Manufacturing, efficacy and safety of recombinant FXIII

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Disclosures for:
Kim Jacobsen

WFH requires the following disclosures be made at each presentation:

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td></td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td>Employee of Novo Nordisk</td>
</tr>
<tr>
<td>Shareholder</td>
<td></td>
</tr>
<tr>
<td>Honoraria</td>
<td></td>
</tr>
<tr>
<td>Advisory Committee</td>
<td></td>
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<tr>
<td>Consultant</td>
<td></td>
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</tbody>
</table>
Agenda

- Factor XIII congenital deficiency
- Manufacturing
- Efficacy in clinical trials
- Safety in clinical trials
- Conclusion
Congenital FXIII Deficiency

- Very rare autosomal recessive bleeding disorder (Orphan Designation)
- All ethnicities, both genders equally affected
- FXIII-A subunit (>95%) and FXIII-B subunit (<5%) deficiency

- Prevalence is ~1 case per 2 million population worldwide
- ~ 400 - 700 subjects diagnosed worldwide (~200 EU, ~100 US)

- Initial clot formation is normal and bleeding stops.
- Lack of FXIII activity → reduced resistance to fibrinolysis
- Bleeding resumes 12-48h after injury ("delayed bleeding")
- Severe bleeding in the majority of cases
Congenital FXIII Deficiency: Characteristic Bleeding Sites

- Umbilicus
- Superficial bruises
- Subcutaneous haematomas
- Mouth and gums
- Intracranial
- Muscles
- Lacerations
- Into and around joints
- After surgery
- Peritoneal
- Epistaxis
- Genital
- Renal
- Peripheral nerves
- Eyes
- Gastrointestinal
- Spleen
- Ears
- Pleural

High risk of ICH (30%)
- Spontaneous or after mild trauma
- Usually at very young age
- Main cause of death and significant morbidity
- Such a high ICH risk not seen in any other congenital bleeding disorder

% reported frequency of bleeding at characteristic sites
Mechanism of Action of FXIII

Activated platelet

Prothrombin II

Xa

Fibrinogen I

Fibrin Ia

Thrombin

Soluble fibrin

Factor XIII A-subunit

Cross-linked fibrin mesh

Haemostatic plug

Intravascular space

Extravascular space

XIIIa

XIII-A2

XIII-B2

Va

Villa

IXa
Agenda

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Recombinant FXIII (rFXIII)

- 1st recombinant FXIII product for use in congenital deficiency
- Identical to human FXIII-A₂
- rFXIII is expressed as the soluble zymogen
- rFXIII is expressed in the intended form, no need for further processing or modifications

pdb-entry 1GGU; Fox et al, J Biol Chem, 1999;274:4917-4923
Production of rFXIII

- Advantages of using *Saccharomyces cerevisiae* as production organism
  - Well-known for pharmaceuticals
  - No use of human or other mammalian blood or tissue components
  - Highly purified protein, does not contain any other coagulation factors
rFXIII manufacturing process

- Expressed as an intracellular, soluble protein in a yeast production strain \textit{(Saccharomyces cerevisiae)}

- Purification with four chromatography steps

- Fermentation process & harvesting

- Freeze-dried rFXIII 2500 IU (15 mg) per vial
The product

rFXIII 2500 IU + Sterile Water for Injection (3.2 ml) = 3 ml reconstituted rFXIII 833 IU/ml
Agenda

Factor XIII congenital deficiency

Manufacturing

**Efficacy in clinical trials**

Safety in clinical trials

Conclusion
Pharmacology and pharmacokinetics

- Normal circulating concentration 50-150 %
- Half-life approximately 12 days
- Designed Phase 3 study for monthly dosing and > 10% trough level after 4 weeks to prevent bleeding
Phase 3 Clinical Programme for rFXIII

- **1725**
  - Efficacy & Safety – 3a

- **3720**
  - Extension – 3b

- **3760**
  - PK Children – 3b

- **3835**
  - Follow up in children – 3b

Year Timeline:
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
Pivotal Phase 3 Efficacy and Safety Trial

- Prospective, open-label, single-arm, bleed prevention trial
- Patients with confirmed Factor XIII A-subunit deficiency
- 41 patients enrolled, 33 patients completed
- Primary endpoint: rate of bleeding episodes requiring treatment with a Factor XIII containing product
23 participating centres in 11 countries
### rFXIII Baseline Demographics

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>26.4 (15.9)</td>
</tr>
<tr>
<td>Median</td>
<td>23.0</td>
</tr>
<tr>
<td>Min; Max</td>
<td>7.0; 60.0</td>
</tr>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (44)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (56)</td>
</tr>
<tr>
<td><strong>Race, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>2 (5)</td>
</tr>
<tr>
<td>White</td>
<td>28 (68)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
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# Treatment Requiring Bleeding Episodes

