CSL Behring: Committed to the bleeding disorders community

8th WFH Global Forum
Montreal, Canada
September 26-27, 2013

Mathias Juers, M.D.
Director Medical Affairs, Commercial Development Coagulation
Committed to saving lives and improving the quality of life for people with rare and serious diseases worldwide.
Coagulation research

- Research area
  - Extension of half-life
  - Reduction of immunogenicity
  - Reduction of bleeding frequency
  - Development of plasma-derived factors

- Development pipeline
  - rFVIII (rVIII-SingleChain)
  - rFIX (rIX-FP)
  - rFVIIa (rVIIa-FP)
  - rVWF (rVWF-FP)
  - Voncento® EU
Half-life extension of coagulation factors: the challenges

- Identify the optimal half-life extension method
  - Acute bleeds ↔ long-term prophylaxis

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

- Immunogenicity and tolerability
  - Safety ↔ improved therapy
Albumin fusion technology: the unique properties of albumin

- Naturally long half-life (≈20 days)
- Highly abundant protein (35–50 g/L)
- Inert carrier protein
- Molecular structure and mode of clearance known

Metzner et al. Thromb Haemost 2009
Preclinical study results

- rIX-FP
- rVIIa-FP
- rVWF-FP
- rVIII-SingleChain
Albumin fusion extends the half-life of coagulation factors

Pharmacokinetics in haemophilia B dogs

- rIX-FP 100 IU/kg (n=3)
- rFIX 100 IU/kg (n=2)

Pharmacokinetics in haemophilia A mice

- NovoSeven, FVII:Ag
- NovoSeven, FVIIa act.
- rVIIa-FP, FVII:Ag
- rVIIa-FP, FVIIa act.

Poster presentation at GTH 2013
..and also works with very complex coagulation factors...

SDS-Agarose gel

PK in rabbits

150 IU/kg rVWF-FP
150 IU/kg pdVWF

Albumin
rVIII-SingleChain

- Very strong affinity to Von Willebrand factor (VWF)
  - Faster and more efficient binding to VWF
    Idea → Improved PK properties and reduction of immunogenicity
- Increased heavy/light chain stability
  - Covalent linkage between heavy and light chain
    Idea → Improved intrinsic stability and room temperature storage stability

![Diagram of rVIII-SingleChain structure]
rVIII-SingleChain: Surface-Plasmon-Resonance (SPR) analysis

rVIII-SingleChain, displayed an increased binding affinity compared to a rFVIII product when rVIII concentrations from 0.125 nM to 1 nM were measured.

Calculated FVIII/ VWF affinity constant

<table>
<thead>
<tr>
<th></th>
<th>KD (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rVIII-SingleChain</td>
<td>43.64</td>
</tr>
<tr>
<td>standard deviation</td>
<td>12.65</td>
</tr>
<tr>
<td>rFVIII</td>
<td>139.42</td>
</tr>
<tr>
<td>standard deviation</td>
<td>11.59</td>
</tr>
</tbody>
</table>

Claar et al. Haemostaseologie 2013. Poster presentation at GTH 2013
PK curves for rVIII-SingleChain and full-length rFVIII in haemophilia A mice

Clinical

• Status of clinical development programs:
  
  - rIX-FP: currently in phase III.
  - rVIIa-FP: phase I finalized.
  - rVIII-SingleChain: currently in phase III.
  - Voncento®: EU registration received.
rIX-FP clinical programme

Phase I
Pharmacokinetic (PK) safety
Completed (NCT01233440)

Phase I/II
PK, long-term safety
Weekly prophylaxis
On-demand treatment
Completed (NCT01361126)

Phase II/III
PK, long-term safety
7–14 days’ prophylaxis
On-demand treatment
Surgical prophylaxis
On-going (NCT01496274)

Phase III Paediatric
On-going (NCT01662531)

Extension

Completed (NCT01361126)

www.clinicaltrials.gov.
Phase I study design and enrolment criteria

First-in-human phase I study conducted between October 2010 and July 2011

**Key enrolment criteria**
- Males, aged 12–65 years
- FIX activity ≤2%
- Received FIX products for >150 exposure days (EDs)
- No confirmed prior history or current FIX inhibitor
- Platelet count ≥100,000/µL
- CD4 count ≥200/mm³
- Adequate liver and renal function
- Signed informed consent/assent

