Pharmacodynamic effects of two recombinant FVIIa products in anticoagulated healthy volunteers

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Background

For many years, recombinant human activated coagulation factor VII (rhFVIIa) has been used for the treatment of haemophilia A or B patients with inhibitors to factor VIII or IX. The effectiveness of treatment is determined by assessment of bleeding cessation, however, a lack of a clear correlation between pharmacodynamic (PD) and pharmacokinetic (PK) parameters hinders dose optimisation and development of new rhFVIIa products. Therefore PK and PD properties of two rhFVIIa products (LR724 and eptacog alfa) were assessed in healthy volunteers, who were pre-treated with fondaparinux to induce an anticoagulated state. LR724 is a novel rhFVIIa product under development.

Methods

- 36 healthy males:
  - placebo (n = 6)
  - rhFVIIa (LR724/eptacog alfa) 15 (6/0), 45 (6/6) or 90 (6/6) µg/kg; actual protein administered for LR724 ≈ 80% of intended dose.
- 5 mg fondaparinux SC (t = -2 h)
- FVIIa/placebo IV-bolus (t = 0)
- Assessments: FVIIa activity and antigen, thrombin generation (TGT), PT, aPTT, and markers of coagulation activation
- Mixed model analysis of variance with fixed factors (treatment, time, treatment by time), subject (random factor), covariates: (1) value before fondaparinux, (2) average of values between fondaparinux and FVIIa
- A PK-PD model for PT and TGT lag time was developed with NONMEM

FIGURE 1 Pharmacokinetic profile

FVIIa activity time-course on linear scale (left), displayed as mean (SD), and observations (dots) over PK-model individual prediction (lines) on logarithmic scale (right). Note: protein content of LR724 ≈ 80% of the labeled content.

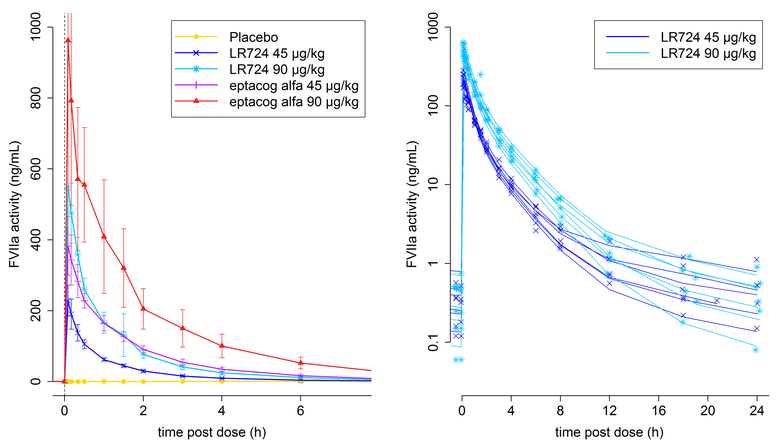
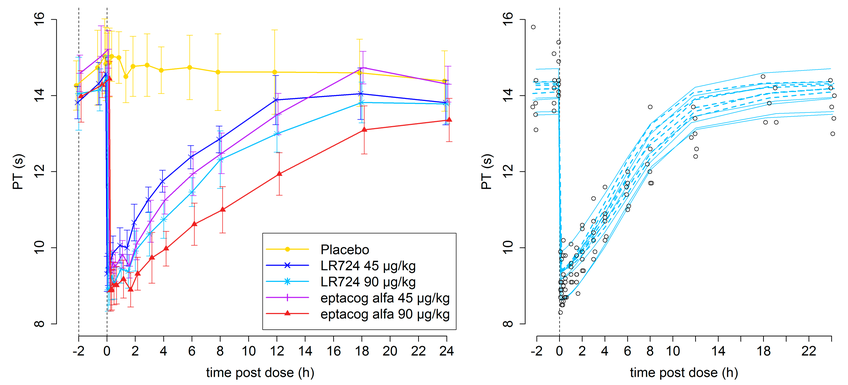


FIGURE 2 Prothrombin time

Mean (SD) (left), and PK-PD-model for LR724 90 µg/kg (right): individual prediction (solid line), population prediction (dotted line), observation (dot).



Results

- **LR724/eptacog alfa**: FVIIa activity (Figure 1), up to 1000x baseline levels (90 µg/kg);
  - Apparent half-life (corrected for baseline activity): 1.9-2.8 h;
  - Protein content of LR724 ≈ 80% of the labeled content.
- Reversal of the fondaparinux-induced anticoagulant state (Table 1):
  - significant reduction in TGT lag time (Figure 3), time to peak, velocity index;
  - significant increase in TGT AUC and peak value.
- Significant decrease in PT (Figure 2).
- Change in aPTT, TAT (Figure 4), and prothrombin fragments 1+2 only significant at 90 µg/kg.
- **PK-model** FVIIa activity (two-compartment kinetics [Figure 1] with endogenous levels as cosine function of time fitted to data from the placebo group): good prediction
- **PK-PD model** (maximum effect model) for PT (Figure 2) and TGT lag time (Figure 3): good prediction of both parameters.
  - Anti-Xa data from the placebo group as 1-compartment PK model described the concentration-dependent effect of fondaparinux on TGT lag time.

