R&D Conference Call
(ISTH 2017)

CHUGAI PHARMACEUTICAL CO., LTD.
Vice President
General Manager of Clinical Development Div.
Hisanori Takanashi

July 11, 2017
Emicizumab (ACE910) Development Programs

- 2015

Phase 1: Healthy adults and patients
→ Phase 1/2 (extension study): Patients

2016

Non-interventional study: Patients
(Main purpose: real-world treatment data)

[HAVEN 1]
Phase 3: Inhibitor QW dosage

[HAVEN 2]
Phase 3: Pediatric inhibitor QW dosage

[HAVEN 3]
Phase 3: Non-inhibitor QW and Q2W dosage

2017

Transfer of eligible patients

2018 -

QW: dosing every week
Q2W: dosing every 2 weeks
Q4W: dosing every 4 weeks

[HAVEN 4]
Phase 3: Non-inhibitor / Inhibitor Q4W dosage

Phase 1 and 1/2: Japanese trials
Others: global trials with Roche
HAVEN 1 Study / HAVEN 2 Study Interim Analysis

Nara Medical College
Department of Pediatrics
Professor Midori Shima, M.D., PhD.

July 11, 2017
HAVEN 1: Emicizumab (ACE910) prophylaxis in patients with hemophilia A with inhibitors – a randomized, multicenter, open-label, phase 3 study to investigate efficacy, safety and pharmacokinetics

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Emicizumab is an investigational product and is not approved or licensed for the treatment of patients with hemophilia A or any other medical condition.
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 study design
Once-weekly subcutaneous emicizumab prophylaxis

Primary analysis:
≥24 weeks follow-up in Arms A and B

Prior episodic
n=53

Arm A
Emicizumab (n=35)

Arm B (Control Arm)
No prophylaxis (n=18)

Arm C
Emicizumab (n=49)

Arm D
Emicizumab

Prior prophylactic
n=49

Persons with hemophilia A (PwHA) with inhibitors aged ≥12 years on treatment with bypassing agents (BPAs) N=109

Emicizumab

Emicizumab

Emicizumab

Emicizumab

Emicizumab

PwHA with inhibitors on episodic/prophylactic treatment with BPAs (from non-interventional study; n=7)

NCT02622321: phase 3, open-label, multicenter, randomized study.
Emicizumab 3 mg/kg/week for 4 weeks; 1.5 mg/kg/week thereafter.
Arm D: Patients unable to enroll into Arms A, B or C before they closed to enrollment.
## Demographics/baseline disease characteristics

**Arm A:** Emicizumab prophylaxis
(prior episodic BPAs)

- n=35

**Arm B:** No prophylaxis

- (prior episodic BPAs; control arm)
- n=18

**Arm C:** Emicizumab prophylaxis
(prior BPA prophylaxis)

- n=49

**Arm D:** Emicizumab prophylaxis
(prior BPAs; episodic or prophylactic)

- n=7

### Total
- N=109

<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><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), years &lt;18 years, n (%)</td>
<td>38.0 (12–68) 4 (11.4)</td>
<td>35.5 (13–65) 2 (11.1)</td>
<td>17.0 (12–75) 26 (53.1)</td>
<td>26.0 (19–49) 0</td>
<td>28.0 (12–75) 32 (29.4)</td>
</tr>
<tr>
<td><strong>Bleeds in 24 weeks prior to study entry, n (%)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≥9</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><strong>Target joints, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Any</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>&gt;1</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><strong>Highest historical inhibitor titer (BU)</strong></td>
<td></td>
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</tr>
<tr>
<td>Median</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>Range</td>
<td>5–1570</td>
<td>18–4500</td>
<td>11–5000</td>
<td>28–2125</td>
<td>5–5000</td>
</tr>
<tr>
<td><strong>Previously treated with ITI, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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

**Annualized bleeding rate (ABR) (95% CI)**

- **Arm B** (No prophylaxis (episodic BPAs only))
  - Annualized bleeding rate: 23.3 (12.33; 43.89)
- **Arm A** (Emicizumab prophylaxis)
  - Annualized bleeding rate: 2.9 (1.69; 5.02)

**87% reduction P<0.0001**

**Median ABR (IQR)**

- **Arm B** (No prophylaxis (episodic BPAs only))
  - Median ABR (IQR): 18.8 (12.97; 35.08)
- **Arm A** (Emicizumab prophylaxis)
  - Median ABR (IQR): 0.0 (0.00; 3.73)

**Patients (%)**

- **Arm B** (No prophylaxis (episodic BPAs only))
  - >10 bleeds: 22.9
  - 4–10 bleeds: 44.4
  - 1–3 bleeds: 5.6 each
  - 0 bleeds: 11.4

