Novel Therapy in Hemophilia

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Introduction

Hemophilia patients are susceptible to **frequent spontaneous bleeding** episodes, which can lead to **joint disease** and **decreased quality of life**\(^1\)

The mainstay of treatment for hemophilia A is FVIII replacement infusions; however, \(~30\%\) of patients develop antibodies (**inhibitors**) to FVIII, which can render this treatment ineffective\(^2\)

Inhibitor patients are at risk of **increased morbidity** and have had **limited treatment options**\(^2\)

Bleeding can be managed by prophylactic or episodic use of BPAs, but these agents are **more costly and less effective than FVIII replacement in patients without inhibitors**

BPAs require frequent infusions,\(^3,4\) which add substantial treatment burden to patients with inhibitors

**Improved therapies to treat patients with inhibitors are needed**\(^2,5\)

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History of available haemophilia A therapies

- Whole blood or fresh plasma
- Cryoprecipitate – Judith Graham Pool (Stanford)
- Freeze-dried (lyophilised) FVIII concentrate
- Viral-inactivated FVIII concentrates
- Recombinant FVIII concentrates
- FEIBA for haemophilia patients with inhibitors
- Recombinant FVIIa concentrate for patients with inhibitors
- Extended half-life FVIII concentrate approved
- New MoAs


- F8 gene cloned and first laboratory production of recombinant FVIII by Genentech
- HCV hepatitis C virus
- HIV human immunodeficiency virus
- MoA mechanism of action

F, factor; FEIBA, factor eight inhibitor bypassing activity; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MoA, mechanism of action

Innovative Strategies for Hemophilia Therapy

- Extended half-life products. (Half-lives – FVIII 12hrs/FIX 24hrs)
- Intrinsic tenase innovations
- Inhibitors of anticoagulant mechanisms
- Gene therapy
1. Modified native protein
   - Single chain covalently linked FVIII (CSL)

2. Molecular conjugates
   - PEGylation (Baxter, Novo Nordisk, Bayer)
   - XTENylation (Biogen)
   - PASylation (Generium)

3. Fusion proteins
   - IgG (Biogen)
   - Albumin (CSL)
Half-Life Extension Technology

- **Fc Fusion**
  - FIX
  - FVIII
  - Immunoglobulin Fc part
  - Binding to FcRn to prevent lysosomal degradation

- **Albumin Fusion**
  - FIX
  - Alb
  - Albumin fusion via linker peptide derived from FIX activation peptide

- **GlycoPEGylation**
  - FIX
  - FVIII
  - Site-directed attachment
  - Cleaved during factor activation
Recycling of IgG

Endothelial cell

IgG binds to FcRn receptor

Non-specific uptake

Bound IgG is recycled

Degradation
Albumin fusion products

Schulte S. Thrombosis Research 128 (Suppl. 1) S9-S12 (2011):

- Marketed as “natural alternative” to PEG, which is not entirely biodegradable
- DNA construct encoding both target protein and albumin in a single recombinant molecule
- Short linker in between to avoid problems due to steric hindrance and ensure retention of maximum potency
Single-chain factor VIII (CSL627):

- Most of B-domain and 4 amino acids of adjacent A3 domain deleted (amino acids 765-1652 of full length molecule)
- Covalent link between heavy and light chains prevents dissociation
- Binding site for VWF also modified to increase affinity twofold
- Very preliminary data suggest $T_{1/2}$ extension of 1.6 fold
- Clinical trials now underway
Pegylation:

When attached to a drug, polyethylene glycol (PEG) polymer chains can sustain bioavailability by protecting the drug molecules from immune responses and other clearance mechanisms. In an aqueous medium, the long, chain-like PEG molecule is heavily hydrated and in rapid motion. This motion causes the PEG to sweep out a large volume and prevent the interference of other molecules.
Clotting Factor Half-Life Extensions

