WFH requires the following disclosures be made at each presentation:

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tbody>
<tr>
<td>Research Support</td>
<td>Employee of CSL Behring</td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td>Employee of CSL Behring</td>
</tr>
<tr>
<td>Shareholder</td>
<td>NA</td>
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<td>Honoraria</td>
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<td>Advisory Committee</td>
<td>NA</td>
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<tr>
<td>Consultant</td>
<td>NA</td>
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</table>
Pioneering designs for recombinant coagulation factors

Debra Bensen-Kennedy, MD
Clinical Research & Development
CSL Behring

23 Sept 2011
A commitment to the treatment of bleeding disorders

CSL Behring has the broadest range of coagulation factor concentrates – plasma-derived and recombinant – in the world, including those for the treatment of rare bleeding disorders.

As a natural evolution of our commitment to the hemophilia and bleeding disorders community, the company is pursuing a number of development activities, including pioneering recombinant technology.
Avenues for improving coagulation factors

• Improved functional activity
• Reduced immunogenicity
• Alternative delivery
• Half-life extension
  • Less frequent injections
  • Improved compliance
  • May enable prophylaxis
Challenge: half-life extension of coagulation factors

- Identify the optimal half-life extension method
  - Chronic therapy ↔ acute therapy

- Preserve biological activity
  - Half-life extension ↔ biological activity

- Immunogenicity and tolerability
  - Safety ↔ improved therapy
Half-life extension of activated factor VII (FVIIa) and factor IX (FIX)

• **Recombinant activated factor VII (rFVIIa)** – indicated for treatment of patients with inhibitors to factor VIII (FVIII) or factor IX (FIX)
  - Half-life ~2.4 h
  - Several infusions required for treatment:
    - Joint bleeding: ≥2
    - Surgery: every 2–3 h for ≥2 days
  → Goal for half-life extension: **one infusion per bleeding event**

• **Recombinant factor IX (rFIX)** – indicated for treatment of hemophilia B
  - Half-life ~20 h
  - 2–3 infusions required per week
  → Goal for half-life extension: **one infusion per week**
Albumin Fusion technology to improve the half-life of coagulation factors

- **Albumin as a recombinant fusion partner**
  - Albumin has a naturally long half-life (~20 days)
  - A carrier protein which is inherently inert to the immune system
  - Clearance mechanism understood
  - Proof of principle shown with fusion with other complex proteins
  - Albumin fusion proteins are expressed as a single recombinant entity

---

Diagram:

- **Recombinant coagulation factor** (Short half-life) + **Recombinant albumin** (Long half-life) = **Recombinant albumin fusion** (Half-life extension)
Generation of recombinant albumin fusion proteins

- Genetic fusion of the coagulation factor with full-length albumin
  - DNA-construct that codes for both proteins
  - Expressed as a single recombinant molecule
- Transfection of the DNA into eukaryotic cell lines
  - Selection
  - Protein is secreted
  - Post-translational modifications
- Fermentation
- Purification
- Characterization
  - Biological activity, pharmacokinetics, efficacy
Albumin extends half-life of recombinant FVIIa (rVIIa-FP): recombinant fusion protein linking coagulation FVIIa with albumin (rVIIa-FP)

![Graph showing % activity increase vs. linker length (aa)]

- FVIIa 406 aa
- Albumin 585 aa

![Bar graph showing total blood loss [μL]]

- Vehicle
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

n=10-70 mean±SEM

![Line graph showing hu FVII [ng/mL]]

- NovoSeven, 0.9 mg/kg
- rVIIa-FP CSL 689, 0.9 mg/kg

species: rat
n=2-4/timepoint
mean ± SD
Albumin extends half-life of recombinant FIX (rIX-FP): recombinant fusion protein linking coagulation FIX with albumin (rIX-FP)

Pharmacokinetic (PK) study with rIX-FP (CSL654) in cynomolagus monkeys

- Recombinant factor IX-fusion protein (rIX-FP) given as an intravenous (IV) dose of 50 or 100 IU/kg (n=4)

- Antigen FIX plasma levels measured for PK profile
rIX-FP (CSL654): PK study in monkeys

CSL Behring. Data on file
rIX-FP (CSL654): PK study in monkeys
>3-fold half-life extension

<table>
<thead>
<tr>
<th></th>
<th>50 IU/kg</th>
<th>100 IU/kg</th>
<th>BeneFIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h*IU/L)</td>
<td>36,800</td>
<td>74,900</td>
<td></td>
</tr>
<tr>
<td>$T_{1/2}$ elim.(h)</td>
<td>41</td>
<td>47</td>
<td>13*</td>
</tr>
</tbody>
</table>

CSL Behring. Data on file
*McCarthy et al. Thromb Haemost 2002; 87: 824–830
rIX-FP (CSL654): PK and pharmacodynamic (PD) study in hemophilia B dogs

- rIX-FP (n=3) or BeneFIX (rFIX, n=2) was given as an IV dose of 100 IU/kg

- Antigen FIX plasma levels measured for PK (area under the curve [AUC], half-life, $C_{\text{max}}$, clearance, 5% level)

- Activated partial thromboplastin time (aPTT) measured as PD parameter
rIX-FP (CSL654): PK study in hemophilia B dogs

CSL Behring. Data on file
rIX-FP (CSL654): study in hemophilia B dogs – aPTT
rIX-FP (CSL654): PK parameters in hemophilia B dogs