- **Arm A** (Emicizumab prophylaxis)
  - >10 bleeds: 62.9
  - 4–10 bleeds: 22.9
  - 1–3 bleeds: 5.6 each
  - 0 bleeds: 11.4

**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.**

Primary analysis data cutoff – October 25, 2016
HAVEN 1 secondary bleed-related endpoints
Consistent statistically significant reductions in ABR

<table>
<thead>
<tr>
<th></th>
<th>Arm B: No prophylaxis (episodic BPAs) (n=18)</th>
<th>Arm A: Emicizumab prophylaxis (prior episodic BPAs) (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All bleeds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR (95% CI)</td>
<td>28.3 (16.79; 47.76)</td>
<td>5.5 (3.58; 8.60)</td>
</tr>
<tr>
<td>% reduction (RR), P-value</td>
<td></td>
<td>80% reduction (0.20), &lt;0.0001</td>
</tr>
<tr>
<td>% patients with 0 bleeds (95% CI)</td>
<td>5.6 (0.1; 27.3)</td>
<td>37.1 (21.5; 55.1)</td>
</tr>
<tr>
<td><strong>Treated spontaneous bleeds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR (95% CI)</td>
<td>16.8 (9.94; 28.30)</td>
<td>1.3 (0.73; 2.19)</td>
</tr>
<tr>
<td>% reduction (RR), P-value</td>
<td></td>
<td>92% reduction (0.08), &lt;0.0001</td>
</tr>
<tr>
<td>% patients with 0 bleeds (95% CI)</td>
<td>11.1 (1.4; 34.7)</td>
<td>68.6 (50.7; 83.1)</td>
</tr>
<tr>
<td><strong>Treated joint bleeds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR (95% CI)</td>
<td>6.7 (1.99; 22.42)</td>
<td>0.8 (0.26; 2.20)</td>
</tr>
<tr>
<td>% reduction (RR), P-value</td>
<td></td>
<td>89% reduction (0.11), 0.0050</td>
</tr>
<tr>
<td>% patients with 0 bleeds (95% CI)</td>
<td>50.0 (26.0; 74.0)</td>
<td>85.7 (69.7; 95.2)</td>
</tr>
<tr>
<td><strong>Treated target joint bleeds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR (95% CI)</td>
<td>3.0 (0.96; 9.13)</td>
<td>0.1 (0.03; 0.58)</td>
</tr>
<tr>
<td>% reduction (RR), P-value</td>
<td></td>
<td>95% reduction (0.05), 0.0002</td>
</tr>
<tr>
<td>% patients with 0 bleeds (95% CI)</td>
<td>50.0 (26.0; 74.0)</td>
<td>94.3 (80.8; 99.3)</td>
</tr>
</tbody>
</table>

ABR calculated using negative binomial regression model.
RR, risk ratio.
Intra-individual comparison: treated bleeds with emicizumab prophylaxis vs prior BPA prophylaxis

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Prior BPA prophylaxis</th>
<th>Emicizumab prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 bleeds</td>
<td>33.3</td>
<td>12.5</td>
</tr>
<tr>
<td>4–10 bleeds</td>
<td>37.5</td>
<td>16.7</td>
</tr>
<tr>
<td>1–3 bleeds</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>0 bleeds</td>
<td>12.5</td>
<td>70.8</td>
</tr>
</tbody>
</table>

- 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

**Median ABR**

<table>
<thead>
<tr>
<th></th>
<th>Prior BPA prophylaxis</th>
<th>Emicizumab prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR (95% CI)</td>
<td>15.7 (11.08; 22.29)</td>
<td>3.3 (1.33; 8.08)</td>
</tr>
<tr>
<td>Median ABR (IQR)</td>
<td>12.0 (5.73; 24.22)</td>
<td>0.0 (0.00; 2.23)</td>
</tr>
</tbody>
</table>
### HAVEN 1 health-related quality of life and health status
Randomized comparison

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number of patients (Arm B/Arm A)</th>
<th>Clinically meaningful difference</th>
<th>Difference in adjusted means (95% CI) (Arm B vs Arm A)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haem-A-QoL (in patients aged ≥18 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>14/25</td>
<td>+10 points</td>
<td>14.01 (5.56; 22.45)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Physical health score</td>
<td>14/25</td>
<td>+7 points</td>
<td>21.55 (7.89; 35.22)</td>
<td>0.0029</td>
</tr>
<tr>
<td><strong>EQ-5D-5L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>16/30</td>
<td>–7 points</td>
<td>–9.72 (–17.62; –1.82)</td>
<td>0.0171</td>
</tr>
<tr>
<td>Index utility score</td>
<td>16/30</td>
<td>–0.07 points</td>
<td>–0.16 (–0.25; 0.07)</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

