Using repeated-time-to-event modelling and simulation of spontaneous bleeding events in the F8 KO rat model for informed decision making of study design

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Objective

- Investigate whether disease progression in terms of bleeding risk in the F8 KO rat model could be described using repeated-time-to-event (RTTE) modelling, and apply stochastic simulation and estimation (SSE) to evaluate three different study designs on the basis of the power to identify a significant treatment effect.

Conclusions

- The occurrence of bleeding events in the F8 KO rat model was well described using RTTE modelling with a surge function.
- The current study, demonstrates the need for frequent dosing and/or high dose treatment to compensate for small group sizes in F8 KO rat efficacy studies.

Introduction

- In haemophilia prophylaxis trials, the primary pharmacodynamic endpoint is reduction in annual bleeding rate (ABR).
- The spontaneously bleeding coagulation factor VIII-gene knock-out (F8 KO) rat model[1], displaying a similar bleeding phenotype to haemophilia A patients, presents a unique opportunity to investigate the exposure-response relationship in close agreement with the clinical setting.
- However, preclinical studies are often limited by small study populations and short study durations which may impede identification of a significant treatment effect.
- In the current study, it was investigated whether disease progression in terms of bleeding risk in the F8 KO rat model could be described using repeated-time-to-event (RTTE) modelling. Secondly, applying stochastic simulation and estimation (SSE), three different study designs were evaluated on the basis of the power to identify a significant treatment effect.

Methods

- The occurrence of spontaneous bleeding events in 89 untreated F8 KO rats, examined daily for bleedings for a period of 52 weeks[1] (Fig. 1), was described by a RTTE model in NONMEM 7.3 (Laplacian estimation method) in conjunction with PsN.
- Several baseline hazard functions were evaluated, including: exponential, Weibull, Gompertz and surge functions[2] (Eq. 1)
- $Hazard = h_0 \cdot e^{\eta} \cdot \left(1 + \frac{SA}{\left(\left(\frac{age-PT}{SW}\right)^N\right)+1}\right)$ (Eq. 1)
- Performance of the RTTE models was evaluated on the basis of the Kaplan-Meier Visual Predictive Check (VPC), precision of parameter estimates and the objective function value
- SSEs (1000 samples) with and without recombinant FVIII treatment were made using the developed RTTE model, a hypothetical one-compartmental intravenous pharmacokinetic model (V_d=30 mL/kg and CL=4.1 mL/h·kg)[3] and a literature derived exposure-response relationship (EC_{50}= 0.0914 IU/mL)[4](Fig. 3)
- For all simulations study duration was set to 16 weeks (week 4 to 20). Different conditions were investigated, including three dosing regimens (50 IU/kg every second day, 50 IU/kg daily and 100 IU/kg daily) and sample sizes ranging from 20 to 100 rats. The power to identify a significant treatment effect was evaluated at a significance level of 0.05 for each study condition, aiming for at least 80% power
- The statistical software R was applied for data processing and model diagnostics.

Results

- The initial increase and subsequent decline in the hazard was accurately described by a surge function as apparent from the Kaplan-Meier VPC (Fig. 2), depicting the time course of the probability of not having a bleeding for each event.
- The highest bleeding risk was observed at week 10 (5 bleeds per year) showing a 6-fold increase relative to baseline.
- A sample size of approximately 30 rats was required to detect a significant reduction in the bleeding risk with a power of at least 80% using a dose regimen of 100 IU/kg daily (Fig. 4). The equivalent sample size at a dose regimen of 50 IU/kg daily and 50 IU/kg every second day was 45 and more than 100, respectively.

Fig. 1 Bleeding frequency

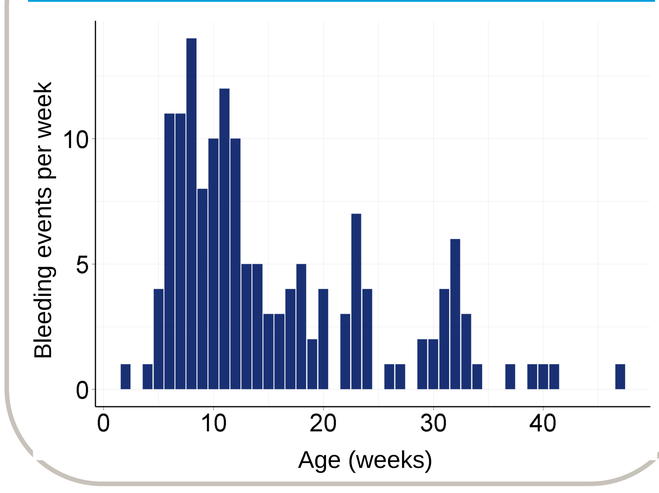
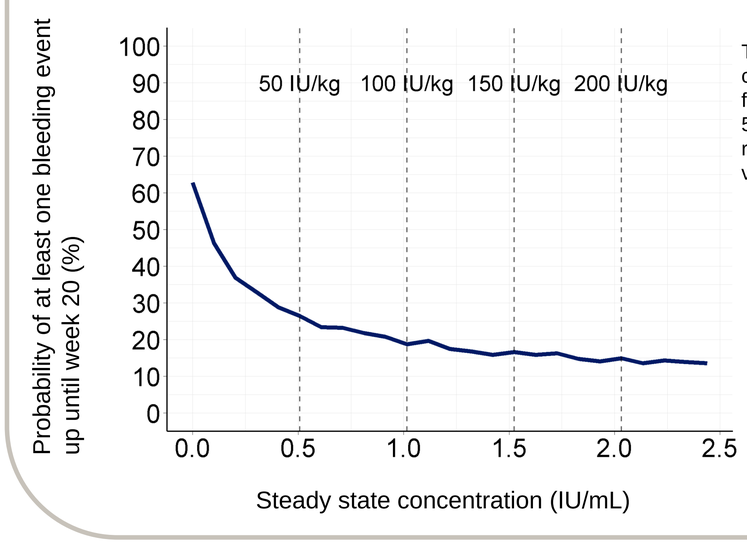


