Phase II dose selection for a hypothetical novel Direct Thrombin Inhibitor (DTI): an integrated approach using experimental and literature competitor data.

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Background

Phase II dose selection includes in general many uncertainties after first healthy volunteers trials, e.g efficacy, safety, dose-regimen and number of doses. However, integrating available knowledge with new experimental data improves dose selection and decision making. Direct Thrombin Inhibitors (DTI's) directly interact with thrombin in the bloodstream and consequently reduce the risk of venous-thrombo-embolism (VTE). The DTI's Dabigatran (DAB) and Ximelagatran (XIM) have been developed (ref 1-6) for this indication. Clinically efficacious and sub-efficacious doses have been described in literature and are publicly available. Also, their pharmacokinetics (PK) and biomarker concentration relationships have been described, especially for the Ecarin Clotting Time (ECT) which specifically reflects the mechanism of action of DTI's.

Objective

- Selecting an active and safe dose range for a Proof of Concept (POC) trial
- By integrating the available competitor literature data
- By integrating experimental data of a hypothetical novel DTI

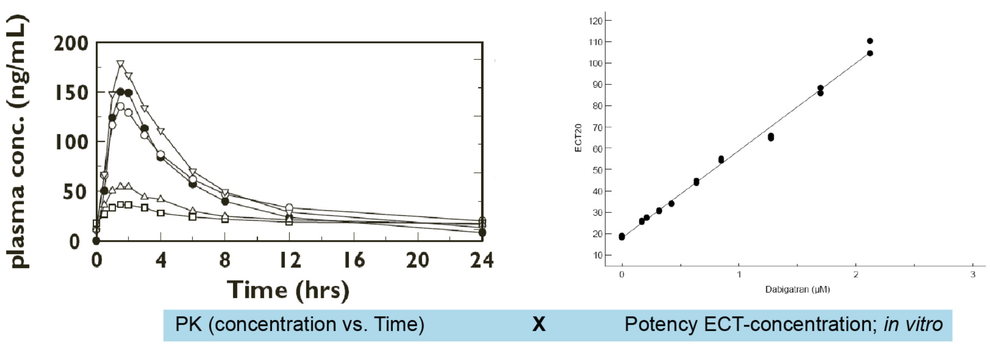
Methods:

- For a hypothetical new DTI, PK and ECT-concentration data were generated. The assumed typical values for a 2 compartment model for the hypothetical DTI were CL/F=600 L/h, V1=200 L, V2=600 L, Q12=60 L/h, Ka=0.75 h (Fig. 2) and the *in vitro* ECT potency at 60 s*L/mg.
- An integrated target value was needed: to relate the available PK and ECT data of the new DTI to the competitor data.
- Assumed was: Exposure (AUC) to a DTI relates to a ECT (potency) response which is related to efficacy.
- The integrated target value was the product AUC_x*$potency_x$=AUE_x (Area-under-ECT-time curve).

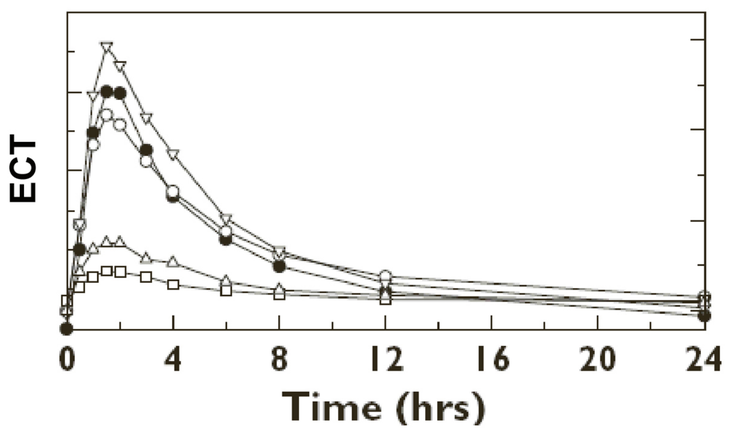
The target AUE range was based on sub-efficacious (SEff) and efficacious (Eff) doses of DAB and XIM as reported from phase II clinical trials (**ref 1-6**).
The AUCs for different doses of DAB and XIM were determined based on published population pharmacokinetics (pop-PK) data. For DAB and XIM, the ECT curves were determined *in vitro*. The linear relationships were described with the difference in slope as a relative potency measure. The target AUE's at the SEff and Eff were calculated by multiplying the AUC with the relative potency value.

- The PK of a hypothetical novel DTI was simulated by a PK model, using NONMEM.
- PD (AUE) was scaled by the *in vitro* relative potency relationship according to **AUC_x*$potency_x$=AUE_x** resulting in an AUE at a certain dose. AUEs for different doses were calculated resulting in a linear AUE-Dose relationship. This AUE-Dose relationship was then used to identify SEff and Eff for the novel DTI.

