Single Dose Pharmacokinetics of Recombinant FIX in Factor IX ko Mice, Rats and Macaques

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Objective

Baxter is developing a new recombinant factor IX (rFIX) product for the potential treatment of patients with hemophilia B.

Our studies evaluated the pharmacokinetic profile of Baxter's rFIX in hemophilia B (FIX ko) mice, Sprague Dawley rats and macaques. These studies were incorporated into a preclinical program including safety and efficacy studies[1,2,3].

Methods

Baxter's rFIX and a commercially available rFIX product were tested at a dose of 75IU/kg in mice and 500µg/kg in rats. Both items were tested at a dose of 150IU/kg in cynomolgus monkeys. 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 FIX activity in FIX ko mice and macaques and human FIX protein (antigen) in all species. 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 rFIX or a licensed rFIX 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 at least 24 before (base line) and 5, 30, 90 minutes, 4, 7 and 10 hours after item administration.

Conscious restrained FIX ko mice (B6.129P2-F9^{tm1Dws}) received Baxter´s rFIX or the commercially available rFIX 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 min, 1, 3, 6, 10 and 16 hours after the administration of the items following a serial sacrifice design.

Four macaques (2m/2f) received Baxter´s rFIX or a licensed rFIX by intravenous (bolus) injection into the saphenous vein. Blood samples were withdrawn from a suitable vein at the following timepoints: base line, 5, 30 min, 1.5, 3, 6, 9, 12, 18, 24 and 36 hours after dosing.

FIX protein (= antigen) was measured by ELISA using commercially available polyclonal paired anti-human factor IX antibodies (Enzyme Research Laboratories, Swansea, UK). FIX activity (= activity) was measured by a chromogenic assay (Biophen Factor IX, Hyphen Biomed, Neuville-sur-Oise, 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. Dietrich et al. (2012) Preclinical safety pharmacology of a new recombinant factor IX, WFH 2012
2. Dietrich et al. (2012) Repeated Application of a new Recombinant Factor IX in Rats and Macaques, WFH 2012
3. Höllriegl et al. (2012) Efficacy of a Recombinant Factor IX in Mouse Models of Hemophilia B, WFH 2012

Results

Results of pharmacokinetic studies of Baxter's rFIX in FIX ko mice, rats and macaques revealed that plasma concentrations of both rFIX activity and rFIX antigen declined in a bi-phasic manner. Terminal elimination half-life ranged from 3.4 to 12.1h for rFIX antigen and 5.5 to 10.4h for rFIX activity. Furthermore, the pharmacokinetic properties of Baxter's rFIX were shown to be similar to those of a commercially available rFIX product.

In mice higher $AUC_{0\text{-tlast}}$ activity levels for Baxter´s rFIX could be observed than with the licensed rFIX product. In contrast, the $AUC_{0\text{-tlast}}$ antigen levels were slightly lower in both rodent species (Tab. 1, Fig. 1).

