Emicizumab safety overview

Emicizumab is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Scope of this module

- Safety data from the emicizumab clinical trials (Phase I through Phase III)
- Safety guidance
- Severe adverse events of interest in haemophilia A
- TEs and TMA events with emicizumab
- Fatalities reported among people receiving emicizumab
- Summary
Safety data from the emicizumab clinical trials (Phase I through Phase III)
The safety of emicizumab has been assessed in several clinical trials over the last 5 years.

- **Chugai studies**
  - Phase I study in healthy volunteers (n = 64)
  - Phase Ib study in Japanese PwHA with or without inhibitors (n = 18)
  - Long-term extension study

- **NIS (NCT02476942)**
  - Phase II study in Japanese PwHA with or without inhibitors (n = 18)
  - Inhibitor, inhibitor paediatric, and non-inhibitor PwHA on-demand (n = 50) and prophylaxis (n = 20) BPA
  - Randomised study of emicizumab vs on-demand BPAs, with separate prophylaxis BPA arm

- **HAVEN 1 (NCT02622321)**
  - Phase III inhibitor
  - Randomised study of emicizumab vs FVIII (on-demand)

- **HAVEN 2 (NCT02795767)**
  - Phase III paediatric inhibitor
  - Non-randomised study (descriptive study)

- **HAVEN 3 (NCT02847637)**
  - Phase III non-inhibitor
  - Randomised study of emicizumab vs FVIII (on-demand)

- **HAVEN 4 (NCT03020160)**
  - Phase III Q4W dosing inhibitor/non-inhibitor
  - Single-arm study with PK run-in (descriptive study)

- **HAVEN 5 (NCT03315455)**
  - Phase III Q4W dosing inhibitor/non-inhibitor
  - Randomised study of emicizumab vs no prophylaxis in Chinese PwHA

- **STASEY (NCT03191799)**
  - Phase IIIb safety study inhibitor
  - Single-arm safety study

BPA, bypassing agent; NIS, non-interventional study; Ph, phase; PK, pharmacokinetics; PwHA, people with haemophilia A; Q, quarter; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks

Updated April 2020
Ongoing study follow-up and RWD analysis will continue to monitor for safety events.

**HAVEN 3 (NCT02847637)**
- **PhIII non-inhibitor**
- Randomised study of emicizumab vs FVIII (on-demand)

**HAVEN 4 (NCT03020160)**
- **PhIII Q4W dosing inhibitor/non-inhibitor**
- Single-arm study with PK run-in (descriptive study)

**HAVEN 6 (NCT04158648)**
- **PhIII QW/Q2W/Q4W dosing mild/moderate non-inhibitor**
- Single-arm study of emicizumab in mild/moderate HA without FVIII inhibitors

**STASEY (NCT03191799)**
- **Phase IIIb safety study inhibitor**
- Single-arm safety study

**RWD/registry analyses**
- HEM-NOR
- EUHASS
- PedNet
- G-THUNDER

BPA, bypassing agent; Ph, phase; PK, pharmacokinetics; PwHA, people with haemophilia A; Q, quarter; QW, once weekly; Q4W, every 4 weeks; RWD, real-world data

Updated April 2020
Emicizumab Phase I study design\(^1\)

- **Design**: Phase I, first-in-human, single-centre, double-blind, randomised, placebo-controlled, inter-individual, dose-escalation study
- **Primary endpoint**: tolerability, safety, PK and PD
- **Study duration**: maximum observation period of 24 weeks

**Part A: Japanese healthy volunteers (n = 40)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>N (drug+placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>0.001 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>A-2</td>
<td>0.01 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>A-3</td>
<td>0.1 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>A-4</td>
<td>0.3 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>A-5</td>
<td>1 mg/kg</td>
<td>6+2</td>
</tr>
</tbody>
</table>

Part B initiated after confirming tolerability and safety of 0.1 mg/kg dose in Part A

