Design of a prospective study on pharmacokinetic-guided dosing of prophylactic factor replacement in hemophilia A and B (OPTI-CLOT TARGET study).


Affiliations below.

DOI: 10.1055/a-1760-0105

Please cite this article as: Goedhart T M, Bukkems L, Coppens M et al. Design of a prospective study on pharmacokinetic-guided dosing of prophylactic factor replacement in hemophilia A and B (OPTI-CLOT TARGET study). . TH Open 2022. doi: 10.1055/a-1760-0105

Conflict of Interest: see manuscript

This study was supported by Innovatiefonds Zorgverzekeraars (http://dx.doi.org/10.13039/501100009248), Project 3216, Nederlandse Organisatie voor Wetenschappelijk Onderzoek (http://dx.doi.org/10.13039/501100003246), NWA.1160.18.038

Trial registration: NTR7523, Netherlands National Trial Register (http://www.trialregister.nl), Prospective cohort study

Abstract:
In resource rich countries, almost all severe hemophilia patients receive prophylactic replacement therapy with factor concentrates to prevent spontaneous bleeding in joints and muscles, to decrease the development of arthropathy and risk of long-term disability. Pharmacokinetic (PK)-guided dosing can be applied to individualize factor replacement therapy, as interindividual differences in PK parameters influence factor VIII (FVIII) and factor IX (FIX) activity levels. PK-guided dosing may therefore lead to more optimal safeguarding of FVIII/FIX levels during prophylaxis and on demand treatment. The OPTI-CLOT TARGET study is a multicenter, non-randomized, prospective cohort study that aims to investigate the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B patients in daily clinical practice. At least 50 patients of all ages on prophylactic treatment using standard half-life (SHL) and extended half-life (EHL) factor concentrates will be included during nine months and will receive PK guided treatment. As primary endpoint, a minimum of four FVIII/FIX levels will be compared to FVIII/FIX levels as predicted by Bayesian forecasting. Secondary endpoints are the association of FVIII and FIX levels with bleeding episodes and physical activity, expectations and experiences, economic analyses and optimization of population PK models. This study will lead to more insight in the reliability and feasibility of PK-guided dosing in hemophilia patients. Moreover, it will contribute to personalization of treatment by greater knowledge of dosing regimens needed to prevent and treat bleeding in the individual patient and provide evidence to more clearly associate factor activity levels with bleeding risk.

Corresponding Author:
Tine M Goedhart, Erasmus MC Sophia Children Hospital, Department of Pediatric Hematology, Rotterdam, Netherlands, m.c.h.j.goedhart@erasmusmc.nl

Affiliations:
Tine M Goedhart, Erasmus MC Sophia Children Hospital, Department of Pediatric Hematology, Rotterdam, Netherlands
Laura Bukkems, Amsterdam University Medical Centres, Hospital Pharmacy - Clinical Pharmacology, Amsterdam, Netherlands
Michiel Coppens, Amsterdam UMC Locatie AMC, Internal Medicine, Amsterdam, Netherlands

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Design of a prospective study on pharmacokinetic-guided dosing of prophylactic factor replacement in hemophilia A and B (OPTI-CLOT TARGET study)


*Shared first and last authorships.

1Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children’s Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands; 2Department of Clinical Pharmacology - Hospital Pharmacy, Amsterdam UMC, University of Amsterdam, Amsterdam; 3Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; 4Pediatric Hematology, Amsterdam UMC, Emma Children’s Hospital, University of Amsterdam, Amsterdam, the Netherlands; 5Department of Hematology, Radboud University Medical Center, Nijmegen, and the Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, the Netherlands; 6Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands; 7Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; 8Department of Hematology, Maastricht University Medical Center, Maastricht, the Netherlands; 9Department of Hematology, Haga Hospital, The Hague, Netherlands; 10Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; 11Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; 12Department of Clinical Pharmacology - Hospital Pharmacy, Amsterdam UMC, University of Amsterdam, Amsterdam.
Keywords

hemophilia, pharmacokinetics, factor VIII, factor IX, prophylaxis

Correspondence to:

