

Wyeth Perspective on Inhibitor Development

Jay M. Feingold, M.D., Ph.D.
Senior Director, Global Medical Affairs

November 21, 2003

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2004N-0033

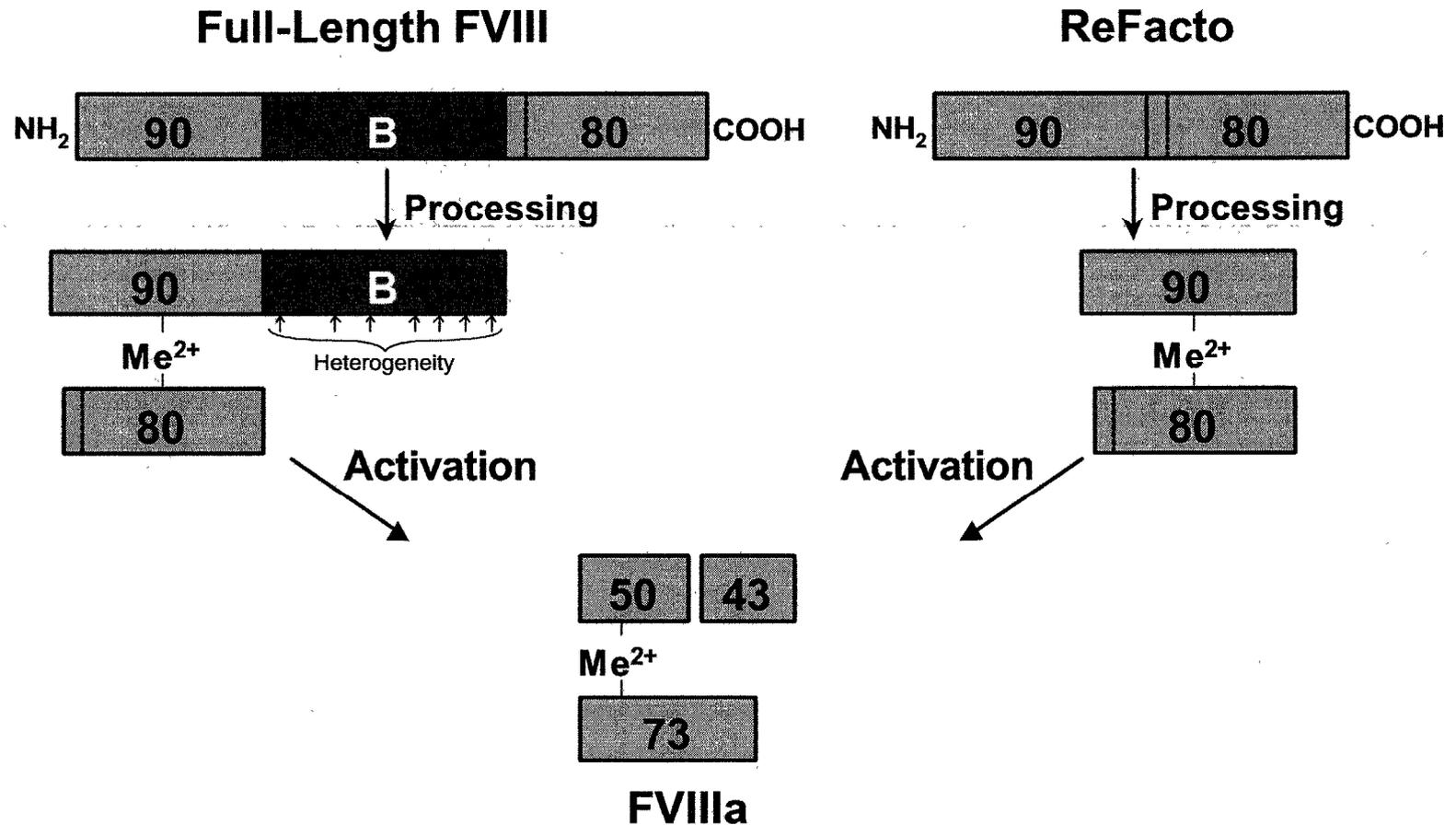
Inhibitors in Hemophilia A

- **Inhibitors are one of the most important safety concerns for all hemophilia patients**
 - ▶ rFVIII and pdFVIII have similar incidence of inhibitors in clinical trials
 - ▶ rFVIII and pdFVIII have low incidence of high-titer inhibitors in PTPs
 - ▶ Literature and registries support these findings
- **Establish uniform standards**
- **Global surveillance program should be implemented for all products**

