Non-factor Treatments of Bleeding Disorders

Char Witmer, MD, MSCE
Normal clotting is a balance!

- **Gas pedal**: Clot
  - Platelet Plug
- **Brake Pedal**: Anti-Coagulant
  - Fibrin Lysis
Procoagulants: “the gas pedal”

Tissue Factor (TF)

(Extrinsic)

TF*VII

TF*VIIa

VIIla

IX

IXa

X

Xa

XII

XI

Kallikrein, HMWK

XIIa

Xla

XI

Prothrombin (II)

V

Va

Thrombin

Fibrinogen

Fibrin
Bispecific Antibody: Emicizumab (ACE910)

- **Antibody** that mimics the role of factor VIII in clotting
  - Human modified Ig antibody

- **Subcutaneous**

- **Schedule**: 1x per week

- **Half-life**: 28-34 days

- **Not** effected by inhibitors

Estimate an equivalent factor VIII activity of 10-30% with 1-3 mg/kg/week dosing.

Emicizumab Prophylaxis Effect on Bleeding: phase 1/2 study

18 subjects with hemophilia

Japanese patients age 12-59 years old with and without inhibitors who received subcutaneous injections of emicizumab once a week for 12 weeks

# Emicizumab (ACE910) US Clinical Trials

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>A Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)</td>
<td>Age &gt;12 years</td>
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<tr>
<td></td>
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<td>Condition: Hemophilia A</td>
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<td>Intervention: Drug: Emicizumab</td>
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<td>2</td>
<td>Recruiting</td>
<td>A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks in Participants With Hemophilia A</td>
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<td>Intervention: Drug: Emicizumab</td>
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<td>3</td>
<td>Recruiting</td>
<td>A Phase III Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Patients With Inhibitors (HAVEN 1)</td>
<td>Age &gt;12 years</td>
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<td>Condition: Hemophilia A</td>
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<td></td>
<td>Intervention: Drug: Emicizumab</td>
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<td>4</td>
<td>Recruiting</td>
<td>A Study of Once-Weekly Emicizumab in Children and Adolescents With Hemophilia A and Factor VIII (FVIII) Inhibitors (HAVEN 2)</td>
<td>Age &lt;12 years</td>
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<td>Condition: Hemophilia A</td>
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<td></td>
<td>Intervention: Drug: Emicizumab</td>
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</table>
Phase III: Preliminary Results

• Media release by Roche December 22, 2016

• Phase III HAVEN 1 study
  – N=109 patients, age >12 years, +inhibitors
  – RCT (2:1) → prophylaxis (A) vs. no prophylaxis (B)
    • Arm C: patients on bypassing agent prophylaxis
  – Met the primary endpoint: reduction in # bleeds in prophylaxis vs. no-prophylaxis (A vs. B)
  – Met all of the secondary endpoints

http://www.roche.com/media/store/releases/med-cor-2016-12-22.htm
Adverse Events

• **Death of a patient in Phase III trial: HAVEN 1**
  – Rectal bleeding: treated with bypassing agents
  – Developed thrombotic microangiopathy (TMA)
  – **Determination:** cause of death related to rectal bleeding and *not* emicizumab.

• **2 other cases of TMA have been reported**
  – Resolved with cessation of drug
  – 1 subject restarted

• **2 other cases of thromboembolic events**
  – Neither required anticoagulation
  – 1 subject restarted
Anticoagulants: “the brakes”

- Tissue Factor (TF)
  - TF*VII
    - TF*VIIa
      - IX
      - VIIIa
      - IXa
      - X
        - Xa
          - Xla
            - XI
              - Xla
                - XII
                  - Kallikrein, HMWK

- TFPI

- Protein C
- Protein S

- Antithrombin III

- Fibrinogen
  - Fibrin
Antithrombin as a target

- **Fitusiran (ALN-AT3)**
  - Synthetic molecule (siRNA) against AT
  - **Suppresses the liver production of antithrombin**
    - Decreased antithrombin levels → “less brakes”
    - Subcutaneous injection

- **Could be used in FVIII or FIX deficiency.**
- **Could be use in patients with or without inhibitors.**

## Ongoing clinical trials

![ClinicalTrials.gov](https://clinicaltrials.gov)

