The journey to extended half-life haemostatic therapies in haemophilia

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Objectives

• Background & limitations of current clotting factor concentrates in haemophilia care

• Bioengineering strategies to prolong coagulation factor half-life

• Non-coagulation factor strategies

• Implications on future of haemophilia care
The Coagulation Cascade

The coagulation cascade can be viewed as an intricate thrombin production regulatory system.

There are four stages to coagulation:

- Stimulus phase
- Initiation phase
- Propagation phase
- Thrombus formation
Regulation of coagulation as potential targets

TFPI=tissue factor pathway inhibitor

Tilman M. Hackeng, Kristin M. Seré, Guido Tans, and Jan Rosing. PNAS 2006
Haemophilia is a musculoskeletal disorder

- Hemophilic arthropathy is the major cause of morbidity due to repeated joint bleeds (20-30/yr)

Life-threatening bleeds (e.g., intracranial hemorrhage) can occur
Treatment

• ‘Prophylaxis’, the provision of regular infusions of factor concentrates aims to prevent bleeding episodes and their pathological consequences

Maintaining a trough of >1% significantly reduces bleeding

Collins et al., J Thromb Haemost 2010
Current available FVIII concentrates in Australia

**Haemophilia A**
- Recombinant
  - Advate
  - Xyntha
- Plasma derived
  - Biostate
- Half-life
  - 8-12h

**Haemophilia B**
- Recombinant
  - Benefix
  - Rixobus
- Half-life
  - 18-24h
Limitations of current haemostatic products

– Short half-life (Compliance & QoL)\(^1,2\)

– Frequent *intravenous* injections
  - Thrice weekly for haemophilia A
  - Ports – infection risk, occlusion etc

– FVIII inhibitors (allo-antibodies)
  - Immune Tolerance Induction costly & <100% effective
  - Short acting “bypass agents”

\(^1\)Hacker Haemophilia 2001; 7: 392–6; \(^2\) Lillicrap Thromb Res 2008; 122 (Suppl. 4): S2–8
Adherence in Severe HA patients on prophylaxis (O/E x 100)

Mason, Parihk, Tran, McRae, submitted to Haemophilia
“Ideal” features for hemostatic product in hemophilia

<table>
<thead>
<tr>
<th>Characteristic of therapeutic agent</th>
<th>Relevance to all hemostatic therapies</th>
<th>Particular relevance to bioengineered coagulation factors in development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Least invasive</strong> mode of administration (Subcutaneous vs IV)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Least requirement for dose manipulation</strong> due to inter-individual differences in response/clearance</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Maximal (i.e, supraphysiologic) <strong>half-life</strong></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>No (or lowest) immunogenicity</strong></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Highest tolerability (safety)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Lowest thrombogenic potential</strong></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lowest cost (aggregate, over a lifetime)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Technologies for haemophilia Treatment

- PEGylation
  - Random
  - Site specific
  - Engineered

- Fusion proteins
  - IgG1-Fc
  - Albumin

- Complexing Antibody
  - (e.g., emicizumab)

- Alternative approaches
  - TFPI
  - ApC
  - AT

- Sequence modifications
  - Site specific e.g., siRNA
PEG-ylation to extend half-life

- Pegylation of proteins
  - Reduce renal clearance
  - Protect against enzyme digestion
  - Blocks interaction with clearance receptors (LRP)
  - E.g., PEG-IFN, PEG-G-CSF, PEG-aspariginase

- Random PEG (multisite)
- Site-specific

Pasut Drug Discovery Today 2005;10(21):1451-8
Fusion protein technology

Protein fused to another protein with natural longer half life in circulation

- Fragment crystalline (Fc) of IgG
- Albumin

Mutations of residues depicted in green improves IgG binding to FcRn, thereby prolongs Fc coupled drugs
Clinical studies with modified long-acting rFIX

