Individualized prophylaxis with *Human-cl rhFVIII* in Adult Patients with Severe Haemophilia A

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Introduction

Prophylactic therapy in patients with severe haemophilia A is aimed to maintain sufficient FVIII:C plasma concentrations between doses to prevent bleeding. Trough FVIII concentrations and duration of FVIII plasma concentration >0.01 IU/mL are mainly determined by the half-life and the infusion interval. The individualization of prophylactic treatment requires knowledge of individual patient's PK profile in response to replacement factor, which is known to vary considerably between patients. Clinical studies with *Human-cl rhFVIII*, a recombinant FVIII concentrate expressed in genetically modified human embryonic kidney (HEK) 293F cells, in adult patients with severe haemophilia A also revealed differences between patients with half-lives ranging from 11.1 to 23.8 hours as analyzed by one-stage clotting assay.[1] Effective prophylaxis with *Human-cl rhFVIII* could be achieved with a mean dose of 32.8 IU/kg (weekly dose 109 IU/kg) given every other day resulting in a low annualized bleeding rate (mean: 2.3).[2]

Objective

This ongoing study is designed to investigate the efficacy and safety of personalized PK-tailored prophylaxis with *Human-cl rhFVIII* in previously treated adult patients with severe haemophilia A. The goal is to find the maximum prophylactic dosing interval that can be achieved with a dose of not more than 60–80 IU/kg and that is capable of maintaining a trough level of ≥0.01 IU/mL.

Methods

Patients

Sixty-five adult patients with severe haemophilia will be enrolled from various countries across Europe.

Inclusion Criteria

- Severe haemophilia A (FVIII:C <1%)
- Male subjects ≥18 years of age
- Previously treated with FVIII concentrate, at least 150 Exposure Days
- Immunocompetence (CD4+ count >200/µL)
- HIV-negative; if positive, viral load <200 particles/µL or <400,000 copies/mL
- Good documentation regarding dosing and bleeding frequency in the 6 months preceding study start
- Freely given written informed consent

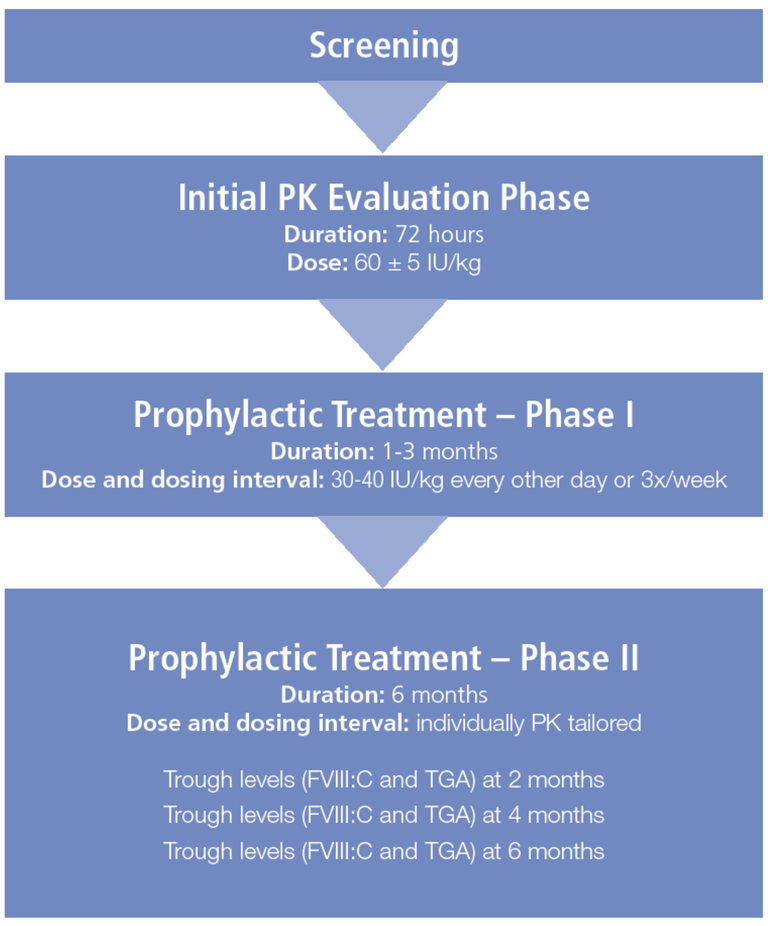
Exclusion Criteria

- Any coagulation disorder other than haemophilia A
- Present or past FVIII inhibitor activity (>0.6 BU)
- Severe liver or kidney disease (ALT and AST levels >5 times of upper limit of normal, creatinine >120 µmol/L)
- Treatment with any investigational medicinal product (IMP) except FVIII IMP within 14 days prior to the screening visit