Factor IX 3 to 5-fold  1 infusion Q7-14 days

(Santagostino et al Blood 2012)
(Negrier et al Blood 2011)
(Shapiro et al Blood 2012)

Factor VIII 1.5 to 1.8-fold  1 infusion Q3-4 days

(Powell et al Blood 2012)
(Coyle et al JTH 2014)
(Mahlangu et al Blood 2014)

FVIII half-life limited by dominance of VWF
# Extended half life factor concentrate

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Technology</th>
<th>Cell line</th>
<th>Molecule length</th>
<th>Pharmacokinetic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eloctate</td>
<td>Biogen</td>
<td>Fc Fusion</td>
<td>HEK</td>
<td>BDD</td>
<td>Age in years: 18-19.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-17: 16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-11: 14.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-5: 12.0</td>
</tr>
<tr>
<td>Bax 855</td>
<td>Baxalta</td>
<td>PEGylation to surface exposed lysine 2× 20 kDa</td>
<td>CHO</td>
<td>Full-length</td>
<td>&gt;12: 16</td>
</tr>
<tr>
<td>Bay 94-9027</td>
<td>Bayer</td>
<td>Site-specific PEGylation to cysteine 1805</td>
<td>BHK</td>
<td>Full-length</td>
<td>&gt;18: 18.6-19.5</td>
</tr>
<tr>
<td>CSL-827</td>
<td>CSL Behring</td>
<td>Covalently linked heavy and light chain with increased affinity for VWF</td>
<td>CHO</td>
<td>BDD</td>
<td>&gt;18: 13.1</td>
</tr>
<tr>
<td>N8 GP</td>
<td>NovoNordisk</td>
<td>Single site-specific PEGylation to O-linked glycan in the B-domain 40 kDa</td>
<td>CHO</td>
<td>BD truncated</td>
<td>&gt;18: 18.4</td>
</tr>
</tbody>
</table>

**Factor IX products**

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Technology</th>
<th>Cell line</th>
<th>Molecule length</th>
<th>Pharmacokinetic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprolix</td>
<td>Biogen</td>
<td>Fc fusion</td>
<td>HEK</td>
<td>Full-length</td>
<td>18: 86.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-17: 83.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-11: 72.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-5: 66.4</td>
</tr>
<tr>
<td>CSL-854</td>
<td>CSL Behring</td>
<td>Albumin fusion</td>
<td>CHO</td>
<td>Full-length</td>
<td>15-58: 89.9</td>
</tr>
<tr>
<td>N9 GP</td>
<td>Novo Nordisk</td>
<td>Site-specific PEGylation to the activation peptide 40 kDa</td>
<td>CHO</td>
<td>Full-length</td>
<td>&gt;21: 92.7</td>
</tr>
</tbody>
</table>

*HEK indicates human embryonic kidney; BDD, B-domain diated; CHO, Chinese hamster ovary; BHK, baby hamster kidney; SHL, standard half-life; and VWF, von Willebrand factor.*
Looking at new targets for haemophilia A therapy

Boost the extrinsic pathway (e.g. by countering the inhibitory action of TFPI)

Replace or replicate the function of missing FVIIIa in the clotting cascade via new means (e.g. monoclonal antibody or gene therapy)

Boost thrombin levels to increase the feedback loop and allow for quicker fibrin formation (e.g. by inhibiting antithrombin)

FVIIIa, activated factor VIII; TFPI, tissue factor pathway inhibitor

Emicizumab

- 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
- Half-life of 4–5 weeks, administered by weekly subcutaneous injection
- Approved in the United States (HEMLIBRA®) for prophylactic treatment of persons with hemophilia A (PwHA) with inhibitors