- Statistically significant, clinically meaningful improvements in HRQoL and health status with emicizumab prophylaxis vs no prophylaxis

HAVEN 1
Emicizumab pharmacokinetics

- Pharmacokinetic/pharmacodynamic modeling predicted emicizumab concentration ≥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

SD, standard deviation.
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

**Total (N=103)**

<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, hemorrhrosis, 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.
HAVEN 1 conclusions (1)

- Once-weekly emicizumab prophylaxis administered subcutaneously successfully prevented or reduced bleeds in PwHA with inhibitors
  - Reduction in bleed rate of 87% vs no prophylaxis
  - Reduction in bleed rate of 79% vs prior prophylactic BPAs
  - 63% of patients randomized to emicizumab prophylaxis and 71% of patients previously on BPA prophylaxis experienced zero bleeds

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

- Risk of TE and TMA events seen with aPCC administered with emicizumab prophylaxis may be mitigated with BPA treatment guidance
  - 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
  - No serious TE or TMA events occurred with emicizumab alone or when rFVIIa alone was used for breakthrough bleed treatment
  - aPCC should be avoided if possible in patients receiving emicizumab
    - If necessary to use, lower doses are indicated and caution should be used
HAVEN 1 conclusions (3)

- Results represent a potential paradigm shift and new standard of care for treatment of hemophilia A with inhibitors, with an effective weekly, subcutaneous, prophylactic therapeutic option.

- Data from this study have been submitted for approval consideration to the EMA and the US FDA.
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 Young1, Johannes Oldenburg2, Ri Liesner3, Victor Jiménez-Yuste4, Maria Elisa Mancuso5, Tiffany Chang6, Marianne Uguen7, Christophe Dhalluin7, Christophe Schmitt7, Sabine Fuerst-Deckenwald7, Midori Shima8, Rebecca Kruse-Jarres9

1Children’s Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; 2Universitätsklinikum Bonn, Bonn Germany; 3North London Paediatric Haemophilia Network, London, UK; 4University Hospital La Paz, Madrid, Spain; 5Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; 6Genentech Inc., South San Francisco, CA, USA; 7F. Hoffmann-La Roche Ltd, Basel, Switzerland; 8Department of Pediatrics, Nara Medical University, Kashihara, Nara, Japan; 9Bloodworks Northwest, Seattle, WA, USA

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HAVEN 2 study design
Once-weekly subcutaneous emicizumab prophylaxis

Pediatric PwHA with inhibitors aged ≥2 to <12 years (or 12–17 years if <40 kg) on episodic or prophylactic treatment with bypassing agent(s) (BPAs)

Primary efficacy analysis
52 weeks after last patient enrolled

Interim data reviews

Weekly SC emicizumab prophylaxis
3 mg/kg/wk for 4 weeks;
1.5 mg/kg/wk thereafter

Potential individual efficacy-guided dose up-titration from week 12

Screening N=20–60

24-week safety follow-up off study drug
OR continue on emicizumab

NCT02795767.
Patients from non-interventional study (NCT02476942) (Cohort B) permitted to enroll.
First interim review – starting maintenance dose evaluated after 3–5 patients dosed for ≥12 weeks.
Second interim review – once ≥10 patients dosed for ≥12 weeks.
SC, subcutaneous.
HAVEN 2
Patient disposition

- No dose up-titrations
- Efficacy analyses include only patients aged <12 years (n=19)
  - Summary statistics on efficacy include patients with ≥12 weeks on study (n=10)
  - Intra-individual comparison includes only those who also participated in the NIS (n=8)
- Safety analyses include all treated patients (n=20)

Enrolled
N=20 (including n=12 from NIS)

Started study treatment
n=20

Discontinued from study and not treated
n=0

Completed 12 weeks on study at time of interim analysis
n=11

NIS, non-interventional study (NCT02476942).
HAVEN 2
Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Emicizumab 1.5 mg/kg QW (N=20)</th>
<th>Emicizumab 1.5 mg/kg QW (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, male, n (%)</strong></td>
<td>20 (100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min–max), years</td>
<td>8.5 (3–12)</td>
<td></td>
</tr>
<tr>
<td>2 to &lt;6 years, n (%)</td>
<td>4 (20.0)</td>
<td></td>
</tr>
<tr>
<td>6 to &lt;12 years, n (%)</td>
<td>15 (75.0)</td>
<td></td>
</tr>
<tr>
<td>≥12 years, n (%)</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Hemophilia severity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild†</td>
<td>1 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>19 (95.0)</td>
<td></td>
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<tr>
<td><strong>Previous ITI, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (85.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>2 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>18 (90.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg), median (min–max)</strong></td>
<td></td>
<td>26.9 (14.2–63.0)</td>
</tr>
<tr>
<td><strong>Bleeds prior 24 weeks, median (min–max)</strong></td>
<td>6.0 (0–35)</td>
<td></td>
</tr>
<tr>
<td><strong>Target joints, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (25.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>3 (60.0)</td>
<td></td>
</tr>
</tbody>
</table>

