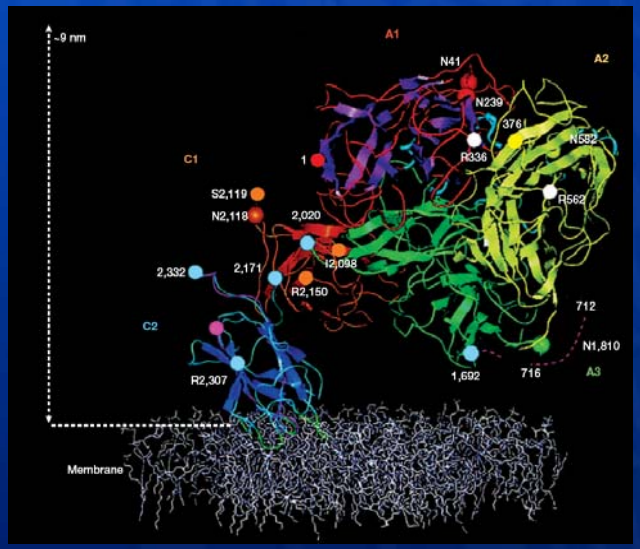
Update Hämophilie Behandlung



Sabine Heine

Universitätsklinik für Kinder- und Jugendmedizin
Universitätsklinikum des Saarlandes

Hämophiliesymposium Homburg / Saar

21.11.2009

ISTH·2009
BOSTON

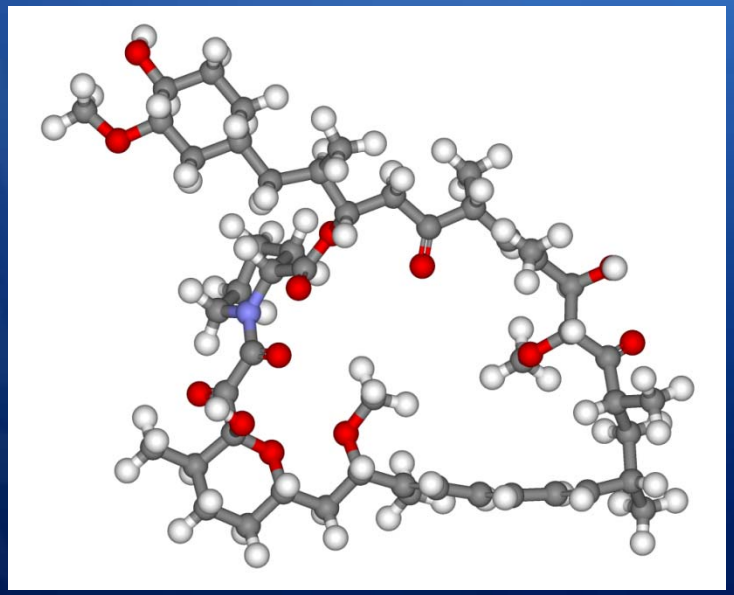
XXII Congress - July 11 - 16, 2009

International Society on
Thrombosis and Haemostasis

B. Moghimi *et al* (Gainesville, FL, USA)

Novel tolerance protocol for factor VIII

- Neues Immuntolerenzprotokoll für Faktor VIII bei hämophilen Mäusen:
- Rapamycin im Futter für vier Wochen vor Gabe von Faktor VIII
  - Keine Inhibitorbildung




