Defining Challenges in Prophylaxis

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Joint Disease in Hemophilia

- Occurs in 90% of severe hemophiliacs
  - 10% to 15% rarely bleed (mild-severe)

- Joint bleeds per year: $15 \pm 12$

- At least 50% of patients have restriction in activity
  - 5% have normal joints

Prophylactic Treatment in Hemophilia: Revised Definitions

Primary Prophylaxis
• Regular infusion of factor concentrates started before the occurrence of joint damage and with the intent of administering prophylaxis continuously, defined as > 45 weeks per year.

Secondary Prophylaxis
• Infusion of factor concentrates after the onset of objectively determined joint damage and with the intent of administering prophylaxis continuously defined as > 45 weeks per year.

## Prophylactic Treatment in Hemophilia: Revised Definitions

<table>
<thead>
<tr>
<th>Model</th>
<th>Revised Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis determined by age</td>
<td>Long-term continuous* treatment started before 2 years of age and prior to clinically evident joint bleeding</td>
</tr>
<tr>
<td>Primary prophylaxis determined by first bleed</td>
<td>Long-term continuous* treatment started prior to the onset of joint damage,† irrespective of age</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>Long-term continuous* treatment not fulfilling the criteria for primary prophylaxis</td>
</tr>
<tr>
<td>Short-term prophylaxis</td>
<td>Short-term treatment to prevent bleeding</td>
</tr>
</tbody>
</table>

*With intent of treating 52 weeks/yr up to adulthood, minimum treatment of 46 weeks/yr.

†Presumptively defined as having had no more than one joint bleed.

“Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.”

“Prophylaxis as currently practiced in countries where there are no significant resource constraints is an expensive treatment and is only possible if significant resources are allocated to hemophilia care.”

“However, it is cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.”

WFH = World Federation of Hemophilia

Prophylaxis: Long-Term Goals

- Prevention of sequelae of chronic disease
- Improvement in individual/family quality of life
- Reduction in long-term societal costs through prevention of disability, improved outcome, maximization of human potential

Prophylaxis in Hemophilia: History

- Initial observation\(^1\)
  - Patients with moderate hemophilia have decreased incidence of musculoskeletal complications

- Initial hypothesis\(^2\)
  - Converting a patient with severe hemophilia to a moderate level through prophylactic therapy will decrease incidence of musculoskeletal complications

\(^1\) Ahlberg A. *Acta Orthop Scand Suppl.* 1965;Suppl 77:3-132.
Prophylaxis - Clinical Studies

- Swedish Studies
  - Astermark, et al 1999

- Dutch Studies
  - Van Der Berg 2001
  - Fisher, et al 2002

- German Study

- Italian Study

- UK Study
  - Yee, et al 2002

- Canadian Study
  - Feldman, et al 2006

- USA Study
  - Manco-Johnson 2007

- USA Study
  - Valentino 2012
When to Start Prophylaxis: The Swedish Experience

Development of arthropathy (n=121)

Proportion with Joint Score = 0

Age at First Joint Score

Conclusion: Prophylaxis should be started before 3 years of age

Prophylaxis: FVIII Optimal Dosing Studies

- **High (Malmö/Sweden)**
  - 25 to 40 IU/kg, minimum frequency 3x per week
  - Pharmacokinetic
- **Low/intermediate (Netherlands)**
  - 15 to 25 IU/kg 2x or 3x per week
- **Incremental/escalating (Petrini/Stockholm; Feldman/Canada)**
  - Once weekly, increased over a period up to 18 months (Sweden) or based on bleeding into joints (Canada) to full-dose prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Netherlands Low/Intermediate Dose</th>
<th>Sweden High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Age at study analysis</td>
<td>21</td>
<td>16 to 22</td>
</tr>
<tr>
<td>Age at start of prophylaxis</td>
<td>4.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Joint bleeds per year</td>
<td>5.3</td>
<td>3</td>
</tr>
<tr>
<td>Pettersson score</td>
<td>6.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Orthopedic joint score (WFH)</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>FVIII consumption (IU/kg/yr)</td>
<td>1828</td>
<td>3713</td>
</tr>
</tbody>
</table>

**Conclusion:** Intermediate dosing results in improvement of long-term clinical outcome with reduced factor consumption.

Data are means.