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Technology</th>
<th>Cell line</th>
<th>$t\text{½}$, hr</th>
<th>$t\text{½}$ vs. rFIX</th>
<th>~ time to 1% trough after 50IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFIX-Fc (Alprolix) (Biogen-Idec)</td>
<td>Fc-Fusion protein (BDD-rFIXFc)</td>
<td>HEK</td>
<td>57-83</td>
<td>3x</td>
<td>10 d (2wks with 100IU/kg)</td>
</tr>
<tr>
<td>N9-GP (NovoNordisk)</td>
<td>Single site specific glycopegylation (40kDa PEG)</td>
<td>CHO</td>
<td>96-110</td>
<td>&gt;5x</td>
<td>2-3 wks</td>
</tr>
<tr>
<td>rIX-FP (Idelvion) (CSL-BEHRING)</td>
<td>Albumin fusion protein</td>
<td>CHO</td>
<td>89-96</td>
<td>&gt;5x</td>
<td>2-3wks</td>
</tr>
</tbody>
</table>
Adult phase 3 study: efficacy of 7, 10 and 14 day prophylaxis

<table>
<thead>
<tr>
<th>Idelvion (rFIX-alb)</th>
<th>Prophylaxis Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-day</td>
</tr>
<tr>
<td></td>
<td>35–50 IU/kg</td>
</tr>
<tr>
<td></td>
<td>(n=40)</td>
</tr>
<tr>
<td>AsBR</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Estimated mean* (95% CI)</td>
<td>0.65 (0.37–1.13)</td>
</tr>
<tr>
<td>Total ABR</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0 (0–1.87)</td>
</tr>
<tr>
<td>Estimated mean* (95% CI)</td>
<td>1.58 (1.02–2.44)</td>
</tr>
</tbody>
</table>

*Assuming Poisson distribution

Study details: Prospective, nonrandomised, open-label, multinational phase 3 clinical study assessing pharmacokinetics, safety and efficacy of IDELVION in previously treated patients (PTPs), 63 males with haemophilia B (≤2% FIX activity), 12–61 years.

ABR, annualised bleeding rate; AsBR, annualised spontaneous bleeding rate; CI, confidence interval; IQR, interquartile range

Adapted from Santagostino et al. 2016

# Long acting recombinant FVIII

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Technology</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rFVIII-Fc</strong> (Eloctate) (Bioverativ)</td>
<td>Fc-Fusion protein (BDD-rFVIIIFc)</td>
<td><strong>Fc -FUSION</strong></td>
</tr>
<tr>
<td><strong>BAX-855</strong> (Adynovate) (Shire)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BAY-94-9027</strong> (Bayer)</td>
<td></td>
<td><strong>PEGYLATED – ALL DIFFERENT</strong></td>
</tr>
<tr>
<td><strong>N8-GP</strong> (NovoNordisk)</td>
<td>Single site specific glycopegylation (<strong>40kDa</strong> PEG) – BDD truncated rFVIII</td>
<td></td>
</tr>
</tbody>
</table>

**Similar pharmacokinetics**

T1/2 (adults) ≈ 19h

1.4-1.7 fold longer than rFVIII
Recombinant Factor VIII Fc Fusion Protein (Eloctate) in Severe Hemophilia A

<table>
<thead>
<tr>
<th></th>
<th>Arm 1: individualized Prophylaxis (n = 117)</th>
<th>Arm 2: weekly prophylaxis (n = 23)</th>
<th>Arm 3: episodic treatment (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR, negative binomial model (95% CI)</td>
<td>2.9 (2.3-3.7)</td>
<td>8.9 (5.5-14.5)</td>
<td>37.3 (24.0-57.7)</td>
</tr>
<tr>
<td>% Reduction vs arm 3 (P)*</td>
<td>92 (&lt;0.001)</td>
<td>76 (&lt;0.001)</td>
<td>—</td>
</tr>
<tr>
<td>ABR by type and location of bleeds, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.6 (0.0, 4.7)</td>
<td>3.6 (1.9, 8.4)</td>
<td>33.6 (21.1, 48.7)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>0.0 (0.0, 2.0)</td>
<td>1.9 (0.0, 4.8)</td>
<td>20.2 (12.2, 36.8)</td>
</tr>
<tr>
<td>Joint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>0.0 (0.0, 1.7)</td>
<td>0.0 (0.0, 3.8)</td>
<td>18.6 (7.6, 29.6)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>0.0 (0.0, 1.2)</td>
<td>0.0 (0.0, 2.0)</td>
<td>3.9 (0.0, 8.6)</td>
</tr>
<tr>
<td>Spontaneous muscle</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>5.1 (1.8, 6.8)</td>
</tr>
<tr>
<td>Subjects with no bleeding episodes, n (%)</td>
<td>53 (45.3)</td>
<td>4 (17.4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Arm 1=individualised **twice weekly** dosing (25 IU/kg on day 1 and 50 IU/kg on day 4 to start, followed by 25-65 IU/kg every 3-5 d); Arm 2=65IU/kg **once weekly**; Arm 3=on demand