Table 1 Population Parameter Estimates and 95% Confidence Intervals Obtained from 2,000 Bootstrap Replicates

Parameters (Unit)	Estimate	95% CI
h_0 (week^{-1})	0.013	0.0018 – 0.020
SA (week^{-1})	6.79	3.73 – 41.46
PT (week)	9.99	8.95 – 14.87
SW (week)	3.85	2.71 – 9.87
N (unitless)	4 (Fixed)	-
$\omega^2_{h_0}$ (%)	67	39.5 – 89.6

Fig. 3 Probability of at least one bleeding event up until the study end (week 20) versus the steady state concentration based on 4,000 simulations.



The steady state concentrations obtained following daily administration of 50, 100, 150 and 200 IU/kg rFVIII are represented by vertical dashed lines

Fig. 2 Kaplan-Meier VPC of the RTTE model, comparing the median of the observed data (solid black line) to the 95% confidence interval of the simulated data (blue area) based on 2,000 simulations.

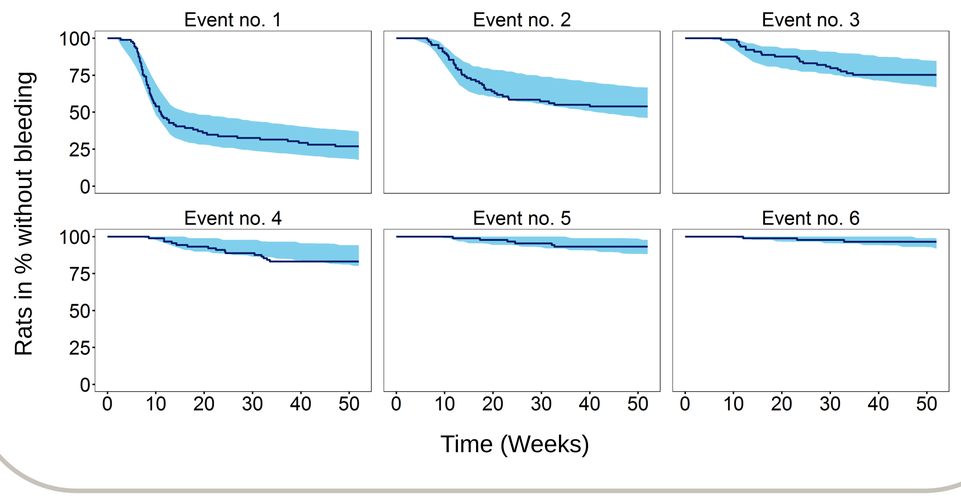
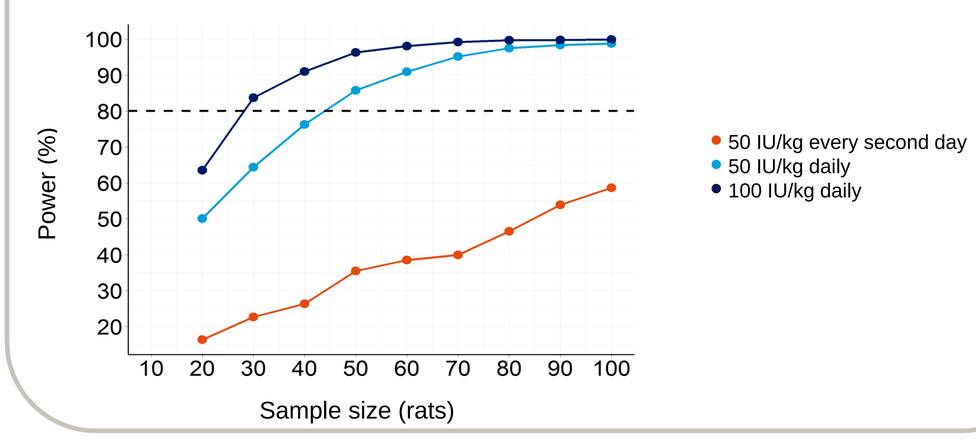


Fig. 4 Study power to identify a significant treatment effect for different dosing regimens versus sample size



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Disclosures

M.S.L, R.V.J, M.K-H and M.K are employed by Novo Nordisk A/S; U.S.H.S, A.K. has no disclosures

References

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2: Plan, E.L., J Pharmacol Exp Ther 2011:339(3): 878-885
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