Novel Treatment Options for Hemophilia treatment

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Bayer Hemophilia Care
FVIII therapy
FVIIa therapy
Summary & Perspectives
The beginning of a new era in Bayer’s approach to Hemophilia

Franchise vision
For people living with and managing hemophilia, Bayer—Hemophilia Care - healthcare partner of choice. Bayer—Hemophilia Care - raising the bar for scientific innovation and research that will help solve unmet clinical needs and improve the standard of care.

Our goal is for all people with hemophilia to confidently live the lives they choose.
Despite several improvements since the first recombinant FVIII in the early 90s, significant unmet needs remain for Hemophilia patients:

- Reduced dosing frequency for prophylaxis
- Elimination of human/animal proteins
- Reduction of inhibitor formation
- Heat stable formulation of products
- Non-invasive administration routes
- Cure (future breakthroughs in gene or stem cell therapies)
Introduction

FVIII therapy

FVIIa therapy

Summary & Perspectives
Bay 94-9027 contains a single site-specific PEGylation that results in:

- Retention of full coagulation activity in preclinical models
- Normal VWF binding in-vitro
- Increased half-life (2x in animal models)
- Prolonged efficacy in bleeding models (2x)
- Reduced pre-clinical immunogenicity

Does PEGylation Block Antigen Uptake?

Adapted from Chirino et al., Drug Discovery Today, 2004
Reduced Internalization of PEG-BDD-rFVIII in Human Dendritic Cells

> 80% reduction in PEG-BDD-rFVIII uptake

Murphy et al, Jul 28, 2011
PEGylation Reduces FVIII’s Immunogenicity by Blocking Antigen Uptake by DC’s

Reduced generation of peptide antigens
Reduced PEG-protein internalization
Hampered presentation of PEGylated peptides
Reduced T cell response
Induction of tolerizing APC
Reduced Ab formation

BAY 94-9027 also shows reduced activation of FVIII-specific T cells from Inhibitor patients

Murphy et al, Jul 28, 2011
PEGylation of FVIII BDD Reduces Antibody Formation in HemA Mice

Ab induction also reduced in rats and rabbits

Ivens et al, Poster # 202, July 26, 2011
BAY 94-9027 PEGylation Results in Reduction of Preclinical Immunogenicity

“Significant reduction in FVIII-specific IgG response in murine and rabbit in vivo models”

“Significant reduction in uptake by human DCs in vitro”

Adapted from Chirino et al., Drug Discovery Today, 2004
An open-label Phase I trial to evaluate the pharmacokinetics and safety profile of BAY 94-9027 following single and multiple dose administration in previously treated male subjects with severe hemophilia A.

Objectives:

- Assess the PK of BAY 94-9027 following administration of single and multiple doses of BAY 94-9027.
- Assess the safety of BAY 94-9027 administered over a period of 8 weeks.
BAY 94-9027: Study 13401 - Design

Multi-center (6 centers), non-randomized, non-blinded parallel-group design.

BAY 94-9027 given in two separate cohorts receiving different dosages with multiple administration over 8 weeks.

Sample size: 12 - 16 (N=~8/cohorts). Minimum number of valid subjects with complete study treatments: 12 subjects
Cohort 1 completed study

- N=7
- 25 IU/kg twice weekly

Cohort 2 enrollment completed

- N=7
- 60 IU/kg once weekly
- 7 subjects completed (LPLV Sept 19)
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BAY 86-6150 – A Novel FVIIa with Improved PK and Localized Efficacy

Bay 86-6150 contains 6 amino acid changes, resulting in:

- Increased binding to activated platelets
- Increased Thrombin generation
- Reduced activity with TF
- Increased efficacy in animal models
- Increased half-life and prolonged efficacy in animal models

Phase I in PWH completed confirming improved PK
BAY 86-6150 has a Wider Thrombogenic Index than rFVIIa in Preclinical Models

Hemophilia mice:

- Joint injury – dosed 10min after injury:
  - 6 fold more potent than rFVIIa as on-demand treatment
  - At efficacious doses, no indication of systemic activation of coagulation

Dosed 1hr prior to injury:

- 25 fold more potent than rFVIIa in tail vein transection model
- 2 fold lower doses required in FeCl artery thrombosis model

Rabbits:

- Cuticle bleeding model in FVIII Ab-induced HemA rabbits
  - ~4 fold more potent than rFVIIa dosed 3min after injury

- Venous stasis model in WT rabbits
  - Thrombus weights and scores similar to wt rFVIIa
Summary and Perspectives

Bayer Pipeline
Committed to research and development of innovative hemophilia treatments and expanding scientific and clinical knowledge that improves patient care
Rich pipeline of hematology compounds that may have potential to increase convenience and help patients remain compliant with their treatment regimen

Key Compounds in Development
Directly PEGylated BDD-rFVIII (BAY 94-9027) has shown extended half-life and efficacy in hemophilic mice and dogs

- Optimizing prophylaxis therapy with long-acting product while preserving efficacy to treat on-demand
- Phase I study ongoing
Summary and Perspectives

Key Compounds in Development, continued

BAY 86-6150 for increased thrombin burst generation at reduced clearance to enable effective bypass therapy

- Phase I study completed successfully
- Phase II/III to start 2012

Other novel clotting factors and bypass compounds are being researched and evaluated
Summary And Perspectives

An emerging pipeline of differentiated products will establish BAYER HEMOPHILIA CARE as a comprehensive hemophilia care provider.

Replacement Factor Era

1969
Plasma-derived Factor VIII and Factor IX Concentrates

1994
KOGENATE® FS/Bayer

2000
KOGENATE® FS/Bayer

2005
KOGENATE® FS/Bayer with BIO-SET®

2011
KOGENATE® FS / Bayer

Comprehensive Care Era

Pipeline

(BAY 81-8973)
(BAY 94-9027)
(BAY 86-6150)
Thank you!