Cabo Norte
Punta San Juan
Maunga Terevaka
Volcán Rana Roi
OSTERINSEL
Cabo O'Higgins
Volcán Rana Roraka
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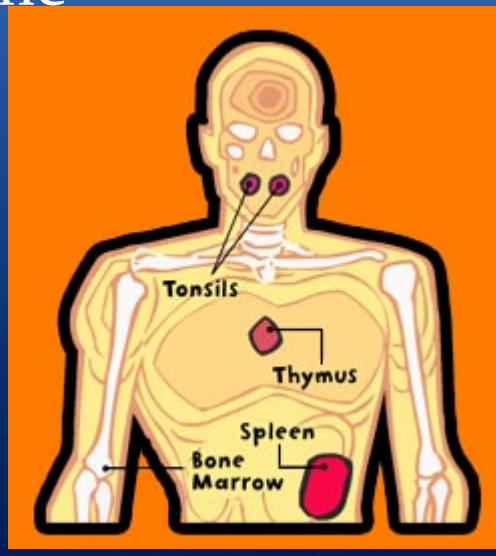
Asunción
Córdoba
Porto Alegre
Santiago
Rosario
Buenos Aires
Montevideo
PAZIFISCHER OZEAN
ATLANTISCHER OZEAN

S. Madoiwa *et al* (Shimotsuke, Japan)

Intrathymic administration of F VIII results in immune tolerance by induction of TREGs

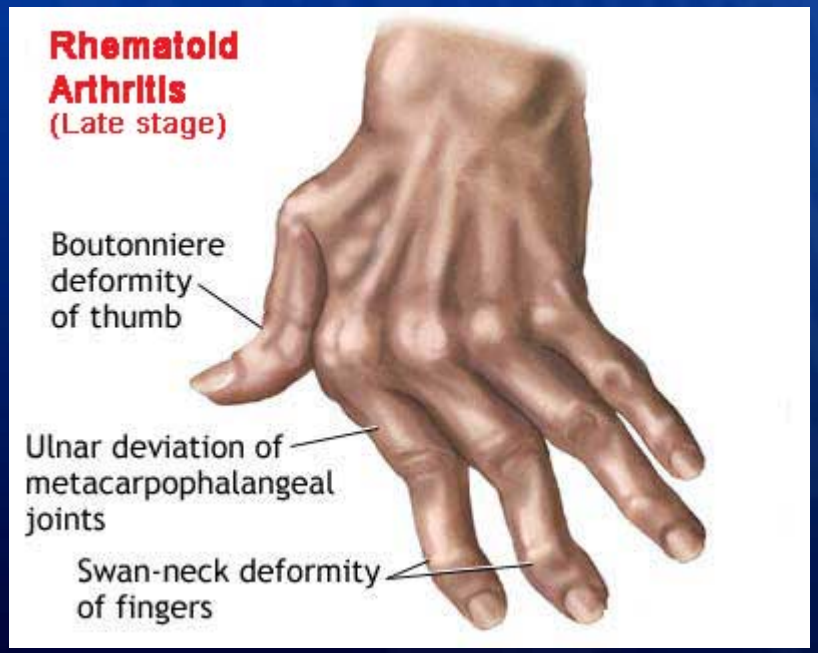
- Injektion von rec F VIII in Thymus von hämophilen Mäusen
- Wesentlich niedrigere Inhibitor Titer
  - Immuntoleranz durch F VIII-spezifische TREGs



J. Sun *et al* (Chapel Hill, NC, USA)

TNF-α antagonists augment factor replacement to prevent arthropathy

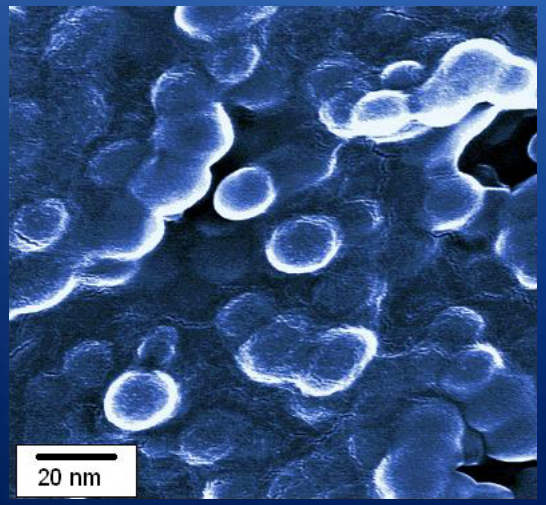
- Bei hämophilen Mäusen verhindert frühzeitige anti-TNF α Gabe die hämophile Arthropathie



