Roche Analyst Event at ISTH 2017

Berlin, Monday, 10 July 2017
Agenda

Welcome
Daniel O’Day, CEO Roche Pharmaceuticals

HAVEN1: Ph3 data of emicizumab (ACE910) prophylaxis in adults with hemophilia A with inhibitors
Prof. Dr. med. Johannes Oldenburg, University Clinic Bonn, Institute of Experimental Hematology and Transfusion Medicine

HAVEN2: Ph3 interim data of emicizumab (ACE910) prophylaxis in pediatrics with hemophilia A with inhibitors; aspects of disease management and emicizumab global development program
Gallia Levy, M.D., Ph.D., Global Development Team Leader emicizumab

Q&A
Welcome

Daniel O’Day
CEO Roche Pharmaceuticals
Roche is committed to innovation

Heavy launch activities

Leading industry with 15 BTDs, 5 recent launches awarded a BTD

BTD=Breakthrough Therapy Designation
Emicizumab: A bispecific monoclonal antibody under investigation for hemophilia A

Bridges factors IXa and X, to activate the natural coagulation cascade and restore the blood clotting process

Expected to avoid the development of factor VIII inhibitors, avoiding a serious complication seen with current factor VIII replacement therapies.

Once weekly subcutaneous injection; less frequent dosing schedules also being evaluated
Emicizumab: Addressing unmet needs in hemophilia A

**Improved treatment benefit**
- Substantially reduced ABR, with zero bleeds in a majority of patients
- Potentially less long-term joint damage and fewer severe /life-threatening bleeds
- Prophylactic treatment offers sustained protection

**Reduced treatment burden**
- Subcutaneous administration
- Less intensive dosing regime

**Improved quality of life**
- Reduced bleeds and reduced treatment burden translate into improved quality of life
HAVEN1: Phase 3 study of emicizumab (ACE910) prophylaxis in adults with hemophilia A with inhibitors

Prof. Dr. med. Johannes Oldenburg
University Clinic Bonn, Institute of Experimental Hematology and Transfusion Medicine
HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors; aspects of disease management and emicizumab global development program

Gallia Levy, M.D., Ph.D.
Global Development Team Leader emicizumab
Aspects of disease management

Safety summary HAVEN1

HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors

Emicizumab global development program
Signs and symptoms of hemophilia

Poor and unpredictable bleed control remains a challenge

Sustained bleeding following minor trauma / surgery

Bruising

Recurrent bleeding into muscles / joints

Spontaneous bleeding
How bleeds have been measured in clinical trials

Self-reporting

Differences in bleeds, disease biology, lifestyle

Bleed definitions

Different calculations

\[ ABR = \frac{\text{number of bleeds} \times 365.25}{\text{number of days}} \]

Negative binomial model

Different measures

Mean ABR

Median ABR

% reduction

% zero bleeds

2014 ISTH Scientific Subcommittee recommendations (Blanchette, Hemostasis Thrombosis 2014)
How bleeds have been measured in HAVEN studies

**Self-reporting**
Handheld device
Record all bleeds and medications

**Bleed definitions**
- Treated bleeds
- All bleeds
- Spontaneous bleeds
- Treated joint bleeds
- Target joint bleeds

**Differences in bleeds, disease biology, lifestyle**

**Different calculations**
Median: traditional ABR calculation
Estimated ABR and % reductions: Negative binomial model

**Different measures**
Median ABR
Estimated ABR
% reduction
% zero bleeds

2014 ISTH Scientific Subcommittee recommendations (Blanchette, Hemostasis Thrombosis 2014)
Aspects of disease management

Safety summary HAVEN1

HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors

Emicizumab global development program
**Safety summary: All emicizumab patients**

<table>
<thead>
<tr>
<th></th>
<th><strong>HAVEN1</strong></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N=103, n (%)</td>
</tr>
<tr>
<td>Total number of AEs, n</td>
<td></td>
</tr>
<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>

No new TMA/thrombotic events occurred when guidance for mitigation was followed

*Additional serious AEs included one event each of: iron deficiency anemia, sepsis, hemorrhosis, muscle hemorrhage, gastrlic ulcer hemorrhage, headache and hematuria. Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision. **Third TMA event occurred after primary analysis data cutoff; 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 patient tested positive for anti-drug antibodies.
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>

TMA=Thrombotic microangiopathy; aPCC=Activated prothrombin complex concentrate; rFVIIa=Activated recombinant FVII
*rFVIIa treatment in TMA #1 included treatment during resolution of the event. **Patient developed TMA following aPCC treatment for recurrent rectal hemorrhage after primary analysis data cutoff. Rectal hemorrhage eventually fatal, death was deemed unrelated to emicizumab. TMA laboratory values (platelets, LDH) showed evidence of improvement of TMA after aPCC discontinuation. Patient also received tranexamic acid.
Common characteristics of TMA/thrombotic events were high cumulative doses of aPCC

All TMA/thrombotic events were seen in cumulative doses of aPCC (>200 U/kg) for ≥24 hours

TMA=Thrombotic microangiopathy; TE=Thromboembolism; aPCC=Activated prothrombin complex concentrate
No TMA/thrombotic events occurred when only rFVIIa was used for breakthrough bleed treatment

*Patients 1301 and 1811 received concurrent aPCC*

No TMA/thrombotic events occurred in patients taking only rFVIIa, despite very high doses in some cases

In patient 1811, some of the rFVIIa doses were administered while TMA was resolving.

