Summary

Although treatment of haemophilia has improved markedly in recent years, suboptimal bleeding prevention remains a serious concern. To address this concern, current research and development (R&D) of novel anti-haemophilic drugs focuses on therapeutic prolongation strategies and alternative administration routes. However, R&D faces several challenges. First, translation of preclinical findings is hampered by the lack of knowledge of how well animal models of haemophilia quantitatively predict pharmacokinetics and efficacy in haemophilia patients. Secondly, historically, clinical trials of haemophilia have been challenged by the limited patient population, event-type efficacy endpoints (bleeding events) with low information content, and potential placebo effect, making it difficult to obtain statistically meaningful outcomes. Finally, effective care remains a challenge due to substantial inter-individual variability in pharmacokinetics (PK) and pharmacodynamics (PD), as well as inadequate monitoring of clinical effectiveness (reduction in bleeding risk) in certain patient-subgroups.

The objective of this thesis was to provide guidance for informed decision-making throughout the different phases of haemophilia R&D through the use of pharmacometric modelling and simulation, explicitly aiming at evaluating the predictive performance of animal models of haemophilia, the impact of trial design and statistical methodology in clinical trials of haemophilia, and the use of rotational thromboelastometry (ROTEM) for predicting bleeding risk in haemophilia patients.

Paper I, “Prediction of human pharmacokinetics of activated recombinant factor VII and B-domain truncated factor VIII from animal population pharmacokinetic models of haemophilia”, evaluated how well various experimental animal models of haemophilia (mice, rats, monkeys and dogs) and scaling principles predicted human PK of activated recombinant factor VII (rFVIIa) and recombinant factor VIII (rFVIII) using population PK modelling and simulation. Here, we demonstrated that the predictive performance of the developed animal PK models of rFVIIa and rFVIII in mice, rats, monkeys and dogs revealed significant species-variation. In general, the PK models of rFVIIa and rFVIII in monkeys and dogs, as well as interspecies allometric scaling demonstrated high predictive performance for human PK and may provide the basis for rational decision-making in future first-in-human trials for rFVIIa and rFVIII variants.

Paper IV, “Impact of target-mediated drug disposition on recombinant factor VIII and von Willebrand factor pharmacokinetics in haemophilia A rats”, adequately described the nonlinear time-course of rFVIII, von Willebrand factor (VWF) and the rFVIII:VWF complex PK following intravenous administration of a broad range of rFVIII doses in haemophilia A rats using target-mediated drug disposition modelling. Additionally, this study provided evidence of VWF depletion following high-dose rFVIII treatment.

Paper III, “Rotational thromboelastometry can predict the probability of bleeding events in haemophilia A rats following gene-based rat FVIIa prophylaxis”, aimed at characterizing the relation between dose of vector genomes, total plasma levels of FVII/FVIIa, clotting time (CT) measured using rotational thromboelastometry (ROTEM), and the probability of bleeding events in haemophilia A rats receiving gene-based rat FVIIa prophylaxis. The
developed model accurately described the vector dose-dependent plasma concentration-time profile of total FVII/FVIIa and the exposure-response relationship between Adeno-associated virus (AAV)-derived FVIIa expression and clotting time. Importantly, the developed model accurately characterized the occurrence of bleeding events over time demonstrating a linear relationship between the predicted change from baseline clotting time and the probability of bleeding events. Using PK-CT-RTTE modelling, we demonstrated that ROTEM parameters could accurately predict the probability of bleeding events in haemophilia A rats.

Paper II, “Impact of trial design on the estimation of drug potency and power in clinical trials of haemophilia with inhibitors”, investigated how the choice of trial design (parallel-group, placebo-controlled and crossover designs), study conditions (study duration, sample size and dose levels) and statistical methodology (RTTE modelling, t-test and negative binomial regression) may affect the precision and accuracy of the estimation of drug potency (EC\textsubscript{50}) along with statistical power in clinical trials of haemophilia with inhibitors. In this study, the crossover designs displayed up to four-fold higher precision of the estimated drug potency, and three-fold higher statistical power relative to the parallel-group trial designs. Furthermore, RTTE modelling demonstrated higher statistical power relative to the traditional statistical methods.

In conclusion, this Ph.D. project demonstrates how pharmacometric modelling and simulation may be utilized in the different phases of haemophilia R&D for informed decision-making and optimization of treatment.