## Emicizumab clinical development plan

<table>
<thead>
<tr>
<th>Emicizumab clinical trials</th>
<th>Key outcome</th>
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| **HAVEN 1** (NCT02622321) primary analysis | ▪ The primary endpoint showed a statistically significant reduction in treated bleeds of 87% with QW emicizumab in PwHA with inhibitors vs no prophylaxis  
▪ All 12 secondary endpoints were positive, including an intraindividual analysis, which showed a statistically significant reduction in treated bleeds of 79% with emicizumab prophylaxis vs prior bypassing agent prophylaxis collected in the NIS before enrollment<sup>1</sup> |
| **HAVEN 2** (NCT02795767) interim analysis | ▪ After a median observation time of 38.1 weeks, 87% of children aged <12 years with PwHA with inhibitors who received QW emicizumab prophylaxis experienced zero treated bleeds  
▪ In an intraindividual analysis, emicizumab prophylaxis substantially reduced bleed rates by 99% vs prior bypassing agent prophylaxis/episodic treatment during the NIS<sup>2</sup> |
| **HAVEN 3** (NCT02847637) | ▪ The primary endpoint showed a statistically significant reduction in treated bleeds with QW emicizumab prophylaxis compared with no prophylaxis in PwHA without inhibitors aged ≥12 years  
▪ Key secondary endpoint showed a statistically significant reduction in treated bleeds with Q2W emicizumab prophylaxis vs no prophylaxis  
▪ In an intraindividual comparison, QW emicizumab prophylaxis was superior to prior FVIII prophylaxis during the NIS |
| **HAVEN 4** (NCT03020160) | ▪ Evaluating emicizumab prophylaxis dosed Q4W in PwHA with and without inhibitors aged >12 years |

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HAVEN 1: Emicizumab Prophylaxis in Adolescent/Adult Patients with Hemophilia A Previously Receiving Episodic or Prophylactic Bypassing Agent Treatment: Updated Analyses from the Study

Maria Elisa Mancuso,1 Johannes Oldenburg,2 Michael U. Callaghan,3 Rebecca Kruse-Jarres,4 Christine L. Kempton,5 Jin Xu,6 Olivier Catalani,7 Elina Asikanius,7 Gallia G. Levy,6 Midori Shima,8 Guy Young9

1Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy; 2Universitätsklinikum Bonn, Bonn, Germany; 3Children’s Hospital of Michigan, Detroit Medical Center, Detroit, MI, USA; 4Washington Center for Bleeding Disorders at Bloodworks Northwest, University of Washington, Seattle, WA, USA; 5Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA; 6Genentech, Inc., South San Francisco, CA, USA; 7F. Hoffmann-La Roche Ltd, Basel, Switzerland; 8Department of Pediatrics, Nara Medical University, Kashihara, Japan; 9Children’s Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
HAVEN 1
Study design

Loading dose: 3 mg/kg/week for 4 weeks
Maintenance dose: 1.5 mg/kg/week starting Week 5†
Elmizumab 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 Asikianis, M.Sc., Gallia G. Levy, M.D.,
Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

Comments open through September 6, 2017
HAVEN 1
Primary endpoint: ABR (treated bleeds)

62.9% of patients experienced zero treated bleeds

87% reduction in ABR
(relative risk, 0.13; \( p < 0.0001 \))

5.6% of patients experienced zero treated bleeds

Primary outcome

ABR (95% CI)

Arm A (emicizumab prophylaxis, n = 35)
2.9 (1.69–5.02)

Arm B (no prophylaxis, n = 18)
23.3 (12.33–43.80)


ABR, annualised bleed rate; CI, confidence interval
<table>
<thead>
<tr>
<th>Event</th>
<th>Overall N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>457</td>
</tr>
<tr>
<td>Total patients with ≥1 AE, n (%)</td>
<td>96 (85.7)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>19 (17.0)</td>
</tr>
<tr>
<td>TMA</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Fatal AEs, n (%)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>AEs leading to withdrawal, n (%)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Grade ≥3 AEs, n (%)</td>
<td>14 (12.5)</td>
</tr>
<tr>
<td>Related AEs, n (%)</td>
<td>32 (28.6)</td>
</tr>
<tr>
<td>Local injection site reactions, n (%)</td>
<td>16 (14.3)</td>
</tr>
</tbody>
</table>
The 5 reported serious AEs of thrombotic microangiopathy (TMA) or thrombosis were attributed to average cumulative doses of aPCC >100 U/kg/day for ≥24 hours for the treatment of breakthrough bleeds during emicizumab prophylaxis.