S. Dhadwar *et al* (Hamilton, Kanada)

Oral administration of chitosan FVIII DNA nanoparticles results in FVIII antigen in blood

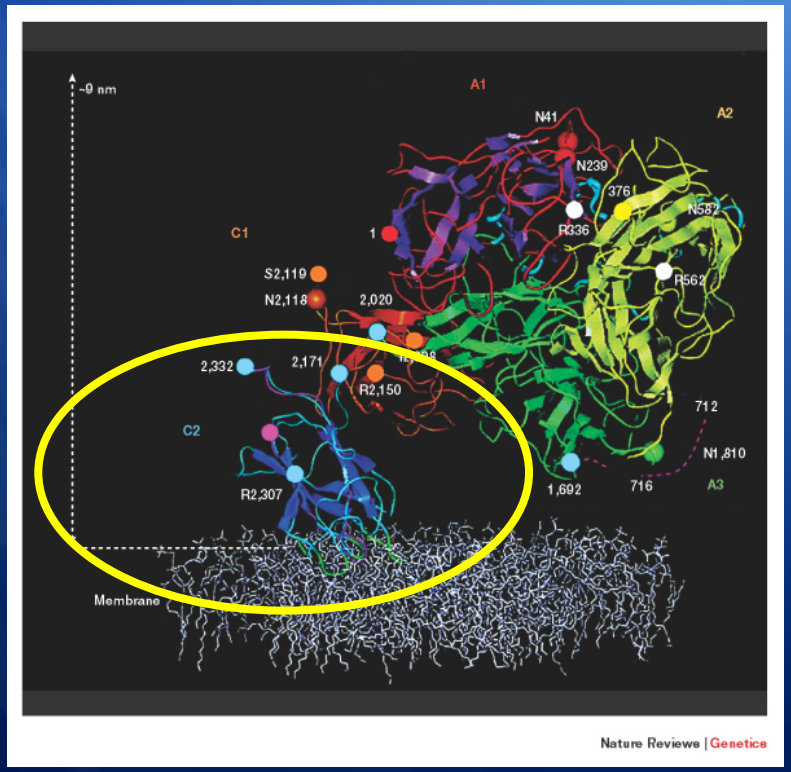
- Orale Gabe von Chitosan Nanopartikeln mit FVIII DNA führte bei hämophilen Mäusen zu
  - Faktor VIII Proteinnachweis im Blut und
  - verminderter Blutungszeit



J. Gilles *et al* (Leuven, Belgien)

Neutralisation of a C2 domain-specific human anti-F VIII inhibitor by an anti-idiotypic AB

- Entwicklung eines Antikörpers <u>gegen</u> FVIII-AK
  - verminderter Blutungszeit



H. Lee *et al*

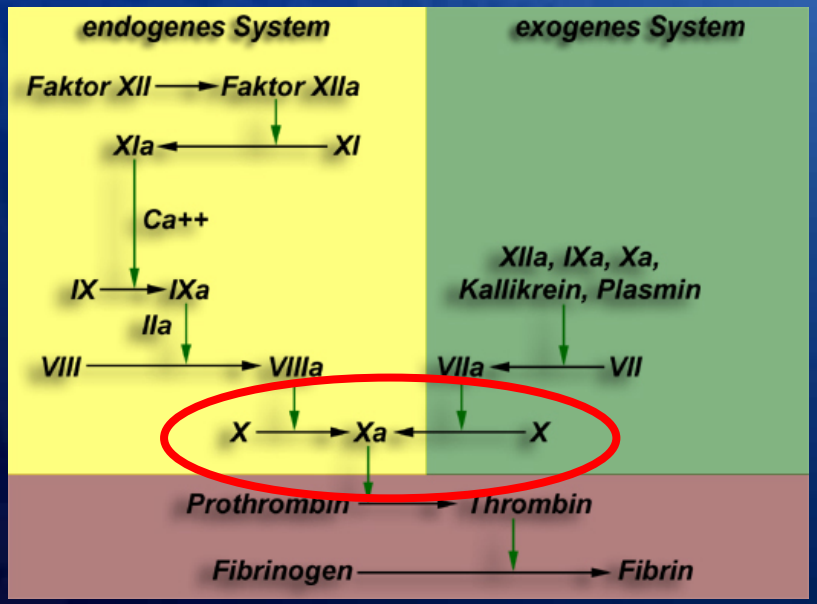
Production of recombinant human vWF in the milk of transgenic pigs

