EXTENDED HALF–LIFE FACTOR VIII CONCENTRATES EXPERIENCE FROM USA
Rebecca Kruse–Jarres, MD/MPH

Washington Center for Bleeding Disorders, Seattle, WA

This session contains presentations on scientific research that has not yet been subject to regulatory filing in Europe
First Blood Transfusion for Haemophilia

1803

First Plasma Transfusion

1840

Cryoprecipitate discovered by Dr. Judith Pool

1936

First Factor Concentrates

1960/70's

First Monoclonal Factor Concentrates

1964

First Recombinant Factor Concentrates

1987

Prophylaxis

1993

First Monoclonal Factor Concentrates

2007

First Recombinant Factor Concentrates

Pan-EMEA Haematology Exchange Forum
Haemophilia Care Today

Active lifestyle
Normal life expectancy

Prophylaxis is standard of care

Chronic

Long-term joint changes

Acute
tissue injury
Bleed
First Blood Transfusion for Haemophilia 1840

First Plasma Transfusion 1823

Cryoprecipitate discovered by Dr. Judith Pool 1936

First Factor Concentrates 1964

First Monoclonal Factor Concentrates 1960/70's

First Recombinant Factor Concentrates 1993

Prophylaxis 2007

Extended half-life factors 2014

Pan-EMEA Haematology Exchange Forum
Recombinant factor Fc fusion

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B


Blood 2014;123:317-325

CLINICAL TRIALS AND OBSERVATIONS

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A

Johnny Mahangu,1 Jerry S. Powell,5 Margaret V. Ragni,5 Pratima Chowdary,5 Neil C. Josephson,5 Ingrid Pabinger,6 Hidenori Hanabusa,7 Nareesh Gupta,8 Roshni Kulakarni,9 Patrick Fogarty,7 David Perry,10 Amy Shapiro,10 K. John Pasi,10 Shashikant Apte,14 Ivan Nesterov,10 Haiyan Jiang,13 Shuanglian Li,13 Sridivya Neelakantan,13 Lynda M. Cristiano,13 Jaya Goyal,13 Jurg M.,13 Jennifer A. Dumont,13 Nigel Dodd,13 Karen Nugent,13 Gloria Vigliani,13 Alvin Luk,13 Aoife Brennan,10 and Glenn F. Pierce,10 for the B-LONG Investigators

FDA approved 3/28/14

FDA approved 6/6/14

Pan-EMEA Haematology Exchange Forum
# Products with phase III data in the U.S.

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIIIFc (Eloctate)</td>
<td>Approved – June 2014</td>
</tr>
<tr>
<td>rFVIII pegylated (BAX855, Adynovate)</td>
<td>Approved – November 2015</td>
</tr>
<tr>
<td>rFVIII pegylated (N8–GP)</td>
<td>Awaiting approval</td>
</tr>
<tr>
<td>rFVIII pegylated (BAY94–9027)</td>
<td>Awaiting approval</td>
</tr>
</tbody>
</table>
Haemophilia treatment goals

• To avoid bleeds
• To treat bleeds
• To avoid joint disease
• To avoid side effects
• To achieve the life they choose
Who should get long acting factor?

High activity

Low activity
Who should get long acting factor?

Who should get long acting factor?
How do we prevent bleeding
How to dose (prophylaxis)

**rFVIIIFc**

- ≥ 6 years
  - 50 IU/kg every 4 days
  - adjust dose based on patient response
    - range 25–65 IU/kg every 3–5 days

- < 6 years of age
  - 50 IU/kg twice weekly
  - adjust dose based on patient response
    - range of 25–65 IU/kg at 3–5 days
    - more frequent or higher doses up to 80 IU/kg may be required

**rFVIII PEG (BAX 855)**

- 40–50 IU/kg 2 times a week
How to dose

- **rFVIIIFc**
  - 2 x 45 IU kg\(^{-1}\) per week (Mo, Th)

- **rFVIII**
  - 3 x 30 IU kg\(^{-1}\) per week (Mo, We, Fr)

**Factor** | **Dose (IU kg\(^{-1}\)) per week**
--- | ---
**rFVIIIFc** | 90
**rFVIII** | 90

**Factor** | **Dose (IU kg\(^{-1}\)) per week**
--- | ---
**rFVIIIFc** | 60
**rFVIII** | 90
How to dose

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dose (IU kg(^{-1})) per week</th>
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</thead>
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<tr>
<td>rFVIIIFc</td>
<td>90</td>
</tr>
<tr>
<td>rFVIII</td>
<td>90</td>
</tr>
</tbody>
</table>

