without treated bleeds (6 months before and after intervention)

Secondary objective:
- Proportion of patients without treated bleeds (12 months before and after intervention)
- Proportion of patients without spontaneous joint- or muscle bleeds (6 and 12 months before and after intervention)
- Annualized bleeding rate (ABR) of treated bleeds, including joint bleeds and sports induced bleeds (6 and 12 months before and after intervention).
- To compare cost-effectiveness between conventional dosing and individualized PK-guided dosing of emicizumab
- To assess the performance of the population PK model
- To investigate whether joint health remains stable when switching to lower-dosed emicizumab treatment
- To investigate whether Health Related Quality of Life (HR-QoL) and sports participation are similar in patients receiving conventional dosing compared with PK-guided dosing of emicizumab
- To investigate whether thrombin generation parameters can be used as a pharmacodynamic (PD) biomarker for emicizumab treatment efficacy
- To assess and monitor pain during emicizumab administration
- To assess the cumulative number of coagulation factor (sc. and/or iv.) of per year.

## Study design

DosEmi study is a multicentre, prospective, open-label, crossover study with >=6 months follow-up on conventional dosing and 12 months follow-up on PK-guided dosing. It was designed as a non-inferiority study powered to detect a 15% clinically relevant decrease in the proportion of patients without treated bleeds during follow-up.The crossover design was chosen to account for

potential imbalanced baseline characteristics, which might occur at treatment start (instable joint health).

Total study duration is 18 months. The study comprimes of 3 phases:
1. Bleeding Assesment Phase (6months): study participants remain at their conventional emicizumab dose and register bleeds
2. PK-guided Dosing Phase (6 months): Depending on emicizumab plasma levels during conventional dosing, a PK-profile will be generated based on a validated maximum a posteriori Bayesian model. During follow-up, patients will be screened for bleeds, joint status and quality of life.
3. Dose Contination Phase (6 months): During the last phase patients dose will be continued according to previous established PK profile in the visits 1 2 or 3. In this phase dose will not be adjusted, patients will be screened for bleeds joint status and quality of life.

In addition to the study, retrospective data collection on bleeding will be performed 6 months prior to inclusion (Clinical Phase).

**Intervention**

The intervention consist of 12 months PK-guided dosing of emicizumab targeted a a Ctrough of 30 µg/mL (± 15 %).

Based on emicizumab levels during visit 1, there a 3 groups:
Intervention group:
- Subjects with emicizumab >= 40 µg/mL: dose will be adjusted using PK-guided dosing of emicizumab targeted at a Ctrough of 30 µg/mL

Non-Intervention group:
- Emcizumab levels 25-39 µg/mL: dose will not be adjusted and study participants continue in follow-up
- Emicizumab levels < 25 µg/mL: dose will be adjusted. Subjects will discontinue from the study no schedules study visits will be performed. Subjects are followed for Selective Safety Data Collection

**Study burden and risks**

Study specific burden consist of:
- 1 or 2 study specific visits in treatment centre (Visit 2 and Visit 3 if applicable); the other visits coincide with visits of standard care
- Monthly contact with researcher for bleeding registration
- Three times completetion of questionnaires (34 questions; 15min per visit)
- Blood- and urine collection at Visit 1 or 2 and 4. Blood collection volume remains beneath maximum allowed for all ages.
- Two times joint status assesment using HJHS and ultrasound

Haemophilia patients are familair with regular blood withdrawal, bleedingregistration, HJHS and ultrasounds.
Based on the results of phase I - III studies and our own experience, we expect that reduction of emicizumab dose to Ctrough target levels of 30u/ml, will cause neglegible or limited risk of increased bleeding. Study participants will be screened for potential bleeding regulary. Furthermore there are strict withdraw rules that have been defined, see protocol 6.4.1.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)

## Inclusion criteria

- Confirmed diagnosis of congenital haemophilia A, with a baseline endogenous FVIII of <6 IU/mL; - Aged > 1 year at inclusion - Receiving conventional dosing of emicizumab (6 mg/kg/4 weeks with varying intervals) for a duration of at least 12 months prior to inclusion; - Having good bleeding control, defined as: i. No spontaneous joint/muscle bleeds in the previous 6 months AND ii. A maximum of two treated (traumatic) bleeds in the previous 6 months. - Willing and able to provide written informed consent, either by the subject or its parents/legal guardian - Willing to provide bleeding assessment information - Willing to adhere to the medication regimen

## Exclusion criteria

Acquired haemophilia A

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Prevention |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 05-09-2022 |
| Enrollment: | 95 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Hemlibra |
| Generic name: | Emicizumab |

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| Registration: | Yes - NL intended use |

## Ethics review

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| Approved WMO Date: | 24-06-2022 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 19-12-2022 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 11-01-2023 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 22-05-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 24-08-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 26-04-2024 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 07-05-2024 |
| Application type: | Amendment |
| Review commission: | METC NedMec |

## Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2024-515528-35-00 |
| EudraCT | EUCTR2021-004039-10-NL |
| CCMO | NL81112.041.22 |