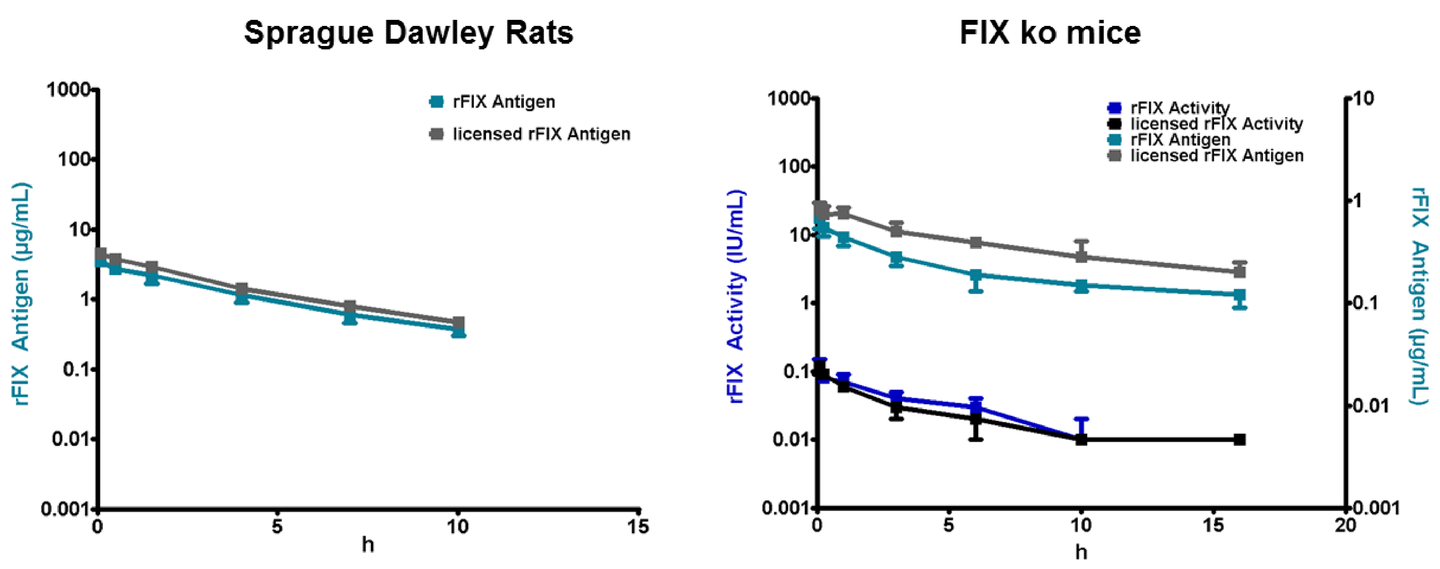

Fig. 1: Activity (blue) and antigen (turquoise) was measured for Baxter´s rFIX, activity (black) and antigen (grey) was measured for the licensed rFIX preparation

Table 1: FIX activity and antigen PK profile of Baxter´s rFIX in rodents

	Hosted by:	$AUC_{0\text{-tlast}}$	MRT [h]	terminal half-life [h]	IVR [%]	CL [mL/h/kg]	Vss [mL/kg]
Rats	FIX antigen	0.0230	7.8	3.4	21	32	249
Mice	FIX activity	0.0067	7.3	5.5	9	131	957
	FIX antigen	0.0174	15.3	11.0	17	37	560

$AUC_{0\text{-tlast}}$ [h*IU/mL / IU/kg] or [h*µg/mL / µg/kg]
Secondary PK parameters are bioequivalent to licensed FIX

In macaques the pharmacokinetic profiles of FIX activity and antigen following a single intravenous bolus injection of Baxter´s rFIX or a licensed rFIX were shown to be similar (Tab. 2, Fig. 2).

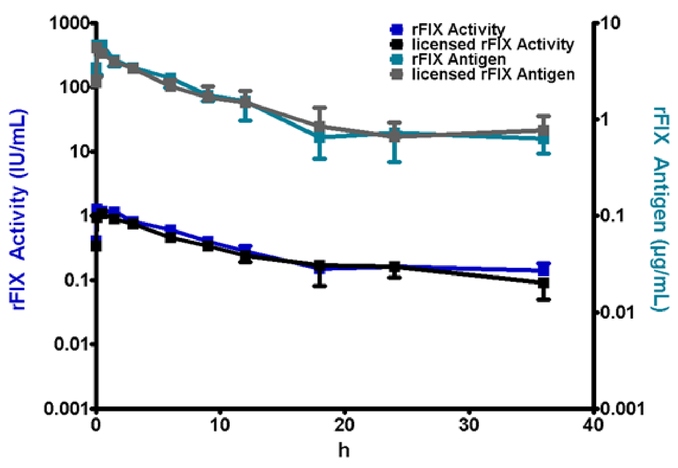

Table 2: FIX activity and antigen PK profile for Baxter´s rFIX

	$AUC_{0\text{-tlast}}$	MRT [h]	terminal half-life [h]	IVR [%]	CL [mL/h/kg]	Vss [mL/kg]
FIX activity	0.0805	15.6	10.4	39.8	11.2	169.5
FIX antigen	0.1330	17.9	12.1	68.8	6.5	113.0

$AUC_{0\text{-tlast}}$ [h*IU/mL / IU/kg] or [h*µg/mL / µg/kg]
All PK parameters are bioequivalent to licensed FIX

Fig. 2: Activity (blue) and antigen (turquoise) was measured for Baxter´s rFIX, activity (black) and antigen (grey) was measured for the licensed rFIX preparation

Conclusions

- The pharmacokinetics of Baxter´s rFIX and a commercially available rFIX were similar in FIX ko mice, Sprague Dawley rats and macaques
- There was no apparent sex-related difference in the extent of systemic exposure of rFIX antigen and rFIX activity

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Disclosure

All authors are employees of Baxter Innovations GmbH

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