**Overall study design**
- A dose-escalation safety segment (25, 50 or 75 IU/kg)
- PK evaluation after a single dose of 25, 50 or 75 IU/kg rIX-FP
- PK evaluation of the previously given FIX product (rFIX or pdFIX) after a single dose of 50 IU/kg

Santagostino et al. Blood 2012
Phase I study: safety and PK of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with haemophilia B

Santagostino et al. Blood 2012
Phase I: conclusions

• rIX-FP demonstrated an excellent safety profile:
  - 18 subjects received one dose, seven subjects received two doses of rIX-FP.
  - All infusions of rIX-FP were well tolerated.
  - No inhibitors to FIX or antibodies against rIX-FP.
  - No serious adverse events (SAEs).
  - Majority of adverse events (AEs) were mild in severity, except one unrelated moderate AE (abdominal pain).

• rIX-FP demonstrated improved PK profile over marketed rFIX product:
  - ~ 44% higher incremental recovery ($p=0.0002$)
  - > 5 times longer $T_{1/2}$ ($p<0.0001$)
  - > 7-fold larger AUC ($p<0.0001$)
  - > 7-fold slower clearance ($p<0.0001$)

Santagostino et al. Blood 2012
Phase I and I/II PK study: baseline-corrected FIX activity following rIX-FP infusion

Conclusions: Phase I/II study

- rIX-FP demonstrated an excellent safety profile (no inhibitors to FIX, no antibodies to FIX-FP, no AEs related to product, 43 moderate-, 3 mild AEs, most common AEs were arthralgia, injury, infection, injection site reaction and headache).

- Comparable PK results with Phase I study.

- All prophylaxis subjects maintained weekly prophylaxis with rIX-FP throughout the study (from 37 to 48 weeks).

- In all treated bleeds
  - 100% bleeding episodes received ≤2 injections of rIX-FP.

Martinowitz et al. Thromb Res 2013
rVIIa-FP Phase I (completed & published)

rVIIa-FP: Phase I in 40 healthy volunteers

- All dose-escalation cohorts in healthy volunteers completed (140, 300, 500, 750 and 1000 µg/kg).
- No SAEs, 1 related AE: pain and hardening of vein at injection site.
- Analysis of PK plasma samples (Staclot®).
- $t_{1/2}$ 8.5 hours.

Questions this study answered

- PK profile established.
- rVIIa-FP $t_{1/2}$ supports on-demand dosing.
- Identified dose equivalency with rFVIIa.
- Early safety evaluation.

Golor et al. JTH 2013
rVIIa-FP phase I: international normalised ratio (INR) reversal by rVIIa-FP

**Prothrombin intl. normalised ratio**

- **Screening**
- **Day -6**
- **Day -5**
- **Day -4**
- **Day -3**
- **Day -2**
- **Add pre day 1**
- **Add pre day 2**
- **Day -1**
- **Day 1**
- **Day 2**
- **Day 3**
- **Day 4**
- **Day 5**
- **Day 6**
- **Day 7**
- **Day 8**
- **Day 9**
- **Day 10**
- **Day 11**
- **Day 12**
- **Day 13**
- **Day 14**
- **Day 15**
- **Day 16**
- **Day 17**
- **Day 18**
- **Day 19**
- **Day 20**
- **Day 21**
- **Day 22**
- **Day 23**
- **Day 24**
- **Day 25**
- **Day 26**
- **Day 27**
- **Day 28**

**Time**

- **60 min**
- **12 hrs**
- **24 hrs**
- **36 hrs**
- **48 hrs**
- **72 hrs**
- **96 hrs**
- **120 hrs**
- **144 hrs**

**Administration of treatment (rVIIa-FP or placebo)**

- **Placebo**
- **140 μg/kg**
- **300 μg/kg**
- **500 μg/kg**
- **750 μg/kg**
- **1000 μg/kg**

Golor et al. JTH 2013
Summary slide

• Albuminfusion is an efficacious and safe method for prolongation of half-life of coagulation factors as supported by preclinical and clinical data.

• Due to its highly abundant presence and its immunological inertness it is expected that further clinical studies will continue to show the excellent efficacy and safety of this procedure.
We would like to thank the patients, the investigators and the whole medical community for their support during the conduct of the studies.