Canadian Prospective Study of Tailored Prophylaxis

STEP 1
50 Units / kg x 1 / week

STEP 2
30 Units / kg x 2 / week

STEP 3
25 Units / kg on alternate days (minimum x 3 / week)

Escalation

n=25

5-year follow-up
- 52% (13/25) of children escalated to Step 2
- 31% (4/13) of children escalated to Step 3
- 40% of children required only once weekly prophylaxis
- 28% required full-dose prophylaxis on alternate days

Enhanced Episodic Treatment of Acute Joint Bleed

- 40 U/kg immediately
- 20 U/kg at 24 & 72 hours
- 20 U/kg qod until complete resolution of pain and normal physical exam, up to 4 weeks

Prophylaxis
rfVIII 25 U/kg qod

Randomize

Enhanced Episodic
No routine infusions

Joint Outcome Study

- Recruit (age 1.6 years)
- Screen for Eligibility
- Obtain Informed Consent

n=65

Prophylaxis
rfVIII 25 U/kg qod

Treatment of Acute Joint Bleed
40 U/kg immediately
20 U/kg at 24 & 72 hours
20 U/kg qod until complete resolution of pain and normal physical exam, up to 4 weeks

Exit: Joint structure on MRI & X-ray at age 6 yrs

Primary Outcome: Proportion of Children with Six Normal Index Joints on MRI at Exit

- Compared with Prophylaxis, RR for Joint Damage on Enhanced Episodic = 6.1 (CI 1.5-24.4) using MRI outcome
- Prophylaxis → 83% risk reduction
- MRI and XR: 97% agreement

Italian Prophylaxis Study (ESPRIT)

Randomized study with similar design and aims as JOS (n=45)

• Prophylaxis arm
  – 25 U·kg⁻¹/3x a week with dose adjustment to maintain trough FVIII levels >1%

• On-demand arm
  – Different infusion schedules depending on severity/site at least 25 U/kg⁻¹ per day

### Outcome Data: ESPRIT Study

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Episodic Tx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bleeding event/pt</td>
<td>37.9</td>
<td>82.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hemarthroses/pt</td>
<td>14.7</td>
<td>40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients w/joint damage</td>
<td>29%</td>
<td>74%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Barriers to Prophylaxis (Patient Perspective)

- Forgetfulness
- Having to deal with hemophilia on a daily basis
- Social/family stresses
- Costs
- Transition to adulthood
- Lack of supervision
- Lack of commitment
- Poor venous access
- Lack of knowledge about importance (patients and payers)

Barriers to Prophylaxis
Global Hemophilia Survey

Survey of 147 nurses from 147 HTCs and 16,115 patients

• Factors affecting patients’ adherence
  – inability to understand potential benefits (75%)
  – denial (67%)
  – poor venous access (66%)
  – lack of parental/family commitment (63%)
  – Interference with lifestyle (62%)
  – teenage rebellion (48%)
  – lack of time (42%)

Why is Adherence Important?

- Decreases arthropathy and prevents other bleeds
- Improves quality of life
- Decreases visits to hospitals, emergency rooms, and clinics
- Increases tolerance to high-activity levels
- Improves academic performance and accomplishments
- Cost-effective
How Can We Measure Adherence?

1. Measure adherence with prophylaxis and on-demand treatment\(^1\)
   
   Based on review of prescribed factor and infusion logs
   
   - 34% of subjects were high adherers  
     - 39% adults; 26% children
   - high intense regimen treatment had lower adherence

2. VERITAS-PRN\(^2\)  
   Multidimensional quantitative measure of adherence
   
   VERITAS-PRO\(^3\)  
   Determines adherence with prophylaxis in children and adults
   
   - 18% of the cohort was non-adherent

3. Patient adherence determined through retrospective evaluation of pharmacy and medical records\(^4\)
   
   - Overall adherence 88.8% ± 27.5 (mean ± SD)

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Ways to Improve Adherence (Patient Perspective)

- Education about prophylaxis
- Communication
  - Internet dialog page
  - more frequent visits
  - reminder telephone calls
- Tracking prophylaxis
  - Diary
  - PC/phone database
- Improvements in factor

Prophylaxis is an effective treatment for prevention of joint disease BUT its effectiveness is in part mediated by adherence to treatment.

We should identify patients at risk for nonadherence and help them overcome the barriers.

Consider using validated adherence measures to test efficacy of interventions.

Target high-risk populations (adolescents and young adults).