- Rekombinanter vWF konnte aus der Milch von transgenen Schweinen gewonnen werden

P. Gueguen *et al.* (Marseille, Frankreich)

Development of a novel tenase-bypassing agent with a prolonged half-life in vivo

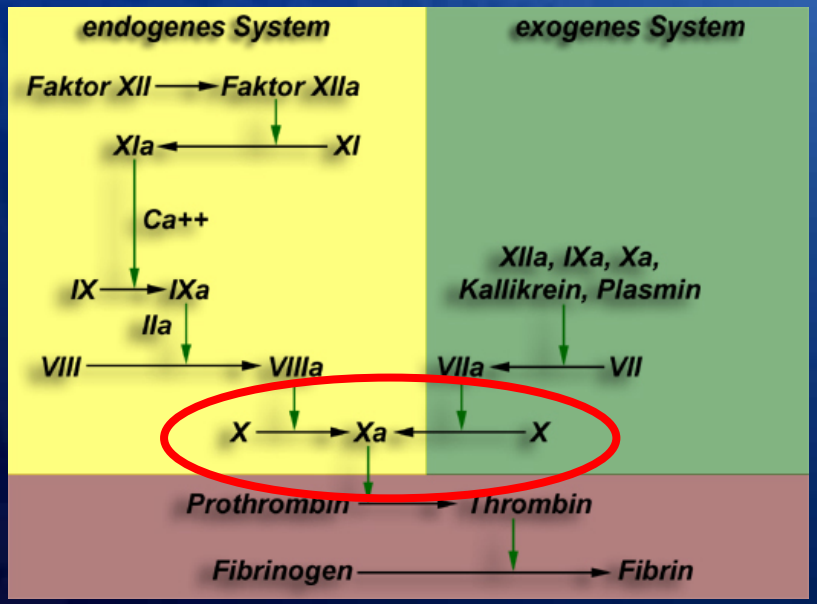
- Synthetischer F X führt bei hämophilen Mäusen zur Thrombusbildung
- FX hat längere Halbwertszeit (40 h) als rFVIIa