A service of the U.S. National Institutes of Health

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<th>Intervention</th>
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<tr>
<td>1</td>
<td>Recruiting</td>
<td>An Open-label Extension Study of an Investigational Drug, ALN-AT3SC, in Patients With Moderate or Severe Hemophilia A or B</td>
<td>Hemophilia A; Hemophilia B</td>
<td>Drug: ALN-AT3SC</td>
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<td>Recruiting</td>
<td>A Phase 1 Study of an Investigational Drug, ALN-AT3SC, in Healthy Volunteers and Hemophilia A or B Patients</td>
<td>Hemophilia A; Hemophilia B</td>
<td>Drug: ALN-AT3SC; Drug: Sterile Normal Saline (0.9% NaCl)</td>
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</tbody>
</table>

Planned phase 2/3 trials in 2017 for patients with hemophilia A and B with and without inhibitors.
**Preliminary Results**

Patients with severe hemophilia A or B with inhibitors

**Part D**

**Phase 1 Study**
- Cohort 1: 50 mg qM x 3 SC, N=6
- Cohort 2: 80 mg qM x 3 SC, N=10

**Phase 2 OLE Study†**
- Patients eligible to roll over onto Phase 2 OLE starting on Day 84
- Individual patient dose adjustment may be allowed (per Safety Review Committee)

**ADVERSE EVENTS**

- No thromboembolic events
- Elevated D-Dimer in some
- No anti-drug antibodies
- ALT >3X ULN in 3 pts
  - All HCV+, reversible

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<thead>
<tr>
<th></th>
<th>50 mg N=6</th>
<th>80 mg N=10</th>
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</thead>
<tbody>
<tr>
<td>Age, years; mean (range)</td>
<td>32 (22-41)</td>
<td>37 (21-65)</td>
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<tr>
<td>Weight, kg; mean (range)</td>
<td>73 (55-100)</td>
<td>73 (52-108)</td>
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<tr>
<td>Hemophilia A with Inhibitors</td>
<td>5</td>
<td>10</td>
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<tr>
<td>Hemophilia B with Inhibitors</td>
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<td>0</td>
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<tr>
<td>Severe</td>
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<td>10</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Medical history of hepatitis C</td>
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</tbody>
</table>

http://www.alnylam.com/web/assets/ASH-2016_Fitusiran_INHIBITORS_03Dec2016_CAPELLA.pdf
AT lowering after monthly dosing in hemophilia patients with inhibitors

[Graph showing mean ± SEM AT activity relative to baseline over days since first dose for Cohort 1 (50 mg, N=6) and Cohort 2 (80 mg, N=10).]

http://www.alnylam.com/web/assets/ASH-2016_Fitusiran_INHIBITORS_03Dec2016_CAPELLA.pdf
Post hoc analysis of thrombin generation by AT lowering quartiles

Boxes denote median and interquartile range

Peak Thrombin Generation (nM)

N=4

Healthy Volunteers

Patients with Hemophilia with Inhibitors

AT Lowering < 25% (N=16)

AT Lowering 25-50% (N=10)

AT Lowering 50-75% (N=14)

AT Lowering >= 75% (N=16)

http://www.alnylam.com/web/assets/ASH-2016_Fitusiran_INHIBITORS_03Dec2016_CAPELLA.pdf
TFPI as a target

**TFPI:**
- BAX499: aptamer that inhibited TFPI
  - *1 Phase 1 trial stopped: increased bleeding*
- Concizumab (anti-TFPI antibody)
  - IV or SQ
Concizumab (anti-TFPI antibody) clinical trials

Per Financial Reports Novo Nordisk is planning on moving forward with phase 2 studies.
http://www.novonordisk.com/bin/getPDF.2075346.pdf
Phase 1 (Explorer 1) Results

• IV and SC
• N=52
  – Healthy volunteers: 28
  – Hemophilia A (no inhibitor): 21
  – Hemophilia B (no inhibitor): 3
• No safety concerns
• No anti-drug antibodies
• TFPI levels decreased in a concentration dependent manner
  – Elevation in D-dimer
• *No bleeding data*

Summary

• Multiple “non-factor” treatments are in clinical trials

• **Emicizumab:**
  – Appears to be effective
  – Appears to have an increased risk of thrombosis/TMA with the concurrent use of aPCC’s

• **Fitusiran and Concizumab:**
  – Early phase clinical trials
  – *Question remain about what will be the best way to treat bleeding without causing thrombosis.*