M. H. Cnossen, MD, PhD
Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children’s Hospital, University Medical Center Rotterdam
P. O. Box 2040
3000 CA Rotterdam, the Netherlands
E-mail: m.cnossen@erasusmc.nl

This study is part of the OPTI-CLOT research programme (Patient tailOred PharmacokeTic-guided dosing of CLOTting factor concentrates and desmopressin in bleeding disorders)”, an (inter)national multicenter study aiming to implement PK-guided dosing of replacement therapy and desmopressin by initiating studies to demonstrate its implications and feasibility, improve PK models and to increase knowledge of patient-tailored PK-guided dosing which is currently part of the SYMPHONY consortium, which aims to unravel the origins of the interindividual variation in bleeding phenotype in order to install personalized treatment in all inherited bleeding disorders.

SUMMARY
In resource rich countries, almost all severe hemophilia patients receive prophylactic replacement therapy with factor concentrates to prevent spontaneous bleeding in joints and muscles, to decrease the development of arthropathy and risk of long-term disability. Pharmacokinetic (PK)-guided dosing can be applied to individualize factor replacement therapy, as inter-individual differences in PK parameters influence factor VIII (FVIII) and factor IX (FIX) activity levels. PK-guided dosing may therefore lead to more optimal safeguarding of FVIII/FIX levels during prophylaxis and on demand treatment. The OPTI-CLOT TARGET study is a multicenter, non-randomized, prospective cohort study that aims to investigate the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B patients in daily clinical practice. At least 50 patients of all ages on prophylactic treatment using standard half-life (SHL) and extended half-life (EHL) factor concentrates will be included during nine months and will receive PK guided treatment. As primary endpoint, a minimum of four FVIII/FIX levels will be compared to FVIII/FIX levels as predicted by Bayesian forecasting. Secondary endpoints are the association of FVIII and FIX levels with bleeding episodes and physical activity, expectations and experiences, economic analyses and optimization of population PK models. This study will lead to more insight in the reliability and feasibility of PK-guided dosing in hemophilia patients. Moreover, it will contribute to personalization of treatment by greater knowledge of dosing regimens needed to prevent and treat bleeding in the individual patient and provide evidence to more clearly associate factor activity levels with bleeding risk.

INTRODUCTION

Hemophilia A and B are X-linked recessive bleeding disorders caused by a deficiency or dysfunction of coagulation factor VIII (FVIII) or factor IX (FIX),
respectively. Severe patients (FVIII/FIX <0.01 IU/mL) and some moderate-severe patients (FVIII/FIX 0.01-0.05 IU/mL) suffer from spontaneous bleeding or bleeding after minimal trauma. Prophylactic treatment by intravenous administration of factor concentrates aims to prevent (spontaneous) bleedings in joint and muscles and subsequent arthropathy with potential long-term disability.\textsuperscript{1,2}

During prophylaxis theoretically, FVIII/FIX trough levels are targeted >0.01 IU/mL. This principle is based on observations by Ahlberg as early as 1965, that bleeding phenotype and joint status are strikingly different between severe and moderate-severe hemophilia patients with only minimal baseline FVIII level differences (<0.01 IU/mL versus 0.01-0.05 IU/mL).\textsuperscript{3} To achieve these FVIII/FIX trough levels during prophylaxis, FVIII/FIX concentrates are mostly prescribed according to bodyweight.\textsuperscript{2} Remarkably, it is still not usual clinical practice to standardly measure and monitor trough FVIII/FIX levels when no bleeding occurs. In order to personalize dosing, information on trough FVIII/FIX levels is of value to establish if prophylaxis is adequate for each individual patient, during follow up and in varying circumstances and when dosing on demand. In addition, the lack of knowledge of achieved FVIII/FIX levels impedes proper switching to novel long-acting factor concentrates due to uncertainties which trough FVIII/FIX target levels should be targeted to prolongate earlier effective prophylactic treatment to prevent bleeding, especially in relation to physical activity or sports.

