Pharmacokinetics of a Recombinant Factor VIIa in Factor VIII ko Mice, Rats and Macaques

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Objective

Baxter is developing a new recombinant factor VIIa (rFVIIa) product for the potential treatment of patients with hemophilia A or B who have inhibitors.

Our studies evaluated the pharmacokinetic profile of Baxter's rFVIIa in hemophilia A (FVIII ko) mice, Sprague Dawley rats and macaques. These studies were incorporated into a preclinical program including safety and efficacy studies[1, 2].

Methods

Baxter's rFVIIa and a commercially available rFVIIa product were tested at a dose of 0.6mg/kg in mice and rats. Both items were tested at a dose of 2.7mg/kg in macaques. The primary endpoint of these studies was dose-adjusted $AUC_{0\text{-tlast}}$ (the area under the concentration vs. time curve from 0 to the last time point measured) for human FVIIa activity in all species and human FVII protein (antigen) in rodents only. Secondary endpoints were in vivo recovery (IVR), half-life, mean residence time (MRT), total clearance standardized per kg body mass (CLs) and volume of distribution at steady state (Vss).

Anesthetized rats received an intravenous bolus injection of Baxter´s rFVIIa or a licensed rFVIIa via the lateral tail vein. A single animal design was used with ten animals (5m/5f) in each group. Blood samples for citrated plasma were drawn from the ventral tail artery 5 – 6 days before (base line FVIIa levels) and 5, 30, 60, 120, 180 and 270min after item administration.

Conscious restrained FVIII ko mice (B6;129S4-*F8*^{tm1Kaz}) received Baxter´s rFVIIa or the commercially available rFVIIa product as a single bolus injection via the lateral tail vein. 10 animals (5m/5f) per time point were bled by cardiac puncture under anesthesia for blood sampling 5, 15, 30, 75, 120, 160, and 200min after the administration of the test item following a serial sacrifice design.

Four macaques (2m/2f) received Baxter´s rFVIIa or a licensed rFVIIa by intravenous (bolus) injection into the saphenous vein. Blood samples were withdrawn from a suitable vein at the following timepoints: base line, 5 min, 15 min, 30 min, 1, 3, 5, 7, 9 and 15 hours after dosing.

FVII protein (= antigen) was measured by ELISA using commercially available polyclonal anti-human factor VII antibodies (Cedarlane, Birlington, Ontario, Canada). FVIIa activity (= activity) was measured by a clotting assay specific for activated FVII (STACLOT VIIa-rTF, Diagnostica Stago, Asnieres, France). All statistical analyses were performed with SAS Version 8.2 for Linux.

All animal experiments accorded with local laws governing animal experimentation and were additionally approved by the Institutional Animal Care and Use Committee (IACUC).

References

1. Schiviz et al. (2012) Efficacy of a New Recombinant Factor VIIa in Animal Models of Hemophilia, WFH 2012
2. Dietrich et al. (2012) Preclinical Safety of a new Recombinant Factor VIIa, WFH 2012

Disclosure

All authors are employees of
Baxter Innovations GmbH

Results

Results of pharmacokinetic studies of Baxter's rFVIIa in FVIII ko mice, rats and macaques revealed that plasma concentrations of both rFVIIa activity and rFVII antigen declined in a bi-phasic manner. Terminal elimination half-life ranged from 0.97 to 1.17h for rFVII antigen and 0.64 to 2h for rFVIIa activity. Furthermore, the pharmacokinetic properties of Baxter's rFVIIa were shown to be similar to a commercially available rFVIIa product.

In <u>rodents</u> a similar pharmacokinetic behavior of FVIIa activity and FVII protein could be observed (Tab. 1, Fig. 1).