T. Liu *et al.* (Richmond, VA, USA)

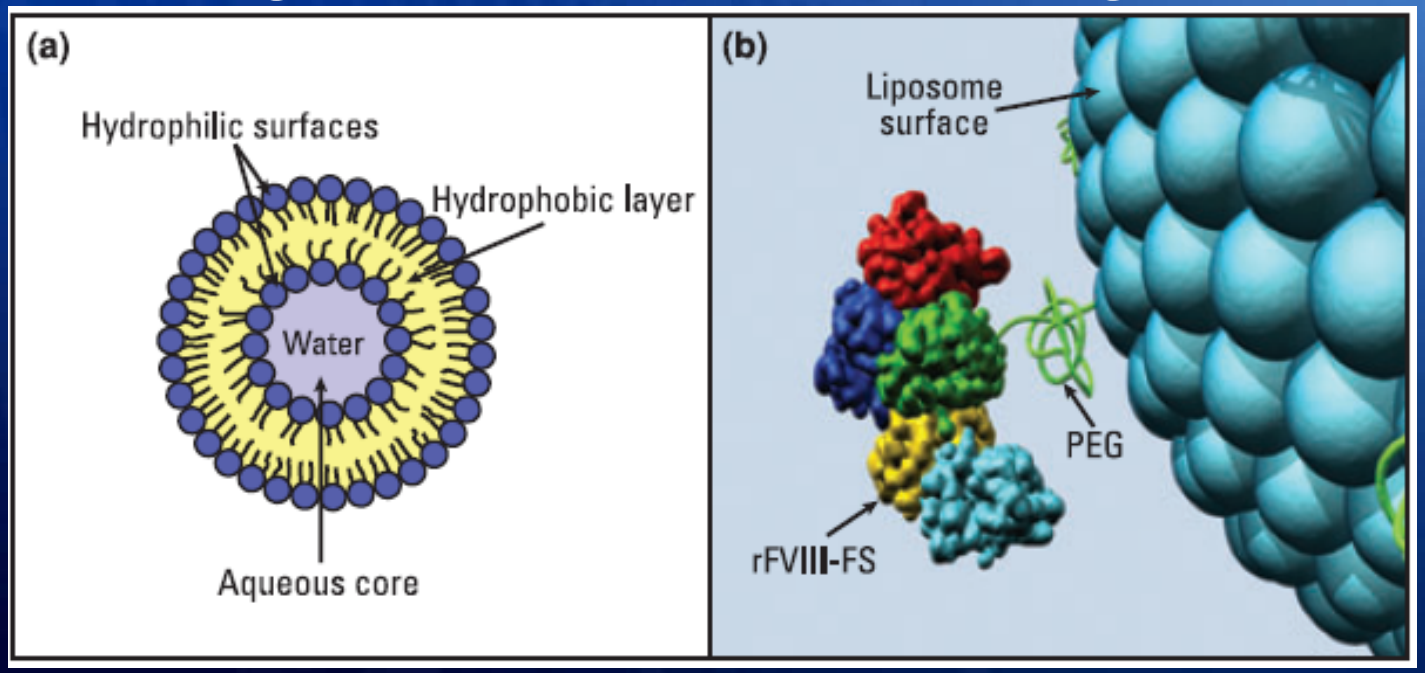
Novel rFVIIa variant (BAY86-6150)

- Neuer rFVIIa bei hämophilen Mäusen
  - in niedrigeren Dosen wirksam
  - längere Halbwertzeit



Strategien für länger wirkenden F VIII

- PEG enthaltender liposomaler Träger für Kogenate
  - 32 PTPs (35 IU/kg) 1*, dann 7 Tage Pause
  - Verlängert Zeit bis zur nächsten Blutung



Kogenate Liplong Study - BAY 79-4980 Compared to rFVIII-FS in Previously Treated Patients With Severe Hemophilia A

This study is currently recruiting participants.
Verified by Bayer, July 2009

First Received: January 9, 2008 Last Updated: July 31, 2009 History of Changes

Sponsor:	Bayer
Information provided by:	Bayer
ClinicalTrials.gov Identifier:	NCT00623727

Purpose

A study to assess treatment with a new formulation of recombinant factor VIII reconstituted with liposomes (Bay 79-4980) to evaluate whether a once-a-week treatment is safe and can prevent bleeds in subjects with severe haemophilia A.

Condition	Intervention	Phase
Hemophilia A	Drug: BAY 79-4980 Drug: BAY 14-2222	Phase II

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study

Official Title: Randomized, Active-controlled, Double-blind, Parallel Design Study to Evaluate the Efficacy and Safety of a Once-a-week Prophylaxis Treatment With BAY 79-4980 Compared to Three Times-per-week Prophylaxis With rFVIII-FS in Previously Treated Patients With Severe Hemophilia A

Further study details as provided by Bayer:

Primary Outcome Measures:

- The primary efficacy variable will be the percentage of subjects with less than 9 total bleeds per year. [Time Frame: 1 year] [Designated as safety issue: No]

Secondary Outcome Measures:

- Number of Bleeds, [Time Frame: 1 year] [Designated as safety issue: No]
- Treatment of bleeds, [Time Frame: 1 year] [Designated as safety issue: No]
- Consumption of FVIII, [Time Frame: 1 year] [Designated as safety issue: No]
- Quality of life [Time Frame: 1 year] [Designated as safety issue: No]

Estimated Enrollment: 260
Study Start Date: June 2008
Estimated Study Completion Date: December 2010
Estimated Primary Completion Date: December 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Arm 1: Experimental	Drug: BAY 79-4980 35 IU/kg body weight IV 1x/week for 52 weeks
Arm 2: Active Comparator	Drug: BAY 14-2222 25 IU/kg body weight IV 3x/week for 52 weeks

Safety and Efficacy of 3 Different Doses of Long Acting Factor VII in Haemophilia A or B Patients With Inhibitors

This study is currently recruiting participants.
Verified by Novo Nordisk, November 2009

First Received: August 3, 2009 Last Updated: November 2, 2009 History of Changes

Sponsor:	Novo Nordisk
Information provided by:	Novo Nordisk
ClinicalTrials.gov Identifier:	NCT00951405

Purpose

This trial is conducted in Asia, Europe, Japan and North America. The aim of this clinical trial is to investigate the safety and the efficacy of a prophylactic treatment option with long acting coagulation factor VII (LA-rFVIIa) for haemophilia patients with inhibitors.

Condition	Intervention	Phase
Haemophilia A or B With Inhibitors	Drug: activated recombinant human factor VII, long acting	Phase II

Study Type: Interventional
Study Design: Prevention, Randomized, Double Blind (Subject, Investigator), Dose Comparison, Parallel Assignment, Safety/Efficacy Study

Official Title: An Exploratory Multi-Centre, Multi-National, Randomised, Double Blinded, Parallel Arm Trial Evaluating Safety, Pharmacokinetics and Dose-finding of Prophylactic Administration of Long Acting rFVIIa (LA-rFVIIa) in Haemophilia A or B Patients With Inhibitors

Further study details as provided by Novo Nordisk:

Primary Outcome Measures:

- Thrombogenecity [Time Frame: at all scheduled visits (1 - 9)] [Designated as safety issue: Yes]
- Immunogenecity: Neutralising Antibody Development [Time Frame: at all scheduled visits (1 - 9)] [Designated as safety issue: Yes]

Arms	Assigned Interventions
A: Experimental	Drug: activated recombinant human factor VII, long acting After an observation period of 3 months, every 2nd day intravenous (i.v.) injection with 25 microgrammes/kg activated recombinant human factor VII, long acting, for 3 months
B: Experimental	Drug: activated recombinant human factor VII, long acting After an observation period of 3 months, every 2nd day intravenous (i.v.) injection with 100 microgrammes/kg activated recombinant human factor VII, long acting, for 3 months
C: Experimental	Drug: activated recombinant human factor VII, long acting After an observation period of 3 months, every 2nd day intravenous (i.v.) injection with 200 microgrammes/kg activated recombinant human factor VII, long acting, for 3 months

Study of Recombinant Porcine Factor VIII (FVIII) in Hemophilia and Inhibitors to FVIII

This study has been completed.

First Received: October 25, 2005 Last Updated: October 2, 2007 History of Changes

Sponsor:	Octagen Corporation
Collaborator:	Biomeasure Inc, Ipsen Group
Information provided by:	Octagen Corporation
ClinicalTrials.gov Identifier:	NCT00245245

Purpose

The ability of a new recombinant porcine coagulation factor VIII, B-domain deleted (called "OBI-1"), to control the non-life- or limb-threatening bleeding episodes patients with hemophilia A commonly develop is being evaluated. Patients with congenital hemophilia A and a low-titer (<20 Bethesda units [Bu]) inhibitory antibody to OBI-1, who meet the inclusion/exclusion criteria, will receive OBI-1 to treat their soft tissue or joint bleeding episode. At least the first two treatment episodes will be performed in the controlled setting of the hemophilia center/clinic/office, where any side effects can be observed. If the patient continues to meet the inclusion/exclusion criteria, has had no serious or severe adverse reactions to OBI-1, and has been in a home care program, the investigator may permit the patient to self-administer OBI-1 at home to treat subsequent bleeding episodes. The study will continue at least until 12 or more patients have received at least 24 treatment episodes in the aggregate.

