Biogen Idec Hemophilia Research Update

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Seventh WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders
Montréal, Canada
Modern Evolution of Hemophilia Treatment

1969
Plasma-derived Factor VIII and Factor IX Concentrates

1993
rFactor VIII

Late 1990s
rFactor IX
rFactor VIIa

2000s
Improved devices for reconstitution
Biosimilar FVIII & FIX
Fusion and Pegylated FVIII & FIX
Pegylated & enhanced rFVIIa

2010s
Investigational Therapies

10 to 20 years of minimal progress
Future Directions

Recombinant Era
The Neonatal Fc Receptor: FcRn

- Structurally related to MHC class I molecules, complexed with β2m
- Expression in endothelial cells across species
- Demonstrated to be responsible for the long circulating half-life of IgG
  - Short half-life in mice with either the β2m gene\(^1\-^3\) or the FcRn gene deleted\(^4\)


3. Israel EJ et al. *Immunology* 1996; 89: 573-8
FcRn Recycling Pathway

FcRn is responsible for the long circulating $t_{1/2}$ life of Fc-containing proteins

- Proteins taken up by endothelial cells via pinocytosis, normally degraded in lysosome
- Fc domain of IgG/Fc-fusion proteins binds to intracellular FcRn in a pH-dependent manner
- FcRn recycles Fc-containing proteins to cell surface, avoiding lysosomal degradation
Traditional Fc fusion proteins are dimeric

- Enbrel® (etanercept)
- Orencia® (abatacept)
- Nplate® (romiplostim)
- Arcalyst® (rilonacept)
- Amevive® (alefacept)

Fc fusion technology has been utilized in approved products for over a decade.
Proprietary ‘Monomer Technology’ was applied to FVIII & FIX

- **rFVIII-Fc**: Single B-domain-deleted rFVIII fused to dimeric Fc region of human IgG1
- **rFIX-Fc**: Single FIX fused to dimeric Fc region of human IgG1
# rFVIII-Fc and rFIX-Fc

## Pharmacokinetics in Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>rFVIII/BDD FVIII</th>
<th>rFVIII-Fc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse, normal</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Mouse, FVIII-def</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Rat</td>
<td>5.5/1.5</td>
<td>8</td>
</tr>
<tr>
<td>Dog, FVIII-def (ELISA)</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Dog, FVIII-def (Activity)</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Mouse, FcRn KO</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Mouse, huFcRn</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>rFIX</th>
<th>rFIXFc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse, normal</td>
<td>12</td>
<td>47±5</td>
</tr>
<tr>
<td>Mouse, FIX-deficient</td>
<td>13</td>
<td>46±10</td>
</tr>
<tr>
<td>Rat</td>
<td>6</td>
<td>35±5</td>
</tr>
<tr>
<td>Dog, FIX-deficient (ELISA)</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Dog, FIX-deficient (Activity)</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Mouse, FcRn KO</td>
<td>16±3</td>
<td>17±2</td>
</tr>
<tr>
<td>Mouse, huFcRn</td>
<td>14±3</td>
<td>53±7</td>
</tr>
</tbody>
</table>

**rFVIII-Fc**

~2-fold longer $t_{1/2}$ in mice, rats and dogs

**rFIX-Fc**

3 to 4-fold longer $t_{1/2}$ in mice, rats, dogs and monkeys
Evaluation of Acute Efficacy in Tail Clip Bleeding Model of Hemophiliac Mice

Tail Clip Bleeding Model in HemA and HemB Mice

- Wide range of bleeding phenotypes
- Dose-response to factor replacement therapy

Dosing

Tail clip (4-10mm)

30-min blood collection

End

5 min

Baseline weight

Time (minutes)

Blood weight

L=4-10mm

L. tail vein

R. tail vein

Central tail artery
Comparable acute activity of rFVIII-Fc vs Advate®, indicating comparable effectiveness in resolving bleeds

n=20 mice/dose/treatment; L=10 mm
Comparable Acute Efficacy of rFIX-Fc vs BeneFIX®: Tail Clip Bleeding Model