FIGURE 3 TGT lag time

Top: change from baseline (95%-CI) after FVIIa/placebo administration (t = 0). Baseline is average of two values under fondaparinux. Bottom: PK-PD-model for LR724 90 µg/kg: individual prediction (solid line), population prediction (dotted line), observation (dot).

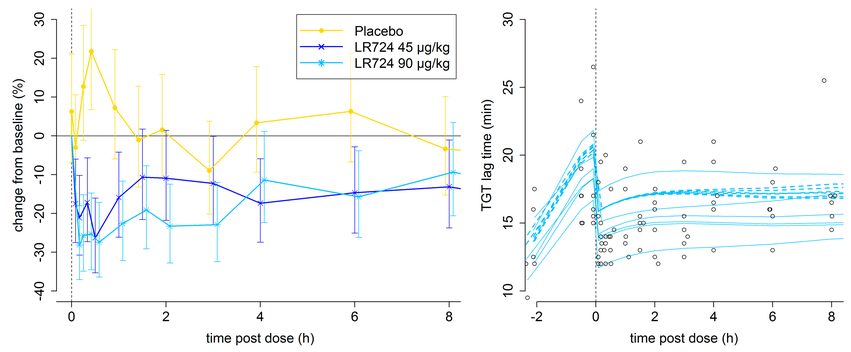


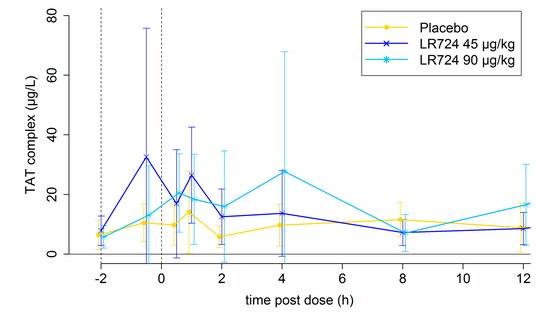
TABLE 1 Pharmacodynamic parameters

Parameter	LR724 45 µg/kg – Placebo	LR724 90 µg/kg – Placebo	LR724/ eptacog alfa 90 µg/kg
TGT lag time*	-15.93	-20.87	0.96
p = 0.0173	(-24.42 – -6.48)	(-28.02 – -13.02)	(0.87 – 1.06)
	p = 0.0027	p = 0.0003	p = 0.4939
TGT time to peak*	-12.87	-19.32	0.96
p = 0.0012	(-20.66 – -4.32)	(-25.61 – -12.50)	(0.88 – 1.05)
	p = 0.0059	p = 0.0002	p = 0.4821
TGT peak value*	37.60	102.36	0.93
p = 0.0018	(4.71 – 80.81)	(61.60 – 153.40)	(0.72 – 1.20)
	p = 0.0240	p < 0.0001	p = 0.6295
TGT AUC (nM x min)	393.30	793.39	0.97
p = 0.0626	(1.93 – 784.67)	(469.80 – 1117.00)	(0.83 – 1.11)
	p = 0.0490	p = 0.0004	p = 0.7236
TGT velocity index*	41.01	133.53	0.95
p = 0.0015	(0.84 – 97.17)	(77.24 – 207.70)	(0.69 – 1.32)
	p = 0.0450	p < 0.0001	p = 0.8066
aPTT*	-1.57	-5.57	0.98
p = 0.0560	(-4.08 – 1.01)	(-7.54 – -3.57)	(0.96 – 1.00)
	p = 0.2179	p = 0.0001	p = 0.1469
PT*	-21.79	-25.97	0.95
p < 0.0001	(-24.52 – -18.96)	(-28.17 – -23.69)	(0.92 – 0.98)
	p < 0.0001	p < 0.0001	p = 0.0092

Contrasts (95%-CI) to placebo over 0-6 hours.
Ratios (90%-CI) between both rhFVIIa products.
P-value beneath each parameter: overal treatment effect.
**As percentage (ln-transformation prior to analysis)*

FIGURE 4 TAT complexes

Mean (SD)



Conclusion

- **PT and TGT lag time are good rhFVIIa PD markers.**
- **Simulations with the PK-PD model: maximal PD effect at 2-3 hour interval (consistent with the way eptacog alfa is used at this time).**