**Part B: Caucasian healthy volunteers (n = 24)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>N (drug+placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1</td>
<td>0.1 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>B-2</td>
<td>0.3 mg/kg</td>
<td>6+2</td>
</tr>
<tr>
<td>B-3</td>
<td>1 mg/kg</td>
<td>6+2</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; PD, pharmacodynamics; PK, pharmacokinetics

Phase I: emicizumab was well tolerated up to 1 mg/kg; no SAEs reported\(^1\)

<table>
<thead>
<tr>
<th>AEs in participants receiving a single SC injection of emicizumab, n (%)</th>
<th>Placebo</th>
<th>Dose of emicizumab (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Japanese participants, n</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Total participants with at least one AE</td>
<td>2 (20.0)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Erythema of eyelid</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Caucasian participants, n</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Total participants with at least one AE</td>
<td>2 (33.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (16.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Bite</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Excoriation</td>
<td>1 (16.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (16.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Bilirubin conjugated increased</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Haemorrhage subcutaneous</td>
<td>1 (16.7)</td>
<td>NA</td>
</tr>
</tbody>
</table>

- In total, 15 AEs were reported in 13 of 48 (27.1%) participants receiving emicizumab; 6 AEs were reported in 4 of 16 (25%) participants receiving placebo.
- All AEs were mild, except for 1 moderate AE: nasopharyngitis in one Caucasian participant receiving 0.1 mg/kg emicizumab.

AE, adverse event; NA, not applicable; SAE, serious adverse event; SC, subcutaneous

Emicizumab Phase Ib study design

**Phase Ib**

- **Cohort 1**
  - 0.3* mg/kg QW emicizumab
  - $n = 6$ (4 with FVIII inhibitors)

- **Cohort 2**
  - 1† mg/kg QW emicizumab
  - $n = 6$ (4 with FVIII inhibitors)

- **Cohort 3**
  - 3 mg/kg QW emicizumab
  - $n = 6$ (3 with FVIII inhibitors)

**Phase Ib/II extension**

- **Cohort 1†**
  - (0.3 mg/kg emicizumab)
  - $n = 6$ (4 with FVIII inhibitors)
  - Median follow-up (range), months: 32.7 (32.2–33.3)

- **Cohort 2†**
  - (1 mg/kg emicizumab)
  - $n = 6$ (4 with FVIII inhibitors)
  - Median follow-up (range), months: 27.1 (8.3–28.5)

- **Cohort 3†**
  - (3 mg/kg emicizumab)
  - $n = 6$ (3 with FVIII inhibitors)
  - Median follow-up (range), months: 21.4 (11.0–22.5)

- **Cohort 2‡**
  - (0.3 mg/kg emicizumab)
  - $n = 6$ (4 with FVIII inhibitors)

- **Cohort 3‡**
  - (1 mg/kg emicizumab)
  - $n = 6$ (3 with FVIII inhibitors)

**Design**: Phase I, non-randomised, open-label, inter-individual dose-escalation study

**Primary endpoint**: ABR during 12-week treatment period and compared with the 6-month period prior to study enrolment

**Major exclusion criteria**: bleeding disorder other than congenital haemophilia A; clinically significant infection other than infection with hepatitis B virus, hepatitis C virus, or HIV; and a value for protein C activity, free protein S antigen level, or anti-thrombin activity that was below the low end of the normal range at screening

**Study duration**: 12 weeks of weekly SC injections with option to be enrolled in extension study

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Phase Ib: weekly emicizumab was well tolerated for a 12-week treatment period

<table>
<thead>
<tr>
<th>AEs reported in ≥2 participants, n (%)</th>
<th>Cohort 1 n = 6</th>
<th>Cohort 2 n = 6</th>
<th>Cohort 3 n = 6</th>
<th>Total n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>16</td>
<td>11</td>
<td>16</td>
<td>43</td>
</tr>
<tr>
<td>No. of patients experiencing any event</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>15 (83)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Contusion</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Excoriation</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Tongue injury</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Injection-site haematoma</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