Comparable dose response of rFIX-Fc vs BeneFIX®, indicating comparable effectiveness in resolving bleeds

n=20 mice/dose/treatment; L=4 mm
Evaluation of Prophylactic Efficacy: Tail Vein Transection Bleeding Model

Tail Vein Transection (TVT) in Hemophilia Mice

...models venous bleeding characteristics of patients with severe hemophilia

Central tail artery
L. tail vein
R. tail vein

Infusion of rFIX-Fc
Infusion of rFVIII-Fc
Infusion of Advate®

Time (hours)

TVT
Hourly observation for survival
(overnight)

Final observation

Infusion of rFVIII-Fc

0 6 12 18 24

-72 -48 -24

Φ=3mm
Prolonged Efficacy of rFVIII-Fc Relative to Advate® In HemA Mice

Advate® and rFVIII-Fc

Survival

12 IU/kg rFVIII-Fc, 24 hrs prior to TVT* (n=19)
12 IU/kg rFVIII-Fc, 48 hrs prior to TVT (n=40)
12 IU/kg Advate®, 24 hrs prior to TVT* (n=39)

*P<0.001 Log-Rank test of survive curves
12 IU/kg rFVIII-Fc vs Advate® 24 hrs prior to TVT
Prolonged Prophylactic Efficacy of rFIX-Fc Relative to rFIX in HemB Mice

Comparable survival curve in mice that received BeneFIX® at 24hrs vs rFIX-Fc at 72 hrs before the injury

Comparable ED$_{50}$ in mice that received BeneFIX® at 24hrs vs rFIX-Fc at 72 hrs before the injury

rFIX-Fc ED$_{50}$ (72 hr) = 17.8 IU/kg
BeneFIX® ED$_{50}$ (24 hrs) = 15.4 IU/kg
## Preclinical Research Summary

<table>
<thead>
<tr>
<th>PK Modeling</th>
<th>The knockout and transgenic mice are valuable for mechanism-based PK modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Comparable acute activity of rFVIII-Fc and rFIX-Fc to the respective marketed product observed in both bleeding model and in vitro ROTEM</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Prolonged PK of rFVIII-Fc and rFIX-Fc correlates well with prolonged prophylactic efficacy in tail vein transection bleeding model and ex vivo ROTEM</td>
</tr>
<tr>
<td></td>
<td>Whole blood ROTEM has the potential as surrogate efficacy marker for rFVIII-Fc and rFIX-Fc</td>
</tr>
<tr>
<td>Further Research</td>
<td>Prolonged activity of rFVIII-Fc and rFIX-Fc are under clinical investigation</td>
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</table>
rFVIII-Fc Phase 1/2a Study Overview

**Design**

- Open-Label, Crossover, Dose-Escalation, and Multi-Center
- Previously Treated Patients with Severe Hemophilia A [FVIII:C <1%]

**Primary Objectives**

- Assessment of safety and tolerability of rFVIII-Fc after single administration
- Low and high rFVIII-Fc doses (25 and 65 IU/kg)

**Secondary Objectives**

- Determine PK parameters of rFVIII-Fc compared to Advate® after a single dose
- PK Parameters: $T_{\text{max}}$, $C_{\text{max}}$, $T_{1/2}$, CL, $V_{\text{ss}}$, AUC, MRT and incremental recovery

Advate® is a registered trademark of Baxter International Inc.
rFVIIIFc Phase I/IIa Study Results

16 PTPs with severe hemophilia A, single dose, 2 dose levels from (25 or 65 IU/kg)*

- No drug-related serious adverse events
- Most adverse events were unrelated to study drug †
- One drug-related AE: dysgeusia (abnormal taste in the mouth)
- No inhibitor or anti-rFVIII-Fc antibody formation after single dose

