Preclinical safety pharmacology of a PEGylated variant of recombinant factor VIII

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Introduction

Factor VIII (FVIII) is a critical component of the intrinsic coagulation pathway. FVIII concentrates are used in patients with hemophilia A to provide a hemostatic FVIII level sufficient to treat and prevent bleeding episodes.
Prophylactic treatment regimens aim to maintain a FVIII level of at least 1% of normal to effectively prevent or reduce spontaneous bleeding episodes.
The desired FVIII level can only be maintained by administering several infusions weekly depending on the individual pharmacokinetic profile, the bleeding phenotype, and the individual life style. A longer acting FVIII concentrate would reduce the frequency of infusions, increase compliance and reduce the number of musculoskeletal bleeds with long-term sequelae and life-threatening bleeds.
Baxter and Nektar have developed BAX 855, a PEGylated form of Baxter's recombinant FVIII (rFVIII) product based on the Advate manufacturing process. The product is derived from a CHO cell line using a plasma-protein-free method and a virus inactivation step.
In this preclinical study program the objective was to evaluate the safety of Baxter's longer acting rFVIII in different species.

Methods

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

Rabbits:

The objective of the study was to evaluate the thrombogenic potential of two preclinical lots of BAX 855, and one lot of the licensed reference item Advate after a single intravenous administration to rabbits. Doses of 900 IU/kg were administered intravenously.
The study consisted of three groups of six animals (three males and three females) and two positive control animals. Control animals were treated intravenously with an activated prothrombin complex preparation at 20 U/kg.

Telemetered Macaques:

Two lots of BAX 855 were tested in eight male, conscious, freely moving macaques to determine the cardiovascular and respiratory effects of BAX 855. The integrated radiotelemetry system (ITS) was used to continuously monitor body temperature, cardiovascular and respiratory variables.
BAX 855 was given at the doses of 150 and 600 IU/kg/day at infusion rates of either 1.1 mL/kg or 4.5 mL/kg. The test item was administered via the intravenous route to mimic the intended clinical administration route.

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Results

Rabbits:

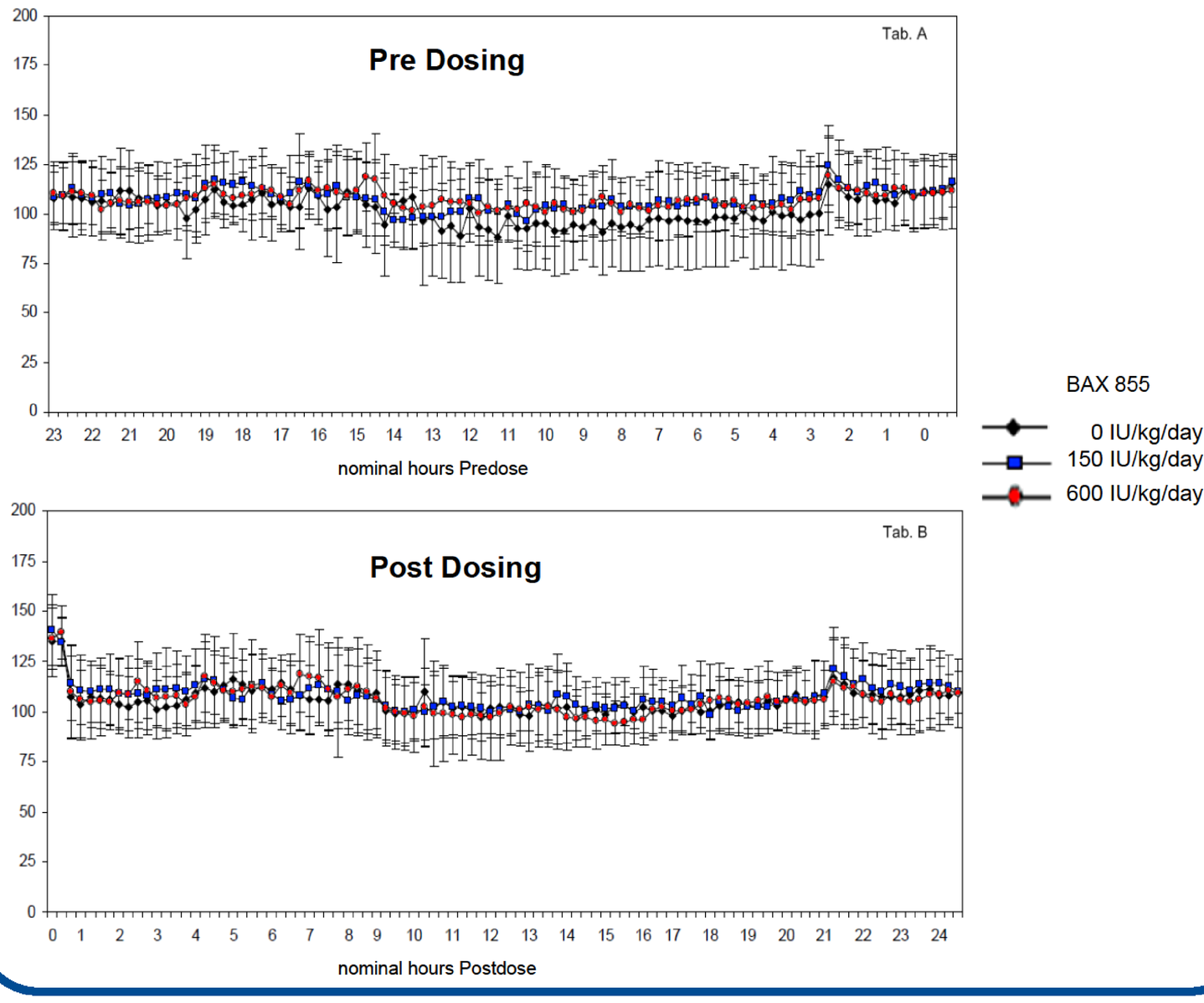
The thrombogenicity of BAX 855 was tested in a rabbit stasis model (Wessler Test).
The Wessler score ranged from 0 to 1 for both lots of BAX 855, similar to scores obtained for Advate (0 – 2), all within in the range of this biological system.
The results of the positive control proved the relevance of the test system.

Target Dose	Item	Score		Individual Scores					
		Range	Mean	♂	♂	♂	♀	♀	♀
900 IU/kg BW	BAX 855 Lot 1	0-1	0.3	0	0	0.5	0	1	0.5
	BAX 855 Lot 2	0-1	0.4	0.5	1	0	1	0	0
	Advate	0-2	0.8	2	0.5	0.5	0	2	0
20 IU/kg BW	positive control	4 to 4	4	4	-	-	4	-	-

Telemetered Macaques:

Two lots of BAX 855 were administered to male monkeys by intravenous administration at two different doses and telemetry was used, to assess effects on cardiovascular and respiratory systems as well as on body temperature. BAX 855 did not cause any adverse clinical effects; furthermore there were no effects on body weight, blood pressure, respiratory rate, body temperature or electrocardiogram data for both batches tested.

Systolic Blood Pressure [mmHg] in Macaques



Conclusions

- There was no evidence of thrombogenic potential after intravenous treatment with the test item, BAX 855 or the active reference item, ADVATE in rabbits.
- BAX 855, given in single intravenous infusions at dose levels of either 150 IU/kg or 600 IU/kg were well tolerated and did not cause any adverse clinical, respiratory or cardiovascular effects in macaques.

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: Christina Piskernik, Barbara Dietrich, Susan Kubik, Hartmut J. Ehrlich, Friedrich Scheiflinger, Hans Peter Schwarz, Eva-Maria Muchitsch are full-time employees of Baxter Innovations GmbH, Vienna, Austria.

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