- 83% (15/18) of participants experienced a total of 43 AEs; all were mild except for 2 moderate events
- No SAEs or thrombotic AEs were reported in the primary analysis
- Both moderate AEs (upper respiratory tract infection in Cohort 2 and headache in Cohort 3) were considered to be unrelated to emicizumab
- AEs related to emicizumab administration were more common in Cohort 3 (3 mg/kg QW emicizumab, with no loading dose)
- Over an extended 33-month treatment period, four SAEs were observed, none of which were related to emicizumab
  - SAEs comprised a left hip joint bleed, appendicitis, mesenteric haematoma*, and subcutaneous haemorrhage of the proglossis; all resolved
  - no TEs or clinically significant abnormalities of coagulation tests were observed
  - of the 18 participants included, seven (39%) experienced a local injection-site reaction; all were manageable

*Led to emicizumab treatment interruption for 6 weeks.

AE, adverse event; QW, once weekly; SAE, serious adverse event; TE, thrombotic event

Safety data from the emicizumab clinical trials
(Phase I through Phase III)

HAVEN studies
HAVEN 1: emicizumab was generally well tolerated

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Primary analysis&lt;sup&gt;1&lt;/sup&gt; (25 October 2016) N = 103</th>
<th>Updated analysis&lt;sup&gt;2&lt;/sup&gt; (8 September 2017) N = 112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs, n</td>
<td>198</td>
<td>457</td>
</tr>
<tr>
<td>Total patients experiencing ≥1 AE</td>
<td>73 (70.9)</td>
<td>96 (85.7)</td>
</tr>
<tr>
<td>SAE</td>
<td>9 (8.7)</td>
<td>19 (17.0)</td>
</tr>
<tr>
<td>TMA</td>
<td>3* (2.9)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>2† (1.9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
<td>1 (0.9)&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>2 (1.9)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>8 (7.8)</td>
<td>14 (12.5)</td>
</tr>
<tr>
<td>Related AE</td>
<td>23 (22.3)</td>
<td>32 (28.6)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>15 (14.6)</td>
<td>16 (14.3)</td>
</tr>
</tbody>
</table>

- Additional SAEs included one event each of: iron deficiency anaemia, sepsis, haemarthrosis, muscle haemorrhage, gastric ulcer haemorrhage, headache and haematuria<sup>1</sup>
- Since the provision of guidance on use of BPAs, no further patients experienced TMA or other serious thrombotic events<sup>2</sup>

*Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal haemorrhage
†Thrombotic events were skin necrosis/superficial thrombophlebitis in one patient, and cavernous sinus thrombosis in a second patient
‡Related to an AE

1. Oldenburg J, et al. ISTH 2017; oral presentation ASY01.1;
HAVEN 1: TEs and TMAs with concomitant use of aPCC

- A total of six TEs and TMAs were reported in five patients enrolled in the HAVEN 1 study

<table>
<thead>
<tr>
<th>TEs</th>
<th>TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two patients experienced TEs; one cavernous sinus thrombosis, one superficial thrombophlebitis and skin necrosis</td>
<td>Two patients experienced a type of TMA, which is a group of rare disorders that can cause damage to the heart, kidneys or other organs, and can be potentially life-threatening</td>
</tr>
<tr>
<td>Neither TE required anti-coagulation therapy</td>
<td>- both cases of TMA observed were transient and resolved after discontinuation of aPCC; one patient restarted emicizumab while the other did not resume emicizumab treatment despite resolution of the TMA</td>
</tr>
<tr>
<td>The individual who experienced cavernous sinus thrombosis resumed emicizumab 28 days after presentation at the emergency department</td>
<td>- Following the primary analysis data cut-off, an additional participant developed TMA following BPA treatment for rectal haemorrhage, which was recurrent and eventually fatal</td>
</tr>
<tr>
<td>The superficial thrombophlebitis and skin necrosis in the second individual was resolving at the time of data cut-off, and no subsequent AEs or BPA use was reported</td>
<td>- As assessed by the investigator, the TMA was resolving at the time of death and the cause of death (rectal haemorrhage) was deemed unrelated to emicizumab</td>
</tr>
</tbody>
</table>

- The common factor in all TEs and TMAs was concomitant aPCC treatment averaging >100 U/kg daily for ≥24 hours