Relative to Advate®, rFVIIIFc demonstrated:
- ~1.5-1.75x increase in half-life, area under the curve and mean residence time
- Comparable incremental recovery

Results of the Phase I/IIa study supported further development in a Phase III study (A-LONG)

* 15/16 PTPs were included for PK analysis (1 subject did not complete PK profiling)
† Adverse events were observed in 11 out of 16 patients
A-LONG: Phase III Pivotal Study

An Open-label, Multi-center Evaluation of the Safety, Pharmacokinetics and Efficacy of rFVIIIFc in the Prevention and Treatment of Bleeding in Previously Treated Severe Hemophilia A Patients

**Primary Objectives**
- Safety and tolerability of rFVIIIFc
- Efficacy of rFVIIIFc for on-demand treatment and during surgery

**Secondary Objectives**
- Characterize PK profile of rFVIIIFc vs. Advate®
- Characterize range of doses and schedules required to adequately prevent bleeding in prophylaxis regimen, maintain hemostasis in a surgical setting, or to treatment of bleeding episodes, in all treatment arms

Study is ongoing
A-LONG Study Design

**Arm 1**
Low Dose Prophylaxis
Surgery subgroup

**Arm 2**
High Dose Regimen
Surgery subgroup

**Arm 3**
On-demand Regimen
Surgery subgroup

Study is ongoing
rFIX-Fc Phase 1/2a Study Overview

Design

• Open-Label, Dose-Escalation, Multicenter
• Previously Treated Patients with Severe Hemophilia B

Primary Objective

• Safety and tolerability of rFIX-Fc between doses 1 to 100 IU/kg
• PEs, VS, ECG, laboratory changes over time, antibody assessments, AEs

Secondary Objective

• PK parameters of rFIX-Fc between 12.5–100 IU/kg

PE=Physical exams, VS=Vital signs, ECG=Electrocardiogram, AE= Adverse events
rFIXFc Phase I/IIa Study Results

14 PTPs with hemophilia B, (FIX:C ≤ 2%), single dose, 6 dose levels from 1 to 100 IU/kg

- There were no drug-related serious adverse events
- Dysguesia (abnormal taste in the mouth; n=1) and headache (on the dosing day; n=1) were reported
- No inhibitor or anti-rFIXFc antibody formation after single dose
- No allergic reaction

Relative to historical data for BeneFIX®, rFIX-Fc demonstrated:
- ~3 X increase in half-life and mean residence time
- 24 % improved incremental recovery
- 2.5 X reduced clearance

Results of the Phase I/IIa study supported further development in a Phase 3 study (B-LONG)
An Open-Label, Multicenter Evaluation of the Safety, Pharmacokinetics and Efficacy of rFIXFc in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia B

Primary Outcome Measures

- Safety/tolerability include clinically notable changes from baseline in PE, vital signs, lab values, and incidence of AEs, including the incidence of inhibitor development
- Number of breakthrough bleeding episodes with rFIXFc

Secondary Outcome Measures

- PK parameter estimates of rFIXFc and BeneFIX at baseline in the Sequential PK subgroup as well as rFIXFc at Week 26
- Efficacy of rFIXFc used on-demand and surgical subgroup
- Subjects' response to treatment
- rFIXFc consumption
B-LONG Study Design

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Low-dose Prophylaxis Regimen</th>
<th>Up to 52 wks</th>
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</thead>
<tbody>
<tr>
<td>Arm 2</td>
<td>High-dose Prophylaxis Regimen</td>
<td>Up to 52 wks</td>
</tr>
<tr>
<td>Arm 3</td>
<td>On-demand Regimen</td>
<td>Up to 52 wks</td>
</tr>
<tr>
<td>Arm 4</td>
<td>Surgery (Dose adjusted to type surgery)</td>
<td>10 surgeries</td>
</tr>
</tbody>
</table>

Study is ongoing