Mahlangu Blood. 2014;123(3):317-325
PROLONG-ATE (rFVIII-PEG): ABR by bleed site and cause*

**Mean (SD)**

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis (N=101)</th>
<th>On-demand (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>41.5 (31.7; 51.1)</td>
<td>21.6 (11.2; 33.2)</td>
</tr>
<tr>
<td>Joint</td>
<td>38.1 (24.5; 44.6)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous/unknown</td>
<td>0 (0.0; 2.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Per protocol analysis set (PPAS)

ABR, annualised bleed rate; Q1, quartile 1; Q3, quartile 3

**Adynovate 45 IU/kg 2x/week for ≥50 EDs or 6 months**

Technologies for half-life extension

Complexing
Antibody
(e.g., emicizumab)
Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D.,
Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D.,
Guy Young, M.D., Elena Santagostino, M.D., Ph.D.,
Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D.,
Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanis, M.Sc.,
Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

Available at http://www.nejm.org
Emicizumab (ACE910)  
Humanized bispecific monoclonal antibody

- Novel humanized bispecific monoclonal antibody
- Bridges activated FIX (FIXa) and FX to restore function of missing FVIIIa
- No structural homology to FVIII – not expected to induce FVIII inhibitors or be affected by presence of inhibitors
- Administered subcutaneously

## HAVEN 1

### Demographics/baseline disease characteristics

<table>
<thead>
<tr>
<th>Arm</th>
<th>Emicizumab prophylaxis</th>
<th>No prophylaxis</th>
<th>Emicizumab prophylaxis</th>
<th>Emicizumab prophylaxis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(prior episodic BPAs)</td>
<td>(prior episodic BPAs; control arm)</td>
<td>(prior BPA prophylaxis)</td>
<td>(prior BPAs; episodic or prophylactic)</td>
<td>N=109</td>
</tr>
<tr>
<td>n=35</td>
<td></td>
<td></td>
<td>n=49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=18</td>
<td></td>
<td></td>
<td>n=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.0 (12–68)</td>
<td>35.5 (13–65)</td>
<td>17.0 (12–75)</td>
<td>26.0 (19–49)</td>
<td>28.0 (12–75)</td>
</tr>
<tr>
<td>&lt;18 years, n (%)</td>
<td>4 (11.4)</td>
<td>2 (11.1)</td>
<td>26 (53.1)</td>
<td>3 (42.9)</td>
<td>32 (29.4)</td>
</tr>
<tr>
<td>Bleeds in 24 weeks prior to study entry, n (%)</td>
<td>24 (68.6)</td>
<td>13 (72.2)</td>
<td>26 (53.1)</td>
<td>3 (42.9)</td>
<td>66 (60.6)</td>
</tr>
<tr>
<td>Target joints, n (%)</td>
<td>25 (71.4)</td>
<td>13 (72.2)</td>
<td>34 (69.4)</td>
<td>4 (57.1)</td>
<td>76 (69.7)</td>
</tr>
<tr>
<td>Any</td>
<td>18 (72.0)</td>
<td>10 (76.9)</td>
<td>24 (70.6)</td>
<td>1 (25.0)</td>
<td>53 (48.6)</td>
</tr>
<tr>
<td>&gt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest historical inhibitor titer (BU)</td>
<td>84.5 (n=32)</td>
<td>102.0 (n=16)</td>
<td>309.0 (n=47)</td>
<td>240.0 (n=6)</td>
<td>180.0 (n=101)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5–1570</td>
<td>18–4500</td>
<td>11–5000</td>
<td>28–2125</td>
<td></td>
</tr>
<tr>
<td>Previously treated with ITI, n (%)</td>
<td>14 (40.0)</td>
<td>7 (38.9)</td>
<td>33 (67.3)</td>
<td>3 (42.9)</td>
<td>57 (52.3)</td>
</tr>
</tbody>
</table>

BU, Bethesda units; ITI, immune tolerance induction.
HAVEN 1 primary endpoint
Randomized comparison of treated bleeds

- Statistically significant, clinically meaningful reduction in bleed rate with emicizumab
- 62.9% of patients experienced zero bleeds with emicizumab prophylaxis
- To date, no patients have discontinued due to lack of efficacy