**Pharmacokinetic -guided dosing**

Large interindividual variability exists in the pharmacokinetics (PK) of FVIII/FIX concentrates as demonstrated by Bjorkman et al. among others.\textsuperscript{4-6} To understand
and predict the consequences of the interindividual variability of factor concentrates in individuals, population PK models have been constructed for prophylaxis and perioperative treatment with standard half-life (SHL) and extended half-life (EHL) FVIII and FIX concentrates for respectively hemophilia A and B patients. With these population PK models, Bayesian forecasting can be performed. Herewith, individual PK parameters are estimated, which are subsequently used to calculate the adequate dose for an individual patient to achieve FVIII/ FIX target levels, both trough and peak. The availability of population PK models has made limited sampling possible, making prior frequent blood sampling (>10 blood samples) and a washout period redundant. PK-guided dosing has also been reported to not only be able to predict dosing requirements to attain certain target FVIII/FIX levels but also to decrease the amount of factor concentrates with concomitant reduction of costs. Carlsson et al. was the first to report a dose and cost reduction of 30% of FVIII factor concentrate without an increase in bleeding events, when PK-guided prophylactic dosing was compared to standard prophylactic dosing in a small patient sample. However, a recent randomized controlled perioperative trial was not able to show a decrease in FVIII concentrate consumption, although achievement of FVIII target ranges was clearly more optimal.

We hypothesize PK-guided dosing leads to individualization of prophylaxis, which is in accordance with the recommendations of the subcommittee on FVIII, FIX and rare bleeding disorders of the ISTH. PK-guided dosing may help achieve higher trough levels more efficiently when clinically indicated, as well as provide guidance when patients switch to alternative replacement factor concentrates, while taking cost and benefit of treatment into account. In addition, PK-guided dosing may lead to increased insight into the association between FVIII/FIX levels, bleeding (risk) and
physical activity levels in individual patients as factor levels can be predicted at any
time point and related to bleeding and activity. Therefore, we aim to prove that
FVIII/FIX trough and peak levels as set by treating physician can be predicted and
achieved reliably by application of PK-guided prophylaxis and that this intervention is
feasible for patients and treatment teams.

**Objective**
Investigate the reliability and feasibility of PK-guided prophylactic dosing of factor
concentrates in hemophilia A and B patients in daily clinical practice.

**METHODS**

**Study design**
The OPTICLOT TARGET study is a multicentre, non-randomized, prospective cohort study.

**Study population**
Patients will be recruited from the two Dutch Hemophilia treatment Centers e.g.
located in the Erasmus MC, University Medical Center Rotterdam and Amsterdam
University Medical Centers.

**Inclusion criteria:**
- Hemophilia A and B patients of all ages on prophylaxis;
- Prophylaxis with SHL or EHL factor concentrates;
- Written (parental) informed consent, according to local law and regulations.

**Exclusion criteria**
- Patients with other severe congenital or acquired hemostatic abnormalities;
- General medical conditions which may interfere with participation in the study;
- Inability to adhere to prophylaxis and/or inability to keep detailed logs on infusion and bleeding episodes;
- Withdrawal of (parental) informed consent.
- Presence of FVIII/FIX inhibitor, leading to alternative treatment with bypassing products, immune toleration induction and/or other immune modulating treatment.

**Outcome measures**

*Primary endpoints are:*

Observed FVIII and FIX levels in comparison to FVIII and FIX levels predicted by Bayesian forecasting. The predictive performance is deemed acceptable when at least 80% of the actual FVIII/FIX levels are within ±25% of the predicted (target) values as stated by treating professional.

*Secondary endpoints are:*

1. Association of (real world or predicted) FVIII/FIX levels with bleeding episodes and daily activities. Additionally, bleeds will be categorized according to sub classifications: total number of bleeds over time, number of spontaneous bleeds, number of traumatic bleeds, number of joint bleeds, number of target joint bleeds, bleed severity.