ReFacto[®] Antihemophilic Factor (recombinant)

- **B-domain deleted recombinant factor VIII (BDDrFVIII)**
- **Produced through a genetically engineered Chinese hamster ovary cell line (CHO)**
- **Designed to correspond to the smallest of the multiple active forms of FVIII found in plasma-derived concentrates**
- **Complexity and heterogeneity have been greatly reduced through the elimination of the B-domain, which is not essential for hemostatic function**

Full-Length Factor VIII and ReFacto



ReFacto Comparable to Full-Length FVIII

- **In vitro functional assessment**

- ▶ vWF binding
- ▶ Thrombin activation
- ▶ Inactivation by activated Protein C
- ▶ FXa generation co-factor activity

- **Detailed structural analysis**

- ▶ Primary protein structure
- ▶ Carbohydrate structure
- ▶ Other post-translational modifications

ReFacto Comparable to Full-Length FVIII

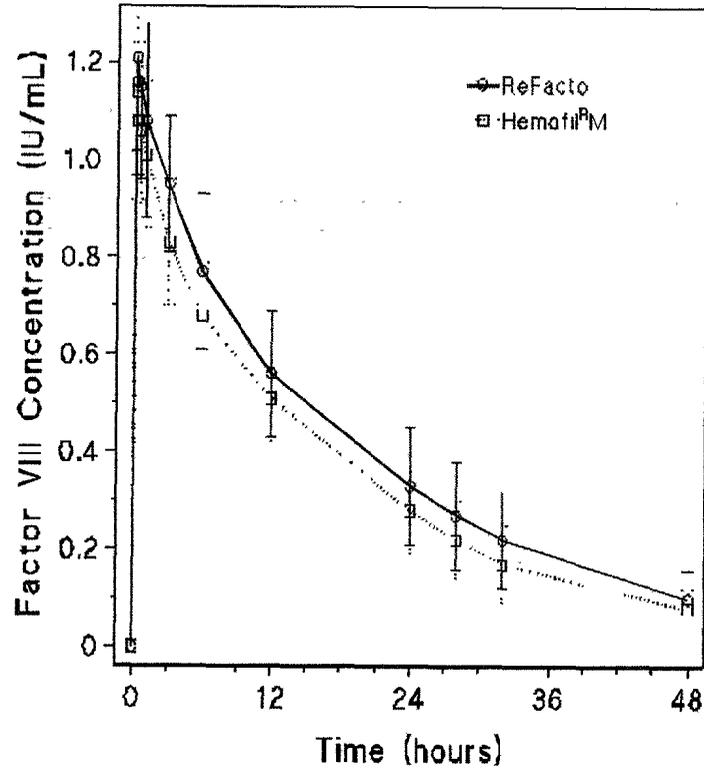
- **Pharmacodynamic studies in canine model of Hemophilia A demonstrate comparability**
 - ▶ Secondary cuticle bleeding times were corrected
 - ▶ Prolonged whole blood clotting times were corrected
 - ▶ Hemostatic correction occurred at the same dose and schedule as full-length FVIII

- **Single and repeated dose toxicity studies demonstrate comparability**
 - ▶ In rat and monkey studies, the toxicity profile is similar to that observed for plasma-derived factor VIII

Extensive Clinical Development Program

- **PK comparability with pdFVIII**
- **Safety / efficacy for bleeding control and prevention**
 - ▶ PTPs
 - ▶ PUPs
 - ▶ Surgery
 - ▶ Routine prophylaxis
 - ▶ On-demand
- **Clinical trials demonstrate ReFacto to be safe and effective**

ReFacto Bioequivalent to FL-pdFVIII



PK Parameters	ReFacto	pdAHF
Elimination half-life (hrs)*	14.5 ± 5.3	13.7 ± 3.4
FVIII activity increase		
IU/dL per IU/kg*†	2.4 ± 0.4	2.3 ± 0.3
In vivo recovery (%)*	118 ± 17	111 ± 14

* Mean ± S.D.