- Dosing guidance for BPA use during emicizumab prophylaxis was provided by the sponsor (October 2016) to mitigate further risk; no additional patients experienced TMA or other serious thrombotic events when this guidance was followed.
HAVEN 1
Conclusions

- With nearly 10 months’ longer follow-up, the updated intra-individual comparisons showed that emicizumab prophylaxis continues to demonstrate a clinically meaningful **reduction in risk of treated bleeds** compared with current standard of care (episodic or prophylactic BPAs)
  - Improvement in emicizumab efficacy over 24-week intervals from the first 24 weeks to weeks 49–72 of treatment was demonstrated by a further reduction in ABR from 3.1 to 0.5, and a further increase in the proportion of patients with zero treated bleeds from 71% to 88%
- Emicizumab prophylaxis was **well tolerated**
- These data support once-weekly subcutaneously administered emicizumab prophylaxis to reduce treatment and disease burden, and **provide a potential new standard of care for the management of PwHA with inhibitors**
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- In an intraindividual comparison, QW emicizumab prophylaxis was superior to prior FVIII prophylaxis during the NIS |
| **HAVEN 4** (NCT03020160) | - Evaluating emicizumab prophylaxis dosed Q4W in PwHA with and without inhibitors aged >12 years |

HAVEN 2: Efficacy, Safety, and Pharmacokinetics of Once-Weekly Prophylactic Emicizumab (ACE910) in Pediatric Patients (<12 Years) with Hemophilia A with Inhibitors: Interim Analysis of Single-Arm, Multicenter, Open-label, Phase 3 Study

Guy Young,¹ Robert F. Sidonio,² Ri Liesner,³ Johannes Oldenburg,⁴ Tiffany Chang,⁵ Marianne Uguen,⁶ Christophe Dhalluin,⁶ Christophe Schmitt,⁶ Gallia G. Levy,⁵ Midori Shima,⁷ Johnny Mahlangu⁸

¹Children’s Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; ²Emory University and Children’s Healthcare of Atlanta, Atlanta, GA, USA; ³Great Ormond Street Hospital for Children, NHS Trust, London, UK; ⁴Universitätsklinikum Bonn, Bonn, Germany; ⁵Genentech, Inc., South San Francisco, CA, USA; ⁶F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁷Nara Medical University, Department of Pediatrics, Kashihara, Japan; ⁸Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa
Pediatric PwHA with inhibitors aged ≥2 to <12 years (or 12–17 years if <40 kg) on episodic or prophylactic treatment with BPAs

Enrollment of those aged <2 years permitted after interim analysis

HAVEN 2 study design
QW SC emicizumab prophylaxis

Primary efficacy analysis
52 weeks after last patient enrolled

Interim data reviews

QW SC emicizumab prophylaxis
3 mg/kg/week for 4 weeks; 1.5 mg/kg/week thereafter

Potential individual efficacy-guided dose uptitration from Week 12

First interim review – starting maintenance dose evaluated after 3–5 patients dosed for ≥12 weeks.
Second interim review – once ≥10 patients were dosed for ≥12 weeks.