Thornburg CD. *JCD* 2009. www.slm-hematology.com
Monitoring and Modifying Treatment Regimens in Hemophilia

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Director, Louisiana Center for Bleeding and Clotting Disorders
Tulane University School of Medicine
New Orleans, LA
Prophylaxis

• Goal of therapy is to convert a severe factor deficiency to a moderate factor deficiency
  – Maintain factor level >1% to 2%

• Typical regimens
  – FVIII tiw or qod
  – FIX biw
Prophylaxis is Easy (In Theory)...

Trough factor level (≥2%)

Low joint bleed rate (target 0)

Good joint function

Good quality of life
But May Be Difficult (In Practice)...

- Difficulty achieving desired trough level
  - Poor recovery or half-life

- Bleeding despite desired trough level
  - Related to activity or trauma
  - Underlying arthropathy or synovitis

- Difficult venous access
  - Indwelling line complications

- Time constraints and inconvenience
And Impossible Without Adherence...

- Achieve low bleed rate
- Maintain trough factor level

Adherence
• Goal is to achieve “moderate hemophilia” status

• Moderate hemophilia patients
  – 30% to 50% have >1 joint bleed/year
  – 40% of adults have at least 1 impaired joint

Annual Bleeding Rate (ABR)

- Can “0” be achieved with prophylaxis?
- Even in an ideal group of patients, probably not….

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis (N=32)</th>
<th>On-demand (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bleeds (#/pt/year)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.27 (6.24)</td>
<td>17.69 (9.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>1.15</td>
<td>17.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Trough Levels and Bleed Rates

- Time spent with trough level <1% associated with higher bleed rates

- In 99 patients with hemophilia A (ages 10 to 65 years) on FVIII 25 to 40 u/kg at least 3 times per week:
  - average 16.5 hr/week with FVIII <1%
  - median bleed rate: 3.3/year
  - ABR increased 1.4% for each hr/week below 1%

- Decreased adherence associated with increase in bleeds

How Many Bleeds Is Too Many?

- How many *joint* bleeds is too many?

<table>
<thead>
<tr>
<th>Total Joint Bleeds (#/pt/y)</th>
<th>Prophylaxis (N=32)</th>
<th>On-demand (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>0.63 (1.35)</td>
<td>4.89 (3.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (SD)</td>
<td>0.20</td>
<td>4.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint damage (%)</td>
<td>2 (7%)</td>
<td>13 (45%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>No joint damage (%)</td>
<td>25 (93%)</td>
<td>16 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Joint ABR

• 4 to 5 joint bleeds per year is too many

• For young patients on primary prophylaxis
  – goal of ≤1 is reasonable in majority of patients

• For older patients on secondary prophylaxis
  – goal of ≤1 joint bleed not achievable in most
  – about 50% of adult patients on optimal prophylaxis have >1 joint bleed per year

Goals of Primary Prophylaxis

- Begin before repeated joint bleeds
- Achieve joint ABR ≤1
- Monitor closely and adjust regimen for breakthrough bleeds

- Obstacles
  - Venous access
  - Family/patient commitment
  - Poor adherence
Goals of Secondary Prophylaxis

- Goal of \( \leq 1 \) joint bleed not achievable in most
- Achieve lowest joint bleed rate possible
- May need other realistic/achievable goals
  - ability to work, attend school
  - begin exercise regimen/physical therapy to improve joint function and pain
  - expand activity levels
  - improve quality of life

- Obstacles
  - Poor adherence
  - Inconvenience, scheduling conflicts
Prophylaxis and Quality of Life

- Prevention of absenteeism (school and work)
  - number of bleeding episodes inversely related to academic achievement

- Quality of life measures in patients on prophylaxis
  - less bodily pain
  - higher scores in mental health and social functioning
Balancing Obstacles With Achievable Goals

- Fewer bleeds, better joints, improved QOL
- Inconvenience, difficult access, cost
Tailoring Treatment: 
Primary Prophylaxis

- Target: ≤1 joint bleed per year
- Safe venous access
- Ideal treatment would be more frequent infusions to maintain higher trough levels
- Must balance with availability of venous access
- 30% of HTCs initiate once weekly prophylaxis in small children to avoid central venous access

Tailoring Treatment: Secondary Prophylaxis

- Target: greatest possible reduction in bleeds

- Consider which secondary outcomes are most important

- If treatment of target joint is main goal, then achieving trough levels >1% to 2% is key
  - requires more frequent infusions