†FVIII activity determined by chromogenic assay

ReFacto Study Design: PUP & PTP Trials

	PUP	PTP
Study Objective	Demonstrate long-term safety & efficacy of prophylaxis / on-demand	
Design	Open-label, non-comparative	
Treatment Plan	Prophylaxis, on-demand, follow-up to 6 years	
Key Eligibility	<ul style="list-style-type: none"> Severe Hemophilia A (< 2% FVIII:C) No history of transfusions with blood products 	<ul style="list-style-type: none"> Severe Hemophilia A (< 2% FVIII:C), age ≥ 7 years >1 year of prophylaxis treatment with FVIII or at least 30 ED / year Absence of past or present inhibitors (≥ 0.6 BU)
Demo-graphics	<ul style="list-style-type: none"> 101 patients Median age: 8 mos (range 0-52) 	<ul style="list-style-type: none"> 113 patients Median age: 26 years (range 8-73)

ReFacto Efficacy

- ReFacto efficacy was demonstrated in PUPs and PTPs
- Duration of treatment

	<u>Years on Study</u>	<u>Percent of Patients</u>
▶ PTPs	4 years	76%
	5 years	64%
	6 years	39%
▶ PUPs	4 years	54%
	5 years	29%
	6 years	5%

- Median ED

▶ PTPs	313 ED
▶ PUPs	197 ED

ReFacto On-Demand Efficacy

	<u>PUP</u>	<u>PTP</u>
Episodes resolved with 1-2 infusions:	85%*	88%
Excellent/Good Ratings:	92%*	92%

* Bleeding episodes in PUPs who were inhibitor-free or until inhibitor detected

ReFacto Prophylaxis Efficacy

Prophylactic dosing reduces the rate of bleeding episodes

	No. bleeding episodes / year	
	On-Demand Periods	Prophylaxis Periods
PUPs		
No. patients	45	45
Mean \pm SD	11.4 \pm 6.0	6.3 \pm 5.2
Median (<i>range</i>)	10.0 (2 - 28)	5.0 (0 - 22)
PTPs		
No. patients	78	85*
Mean \pm SD	24.5 \pm 24.6	10.3 \pm 9.8
Median (<i>range</i>)	20 (0 - 135)	7 (0 - 42)

* Seven (7) patients received prophylactic treatment for their entire time on study.

Factor VIII Inhibitor Testing During Clinical Trials

- **Extensive inhibitor monitoring**
- **Classic Bethesda Inhibitor Assay (BIA)**
 - ▶ Method precision: within 11%
 - ▶ Limit of Quantitation: 0.6 BU/ml
 - ▶ “No inhibitor” < 0.6 BU/ml
- **Three (3) independent BIAs performed centrally**
 - ▶ Normal human plasma test base
 - ▶ ReFacto test base
 - ▶ Nijmegen inhibitor assay

FVIII Inhibitors: ReFacto Clinical Trial Experience Similar to Full-Length FVIII for PUPs and PTPs

PUPs

- **32% (32 out of 101) of patients developed inhibitors**
 - ▶ 16 were low-titer (<5 BU)
 - ▶ 16 were high-titer (\geq 5 BU)
- **Consistent with other clinical trials with other rFVIII products**
- **Number of exposure days prior to inhibitor development**
 - ▶ Median = 12 EDs (range 3 to 49)
- **Inhibitor resolved (0 BU) in 25 of 32 patients (78%)**
 - ▶ 20 of 25 patients who received ITT (Immune Tolerance Therapy)
 - ▶ 5 of 7 patients who did not receive ITT

PTPs

- **1 of 113 (0.9%) patients developed an inhibitor**
 - ▶ Low-titer inhibitor of 1.2 BU at 98 ED
 - ▶ After 18 months, titer increased to 13 BU
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Similar Inhibitor Rates in PTP Clinical Trials

- Schwartz et al., *NEJM* 1990 (1st generation FL rFVIII)
 - ▶ High-titer *de novo* inhibitors developed in 2 of 86 PTP patients (2.3%; CI=0.28- 8.15)*
 - In one of these patients, Western blot analysis of baseline samples detected antibody to factor VIII
- White et al., *Thromb Haemost* 1997 (1st generation FL rFVIII)
 - ▶ Inhibitors developed in 2 of 69 PTP patients (2.9%; CI=0.35-10.08)*
 - 1 patient with a remote history of a previous low-titer inhibitor
 - 1 patient with a low-titer inhibitor at baseline that became a high-titer inhibitor
- Abshire et al., *Thromb Haemost* 2000 (2nd generation FL rFVIII)
 - ▶ Inhibitor developed in 1 of 71 PTP patients (1.4%; CI=0.04-7.60)*
 - This patient had a low-titer inhibitor (0.39 BU) prior to study entry, considered *anamnestic*
- Courter and Bedrosian, *Seminars in Hematology* 2001 (2nd generation BDD rFVIII)
 - ▶ 1 in 113 PTP patients (0.9%; CI=0.02- 4.83) developed an inhibitor