ClinicalTrials.gov, NCT02795767. Patients from the noninterventional study (NIS; NCT02476942; Cohort B) were permitted to enroll.
HAVEN 2
Patient disposition

- No dose uptitrations
- Overall, 57 patients were aged <12 years
  - 3 patients were aged 12–17 years
- Efficacy analyses include patients aged <12 years with ≥12 weeks on study (n=23)
- Intraindividual comparison includes only those who also participated in the NIS (n=13)
- Safety analyses include all treated patients (N=60)

Enrolled
N=60 (including n=19 from the NIS)

Started study treatment
n=60

Discontinued from study and not treated
n=0

Completed ≥12 weeks on study at time of present analysis
n=24
HAVEN 2
Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emicizumab 1.5 mg/kg QW N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>60 (100.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (min–max)</td>
<td></td>
</tr>
<tr>
<td>&lt;2, n (%)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>2 to &lt;6, n (%)</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>6 to &lt;12, n (%)</td>
<td>38 (63.3)</td>
</tr>
<tr>
<td>≥12, n (%)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Hemophilia severity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Mild‡</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>57 (95.0)</td>
</tr>
<tr>
<td>Previous ITI, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43 (71.7)</td>
</tr>
<tr>
<td>No</td>
<td>17 (28.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emicizumab 1.5 mg/kg QW N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>44 (73.3)</td>
</tr>
<tr>
<td>Median (min–max) weight (kg)</td>
<td>22.9 (9.5–63.0)</td>
</tr>
<tr>
<td>Median (min–max) number of bleeds in previous 24 weeks</td>
<td>6.0 (0–155)</td>
</tr>
<tr>
<td>Target joints, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (38.3)</td>
</tr>
</tbody>
</table>

*Ages 14.7 and 22.9 months. †<40 kg body weight if aged ≥12 years. ‡Mild disease at baseline, severe disease at study entry.
HAVEN 2 intraindividual comparison
Emicizumab prophylaxis vs prior BPA treatment

- 2 treated bleeds reported for 13 patients receiving emicizumab (efficacy period, 106–291 days)
- Overall reduction in ABR of 99% with emicizumab prophylaxis vs prior BPA treatment

Data sorted by emicizumab ABR in descending order and then by descending efficacy period duration. Intraindividual comparison performed for 13 NIS patients on HAVEN 2 study for ≥12 weeks.
HAVEN 2
Health-related outcomes and caregiver burden

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) change from baseline to Week 25‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemo-QoL-SF (n=7)*</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−10 (11)</td>
</tr>
<tr>
<td>Physical health domain</td>
<td>−20 (25)</td>
</tr>
<tr>
<td>Adapted InhibQoL (n=16)*;†</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−22 (12)</td>
</tr>
<tr>
<td>Physical health domain</td>
<td>−32 (22)</td>
</tr>
</tbody>
</table>

- Substantial improvements in health-related quality of life and aspects of caregiver burden with emicizumab prophylaxis vs prior BPA treatment

*Higher scores indicate greater impairment, decrease in score indicates decrease in impairment; only completed in patients aged ≥8 years. †Adapted InhibQoL with Aspects of Caregiver Burden; completed by caregivers of children and reflects caregiver’s perception of health of child. ‡Only includes patients with data at both baseline and Week 25.
## HAVEN 2
### Safety summary

<table>
<thead>
<tr>
<th>AEs</th>
<th>Emicizumab 1.5 mg/kg QW N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>201</td>
</tr>
<tr>
<td>Total number of patients with ≥1 AE, n (%)</td>
<td>40 (66.7)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Related AE</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>Local injection site reaction</td>
<td>10 (16.7)</td>
</tr>
</tbody>
</table>

- **Serious AEs:**
  - Muscle hemorrhage
  - Eye pain
  - Catheter site infection
  - Device-related infection
  - Mouth hemorrhage
  - Appendicitis

- **Most related AEs** were mild injection site reactions

- **No thromboembolic or thrombotic microangiopathy events** reported

- **No patients** tested positive for antidrug antibodies

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Target emicizumab exposure was $\geq 45 \, \mu g/mL$\(^1\)

Mean steady-state trough emicizumab plasma concentrations $\sim 50 \, \mu g/mL$ were maintained with longer follow-up