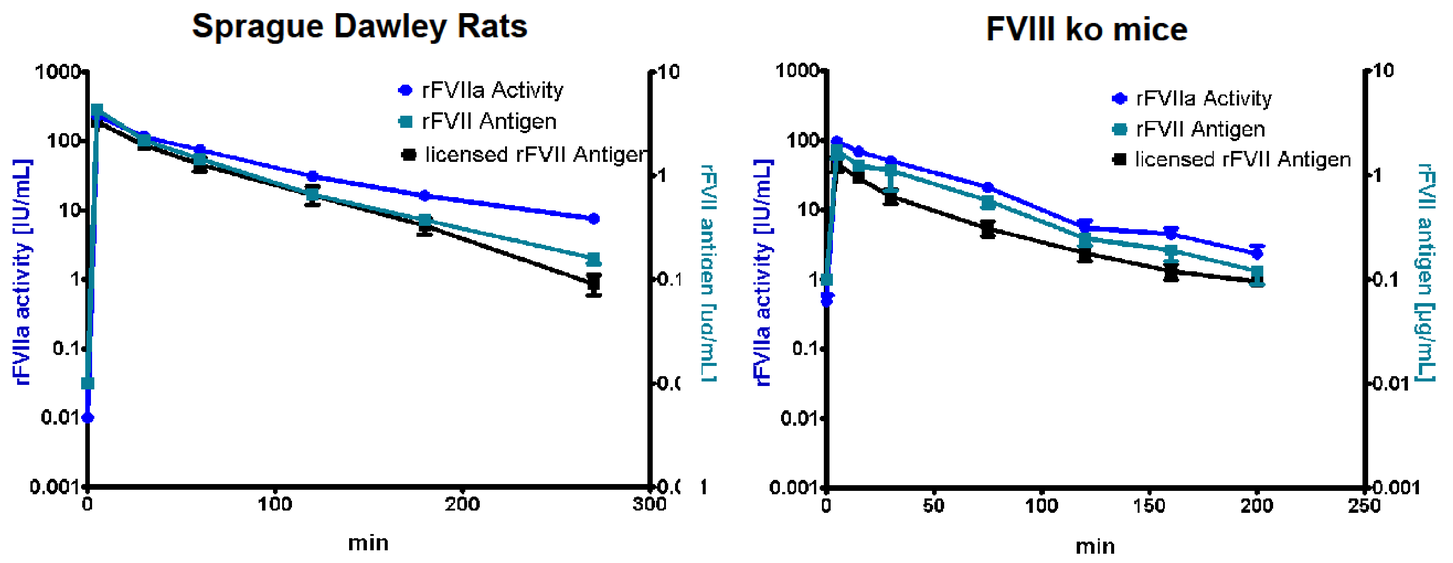

Fig. 1: Activity (blue) and antigen (turquoise) was measured for Baxter´s rFVIIa, antigen (black) was measured for the licensed rFVIIa preparation

Table 1: FVIIa activity and antigen PK profile of Baxter´s rFVIIa in rodents

		$AUC_{0\text{-tlast}}$	MRT [h]	terminal half-life [h]	IVR [%]	CL [mL/h/kg]	Vss [mL/kg]
Rats	FVIIa activity	0.56	1.29	1.17	30.0	103	132
	FVII antigen	0.58	1.38	1.17	29.5	98	136
Mice	FVIIa activity	0.24	0.80	0.64	25.2	245	195
	FVII antigen	0.23	1.28	0.97	18.5	235	301

$AUC_{0\text{-tlast}}$ [h*IU/mL / IU/kg] or [h*µg/mL / µg/kg]

In <u>macaques</u> the pharmacokinetic profiles of FVIIa activity following a single intravenous bolus injection of Baxter´s rFVIIa or a licensed rFVIIa were shown to be similar (Tab. 2, Fig. 2).

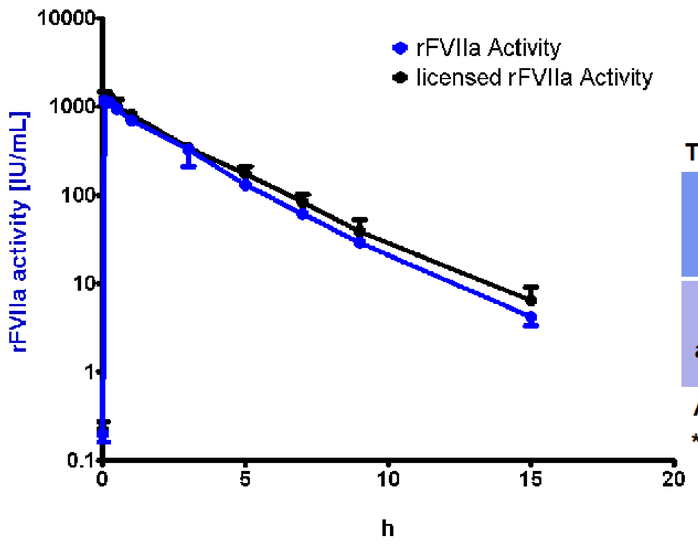

Fig. 2: Activity for Baxter´s rFVIIa (blue) and for the commercially rFVIIa preparation (black) was measured

Table 2: FVIIa activity PK profile for Baxter´s rFVIIa

	$AUC_{0\text{-tlast}}$	MRT [h]	terminal half-life [h]	IVR [%]	CL [mL/h/kg]	Vss [mL/kg]
FVIIa activity	0.0297*	2.45	2.00	49.7	34	82

$AUC_{0\text{-tlast}}$ [h*IU/mL / IU/kg]
* Sample size too small for statistical evaluation of bioequivalence

Conclusions

- The pharmacokinetics of Baxter´s rFVIIa and a commercially available rFVIIa were similar after IV administration to FVIII ko mice, Sprague Dawley rats and macaques
- There was no apparent sex-related difference in the extent of systemic exposure of rFVII antigen and rFVIIa activity

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