Study Design

First, each eligible patient will undergo a PK assessment using a dose of 60 ± 5 IU/kg. Blood samples will be collected over a 72-hour period and FVIII coagulant activity (FVIII:C) will be measured by validated chromogenic substrate and one-stage clotting assays in a central laboratory, which also assigned actual drug potency with the same assays. The patients will enter Phase-I of the study during which they will be treated with a dose of 30-40 IU/kg every other day or 3 times per week for 1 to 3 months until the patient's individual PK has been analyzed (based on FVIII:C one-stage results) and discussed with the investigator. Then, patients will be treated prophylactically for 6 months whereby the dose and the dosing interval are recommended for each patient based on the analysis of individual PK data. In case of unacceptable frequent and/or severe spontaneous breakthrough bleeds, the dose may be adapted. If patients still experience unacceptable bleeding episodes, the dosing interval will be shortened. After 2 and 4 months as well as at the study end the FVIII:C trough level will be determined. For comparison, also the thrombin generation assay (TGA) is performed at these time points as well as during the PK assessment.

Figure 1. Study design



Hemostatic efficacy

In case of break-through bleeds, treatment efficacy of *Human-cl rhFVIII* will be assessed by the patient using a 4-point efficacy scale with objective criteria ranging from "none" to "excellent" mainly based on the number of infusions needed to manage the bleed and time until pain relief.

Inhibitors

Inhibitors will be measured before first exposure to *Human-cl rhFVIII* and at study end by the modified Nijmegen assay using FVIIII-depleted plasma spiked with *Human-cl rhFVIII* as test base.

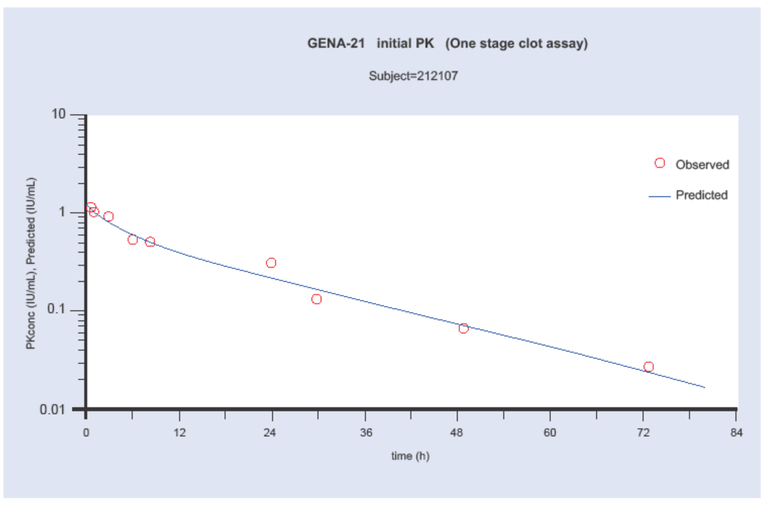
Status of study and preliminary results

The study protocol and informed consent were approved by the Independent Ethics Committee of each participating institution and the regulatory agencies of each country. Written informed consent was obtained from the patient prior to any trial-related activity.

As of March 14, 2014, 60 patients from 17 study centers in 8 countries have undergone PK assessment and dosing recommendations for the personalized prophylaxis (Phase-II) were provided for 41 patients. An example for a dose recommendation is shown below (Figure 2).

Figure 2. FVIII:C plasma concentrations after a dose of 60 IU/kg

2-Compartment Model
Half-life = 15.2 hours
Recommendation: 42 IU/kg twice per week



As of March 2014, based on PK analyses for 41 patients, the median recommended dose interval was 3.5 days and the median weekly dose was 96 IU/kg. It remains to be seen whether patients will be compliant with the personalized treatment protocol. By September 2014 we will have data on bleeding rate and FVIII consumption data for at least 30 completed patients allowing us a first evaluation on the validity of this treatment approach. No related adverse events have been reported so far.

References

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2. Knaub S, Lissitchkov T, Hampton K, von Depka M, Rangarajan S, Hay C, Tuddenham EDG, Collins PW, Holstein K, Huth-Kühne A, Pabinger I, Bichler J, Oldenburg J. Human-cl rhFVIII effectively and safely prevents bleeding episodes in previously treated adult patients with severe haemophilia A. Poster presented at the 2012 ASH Annual Meeting.

Conclusion

- The preliminary data suggest that twice per week prophylaxis might be possible with *Human-cl rhFVIII*
- The results of this study may improve the practice of preventing bleeds in haemophilia A patients.

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