### Median ABR

- **Arm A:** Emicizumab prophylaxis
  - Annualized bleeding rate (ABR) (95% CI): 23.3 (12.33; 43.89)
  - Median ABR (IQR): 18.8 (12.97; 35.08)
- **Arm B:** No prophylaxis (episodic BPAs only)
  - Annualized bleeding rate (ABR) (95% CI): 2.9 (1.69; 5.02)
  - Median ABR (IQR): 0.0 (0.00; 3.73)

### Comparative Analysis

- **Arm A:** Emicizumab prophylaxis
  - 87% reduction in ABR
  - P < 0.0001

- **Arm B:** No prophylaxis (episodic BPAs only)
  - Mean ABR: 2.9
  - Median ABR: 0.0

- **Arm A:** Emicizumab prophylaxis
  - 62.9% of patients experienced zero bleeds
  - To date, no patients have discontinued due to lack of efficacy

Primary analysis data cutoff – October 25, 2016

ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.
CI, confidence interval; IQR, interquartile range.
HAVEN 1 safety summary
All emicizumab patients

- Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal hemorrhage
- Thrombotic events were skin necrosis/superficial thrombophlebitis in one patient, and cavernous sinus thrombosis in a second patient
- No patients tested positive for anti-drug antibodies

<table>
<thead>
<tr>
<th>Total number of adverse events (AEs), n</th>
<th>198</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients ≥1 AE, n (%)</td>
<td>73 (70.9)</td>
</tr>
<tr>
<td>Serious AE*</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (TMA)**</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Death**</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Related AE</td>
<td>23 (22.3)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>15 (14.6)</td>
</tr>
</tbody>
</table>

**Additional serious AEs included one event each of: iron deficiency anemia, sepsis, hemarthrosis, muscle hemorrhage, gastric ulcer hemorrhage, headache and hematuria.
Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision.
HAVEN 1
Characteristics of TMA and thrombotic events

<table>
<thead>
<tr>
<th>Event</th>
<th>Received BPA prior to event?</th>
<th>Anti-coagulation</th>
<th>Resolution</th>
<th>Additional treatment</th>
<th>Restarted emicizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis #1</td>
<td>aPCC</td>
<td>No</td>
<td>Resolved</td>
<td>Supportive care only</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombosis #2</td>
<td>aPCC</td>
<td>No</td>
<td>Resolving</td>
<td>Supportive care only</td>
<td>No</td>
</tr>
<tr>
<td>TMA #1</td>
<td>aPCC/rFVIIa</td>
<td>N/A</td>
<td>Resolved</td>
<td>Plasmapheresis</td>
<td>No</td>
</tr>
<tr>
<td>TMA #2</td>
<td>aPCC</td>
<td>N/A</td>
<td>Resolved</td>
<td>Supportive care only</td>
<td>Yes</td>
</tr>
<tr>
<td>TMA #3</td>
<td>aPCC/rFVIIa</td>
<td>N/A</td>
<td>Resolving*</td>
<td>Plasmapheresis</td>
<td>No</td>
</tr>
</tbody>
</table>

- Commonality among all cases was high cumulative doses of aPCC over multiple days prior to event and improvement shortly after discontinuing aPCC
- TMA events in two patients were short-lived; resolved soon after aPCC treatment was stopped
  - rFVIIa treatment in TMA #1 included treatment during resolution of the event
- *Patient treated for rectal hemorrhage, which was eventually fatal; death was deemed unrelated to emicizumab

aPCC, activated prothrombin complex concentrate; rFVIIa, activated recombinant FVII.
HAVEN 1 updated data
Assessment of interaction between emicizumab and aPCC

- TMA/thrombotic events only occurred with aPCC treatment averaging >100 U/kg daily for ≥24 hours
- aPCC contains activated and non-activated coagulation factors, including FII, FVII, FIX and FX, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date

- Two patients also received rFVIIa prior to/during the event.

TE, thromboembolism.