2. Expectations, feasibility and experience with PK-guided dosing with the different factor concentrates (SHL versus EHL) as reported by patient/caretakers and physician will be measured using a visual analogue scale (VAS) questionnaire at the start and end of the study.
3. Economic analysis in which costs and benefits of standard prophylactic treatment and PK-guided prophylaxis are compared.

4. Analysis of described modifiers effecting PK parameters of FVIII/FIX concentrate in order to further optimize population PK models. Modifiers include demographics (such as lean body mass) and laboratory measurements (such as Von Willebrand Factor levels).

**Interventions**

Study interventions are depicted in the flowchart (Figure 1.) Patients will be categorized into strata according to type of hemophilia and type of factor concentrate (SHL or EHL). For all patients, the following patient characteristics and demographics will be collected: type of hemophilia, endogenous factor level, DNA mutation, age, height (cm), weight (kg), body mass index (BMI; kg/cm2), lean body mass (kg), blood group, current other medication, activity patterns.

Patients/caretakers will fill in the Hemophilia Activities List (HAL) and/or pediatric HAL (PedHAL) before initiation. Moreover, the Hemophilia Joint Health Score (HJHS) will be performed or must have been performed <12 months prior inclusion.

The validated PedHAL/HAL questionnaire and the HJHS are included as clinical parameters to systematically establish baseline values of functional outcome from the patient’s perspective and to be informed of joint status, respectively. These clinical parameters may help to evaluate outcomes after implementation of PK-guidance.

Furthermore, both patients/caretakers and the treating physician will fill in a specifically developed questionnaire using VAS scales, before the implementation of PK-guided dosing considering the expectations with PK-guided dosing of prophylaxis. More specifically, in the questionnaire questions are asked about
satisfaction, being informed of factor levels and expected burden of PK-guidance. Moreover, when patients switch to an EHL factor concentrate, the reason for switching are also asked.

An individual PK profile will be constructed after a factor concentrate dose of 35-50 IU/kg, depending on hemophilia type and age of the patient. The frequency and timing of blood sampling during PK profiling is depending on type of hemophilia and type of factor concentrate (Figure 2). No wash out period is required if three prior infusions and time points of infusion are documented. During sampling of the PK profile, laboratory tests will be performed according to table 1, 2 and 3.

Dosing will be advised by clinical pharmacologist on the basis of FVIII/ FIX target trough levels as set by treating physician, in accordance to patient characteristics, previous trough levels (if a patient switches between factor concentrates), bleeding history, activity pattern and in consultation with patient/ caretakers. If desirable, physicians are also able to set FVIII/FIX target peak levels during intensive physical activities. In this way, treatment is truly customized and tailored to the needs and lifestyle of each individual as personalization is meant to be. Retrospective data of a patient, such as previous trough levels and factor levels at onset of a bleed or during sport activities, can be informative to the physician to set target levels.

Thereafter, patients will initially be on PK-guided treatment for 12 weeks. During these 12 weeks, a minimum of three factor levels will be measured and compared to predicted FVIII/ FIX values to validate predicted dosing regimen. Patients on EHL will be on iterative PK-guided treatment with dose adjustment if needed based on both factor levels and bleedings. Iterative treatment is desirable in these patients as most patients initiate treatment with EHL factor concentrates after being on prophylaxis with SHL factor concentrates. Because of the lack of knowledge of most optimal
(frequency and dose of) EHL factor concentrate, this period has a dose finding perspective.

For patients on SHL predicted FVIII/FIX values will be blinded to the treating physician and dosages will not be adjusted during the first 10 weeks. Thereafter, dose adjustment can be made.

A subsequent follow up period of 24 weeks on PK-guided treatment is necessary to further collect data to establish the associations between FVIII/FIX levels and bleeding events. Only if clinically indicated, FVIII/FIX levels will be measured during bleeds. At the end of this follow-up period, one final blood sample will be taken to compare the factor level with the predicted value. Patients/caretakers will again fill in the HAL or PedHAL questionnaire and the physiotherapist will perform the HJHS, to evaluate outcomes after implementation of PK-guidance.