Emicizumab’s pharmacokinetic profile was consistent across age groups and body weight, and comparable with that seen in adolescent/adult PwHA

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The safety profile of emicizumab was favorable and well tolerated
- No thromboembolic or thrombotic microangiopathy events reported

Updated results from the HAVEN 2 study confirm prior efficacy results
- Emicizumab successfully prevented or reduced bleeds
- Clinically meaningful reductions in ABR shown with emicizumab vs. prior BPA treatment (from the NIS)
Emicizumab clinical development plan

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  6. HAVEN 3 (NCT02847637)  
  7. The primary endpoint showed a statistically significant reduction in treated bleeds with QW emicizumab prophylaxis compared with no prophylaxis in PwHA without inhibitors aged ≥12 years  
  8. Key secondary endpoint showed a statistically significant reduction in treated bleeds with Q2W emicizumab prophylaxis vs no prophylaxis  
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  10. HAVEN 4 (NCT03020160)  
  11. Evaluating emicizumab prophylaxis dosed Q4W in PwHA with and without inhibitors aged >12 years |

FVIII, factor VIII; NIS, noninterventional study; PwHA, persons with hemophilia A; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, once weekly. 
Patient population: ~145 patients aged ≥12 years with haemophilia A without inhibitors against FVIII

Objectives:
- Non-inhibitor patients prophylaxis vs no prophylaxis
- 1.5 mg/kg/week and 3 mg/kg/2 weeks

Primary endpoints
Efficacy Objective
- Bleed rate – (the number of bleeds over time )
  - Arm A vs C
  - Arm B vs C

Key secondary/other endpoints
- Efficacy – joint bleed rate, target joint bleed rate, HRQoL/health status, bleed rate in prophylaxis arm D patients
- Safety – incidence of anti-emicizumab antibodies, thromboembolic events
- Exploratory – days of missed school/work, days hospitalised, biomarkers
Emicizumab clinical development plan

<table>
<thead>
<tr>
<th>Emicizumab clinical trials</th>
<th>Key outcome</th>
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| HAVEN 1 (NCT02622321) primary analysis | ▪ The primary endpoint showed a statistically significant reduction in treated bleeds of 87% with QW emicizumab in PwHA with inhibitors vs no prophylaxis  
▪ All 12 secondary endpoints were positive, including an intraindividual analysis, which showed a statistically significant reduction in treated bleeds of 79% with emicizumab prophylaxis vs prior bypassing agent prophylaxis collected in the NIS before enrollment¹ |
| HAVEN 2 (NCT02795767) interim analysis | ▪ After a median observation time of 38.1 weeks, 87% of children aged <12 years with PwHA with inhibitors who received QW emicizumab prophylaxis experienced zero treated bleeds  
▪ In an intraindividual analysis, emicizumab prophylaxis substantially reduced bleed rates by 99% vs prior bypassing agent prophylaxis/episodic treatment during the NIS² |
| HAVEN 3 (NCT02847637) | ▪ The primary endpoint showed a statistically significant reduction in treated bleeds with QW emicizumab prophylaxis compared with no prophylaxis in PwHA without inhibitors aged ≥12 years  
▪ Key secondary endpoint showed a statistically significant reduction in treated bleeds with Q2W emicizumab prophylaxis vs no prophylaxis  
▪ In an intraindividual comparison, QW emicizumab prophylaxis was superior to prior FVIII prophylaxis during the NIS |
| HAVEN 4 (NCT03020160) | ▪ Evaluating emicizumab prophylaxis dosed Q4W in PwHA with and without inhibitors aged >12 years |

PK run-in cohort (n=7)
- PwHA aged ≥12 years
- (previous episodic treatment)
- Emicizumab 6 mg/kg Q4W for ≥24 weeks