- **rFVIIIFc**: 3 x 30 IU kg\(^{-1}\) per week (Mo, Th)
- **rFVIII**: 3 x 30 IU kg\(^{-1}\) per week (Mo, We, Fr)

Factor VIII activity (IU/dL\(^{-1}\))

- Mon: 5
- Tue: 3
- Wed: Pre dose
- Thu: 1
- Fri: 1
- Sat: 1
- Sun: 1
- Mon: 1

**Graph:**
- Mon - Tue: Decrease to 3 IU/dL
- Wed: Pre dose
- Thu - Fri: Decrease to 1 IU/dL
- Sat - Sun: Continue decreasing
- Mon: Minimum level reached

**Table:**

<table>
<thead>
<tr>
<th>Day</th>
<th>Factor VIII Activity (IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>5</td>
</tr>
<tr>
<td>Tue</td>
<td>3</td>
</tr>
<tr>
<td>Wed</td>
<td>Pre dose</td>
</tr>
<tr>
<td>Thu</td>
<td>1</td>
</tr>
<tr>
<td>Fri</td>
<td>1</td>
</tr>
<tr>
<td>Sat</td>
<td>1</td>
</tr>
<tr>
<td>Sun</td>
<td>1</td>
</tr>
<tr>
<td>Mon</td>
<td>Minimum level reached</td>
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</table>
NHF’s Medical and Scientific Advisory Council (MASAC) 2/28/16

• Prophylaxis should be considered optimal therapy for individuals with severe haemophilia A or B (factor VIII or factor IX <1%)

• Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding), with the aim of keeping the trough FVIII or FIX level above 1% between doses

• Optimal dosing and frequency should be determined for each individual by appropriate laboratory monitoring

• Recommended that individuals on prophylaxis have regular follow-up visits
  - evaluate joint status
  - document any complications such as inhibitors
  - record any bleeding episodes that occur during prophylaxis
Prophylaxis should be considered optimal therapy for individuals with severe haemophilia A or B (factor VIII or factor IX <1%).

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Recommended that individuals on prophylaxis have regular follow-up visits:
- evaluate joint status
- document any complications such as inhibitors
- record any bleeding episodes that occur during prophylaxis
Should we do pharmacokinetic (PK) testing?

• Ellis Neufeld – Harvard, MA
  - Used to reserve PKs for patients with breakthrough bleeds
  - Those aren’t the only patients that PK studies would be valuable for
  - Center now takes PKs on all prophy patients

• Steve Pipe – Ann Arbor, Michigan
  - We tend to tease out the inherent pharmacokinetics in a patient because we do an escalating initiation of prophy
    - starting infants on weekly prophylaxis, then building up to twice weekly and then three times per week, the center can evaluate the impact of infusion frequency and dosing
  - Breakthrough bleeds in a patient who is receiving optimal dosing would warrant further evaluation –> That’s where a PK study evaluation can be helpful
Methods used to determine pharmacokinetic profile

• Gold standard: ISTH SSC protocol
  - 10 or 11 samples over 32–48 hours\(^1\)
  - Difficult to use in clinical practice

• Realistic approach
  - Use sparse sampling and Bayesian analysis\(^2,3\)

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Do we know the time to 1%??
Do we know the “terminal” $t_{1/2}$??
NEQAS Report: Accuracy of FVIII:C Measurement

- Sample from same patient sent to 346 laboratories
- FVIII:C (Median, 26.8 IU/dL; range, 14.4–78.3 IU/dL)
## Cost considerations

<table>
<thead>
<tr>
<th></th>
<th>Prescribed prophylaxis regimens Standard factor replacement</th>
<th>Label prophylaxis regimens EHL factor replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII</td>
<td>Strategy #1 25 IU kg(^{-1}) every other day(^*)</td>
<td>Strategy #1 25 IU kg(^{-1}) every 3(^{rd}) day</td>
</tr>
<tr>
<td></td>
<td>Strategy #2 30 IU kg(^{-1}) every other day</td>
<td>Strategy #2 50 IU kg(^{-1}) every 4(^{th}) day</td>
</tr>
<tr>
<td>Price per unit</td>
<td>$1.10(^†)</td>
<td>$1.98(^‡)</td>
</tr>
<tr>
<td>Factor cost per year per adult patient (70 kg)</td>
<td>$350,350</td>
<td>$422,730</td>
</tr>
<tr>
<td>Factor cost per year per pedi patient (25 kg)</td>
<td>$125,125</td>
<td>$150,975</td>
</tr>
<tr>
<td>Comparative premium cost</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Number of infusions saved per year</td>
<td>Baseline</td>
<td>–</td>
</tr>
<tr>
<td>Anticipated factor activity trough(^**)</td>
<td>2%</td>
<td>2–3%</td>
</tr>
</tbody>
</table>