Finally, at study end both patients/caretakers and the treating physician will fill in the VAS questionnaire considering the experience with PK-guided dosing and EHL factor concentrate when patients have switched to an EHL factor concentrate.

Importantly, hemophilia patients who have undergone individual PK-profiling prior to study inclusion or who already receive PK-guided treatment on SHL or EHL concentrate, are also able to participate in the study. PK profiling is required to be performed with a maximum of one year prior to study inclusion when <12 years of age and a maximum of three years prior to study inclusion when 12 years and older. Patients who already received PK guidance prior to study inclusion, will only complete the VAS questionnaire at the end of the study period, since asking the patient questions with regard to expectations on PK guided dosing at the start of the study, would lead to recall bias. Also, the HJHS will not be performed in these patients and the (PedHAL) will not be completed in this subgroup as results after
body weight (and bleeding) based prophylaxis and PK-guided therapy cannot be compared.

In parallel with the prospective study, retrospective data analysis will be performed over a 12-month period prior to inclusion (if no PK profiling has been performed) or from PK profiling prior to inclusion. These data will be utilized as “real world data” to construct and enrich available population PK models. Moreover, if patients kept a detailed patient logon infusion dates and timing and bleeding episodes, FVIII/ FIX trough levels and FVIII/FIX levels during physical activities and at the onset of a bleed can be calculated.

Factor activity levels will be measured by local laboratories, as this reflects the real world setting of standard clinical practice. Plasma samples are stored in case centralized measurements are deemed necessary Laboratory specifications (assay, reagents, deficient plasma, analyser) applied in local laboratory will be recorded precisely. Preferably, the local laboratory assays match with the assays as used during population PK model construction.

Bayesian forecasting

Bayesian forecasting will be performed with the NONMEM® software (Icon, Dublin, Ireland); individual PK parameters will be assessed with a limited number of blood samples. Available population PK models in literature and new models that will become available, will be used. Based on the estimated individual PK parameters and the FVIII/ FIX target trough and peak values as set by the physician, dosing schedules will be calculated.

Sample size calculation
In this prospective study, we aim to evaluate the predictive performance of PK-guided dosing in hemophilia patients. It is not common practice to calculate a sample size for prognostic models, and to our knowledge, it is not possible to calculate a sample size for the determination of predictive performance. What we do know, is that characteristics such as age, bodyweight, activity pattern and bleeding phenotype are not part of the in- or exclusion criteria, the study population will be a reflection of the real world and thus a heterogeneous hemophilia population. However, we aim to enroll a minimum of 50 patients in all strata together, to explore the predictive performance of PK guided dosing in real life.

Statistical analysis

Continuous data will be expressed as mean and standard deviation when normally distributed or median and interquartile range when not normally distributed. Categorical data will be expressed as frequency and percentage.

As described in the primary study endpoint, the predictive performance of PK-guided dosing is deemed acceptable when at least 80% of the actual FVIII/FIX levels are within ± 25% of the predicted (target) values as stated by treating professional. Both the mean error between the predicted and observed factor level and the mean absolute difference of the predicted level will be calculated. No significant bias is present as zero is included in the 95% confidence interval (CI) of the mean error. Moreover, differences between the predictive performance of different factor concentrates and age groups will be investigated and described.

Association of factor levels with bleedings will be described according to sub classifications. Comparisons of the ABR and joint status before and during PK-
guidance will be analyzed using a paired t test or Wilcoxon test, depending on the distribution.

R (version 4.0.3) will be used for statistical analysis.

**Ethical considerations**

The study protocol was approved by the Medical Ethics Board of the Erasmus MC, University Medical Center Rotterdam, the Netherlands and approved by all boards of all participating hospitals.

**Registration**

The trial is registered at the Dutch Trial register with trial number NTR7523 (www.trialregister.nl)

**CONCLUSION**

The proposed study aims to investigate the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B patients in daily clinical practice. Moreover, the collected real world data will lead to enrichment of current population PK models and an increased insight in the association of FVIII/FIX levels with bleeding episodes and daily activities.