<40 kg body weight if ≥12 years.
Patient with mild disease at baseline had severe disease at study entry.
## HAVEN 2
### Bleed-related endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean ABR (95% CI) N=10</th>
<th>% zero bleeds (95% CI) N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated bleeds</td>
<td>0.4 (0.00; 4.51)</td>
<td>94.7 (74.0; 99.9)</td>
</tr>
<tr>
<td>All bleeds</td>
<td>3.7 (0.94; 9.81)</td>
<td>63.2 (38.4; 83.7)</td>
</tr>
<tr>
<td>Treated spontaneous bleeds</td>
<td>0.4 (0.00; 4.51)</td>
<td>94.7 (74.0; 99.9)</td>
</tr>
<tr>
<td>Treated joint bleeds</td>
<td>0.0 (NA; 3.69)</td>
<td>100 (82.4; 100.0)</td>
</tr>
<tr>
<td>Treated target joint bleeds</td>
<td>0.0 (NA; 3.69)</td>
<td>100 (82.4; 100.0)</td>
</tr>
</tbody>
</table>

- Median (range) observation time for 19 patients aged <12 years, 12.1 (7–14) weeks
- In total, 14 bleeds reported in 7 patients
  - Only 1 was treated – spontaneous bleed
  - None occurred in a joint or muscle

- Majority of patients receiving emicizumab prophylaxis reported zero bleeds

Efficacy analyses include only patients <12 years of age. ABR, annualized bleeding rate; NA, not available.
Intra-individual comparison performed for 8 NIS patients on HAVEN 2 study ≥12 weeks
Zero bleeds reported for all 8 patients receiving emicizumab (efficacy period 85–99 days)
Substantial reductions in treated bleed rates with emicizumab prophylaxis vs prior BPA treatment
HAVEN 2 safety summary

- Serious AEs: mouth hemorrhage, appendicitis, catheter-site infection
- **All related AEs were mild injection-site reactions (3 patients; 9 events)**
- No thromboembolic or thrombotic microangiopathy events observed
- No patients tested positive for anti-drug antibodies

### Adverse events, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Emicizumab 1.5 mg/kg QW (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of AEs</strong></td>
<td>43</td>
</tr>
<tr>
<td><strong>Total patients experiencing ≥1 AE, n (%)</strong></td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td><strong>Related AE</strong></td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>
HAVEN 2
Emicizumab pharmacokinetics

- Target emicizumab exposure was ≥45 µg/mL
- Emicizumab PK profile comparable with that seen in adolescent/adult PwHA
- With weekly subcutaneous dosing, mean trough emicizumab plasma concentrations >50 µg/mL were achieved and sustained once at steady-state

SD, standard deviation.
HAVEN 2
Emicizumab pharmacokinetics by age group and body weight

- Mean trough emicizumab concentrations in plasma were consistent across age groups and body weight.

Four loading doses of emicizumab 3 mg/kg/wk followed by maintenance doses of 1.5 mg/kg/wk. SD, standard deviation.
HAVEN 2 conclusions (1)

- At 12-week follow-up, efficacy results are promising and clinically meaningful in pediatric PwHA with inhibitors
  - Emicizumab successfully prevented or reduced bleeds
  - Clinically meaningful reductions in annualized bleeding rate shown with emicizumab versus prior regimen (from non-interventional study)

- Safety profile of emicizumab was favorable and well tolerated, with no thromboembolic or thrombotic microangiopathy events reported

- Target exposure was achieved at 50 μg/mL in pediatric population (>2 years of age), with PK profile consistent with adolescent/adult population
  - Pediatric dose confirmed to be the same as adult dose
HAVEN 2 conclusions (2)

- Emicizumab has the potential to provide a paradigm shift in the treatment of pediatric PwHA with inhibitors, with an effective weekly, subcutaneous therapeutic option.

- Study continues with a total of 62 patients enrolled, including 4 patients <2 years of age; patients will be followed ≥52 weeks.

- Data from this study have been submitted for approval consideration to the EMA and the US FDA.
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