\(^*\) Boston Hemophilia Center typical prophylaxis strategy

\(^†\) Disclosures by the manufacturer of the currently licensed EHL products suggest that pricing was adjusted to give ‘annual price parity’ between ‘Label strategy\(^†\)’ for each product to a putative community standard factor use, based on proprietary pharmacy and prescriber surveys. We have imputed price per unit of the standard factor product (left-hand columns) based on this manufacturer claim. Actual prices available in the community vary but may be substantially lower in some circumstances.

\(^‡\) Based on launch price data for paediatric- and adult-sized patients. Price per unit of the EHL factors (right hand columns) is based on publically available market prices. Cost to specific pharmacies and individual patients vary.

\(^**\) Based on half-life of 10.5 h for standard FVIII and 1.5 x increase with EHL product.
Haemophilia treatment goals

• To avoid bleeds

• To treat bleeds

• To avoid joint disease

• To avoid side effects
  - Inhibitor
  - Infection

• To achieve the life they choose
Open questions

• Treatment of acute bleeds
  - Limited data for on demand treatment
  - Prefer only one product in the home
  - No guidelines for dosing available
    - My recommendations for major bleeding:
      - Review PK studies with patient
      - If bleeding within the 1st 24 hours – take a 50% corrective dose
      - Of bleeding > 24 hours after prophy – take 100% corrective dose
  - Need new patient education
Open questions

• Surgery
  - rFVIIIIfc peri–operatively¹
    - Perioperative dosing regimens were determined by investigators with guidance based on pharmacokinetic data and recommendations from a clinical dosing committee
    - 75 surgeries (minor and major)
    - Of the surgeries assessed for haemostatic response (n=54), all were rated as excellent or good by the investigator/surgeon
    - Well tolerated
  
  - rFVIII PEG (BAX 855) peri–operatively²
    - 15 surgeries (minor and major)
    - Efficacious for peri–operative control of haemostasis in patients with severe haemophilia A
    - No safety concerns

Haemophilia treatment goals

• To avoid bleeds
• To treat bleeds
• To avoid joint disease
• To avoid side effects
  - Effects of PEGylation
  - Inhibitor formation
• To achieve the life they choose
• Hypothetical degradation and elimination pathways of PEG-rFVIII conjugate

• PEG-acid is the final degradation product, which is primarily eliminated via kidney and liver

- Increasing overall size of PEG conjugate limits renal clearance
- PEGs <30 kDa expected to be secreted via the kidney

ATHN 2: Factor switching study

- Patients in Hemophilia Treatment Centers in the U.S.
- Longitudinal, observational study of patients with Haemophilia A or B who are planning to switch to a newly approved coagulation factor replacement product, or who have recently switched factor products
- Will follow each patient for up to 1 year
- Primary outcome – Inhibitor development
- ClinicalTrials.gov – NCT02546622
Immunogenicity – is it reduced?

Recombinant factor VIII Fc (rFVIIIFc) fusion protein reduces immunogenicity and induces tolerance in hemophilia A mice

Sriram Krishnamoorthy a,*, Tongyao Liu a, Douglas Drager a, Susannah Patarroyo-White a, Ekta Seth Chhabra a, Robert Peters a, Neil Josephson b, David Lillicrap c, Richard S. Blumberg d, Glenn F. Pierce a, Haiyan Jiang a, *

Cellular Immunology 301 (2016) 30–39

- INHIBIT Trial (PI – Ragni)
  - Phase II Single-Arm Trial of Preemptive Prophylaxis With Long-Acting Recombinant Factor VIII Fc Fusion Protein (Eloctate) to Prevent Inhibitor Formation in Children With Severe Haemophilia A
  - Not yet open
  - ClinicalTrials.gov – NCT02196207
Haemophilia treatment goals

• To avoid bleeds
• To treat bleeds
• To avoid joint disease
• To avoid side effects
• To achieve the life they choose
What do we recommend?

What is the right trough?

How do we monitor bleeding?

How do we monitor PK?

Are we worried about micro-bleeds?

How do we monitor joints?
Thanks for letting me share my U.S. perspective....