**AE, adverse event; aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; TE, thrombotic event; TMA, thrombotic microangiopathy**

HAVEN 2: paediatric safety profile reflects that seen in the adult population¹

|                                             | Emicizumab  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 88</td>
</tr>
<tr>
<td>Total number of AEs, n (%)</td>
<td>712</td>
</tr>
<tr>
<td>Total patients with ≥1 AE, n (%)</td>
<td>82 (93.2)</td>
</tr>
<tr>
<td>Fatal AE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SAE</td>
<td>17 (19.3)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>15 (17.0)</td>
</tr>
<tr>
<td>Related AE</td>
<td>30 (34.1)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>27 (30.7)</td>
</tr>
<tr>
<td><strong>AEs of special interest, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic hypersensitivity / anaphylactic / anaphylactoid reaction</td>
<td>1 (1.1)*</td>
</tr>
<tr>
<td>TE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TMA</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

• Seventeen participants experienced 21 SAEs, only one of which (development of an ADA with neutralising potential) was considered related to emicizumab

• The most common AEs (>10% incidence) were:
  – nasopharyngitis: 37.5%
  – injection-site reaction: 30.7%
  – pyrexia: 23.9%
  – upper respiratory tract infection: 23.9%
  – cough: 23.9%
  – diarrhoea: 15.9%
  – vomiting: 15.9%
  – headache: 14.8%
  – contusion: 12.5%
  – fall: 12.5%
  – influenza: 10.2%

• All injection-site reactions were mild, and no participants discontinued due to injection-site reactions

*Cough and abdominal pain; not considered to be a true hypersensitivity reaction.
ADA, anti-drug antibody; AE, adverse event; SAE, serious adverse event; TE, thrombotic event; TMA, thrombotic microangiopathy

HAVEN 3: emicizumab had a favourable safety profile in all treatment arms\textsuperscript{1,2}

<table>
<thead>
<tr>
<th></th>
<th>Arm A: emicizumab QW\textsuperscript{n = 36}</th>
<th>Arm B: emicizumab Q2W\textsuperscript{n = 35}</th>
<th>Arm C: emicizumab Q2W\textsuperscript{*n = 16}</th>
<th>Arm D: emicizumab QW\textsuperscript{n = 63}</th>
<th>Total N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs, n</td>
<td>143</td>
<td>145</td>
<td>19</td>
<td>236</td>
<td>543</td>
</tr>
<tr>
<td>Total patients with ≥1 AE, n (%)</td>
<td>34 (94.4)</td>
<td>30 (85.7)</td>
<td>8 (50.0)</td>
<td>55 (87.3)</td>
<td>127 (84.7)</td>
</tr>
<tr>
<td>Number of serious AEs</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Emicizumab-related SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Selected AEs occurring in ≥5% of all patients, n (%)\textsuperscript{†}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction\textsuperscript{‡}</td>
<td>9 (25)</td>
<td>7 (20)</td>
<td>2 (12)</td>
<td>20 (32)</td>
<td>38 (25)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (11)</td>
<td>4 (11)</td>
<td>0</td>
<td>8 (13)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Patients with AE leading to withdrawal, n (%)</td>
<td>0</td>
<td>1 (3)\textsuperscript{§}</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AE leading to withdrawal</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Includes emicizumab Q2W prophylaxis time period only; at clinical cut-off date, 1 participant was lost to follow-up and another was waiting to start emicizumab. \textsuperscript{2}Other AEs in ≥5% of all participants: arthralgia (19%), nasopharyngitis (12%), headache (11%), and influenza (6%). \textsuperscript{3}Grades 1–2 AE. 1 additional patient in Arm D (and total column) reported an ‘injection-site erythema’ not ‘injection-site reaction’ as the Preferred Term. \textsuperscript{4}Participant in Arm B discontinued due to multiple mild AEs (insomnia, hair loss, nightmare, lethargy, depressed mood, headache and pruritus); 2 patients were lost to follow-up (Arms A and C, 1 patient each). AE, adverse event; F, factor; IU, international units; QW, once weekly; Q2W, once every two weeks; SAE, serious adverse event; TE, thrombotic event; TMA, thrombotic microangiopathy