* Based on Wyeth analysis of article

Similar Inhibitor Rates in PTP Post-Marketing Observational Studies

- **McMillan et al., *Blood* 1988 (pdFVIII)**
 - ▶ 3.2% of patients developed inhibitors (n=919)
 - ▶ 26 with ≥ 25 EDs
 - ▶ 14 PTP (1.6%) with high-titer inhibitors (> 5 BU)
 - **Giles et al., *Transf Sci* 1998 (large Canadian experience in PTPs)**
 - ▶ PTP patients switching from plasma-derived factor VIII to recombinant factor FVIII
 - ▶ 1.9% of patients developed inhibitors at 1 year (n=478)
 - ▶ 3.0% of patients developed inhibitors at 2 years (n=339)
 - **NHF (MASAC) 2003 (survey on high-titer inhibitors in PTPs)**
 - ▶ 45 centers responded (approximately 3500 patients)
 - ▶ 12 PTPs (0.35%) with >50 EDs developed high-titer inhibitors in last 3 years
 - 10 recombinant; 2 plasma derived product
 - ▶ 6 of 12 inhibitor patients had more than 250 EDs
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Conclusions from Literature Review

- Reported range for inhibitor development in PTPs: 0.9-3.2%
 - Reported range for high titer inhibitors: 0-2.3%
 - Broad and overlapping confidence intervals exists
 - Definitions for inhibitors vary among reports
 - ▶ High vs. low-titer
 - ▶ *De novo* vs. anamnestic
 - Need for a consistent standard for reporting inhibitors
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Wyeth Post-Marketing Inhibitor Surveillance

- **Wyeth reports any spontaneous event of inhibitor development with or without supportive clinical or laboratory data**
 - ▶ Extensive follow-up data collection
 - Inhibitor specific questionnaire sent to all reporters
 - Follow-up telephone calls
 - **Wyeth definitions for post-marketing inhibitor reports**
 - ▶ No central laboratory testing performed
 - ▶ Positive titer: ≥ 0.6 BU
 - ▶ High-titer: ≥ 5.0 BU
 - ▶ Positive history of inhibitor: any previous titer ≥ 0.6 BU
 - ▶ *De novo*: no prior history of inhibitor ≥ 0.6 BU
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Post-Marketing Experience with ReFacto*

- **Estimated 5800 patients treated worldwide**
 - ▶ 1450 PUPs
 - ▶ 4350 PTPs
- **83 reports of inhibitors**
 - ▶ 31 PUPs
 - ▶ 24 classified as:
 - 12 unknown ED or < 50 ED to all FVIII products
 - 7 history of inhibitor prior to ReFacto therapy
 - 4 inadequate medical history information
 - 1 no titer obtained
- **Therefore, 28 *de novo* inhibitors in PTPs with >50 ED to all FVIII products**
 - ▶ 20 low-titer (0.5%)
 - ▶ 8 high-titer (0.2%)

* Through April 2003

Initiatives in PTP Inhibitor Monitoring

- **Data in PTPs reporting inhibitors has led to a broad discussion**
 - ▶ Canadian prospective inhibitor surveillance
 - 3% incidence at two years
 - ▶ Review of UK inhibitor database
 - No product specificity
 - ▶ MASAC survey
 - High-titer inhibitors seen with pdFVIII and rFVIII
 - ▶ ISTH – interest in global surveillance program

Conclusions/Recommendations

- **Clinical trials, literature, and registries support:**
 - ▶ rFVIII and pdFVIII products have similar incidence of inhibitors
 - ▶ rFVIII and pdFVIII products have low incidence of high-titer inhibitors in PTPs
- **Global prospective surveillance needed to assess incidence of inhibitor development**
 - ▶ Defined period of patient observation
 - ▶ Standardized data collection techniques and definitions
 - ▶ Gathering of complete patient information including serial inhibitor testing, genotyping and other relevant data
- **Standardized spontaneous data collection leading to data-driven labeling**