Expansion cohort (n=41)
- Loading dose: Emicizumab 3 mg/kg QW for 4 weeks, followed by
- Maintenance dose: Emicizumab 6 mg/kg Q4W for ≥24 weeks

Analyses
- PK and safety
- (last patient at Week 6 of treatment)
- Efficacy, safety, PK/PD

PK run-in phase:
- Eligible persons were aged ≥12 years with congenital hemophilia A with or without inhibitors; episodic treatment (FVIII or bypassing agents) at study entry and documentation of episodic treatment for ≥24 weeks before study entry
- Preplanned interim analysis of PK and safety when last patient reached 6 weeks of treatment
- Data cutoff: April 10, 2017 (median [range] follow-up, 8 [6–10] weeks)

PD, pharmacodynamic; PK, pharmacokinetic.
Conclusions: Emicizumab

- Emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis or previous prophylactic treatment with bypassing agents among patients with hemophilia A with inhibitors, and it improved health-related quality of life.

- Emicizumab was safe when administered alone or in conjunction with recombinant factor VIIa alone.

- Clinical data support once-weekly subcutaneously administered emicizumab prophylaxis to reduce treatment and disease burden, and provide a potential new standard of care for the management of PwHA with inhibitors
HAEMOPHILIA
People with haemophilia do not produce enough factor VIII or factor IX, proteins that play a crucial part in clotting.

FACTOR REPLACEMENT TREATMENT
To prevent and staunch bleeding, physicians typically give patients with haemophilia infusions of the factors they lack. Adding these extra factors restores the balance between bleeding and clotting.

ANTICOAGULANT INHIBITION TREATMENT
An approach under development restores balance instead by inhibiting the proteins that prevent clotting – natural anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin.

Alpha-1-antitrypsin variant RNAi therapy specifically targets antithrombin messenger RNA.

David A. Lane Blood 2017;129:10-11
Re-balanced Hemostasis

**Fitusiran - Antithrombin siRNA**

- FXII
- FIX
- FXI
- FX
- FVII
- FII
- Fibrinogen

- AT
- PS
- PC
- TFPI

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**Concizumab – Anti-TFPI Ab**

- FXII
- FIX
- FXI
- FX
- FVII
- FII
- Fibrinogen

Bayer
Pfizer

- AT
- PS
- PC
- TFPI

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Ragni M. NEJM 2015; 373
Re-balanced Hemostasis

“Re-Balanced Hemostasis”

Inhibiting Antithrombin
- Reducing its production
  - siRNA
- Inhibiting its function
  - Antibody/Aptamer/Peptide

Inhibiting TFPI
- Anti-TFPI antibodies

Inhibiting Activated Protein C
- Novel bioengineered Anti-APC Serpin

Ragni M. NEJM 2015; 373
Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy


August 31, 2017


SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
Interim Fitusiran Phase 1 (Part D) Study Results*  
AT Lowering in Patients with Inhibitors

AT lowering after monthly dosing in hemophilia patients with inhibitors

Peak Thrombin Levels Achieved in Hemophilia A and B Patients Treated with Fitusiran
Alnylam Pharmaceuticals News Release
Sept 7th 2017

“Alnylam is reporting a fatal thrombotic event in a patient with hemophilia A without inhibitors in the Phase 2 open-label extension (OLE) study of fitusiran.”

“.....investigation of the SAE, including review of the patient’s CT scans by three independent neuro-radiologists, who all confirmed on September 1, 2017, that the initiating event was a cerebral venous sinus thrombosis.”

Annualized Bleed Rates in Hemophilia Patients with Inhibitors Treated with Fitusiran

Follow up 43-147 days
Conclusions

- EHL factor concentrates decrease frequency of injections and improve quality of life in hemophilia patients.
- Novel therapy eg. emicizumab can decrease bleeding symptom in both hemophilia with and without inhibitor, change of treatment paradigm in hemophilia patients.
- Thrombotic complication, long term safety esp. in children should be monitored.
Thank you for your attention

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