- Of 215 events of co-exposure to FVIII and emicizumab in 64 patients, 43 included an average FVIII dose ≥50 IU/kg/24 hours, of which eight events lasted >24 hours
  - co-exposure to emicizumab and FVIII was not related to SAEs, TEs or TMAs at the time of primary analysis; however, since data cut-off, one TE has been reported\textsuperscript{3}
- No deaths, ADAs, or de novo FVIII inhibitors have been reported in HAVEN 3
- SAEs include: bleeding event (n = 4); cardiac disorder (n = 1); infection (n = 3); musculoskeletal disorder (n = 3); loosening of an orthopaedic device (n = 1); psychiatric disorder (n = 1); trauma (n = 1)
  - no SAEs were considered related to emicizumab treatment

\textsuperscript{1}Mahlangu J, et al. WFH 2018 (oral presentation);
\textsuperscript{2}Mahlangu J, et al. NEJM 2018;379:811–22;
\textsuperscript{3}F. Hoffmann-La Roche, data on file.
HAVEN 4 PK run-in: no treatment-related AEs were reported

<table>
<thead>
<tr>
<th>Elicizumab 6 mg/kg Q4W*</th>
<th>N = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>14</td>
</tr>
<tr>
<td>Total participants experiencing ≥1 AE, n (%)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Related AE</td>
<td>0</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>0</td>
</tr>
</tbody>
</table>

- No AEs led to treatment withdrawal or dose modification / interruption
- No unexpected changes in vital signs (except elevated blood pressure in one patient†) or electrocardiogram
- No haematology findings and only mild (Grade 1) changes in blood chemistry
- Grade 3 serious AE was a worsening of pre-existing hypertension, which was not considered related to elicitizumab treatment

*Unlike the later expansion phase, participants in the PK run-in phase did not receive a loading dose before the 6 mg/kg dose was given;  
†The participant had elevated blood pressure at study entry and experienced another episode of Grade 2 (moderate) hypertension.

AE, adverse event; PK, pharmacokinetic; Q4W, once every 4 weeks; SAE, serious adverse event

1. Jiménez-Yuste et al. ASH 2017; oral presentation 86.
HAVEN 4 expansion phase: emicizumab was well tolerated when administered every 4 weeks\(^1\)

<table>
<thead>
<tr>
<th>Emicizumab 6 mg/kg Q4W (N = 41)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>148</td>
</tr>
<tr>
<td>Total participants with ≥1 AE, n (%)</td>
<td>30 (73.2)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Related AE</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic event / TMA</td>
<td>0</td>
</tr>
</tbody>
</table>

- 73.2% of participants experienced ≥1 AE
- Only one serious (Grade ≥3) AE was reported (rhabdomyolysis; unrelated to emicizumab)
- No AEs leading to emicizumab discontinuation or withdrawal from the study were reported
- Injection-site reactions were the most common emicizumab-related AE (22.0% of participants) – consistent with other HAVEN studies\(^2,3\)
- No thrombotic events, TMAs, or unexpected safety signals were reported

Data cut-off: 15 December 2017

AE, adverse event; Q4W, once every 4 weeks; SAE, serious adverse event; TMA, thrombotic microangiopathy

No new safety concerns were observed in the HAVEN studies with long-term emicizumab prophylaxis¹

<table>
<thead>
<tr>
<th>Total number of participants with ≥1 AE, n (%)</th>
<th>Total (N=399)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>373 (93.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total number of patients, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>71 (17.8)</td>
<td></td>
</tr>
<tr>
<td>5 (1.3)</td>
<td></td>
</tr>
<tr>
<td>73 (18.3)</td>
<td></td>
</tr>
<tr>
<td>134 (33.6)</td>
<td></td>
</tr>
<tr>
<td>107 (26.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events of special interest</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypersensitivity/anaphylactic/anaphylactoid reaction</td>
<td>1 (0.3)†‡</td>
</tr>
<tr>
<td>TMA event related to concomitant aPCC and emicizumab</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>TE related to concomitant aPCC and emicizumab</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Other TE (grade 1 device occlusion)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

*The safety population only included those patients who received emicizumab. One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analyses
†All ISRs were mild in severity. ‡Assessed using the Sampson Criteria and include all participants that experienced indicative symptoms. One participant experienced symptoms of abdominal pain and cough that were identified as a potential systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the protocol-defined search criteria; however, medical review of the case confirmed that this was not indicative of a systemic hypersensitivity, anaphylactic, or anaphylactoid reaction.