- If achieving work goals or activity goals are most important and adherence is a concern
  - less frequent infusions may be effective
Assessing Efficacy of Prophylaxis

**Primary Prophylaxis**
- Maintenance of trough factor level >1% to 2%
- Bleed rate
  - ABR (annual bleed rate)
  - Joint bleed rate
- Joint preservation
- QOL

**Secondary Prophylaxis**
- Maintenance of trough factor level >1% to 2%
- Bleed rate
  - ABR
  - Joint bleed rate
  - Target joint bleed rate
- Joint improvement and preservation
- QOL
Adherence

• Recent survey of HTC physicians and nurses in the US
  – 87% prescribe prophylaxis
  – 34% had discontinued prophylaxis for poor adherence in the previous year

• Adherence can be regularly assessed by
  – Handwritten logs
  – Pharmacy records
  – Trough levels
  – Joint bleeds

Summary

- Efficacy of prophylaxis established in randomized controlled trials
- Broad acceptance of prophylaxis among clinicians as best practice

But...
- Prophylaxis is a costly, high-complexity, high-intensity treatment regimen
- Adherence is crucial but difficult
- Most patients will require a tailored approach and careful follow-up to best meet their needs
Translating Advances in Hemophilia into Clinical Practice

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Director, Penn Comprehensive Hemophilia and Thrombosis Program
Hospital of the University of Pennsylvania
Division of Hematology/Oncology
Philadelphia, PA
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic (&quot;on demand&quot;) treatment</td>
<td>Treatment given at the time of clinically evident bleeding</td>
</tr>
<tr>
<td>Continuous prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years**</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies</td>
</tr>
<tr>
<td>Tertiary prophylaxis</td>
<td>Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints</td>
</tr>
<tr>
<td>Intermittent (&quot;periodic&quot;) prophylaxis</td>
<td>Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year</td>
</tr>
</tbody>
</table>

* continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

**large joints = ankles, knees, hips, elbows and shoulders

Half-Life Extension

Increased Potency

Lower Immuno-Genicity

Improved Delivery
Bioengineering for Half-Life Extension

Glyco-PEGylation

- Conjugation is site-directed
- Cleaved, released upon activation

Fc Fusion

- Fusion to Fc of IgG1
- FcRn recycling

Albumin Fusion

- Fusion to rAlb
- Linker peptide cleaved during FIX activation

PEGylation

- Site-specific PEG (Cysteine resides)
- Activation peptides (cleaved, excised)
- Hydrophilic polymer
- Shield around protein
- ↓ degradation, ?

Immune effector cells

N9-GP

### Clinical Investigation

<table>
<thead>
<tr>
<th></th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAX855</td>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY94-9027</td>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N8-GP</td>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFVIII Fc</td>
<td>Completed*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9-GP</td>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFIXFP</td>
<td>Completed</td>
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<tr>
<td>rFIX Fc</td>
<td>Approved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BLA filed with FDA

Extended Half-Life rFVIII

Half-Life Extension: 1.5 to 1.8 fold

- rFVIII: 11 hours
- BAX855: 19 hours
- rFVIII: 13 hours
- BAY94-9027: 18.3 hours
- rFVIII: 11.7 hours
- N8-GP: 19 hours
- rFVIII: 12 hours
- rFVIII Fc: 19 hours

Extended Half-Life rFIX

Half-Life Extension: 3- to 5-fold

- rFIX: 19 hours (Extended 33 hours)
- rFIXFc: 17 hours (Extended 39 hours)
- rFIXFP: 56 hours (Extended 86 hours)
- rFVIII: 18 hours (Extended 32 hours)
- N9-GP: 92 hours (Extended 93 hours)

N9-GP

Time to <1%: 22.5 d*

*50U/kg


rFIX-FP

Time to <5%: 14 d*

*50U/kg


FVIII:Fc

Time to <1%: 4.9 d*


N8-GP

Time to <1%: 6.5 d*

## Phase 3 Results: FVIIIIFc

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosing</th>
<th>Annualized bleeding rate (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individualized</td>
<td>25 to 65 IU/kg every 3 to 5 days</td>
<td>2.9 (2.3 to 3.7)*</td>
</tr>
<tr>
<td>Weekly</td>
<td>65 IU/kg every 7 days</td>
<td>8.9 (5.5 to 14.5)*</td>
</tr>
<tr>
<td>On-demand</td>
<td>10-50 IU/kg per dose</td>
<td>37 (24 to 58)</td>
</tr>
</tbody>
</table>