Updated data cutoff – April 21, 2017, including 8 additional patients.
Pharmacokinetic/pharmacodynamic modeling predicted emicizumab concentration \( \geq 45 \) µg/mL would result in >50% of patients achieving zero bleeds

- Target met with weekly subcutaneous dosing: mean trough plasma concentrations >50 µg/mL achieved and sustained once steady-state was reached

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SD, standard deviation.
HAVEN 1 conclusions (1)

Once-weekly emicizumab prophylaxis administered subcutaneously

- **Reduction in bleed rate of 87% vs no prophylaxis**
  - 63% of patients randomized to emicizumab prophylaxis & 71% of patients previously on BPA prophylaxis experienced **zero bleeds**

- Substantial reduction in bleeds associated with clinically meaningful benefits in HRQoL and health status
HAVEN 1 conclusions (2)

- Serious thrombotic and TMA events were seen when aPCC was administered at repeated doses (>100 U/kg/day on average for ≥24 hours) to treat breakthrough bleeds during emicizumab prophylaxis.

- aPCC should be avoided if possible in patients receiving emicizumab.
  - If necessary to use, lower doses are indicated and caution should be used.

- Risk of TE and TMA events seen with aPCC administered with emicizumab prophylaxis may be mitigated with BPA treatment guidance.
Technologies for half-life extension

Alternative approaches

AT= antithrombin
TFPI – tissue factor pathway inhibitor
Fitusiran (siRNA-AT)

- **Investigational RNAi Therapeutic for the Treatment of Hemophilia**

  - **Fitusiran (ALN-AT3)**
    - **SC-administered** small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
      - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—the site of AT synthesis
      - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

  - **Therapeutic hypothesis**
    - Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
    - Fitusiran is designed to lower AT, with the goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
      - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia
      - Supported by pre-clinical data and emerging Phase 1 clinical results

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Coexistence of FVIII and antithrombin (AT) deficiency reduces bleeding

- “Clinically mild” bleeding phenotype:
  - FVIII<1% yet <2 bleeds/infusions over previous 5yrs and no severe joint deformity

- ?Inhibition of AT could be used as haemostatic therapy

<table>
<thead>
<tr>
<th>age/age at Dx</th>
<th>Factor deficiency</th>
<th>ABE/AI</th>
<th>Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 29/15</td>
<td>VIII</td>
<td>0.4/0.2</td>
<td>AT=36%</td>
</tr>
<tr>
<td>2 54/23</td>
<td>VIII</td>
<td>0.4/0</td>
<td>AT=51%</td>
</tr>
</tbody>
</table>

ABE, ave number of bleeds last 5 years
AI, ave number of infusions last 5 years

Shetty Br J Haematol 2007;138:541-44
Potential benefits of RNAi in hereditary bleeding disorders

- **Subcutaneous** administration
- Long duration of effect (2-4 weekly dosing, ?longer)
- Synthetic siRNA – no inhibitors
- Prophylaxis for **both HMA & HMB without and with inhibitors**
  - ?Breakthrough bleeds can be safely managed with FC replacement
    - Thrombosis - rescue with antithrombin concentrate?
- ?benefit for rarer bleeding disorders
Interim Fitusiran Phase 1 Study Results*

- Exploratory Analysis of Bleed Events, Part C†

**Summary of Median ABR (All Cohorts)**

<table>
<thead>
<tr>
<th>ABR</th>
<th>PPx</th>
<th>OD</th>
<th>Onset</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-study‡</td>
<td>28</td>
<td>6</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

**Summary of Median ABR (80 mg)**

<table>
<thead>
<tr>
<th>ABR</th>
<th>PPx</th>
<th>OD</th>
<th>Onset</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Study‡</td>
<td>6</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**All Part C patients^**

- Median ABR, Pre-study period: 2 (PPx); 28 (OD)
- Median ABR, Observation period: 0
  - 53% of patients report no bleeds
  - 82% of patients report no spontaneous bleeds

**Part C, 80 mg MONTHLY dosing cohort ^**

- Median ABR, Pre-Study (all PPx patients): 6
- Median ABR, Observation period: 0

---

*Data transfer: 30Jun2016
PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate;
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier; ‡Pre-study ABR derived from medical records; ^Patient C5-4 withdrawn, excluded from analysis
Interim Fitusiran Phase 1 Study Results*

- No SAEs related to study drug
- 11 (35%) patients reported drug-related ISRs, all mild
  - Mostly pain and/or erythema at injection site

- No thromboembolic events
  - (or laboratory evidence of pathologic clot formation)

- Bleed events successfully managed with infusion of standard replacement factor or bypass agents

*Data transfer up to 11 July 2016
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
## Study Comparison