- No deaths, TE or TMA events were observed in the HAVEN studies beyond those reported in the HAVEN 1 primary analysis²
- 103 SAEs were reported in 71 participants
  - SAEs reported by ≥5 participants were haemorrhage (n=7, 1.8%) and haemarthrosis (n=5, 1.3%)
- The most common treatment-related AEs were ISRs (n=104; 26.1%)
- ADAs with neutralising potential were observed in <1% (3/398) of all participants³

ADA, anti-drug antibody; AE, adverse event; aPCC, activated prothrombin complex concentrate; ISR, injection-site reaction
SAE, serious adverse event; TE, thrombotic event; TMA, thrombotic microangiopathy

STASEY interim analysis: emicizumab once weekly is well tolerated in PwHA with FVIII inhibitors\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Emicizumab 1.5 mg/kg QW N = 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>234</td>
</tr>
<tr>
<td>Total participants with ≥1 AE, n (%)</td>
<td>66 (75.0)</td>
</tr>
<tr>
<td>SAE</td>
<td>10* (11.4)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>14 (15.9)</td>
</tr>
<tr>
<td>Related AE</td>
<td>18 (20.5)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>13 (14.8)</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic event / TMA</td>
<td>0</td>
</tr>
</tbody>
</table>

- The only SAE deemed treatment-related by the investigator was one case of catheter-site abscess
- No AEs leading to emicizumab discontinuation or withdrawal from the study were reported
  - three participants had a temporary dose interruption
- **As in the HAVEN studies, injection-site reactions were the most common emicizumab-related AE** (14.8% of participants)
- One patient died during the study due to polytrauma with fatal head injury, which was unrelated to emicizumab
- A second patient has died since the time of this analysis, due to septic shock after infectious complications following surgery, unrelated to emicizumab\(^2\)
- No thrombotic events, TMAs, or unexpected safety signals were reported at the time of this interim analysis
  - a single TE has been reported since this analysis, in a patient with multiple known risk factors for TE\(^2\)

---

Data cut-off: 15 October 2018

*10 participants experienced 13 SAEs (3 events [pneumonia, diverticulum intestinal haemorrhagic and gastrointestinal haemorrhage] occurred in one participant and 2 events [wound hematoma and femur fracture] occurred in another participant)

\(^{1}\) Jimenez-Yuste V, et al. ISTH 2019; oral presentation 60.3;

\(^{2}\) F. Hoffmann-La Roche, data on file.
**STASEY: SAEs were infrequent and the most common treatment-related AEs were ISRs**

<table>
<thead>
<tr>
<th>SAEs, n (%)</th>
<th>N=88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with ≥1 SAE</td>
<td>10 (11.4)</td>
</tr>
<tr>
<td>Overall total number of serious events</td>
<td>13*</td>
</tr>
<tr>
<td>Catheter-site abscess†</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Pneumonia‡</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Diverticulum intestinal haemorrhagic‡</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage‡</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Wound haematoma§</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Femur fracture§</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Polytrauma with fatal head injury</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Retroperitoneal haematoma</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Muscle haemorrhage</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Generalised tonic-clonic seizure</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Renal pain</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Leg amputation</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

- The most common non-serious AEs (seen in ≥10% of patients) were ISRs (14.8%), arthralgia (13.6%), headache (11.4%) and nasopharyngitis (11.4%)

- The most common emicizumab-related AEs were ISRs (n=12; 13.6%)