* Significantly different from on-demand group ($P<.001$)
### Phase 3 Results: FVIIIIFc

<table>
<thead>
<tr>
<th>rFVIIIIFc dose, IU/kg</th>
<th>Twice weekly</th>
<th>Every 3 d</th>
<th>Every 4 d</th>
<th>Every 5 d</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0 (0)</td>
<td>2 (2.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>30</td>
<td>0 (0)</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>35</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>25/50†</td>
<td>34 (29.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>34 (29.1)</td>
</tr>
<tr>
<td>40</td>
<td>0 (0)</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>45</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>50</td>
<td>0 (0)</td>
<td>20 (17.1)</td>
<td>2 (1.7)</td>
<td>34 (29.1)</td>
<td>56 (47.9)</td>
</tr>
<tr>
<td>60</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>65</td>
<td>0 (0)</td>
<td>10 (8.5)</td>
<td>2 (1.7)</td>
<td>4 (3.4)</td>
<td>16 (13.7)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (29.9)</td>
<td>39 (33.3)</td>
<td>4 (3.4)</td>
<td>39 (33.3)</td>
<td>117 (100)</td>
</tr>
</tbody>
</table>

† Initial twice-weekly dosing regimen of 25 U/kg on D1 followed by 50 U/kg on D4

## Phase 3 Results: FIXFc

<table>
<thead>
<tr>
<th>Group</th>
<th>Interval</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Fixed weekly</td>
<td>Adjusted, starting 50 IU/kg</td>
</tr>
<tr>
<td>Group 2</td>
<td>Adjusted, starting every 10 days</td>
<td>Fixed 100 IU/kg</td>
</tr>
<tr>
<td>Group 3</td>
<td>On-demand</td>
<td>20 to 100 IU/kg</td>
</tr>
<tr>
<td>Group 4</td>
<td>Surgical prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>

### Phase 3 Results: FIXFc

<table>
<thead>
<tr>
<th>Group</th>
<th>Actual Dosing</th>
<th>Annualized bleeding rate (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed interval</td>
<td>45 IU/kg (25 to 74) weekly</td>
<td>3.1 (2.5 to 4.0)*</td>
</tr>
<tr>
<td>Fixed dose</td>
<td>Every 12.5 days (7.8 to 15.9) x 100 IU/kg</td>
<td>2.4 (1.7 to 3.5)*</td>
</tr>
<tr>
<td>On-demand</td>
<td></td>
<td>18.7 (14 to 25)</td>
</tr>
</tbody>
</table>

* Significantly different from on-demand group ($P<.001$)

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## Prophylaxis Using EHL – Efficacy

<table>
<thead>
<tr>
<th>Molecule</th>
<th>n*</th>
<th>Dose</th>
<th>ABR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rFIX (Extended Half-Life)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIXFc¹</td>
<td>63</td>
<td>50 U/kg/wk + pK</td>
<td>2.95</td>
<td>23%: no bleeds</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>100 U/Kg/10d</td>
<td>1.38</td>
<td>42.3%: no bleeds</td>
</tr>
<tr>
<td>N9-GP²</td>
<td>≥25</td>
<td>40 U/kg/wk</td>
<td>1</td>
<td>2/3: no target joint bleeding</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td>10 U/kg/wk</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td><strong>rFVIII (Extended Half-Life)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVIIIFc³</td>
<td>118</td>
<td>25-65 U/kg Q3-5D</td>
<td>1.6</td>
<td>45.3%: no bleeds</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>65 U/kg/wk</td>
<td>3.6</td>
<td>17.4%: no bleeds</td>
</tr>
<tr>
<td>BAY 94-9027⁴</td>
<td>43</td>
<td>Q5d dosing</td>
<td>1.9</td>
<td>44%: no bleeds</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>Q7d dosing</td>
<td>3.9</td>
<td>37%: no bleeds</td>
</tr>
</tbody>
</table>

*prophylaxis arms only

Tenase Facilitation

- ACE910, bispecific Ab
- SC administration
- $t_{1/2} = 2$ weeks

AT

- siRNA (AT mRNA)
- ASGPR-specific ligand (liver)
- 1 to 2x/mo admin
- Normalization of ETP in hemophilia B mice