Calculation of the integrated target value for Dabigatran at the efficacious dose (EFF) and sub-efficacious dose (SEff)



PK (concentration vs. Time) **X** Potency ECT-concentration; *in vitro*



ECT-time relationship for different doses of Dabigatran

Evaluation of Phase II trials showed that two doses were either efficacious (EFF) or sub-efficacious (SEff) for both XIM and DAB. The corresponding AUEs were calculated, multiplying the AUC and the ECT potency at the particular dose.

For the hypothetical DTI, PK and ECT data have been simulated. Thus, for each dose, AUEs were calculated for the dose-range tested (25-150 mg) using the potency of 60 s*L/mg. This provided the dose-AUE relationship (Fig. 2)

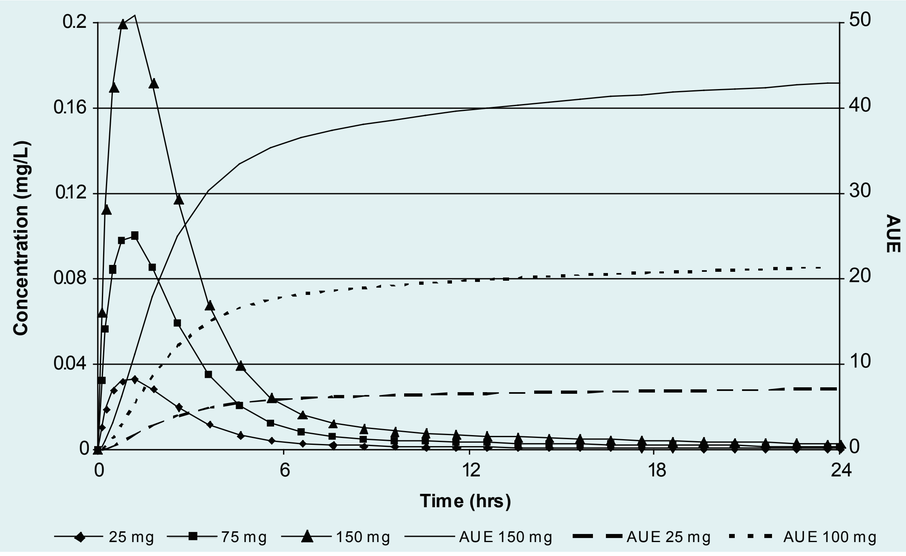


Figure 1. Concentration time relationship of hypothetical DTI and the AUE for 3 different doses

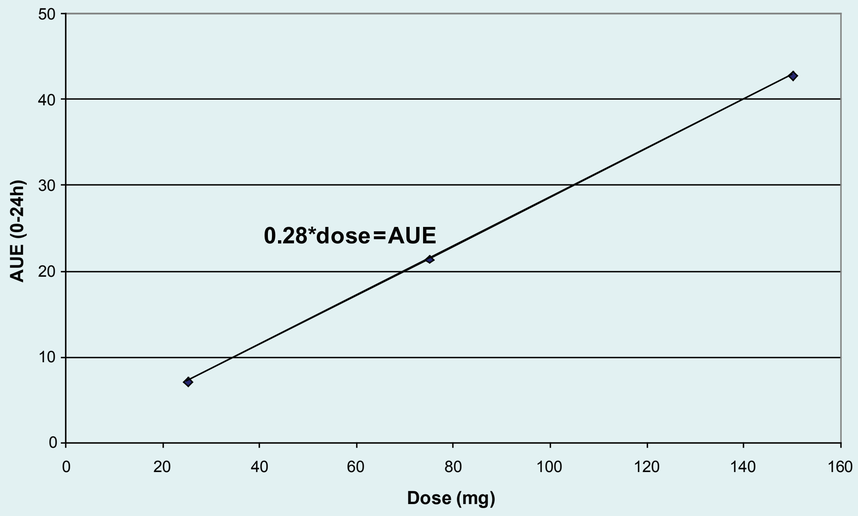


Figure 2. Dose-AUE relationship for new DTI

Results

Integrating experimental and literature data for DAB and XIM resulted in the following parameters:

DTI	SEff (mg)	Eff (mg)	ECT potency (s*L/mg)	CL/F (L/h)	AUC SEff (L/h)	AUC Eff (L/h)	AUE (s*h) SEff	AUE (s*h) Eff
DAB	100	150	84	103	0.98	1.45	82	122
XIM	24	48	56	27.3	0.88	1.76	49	99

- The integrated target value AUE based on XIM and DAB for the hypothetical DTI: 49 to 122 s*h to achieve sub-efficacy or efficacy in a phase II PoC trial
- Tthe slope of the linear relationship (AUE-Dose) of the hypothetical DTI was 0.28.
- Thus the active dose-range for the DTI in the POC trial would be 175-293 mg for SEff and 353 to 435 mg for Eff.

Conclusion

- **Experimental and literature data from a novel hypothetical Direct Thrombin Inhibitor and two existing competitors were successfully pooled in an integrated analysis.**
- **This approach allowed the selection of a dose range of 200 -400 mg, which is anticipated to be effective in a POC trial patient population.**

References
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