Preclinical Safety Pharmacology of a new Recombinant Factor IX

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Introduction

Baxter is developing a recombinant FIX (rFIX) product for the treatment of patients with hemophilia A or B who have inhibitors. Baxter's new rFIX is produced by a genetically engineered Chinese hamster ovary (CHO) cell line in a cell culture medium free from any animal or human proteins.
The objective of this preclinical study program was to evaluate the safety of Baxter's rFIX in different species.

Methods

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

Thrombogenic Potential (Wessler Test) in Rabbits

The thrombogenic potential of Baxter' s recombinant FIX has been tested at a dose of 750 IU/kg in three male and female NZW rabbits per group. The thrombogenicity is evaluated after a single administration. Plasma-derived FIX (pd FIX) and commercially available recombinant FIX were used as the reference items.

Cardiovascular Effects in Telemetered Macaques

Two different Doses (75 and 250 IU/kg bodyweight) were administered to four male and four female animals per group. Animals were radio telemetered 24h pre- and post dosing. Plasma-derived FIX (pd FIX) and commercially available recombinant FIX were used as the reference items.

Endpoints	
Macaques	**Rabbits**
body temperature, blood pressure, respiratory variables or ECG (QT, QTcf, PR and/or QRS intervals) and respiratory system (intra-thoracic pressure)	thrombus formation in isolated jugular vein segments using the qualitative Wessler score scala ranging from 0 (no thrombus formation) to 4 (maximum score for thrombogenicity)

Conclusions

- Studies on safety pharmacology with Baxter's new rFIX revealed an excellent safety profile
- A high dose (750 IU/kg) of Baxter's new rFIX was non-thrombogenic in rabbits
- Baxter's rFIX did not cause any adverse clinical, respiratory or cardiovascular effects and was very well tolerated at all dose levels in macaques
- Our studies on the safety profile of Baxter's new rFIX provide the evidence necessary for proceeding with trials in humans

Results

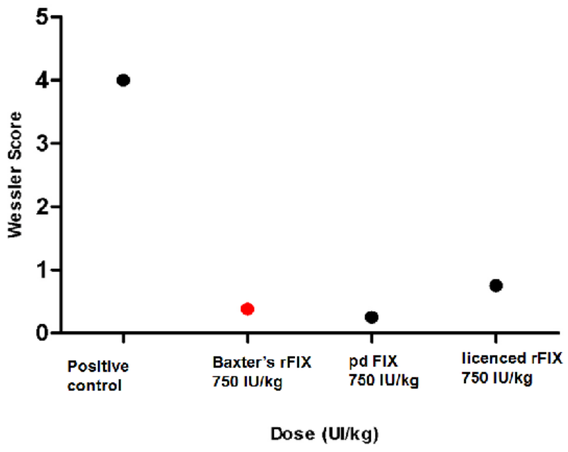
Thrombogenicity in rabbits

Baxter's rFIX was not thrombogenic in the rabbit stasis model at a dose of 750 IU/kg, representing 10-fold the prophylactic dose intended for humans.
The mean Wessler scores (n=6/group) for all three products were <1.

Comparative evaluation of thrombogenicity of Baxter's new rFIX in a Wessler stasis model with licensed rFIX or pd FIX

Wessler Score for Test Items:

Positive control	Baxter's rFIX	pd rFIX	licenced rFIX
4	0.38	0.25	0.75

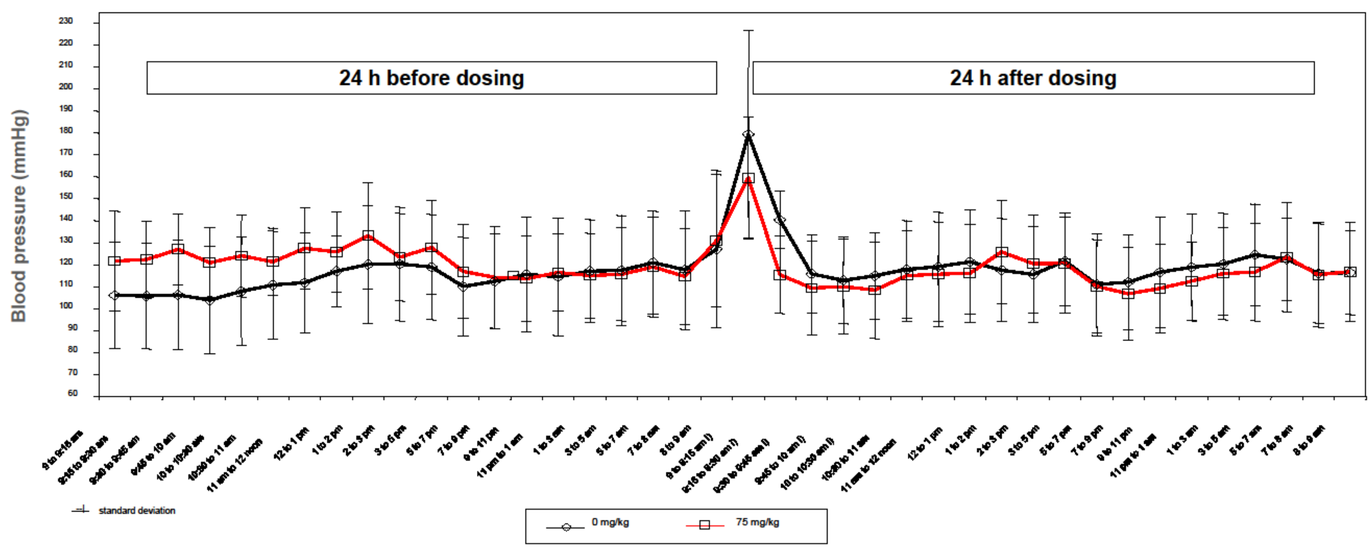


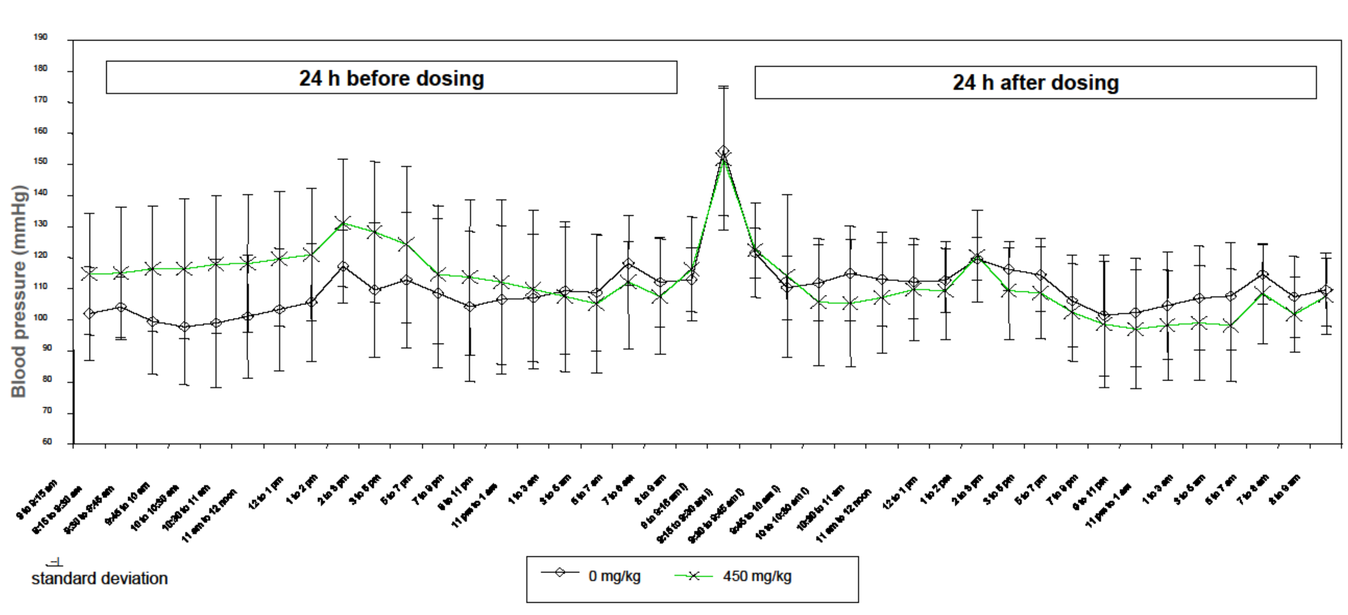
- Thrombogenicity of Baxter's new rFIX in the Wessler stasis model in rabbits with normal hemostasis is similar to that of plasma-derived or licensed rFIX

Cardiovascular and respiratory function in macaques

No clinical, respiratory or cardiovascular adverse effects were observed in monkeys at doses up to 450 IU/kg, representing the 6-fold prophylactic doseintended for humans.
There was no adverse effect of Baxter's rFIX on body weight, body temperature, blood pressure, respiratory variables or ECG (QT, QTcf, PR and/or QRS intervals) at doses of 75 and 450 IU/kg.
Baxter's rFIX was very well tolerated at all dose levels.

Radio Telemetry of Baxter's New rFIX – Systolic Blood Pressure (mmHg)





- No physiologically relevant effect on any of the respiratory variables
- No adverse effect on any of the cardiovascular variables

Disclosure The authors of this presentation make the following disclosure of financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: Barbara Dietrich, Susan Kubik, Hartmut J. Ehrlich, Friedrich Scheiflinger, Hans Peter Schwarz and Eva-Maria Muchitsch are full-time employees of Baxter Innovations GmbH, Vienna, Austria.

Poster presented at the World Federation of Hemophilia 2012 World Congress, July 2012, Paris

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DOI: 10.3252/pso.eu.WFH2012.2012