**Acknowledgements**
All authors would like to thank the OPTI-CLOT study group as a whole for their support and Iris van Moort and Jessica Heijdra for their involvement and participation.

The SYMPHONY consortium which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, healthcare professionals and translational & fundamental researchers specialized in inherited bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, workpackages (WP) have been organized according to three themes e.g. Diagnostics (WPs 3&4), Treatment (WPs 5-9) and Fundamental Research (WPs 10-12). This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project manager: Dr. S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus MC and Erasmus MC Sophia Children’s Hospital, University Medical Center Rotterdam, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

Conflict of interest
M.H. Cnossen has received grants from governmental and societal research institutes e.g. NWO-ZonMW, NWO-NWA, Innovation fund, from private funds, institutional grants and unrestricted investigator research grants/educational and travel funding from the following companies over the years: Pfizer, Baxter/ Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, Nordic Pharma and Roche, and has served as a member on steering boards of Roche and Bayer. All grants, awards and fees go to the Erasmus MC as an institution.

R.A.A. Mathôt has received governmental and societal research institutes such as NWO, ZonMW, and Innovation Fund and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, and Sobi. He has served as an advisor for Bayer, CSL Behring, Merck Sharp & Dohme, and Baxter/Baxalta/Shire/Takeda. All grants and fees were paid to the institution.

J. Eikenboom received research support from CSL Behring outside the scope of this project and fees for educational activities from Roche and Celgene, which fees go to the institution.

F.W.G. Leebeek received unrestricted research grants from CSL Behring, Shire/Takeda, SOBI and UniQure. He is a consultant for CSL Behring, Takeda, Biogen and UniQure, of which the fees go to the Erasmus MC as an institution. He served as DSMB member of a study sponsored by Roche.

K. Meijer reports speaker fees from Bayer and Alexion, participation in trial steering committee for Bayer, consulting fees from UniQure, participation in data monitoring
and endpoint adjudication committee for Octapharma. All fees are paid to the institution.

REFERENCES


**Figure 1: Flowchart.**

EHL, extended half-life; HAL, Hemophilia Activity List; HJHS, Hemophilia Joint Score; PedHAL, pediatric HAL; PK, pharmacokinetic(s); SHL, standard half-life; VAS, Visual Analogue Scale

*Non severe hemophilia patients will be analysed separately.

** In parallel with the prospective study, retrospective data analysis will be performed over a 12 month period prior to inclusion (if no PK profiling has been performed) or from PK profiling prior to inclusion.
Patients in stratum 2 could undergo PK profiling during SHL prophylaxis as well as during EHL prophylaxis.

Figure 2. Time points (T) of laboratory tests during individual PK-profiling. A pre-infusion, t=15-30min and t=4h sample (left) are performed in all patients. The other time points (right) depend on hemophilia type and brand of factor concentrate.

EHL, extended half-life; SHL, standard half-life.
Flowchart “OPTI-CLOT:TARGET”

A

Hemophilia patients on prophylaxis → Inclusion criteria? → No → Exclusion

Yes → Informed consent → Treatment allocation → Data collection including retrospective analysis → VAS (start of the study), NH3, HAL, or PediHAL

Stratum 1
Hemophilia A → Stratum 1B → Hemophilia B

Stratum 2
Hemophilia A → Stratum 2B → Hemophilia B

B

Individual PK profile → Individual PK profile

C

Blinded PK-guided treatment → Blinded PK-guided treatment → Blinded PK-guided treatment

Iterative PK-guided treatment → Iterative PK-guided treatment → Iterative PK-guided treatment

2 weeks → 12 weeks → 12 weeks

D

Follow-up treatment under PK-guidance → VAS (end of the study), NH3, HAL, or PediHAL

Screening period: 2-4 weeks
Study period: 35 weeks
Pre-infusion, T=15-30min, T=4h

Hemophilia A
- SHL T=24h, T=48-72h
- EHL T=24h, T=48-72h, T=72-96h

Hemophilia B
- SHL T=48-56h, T=72-80h
- EHL T=24h, T=72-120h, T=168h