<table>
<thead>
<tr>
<th></th>
<th>ALN-AT3SC-003</th>
<th>ALN-AT3SC-004</th>
<th>ALN-AT3SC-005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemophilia A / B</strong></td>
<td>A &amp; B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitor Status</strong></td>
<td>With Inhibitors</td>
<td>Without Inhibitors</td>
<td>With and Without Inhibitors</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>Open to Youth 12-18 years old and Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Assignment</strong></td>
<td>On Demand ⇒ 2:1 Fitusiran:SOC Prophylaxis ⇒ Fitusiran</td>
<td></td>
<td>All Open Label Fitusiran</td>
</tr>
<tr>
<td><strong>Fitusiran Administration</strong></td>
<td>Q4W in Clinic</td>
<td></td>
<td>Q4W in Clinic, or Home Nursing</td>
</tr>
<tr>
<td><strong>Study Duration</strong></td>
<td>Screening: Up to 2 Months Treatment: 8 Months Safety F/U: Until 60% Baseline AT OR Rollover to OLE</td>
<td>Screening: 3 Months Treatment: 24 Months Safety F/U: Until 60% Baseline AT OR Available Commercial Therapy</td>
<td></td>
</tr>
</tbody>
</table>
What are the implications of half-life extension?

- Clinical
  - Reduction in bleeds
    - Quality of life
      - Contributes to society

- Laboratory
How will EHL concentrates impact on prophylaxis?

**Fewer infusions**
- Improved vein health
- Less need for CVC
- Convenient dosing times
- Increased uptake of appropriate prophylaxis

**Higher troughs**

\[(\text{FVIII}>12\% = \text{no Joint bleeds})\]

Combination of both

*Den Uijl Haemophilia 2011 17(1);1:41-44
EHL Factor concentrate means fewer infusions

## Haemophilia A

<table>
<thead>
<tr>
<th>Dosing regime</th>
<th>Number of infusions per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three times weekly</td>
<td>184</td>
</tr>
<tr>
<td>Twice weekly</td>
<td>104</td>
</tr>
<tr>
<td>Every 5 days</td>
<td>73</td>
</tr>
<tr>
<td>Once weekly</td>
<td>52</td>
</tr>
</tbody>
</table>

## Haemophilia B

- **Dose once 10-21d and still keep trough >1%**
  
  rFIXFc administered 50 iu/kg weekly and 100 iu/kg every 10 d would maintain steady-state FIX trough levels ≥1 iu/dl in 95.4% and 89.2% of subjects

- **Reduce from 104 infusions per year to 18-36 per year**

*Powell Br J Haematol. 2014 Sep 11*
Relationship between subjects’ prestudy (FVIII) and on-study (rFVIIIFc) regimens

Frequency of infusion

Weekly factor consumption

N=80

ABR, 2.1 overall and 0.0 in last 2m on study
Significantly lower than 12m pre study
Framework for Tailoring Treatment through Outcome Based Tailored Care (OBTC)

ADVATE Prophylaxis Study (Standard prophylaxis arm - Q2days)

High Bleeders; trough > 3% and ABR > 1 (15%)

High bleeder; low trough and ABR > 1 (10%)

0-1 ABR w/ trough > 3% (25%)

0-1 ABR w/ trough < 3% (50%)
ADVATE Prophylaxis Study (Standard prophylaxis arm - Q2days)

- **Goal: Increase dose to target trough**
  - High bleeders; low trough and ABR > 1 (10%)

- **Goal: PK-tailoring based on individual target**
  - High Bleeders; trough > 3% and ABR > 1 (15%)

- **Goal: Maintain**
  - 0-1 ABR w/ trough ≤ 3% (50%)

- **Goal: Optimise dose to decrease utilisation/maintain effectiveness**
  - 0-1 ABR w/ trough > 3% (25%)

**Framework for Tailoring Treatment through Outcome Based Tailored Care (OBTC)**

Goal: Increase dose to target trough

Goal: PK-tailoring based on individual target

Goal: Maintain

Goal: Optimise dose to decrease utilisation/maintain effectiveness
Conclusion

- Different technologies extend half-life of haemostatic agents
- PEG/Fc/albumin technologies might have “ceiling” half-lives and remain as *intravenous* administration
- Small molecules (e.g., bispecific antibody) with extended half-lives will provide alternate *subcutaneous* route of administration
- Longer acting products will improve prophylaxis outcomes through personalised treatment & better adherence & QoL
Thank you & Questions