Condition	Intervention	Phase
Hemophilia A	Drug: recombinant porcine coagulation factor VIII (OBI-1)	Phase II

Study Type: Interventional
Study Design: Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study

Official Title: An Open-Label Study of the Hemostatic Activity, Pharmacokinetics and Safety of OBI-1 (B-Domain Deleted Recombinant Porcine FVIII), When Administered by Intravenous Injection, to Control Non-Life and Non-Limb Threatening Bleeding Episodes in Congenital Hemophilia A Patients With an Inhibitor to Human FVIII

Further study details as provided by Octagen Corporation:

Primary Outcome Measures:

- The percentage of successful treatment episodes, defined as having achieved control of the bleeding episode within One Loading Dose and 8 or fewer Treatment Doses, with a dose limit of 1000 U/kg in 24 hours

Secondary Outcome Measures:

- Adverse events and serious adverse events observed throughout course of study
- Pattern of inhibitory antibody response to OBI-1 following treatments
- The percentage of patients who continue to qualify because their anti-OBI-1 titer remains at 20 Bu or less
- Pharmacokinetics of OBI-1 when it is administered for treatment of a qualifying bleeding episode, in the absence of an inhibitory antibody to OBI-1

Estimated Enrollment: 12
Study Start Date: May 2005
Study Completion Date: June 2007

Pharmacokinetic, Safety and Tolerability Study of Recombinant Von Willebrand Factor / Recombinant Factor VIII Complex in Type 3 Von Willebrand Disease

This study is currently recruiting participants.
Verified by Baxter Healthcare Corporation, October 2009

First Received: January 2, 2009 Last Updated: October 15, 2009 History of Changes

Sponsor:	Baxter Healthcare Corporation
Information provided by:	Baxter Healthcare Corporation
ClinicalTrials.gov Identifier:	NCT00816660

Purpose

The objectives of this study are to evaluate the immediate tolerability and safety of rVWF:rFVIII in subjects with Type 3 Von Willebrand Disease after administration of various dosages of VWF:RCo.

Condition	Intervention	Phase
Von Willebrand Disease	Biological: Recombinant von Willebrand factor : recombinant FVIII (rVWF:rFVIII) Biological: Marketed plasma-derived VWF/FVIII concentrate	Phase I

Study Type: Interventional
Study Design: Randomized, Single Blind (Subject), Active Control, Crossover Assignment, Safety Study

Official Title: Recombinant Von Willebrand Factor / Recombinant Factor VIII Complex (rVWF:rFVIII): A Phase 1 Study Evaluating the Pharmacokinetics (PK), Safety, and Tolerability in Type 3 Von Willebrand Disease (VWD)

Further study details as provided by Baxter Healthcare Corporation:

Primary Outcome Measures:

- To demonstrate the immediate tolerability and safety after single-dose injections of rVWF:rFVIII at various doses [Time Frame: Up to 30 days after the last investigational product infusion] [Designated as safety issue: Yes]

Estimated Enrollment: 31
Study Start Date: December 2008
Estimated Primary Completion Date: March 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
1: Experimental	Biological: Recombinant von Willebrand factor : recombinant FVIII (rVWF:rFVIII) Single dose, dose escalation, various cohorts
2: Active Comparator	Biological: Recombinant von Willebrand factor : recombinant FVIII (rVWF:rFVIII) Single dose, dose escalation, various cohorts Biological: Marketed plasma-derived VWF/FVIII concentrate Cross-over: recombinant FVIII (rVWF:rFVIII) and marketed plasma-derived VWF/FVIII concentrate