<table>
<thead>
<tr>
<th></th>
<th>rIX-FP (100 IU/kg)</th>
<th>BeneFIX (100 IU/kg)</th>
<th>Effect ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h*IU/L)</td>
<td>35,600</td>
<td>10,700</td>
<td>3.3</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (IU/L)</td>
<td>961</td>
<td>608</td>
<td>1.6</td>
</tr>
<tr>
<td>T&lt;sub&gt;½&lt;/sub&gt; elimination (h)</td>
<td>54</td>
<td>33</td>
<td>1.6</td>
</tr>
<tr>
<td>Clearance (mL/kg/h)</td>
<td>2.8</td>
<td>9.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Days above 5%</td>
<td>7.1</td>
<td>2.3</td>
<td>3.1</td>
</tr>
</tbody>
</table>

CSL Behring. Data on file
rIX-FP (CSL654): pharmacology/toxicology studies completed

- No adverse effects of treatment observed following intravenous administration of rIX-FP in all species tested
  - Rat, rabbits and monkeys
  - 75, 150 and 500 IU/kg

- PK and PD studies performed in hemophilia B dogs
  - Whole blood clotting time (WBCT) and aPTT reduced
  - >3-fold higher AUC than BeneFIX

- PK study performed in monkeys
  - >3-fold half-life extension observed

Phase I PK and Phase I/II study listed on www.clinicaltrials.gov

CSL Behring. Data on file
CSL627: Single chain recombinant factor VIII (rFVIII)
Single chain rFVIII: CSL’s approach for an improved FVIII

- FVIII’s physiological partner in plasma is von Willebrand factor (VWF)\(^1\)
  - The FVIII/VWF complex plays an important role in the physiological activity and clearance of FVIII and has been shown to have an influence on the presentation of FVIII to the immune system.
  - **Aim: Improve binding with VWF**

- FVIII is an unstable molecule in the manufacturing environment
  - Possible dissociation of FVIII heavy and light chain may affect on stability and potency
  - **Aim: Improve molecular stability**
CSL627: Single chain rFVIII

- **Increased heavy/light chain association**
  - Covalent linkage between heavy and light chain.
  - Expressed as a single chain rFVIII
  - Enhanced molecular integrity demonstrated

- **Very strong affinity to von Willebrand factor (VWF)**
Single chain rFVIII (CSL627): surface plasmon resonance (SPR) analysis

Binding to plasma-derived (pd) VWF

Comparison of VWF affinity constants

CSL Behring. Data on file
Single chain rFVIII (CSL627): summary & conclusions

• Unique rFVIII design
  • Very strong affinity for VWF with faster and more efficient binding
  • Improved stability
• Comparable efficacy
  • Tail tip bleeding model
• Entering formal development phase
Biostate®
Clinical Development Program

SWIFT
Studies with von Willebrand Factor/Factor VIII
Biostate®

• A highly active plasma derived VWF/FVIII concentrate
  • VWF/FVIII ratio ≈ 2.2:1
  • High content of High Molecular Weight VWF Multimers

• Launched in Australia in 2003 in Haemophilia A

• Registered in Australia and New Zealand since September 2008 in von Willebrand Disease (vWD)

• Current trial program will enable EU centralized approval
## Biostate® - SWIFT Program

<table>
<thead>
<tr>
<th>Study</th>
<th>VWD SWIFT-VWD</th>
<th>VWD SWIFTLY-VWD</th>
</tr>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>• Approximately 25 Patients with VWD (type 1, 2a or 3)</td>
<td>• Approx. 12 patients (0-12yrs) with VWD (type 1, 2a or 3)</td>
</tr>
<tr>
<td></td>
<td>• 12 years and older</td>
<td></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td><strong>Primary Study Objectives</strong></td>
<td><strong>Primary Study Objectives</strong></td>
</tr>
<tr>
<td></td>
<td>• PK profile</td>
<td>• Haemostatic efficacy in subjects with vWD</td>
</tr>
<tr>
<td></td>
<td>• Haemostatic efficacy in subjects with VWD to control a non-surgical bleeding event (NSB)</td>
<td>• PK profile</td>
</tr>
<tr>
<td></td>
<td>• Effectiveness of a prophylaxis regime as compared to on-demand therapy in preventing NSB event</td>
<td><strong>Secondary Study Objectives:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Safety of Biostate®</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary Study Objectives:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Safety when used as on-demand therapy to treat NSB events and as prophylactic therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Haemostatic efficacy for subjects who undergo surgical procedures during the study period</td>
<td></td>
</tr>
</tbody>
</table>
## Biostate® - SWIFT Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Hemophilia A SWIFT-HA</th>
<th>Hemophilia A SWIFTLY-HA</th>
</tr>
</thead>
</table>
| Patients | • Approx. 80 male patients with severe hemophilia A  
• 12 years and older | • Approx. 20 male patients (0-12yrs) with severe hemophilia A |
| Objectives | Primary Study Objectives  
• Efficacy  
• Comparability of the PK of Biostate® [RP] and Biostate® [SP]  
Secondary Objectives  
• Safety of Biostate® [SP] | Primary Study Objectives  
• Haemostatic efficacy in subjects with hemophilia A  
• PK profile  
Secondary Study Objectives:  
• Safety of Biostate® |
Thank you