TMA=Thrombotic microangiopathy; rFVIIa=Activated recombinant FVII; aPCC=Activated prothrombin complex concentrate
Interaction between emicizumab and aPCC

Five patients experienced TE or TMA

111 inhibitor patients treated with emicizumab

- 37 patients treated with rFVIIa
- 140 treatment episodes
- No TMA/TE with emicizumab + rFVIIa treatment alone

- 20 patients treated with aPCC
- 78 treatment episodes

≤100 U/kg/day

- 52 treatment episodes
  - No TMA or TE
  - < 24 h

>100 U/kg/day

- 13 treatment episodes
  - No TMA or TE
  - ≥24 h

- 5 treatment episodes
  - No TMA or TE
  - 8 treatment episodes
  - 5 TMA/thrombosis*

TE #1 received aPCC

TE resolved
Emicizumab restarted

TE #2 received aPCC

TE resolving

TMA #1 received aPCC/rFVIIa

TMA resolved

TMA #2 received aPCC

TMA resolved
Emicizumab restarted

TMA #3** received aPCC/rFVIIa

TMA resolving

Risk of TMA/thrombotic events may be mitigated with BPA dosing guidance

No further events in >350 patients treated in emicizumab development program to date

TE = Thromboembolism; TMA = Thrombotic microangiopathy; aPCC = Activated prothrombin complex concentrate; BPA = Bypassing agent

*Two patients also received rFVIIa prior to during the event. **Patient developed TMA following aPCC treatment for recurrent rectal hemorrhage after primary analysis data cutoff. Rectal hemorrhage eventually fatal, death was deemed unrelated to emicizumab. TMA laboratory values (platelets, LDH) showed evidence of improvement of TMA after aPCC discontinuation. Patient also received tranexamic acid.
Potential mechanism for combination effects of emicizumab with bypassing agents

**aPCC characteristics**
- Prothrombin, FVII, FIX and FX
- Low levels of thrombin, FIXa and FXa, FVIIa and FVIIIa
- Factor half life up to 65 hrs leads to accumulation with repeated dosing

**rFVIIa characteristics**
- Recombinant activated FVII
- 2.3–6 hour half life

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Intra-individual comparison: Treated bleeds with emicizumab prophylaxis vs prior BPA prophylaxis

**Bleed reduction**

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<tr>
<th></th>
<th>Prior BPA prophylaxis</th>
<th>Emicizumab prophylaxis</th>
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<tbody>
<tr>
<td>ABR (95% CI)</td>
<td>15.7</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>79% reduction</strong></td>
<td></td>
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<td>( P=0.0003 )</td>
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Statistically significant, clinically meaningful reduction in bleed rates with emicizumab prophylaxis vs prior BPA prophylaxis.

70.8% of patients with zero bleeds on emicizumab prophylaxis.

1 Intra-individual comparison for 24 patients from NIS who had been on HAVEN1, Arm C
*Of 7 patients experiencing bleeds, 5 had reduced bleed rate compared to prior BPA prophylaxis; Primary analysis data cutoff – October 25, 2016
Median efficacy period: Prior BPA prophylaxis, 32 weeks; emicizumab prophylaxis, 30 weeks; ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.
ABR=Annualized bleeding rate; BPA=Bypassing agent; NIS=Non-interventional study
Aspects of disease management

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Emicizumab global development program
Emicizumab’s phase III clinical development plan covers entire hemophilia A patient population

HAVEN1
- Met primary endpoint in Q4 2016
- 113 patients
- Inhibitor adults/adolescents (≥12 years old), qw

HAVEN2
- Positive interim results Q2 2017; Fully enrolled
- 62 patients
- Inhibitor children (0–11 years old), qw

HAVEN3
- Fully enrolled
- 152 patients
- Non-inhibitor adults/adolescents (≥12 years old), qw and q2w

HAVEN4
- Fully enrolled
- 48 patients
- Non-inhibitor/inhibitor adults/adolescents, q4w

HAVEN1 and HAVEN2 filed in US and EU

Status of studies as of July 10, 2017
Doing now what patients need next