TFPI Inhibition

- NNC172-2021
- mAb disrupting Fxa-TFPI interaction
- SC Administration
- Preclinical (rabbit)

- Phase 1b (Japan)


Akinc, et al., WFH Poster, 2012

Putting New Molecules into Practice: Additional Considerations

- Toxicity
- Transitioning (traditional → EHL)
- Implications of EHL on prophylaxis
- Monitoring
# EHL Products – Immunogenicity

- Conjugate/fusion protein, effector molecule

<table>
<thead>
<tr>
<th>Product</th>
<th>Modification</th>
<th>Observation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9-GP</td>
<td>Site-directed PEGylation (40kDa)</td>
<td>Hypersensitivity (Face swelling/ chest tightness)</td>
<td>No anti-N9 Abs, tolerated pdFIX later</td>
</tr>
<tr>
<td>FVIII:Fc</td>
<td>Fc fusion</td>
<td>Non-neutralizing Abs</td>
<td>NNAs in some patients</td>
</tr>
<tr>
<td>BAY 86-6150 (rVIIa)</td>
<td>N-glycans, Gla domain</td>
<td>Neutralizing Antibody</td>
<td>Discontinued in Phase II/III</td>
</tr>
</tbody>
</table>

• Accumulation?
  – Renal tubular vacuolization (rat)

• Certolizumab Pegol
  – Crohn’s/RA; since 2007
  – Higher cumulative dose than N9-GP PPX regimen

Switching: Instructions?

Conversion from epoetin alfa to darbepoetin alfa in patients with CKD on dialysis

- “…darbepoetin…once weekly in patients who were receiving epoetin…BIW-TIX”
- “…darbepoetin…once every 2 weeks in patients who were receiving epoetin…QW”

<table>
<thead>
<tr>
<th>Previous Weekly Epoetin alfa Dose (Units/week)</th>
<th>Darbepoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>&lt;1,500</td>
<td>6.25</td>
</tr>
<tr>
<td>1,500 to 2,499</td>
<td>6.25</td>
</tr>
<tr>
<td>2,500 to 4,999</td>
<td>12.5</td>
</tr>
<tr>
<td>5,000 to 10,999</td>
<td>25</td>
</tr>
<tr>
<td>11,000 to 17,999</td>
<td>40</td>
</tr>
<tr>
<td>18,000 to 33,999</td>
<td>60</td>
</tr>
<tr>
<td>34,000 to 89,999</td>
<td>100</td>
</tr>
<tr>
<td>≥ 90,000</td>
<td>200</td>
</tr>
</tbody>
</table>

http://www.aranesp.com/
Prophylaxis and Longer-Acting Products

↑ Time spent below a specified factor level?

Turning severe into moderate haemophilia by prophylaxis: are we reaching our goal?

Ingrid den Uijl¹,², Douwe Biesma³, Diederick Grobbee², Kathelijn Fischer¹,²

¹van Creveldkliniek, Department of Haematology; ²Julius Centre for Health Sciences and Primary Care; ³Department of Haematology, Medical University Centre Utrecht, Utrecht, The Netherlands

- Single-center, n=80 severe, n=40 moderate HA
- All sHA, 25% modHA on “intermediate-dose ppx”
- FVIII level (median): PPX pts 2 IU/dL, demand 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Severe HA</th>
<th>Moderate HA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR*, median (IQR)</td>
<td>2.0 (0.8 to 3.7)</td>
<td>0.8 (0 to 1.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Joint Score** (IQR)</td>
<td>8 (3 to 15)</td>
<td>2 (0 to 6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Joints **Haemophilia Joint Health Score (HJHS)

Monitoring Extended Half-Life Products

- Field Study, Fc-fusion vs commercial standard
- Potencies: .05, .20, .80 IU/ml

<table>
<thead>
<tr>
<th>Label activity, IU mL⁻¹</th>
<th>Mean recovery, % of label (n = 29–30 per level)</th>
<th>Mean intra-laboratory % CV (n = 3 per laboratory)</th>
<th>Inter-laboratory % CV (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advate® 0.80</td>
<td>96.7</td>
<td>6.3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>110.2</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>118.1</td>
<td>7.4</td>
</tr>
<tr>
<td>rFVIII Fc 0.87</td>
<td>94.6</td>
<td>6.0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>106.0</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>115.7</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Conducted in 30 laboratories.

One-stage FVIII Assay have comparable activity

Thank You

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