<table>
<thead>
<tr>
<th>Pivotal Trial (Trial 1725)</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>41</td>
</tr>
<tr>
<td>Number of patients with bleeds</td>
<td>4</td>
</tr>
<tr>
<td>Total number of bleeds</td>
<td>5</td>
</tr>
<tr>
<td>Mean yearly bleeding rate</td>
<td>0.138</td>
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<tr>
<td>Mean observation period (days)</td>
<td>322</td>
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</tbody>
</table>

p < .0001
## Treatment- requiring Bleeding Episodes in Pivotal Trial

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender, Age at Baseline</th>
<th>Cause of Bleed</th>
<th>Location of Bleeding</th>
<th>Time Since First Dose of rFXIII (days)</th>
<th>Time Since Last Dose of rFXIII (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>xx001</td>
<td>Female, 8</td>
<td>Trauma</td>
<td>Lip</td>
<td>183</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>xx002</td>
<td>Male, 10</td>
<td>Trauma</td>
<td>Soft tissue</td>
<td>208</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>xx202</td>
<td>Male, 16</td>
<td>Trauma</td>
<td>Soft tissue</td>
<td>358</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>xx102</td>
<td>Female, 19</td>
<td>Trauma</td>
<td>Nose bleeding</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bruises to nose and face</td>
<td>190</td>
<td>27</td>
</tr>
</tbody>
</table>
Circulating FXIII Trough Level
Well Above 10%

n=41 patients for 471 doses

Red dashed line indicates 10% level
Historical Control Rate

- Methodology discussed with FDA

- Based on 2005 retrospective data collection
  - On-demand treatment
  - Range of bleeding 0 to 12 bleeds per year
  - Most severe patients were already on prophylaxis

- Bleeding rate of 2.91 per year
Efficacy Results

- Pivotal Trial
  - 0.138 vs 2.91 bleeds/patient/year
- Highly significant reduction vs historical control
- No severe bleeds
Efficacy Summary

- No intracranial or life-threatening bleeds
- No patients withdrawn due to lack of efficacy
- rFXIII highly efficacious in preventing bleeds
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Adverse Events of Special Interest

- Antibody formation
- Thromboembolic events
- Anaphylactic reaction
- Lack of efficacy
### Serious Adverse Events

<table>
<thead>
<tr>
<th>Patient Age (years)</th>
<th>Preferred Term</th>
<th>Days From Dosing to Onset</th>
<th>Relation to Trial Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Road traffic accident</td>
<td>27</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac chest pain</td>
<td>23</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>24</td>
<td>Unlikely</td>
</tr>
<tr>
<td>57</td>
<td>Diverticulitis</td>
<td>3</td>
<td>Unlikely</td>
</tr>
<tr>
<td>14</td>
<td>Small intestinal obstructions</td>
<td>4</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Antibody test positive</td>
<td>17</td>
<td>Possible</td>
</tr>
<tr>
<td>16</td>
<td>Antibody test positive</td>
<td>17</td>
<td>Possible</td>
</tr>
<tr>
<td>7</td>
<td>Antibody test positive</td>
<td>15</td>
<td>Probable</td>
</tr>
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</table>
Patients Withdrawals

41 Patients Enrolled in Pivotal Trial

- 5 Withdrawn from Trial
  - 2 pregnancies
  - 1 inconvenience
  - 1 worsening of leukopenia
  - 1 personal reasons

- 3 discontinued Treatment
  - 3 non-neutralizing antibodies

33 patients Completed the Pivotal Trial and Enrolled in the Extension Trial
Immunogenicity in Phase 3 Program

- 4 cases of transient, non-neutralizing antibodies
- No clinically relevant antibodies
- No rFXIII inhibitors
  - No changes in PK
- No clinically relevant immunogenicity to rFXIII
4 Cases of Transient, Non-neutralizing Antibodies

**Patient xx401, 16-year old Female**

- Antibody positive
- Limit of detection

**Patient xx402, 14-year old Male**

**Patient xx003, 8-year old Male**

**Patient xx002, 8-year old Male**

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**Patient xx401, 16-year old Female**

- Antibodies
- FXIII dosing
- Cryoprecipitate

**Patient xx402, 14-year old Male**

- Antibodies
- FXIII dosing
- Cryoprecipitate

**Patient xx003, 8-year old Male**

- Antibodies
- FXIII dosing
- Fibrogammin

**Patient xx002, 8-year old Male**

- Antibodies
- FXIII dosing
Safety Summary

- No deaths
- No clinically relevant safety findings
- No clinically relevant changes in laboratory parameters
Safety Conclusion

- rFXIII provides a safe treatment option for patients with FXIII A-subunit deficiency.
Agenda

- Factor XIII congenital deficiency
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- Safety in clinical trials
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Summary and Conclusion

- rFXIII is efficacious in bleed prevention
- rFXIII is safe when administered monthly in patients with congenital Factor XIII deficiency