- All ISRs were mild (n=12; 13.6%) or moderate (n=1; 1.1%) in severity

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*SAE rate per 100 patient-years (95% CI): 19.68 (10.48, 33.66); †The only SAE deemed treatment-related by the investigator was one case of catheter-site abscess; ‡These 3 SAEs occurred in a single patient; §These 2 SAEs occurred in a single patient AE, adverse event; CI, confidence interval; ISR, injection-site reaction; SAE, serious adverse event

### Summary of safety data for HAVEN studies and STASEY

<table>
<thead>
<tr>
<th>Study</th>
<th>Emicizumab Dose</th>
<th>N</th>
<th>Total number of AEs</th>
<th>Total participants with ≥1 AE, n (%)</th>
<th>Related AE</th>
<th>Local injection-site reaction</th>
<th>AEs of special interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAVEN 1</strong> Emicizumab 1.5 mg/kg QW&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>112</td>
<td>457</td>
<td>96 (85.7)</td>
<td>32 (28.6)</td>
<td>16 (14.3)</td>
<td></td>
</tr>
<tr>
<td><strong>HAVEN 2</strong> Emicizumab Paediatric All doses&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>88</td>
<td>712</td>
<td>82 (93.2)</td>
<td>30 (34.1)</td>
<td>27 (30.7)</td>
<td></td>
</tr>
<tr>
<td><strong>HAVEN 3</strong> Emicizumab 1.5 mg/kg QW or 3 mg/kg Q2W&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>150</td>
<td>543</td>
<td>127 (84.7)</td>
<td>NR</td>
<td>38 (25.3)</td>
<td></td>
</tr>
<tr>
<td><strong>HAVEN 4</strong> Emicizumab 6 mg/kg Q4W&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td>41</td>
<td>148</td>
<td>30 (73.2)</td>
<td>12 (29.3)</td>
<td>9 (22.0)</td>
<td></td>
</tr>
<tr>
<td><strong>STASEY</strong> Emicizumab 1.5 mg/kg QW&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td>88</td>
<td>234</td>
<td>66 (75.0)</td>
<td>18 (20.5)</td>
<td>13 (14.8)</td>
<td></td>
</tr>
</tbody>
</table>

* The most common emicizumab-related AEs across all studies were injection-site reactions

---

<sup>1</sup> 10 participants had 13 SAEs; †Cough and abdominal pain; not considered to be a true hypersensitivity reaction; ‡Zero TEs at the time of published analysis; however, one TE has now been reported in both HAVEN 3 and STASEY; AE, adverse event; NR, not reported; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TMA, thrombotic microangiopathy

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Safety guidance
Guidance on the management of breakthrough bleeds

• In the emicizumab clinical trials, the following guidance was given to investigators in relation to the management of breakthrough bleeds in PwHA without FVIII inhibitors:¹

  ❑ Breakthrough bleeds should be treated with the lowest FVIII dose expected to achieve haemostasis; this may be lower than the patients’ prior FVIII dose
    ❑ investigators should review the dose used to treat breakthrough bleeds with the individual patient
  ❑ If breakthrough bleeding does not resolve after the first dose of FVIII, patients should be instructed to contact their treatment centre before infusing multiple FVIII doses
  ❑ Investigators and patients should consider obtaining objective verification of breakthrough bleeds

F, factor; PwHA, people with haemophilia A

1. F. Hoffmann-La Roche Ltd. HAVEN 3 BH30071 protocol v3.
Guidance to mitigate risk of TEś and TMA

• During HAVEN 1, serious TEś and TMAś were reported in five patients\(^1\)
  – all were associated with aPCC doses averaging >100 U/kg/day given for ≥24 hours for treatment of breakthrough bleeds during emicizumab prophylaxis
  – no events were reported when emicizumab was given alone, or in conjunction with rFVIIa alone

• To mitigate further risk, study investigators were provided with the following guidance:

- Exercise caution when using rFVIIa
- Breakthrough bleeds should preferably be treated with the lowest rFVIIa dose expected to achieve haemostasis, using ≤90 µg/kg as the initial dose
- Avoid the use of aPCC
- If aPCC is the only available BPA, use the lowest dose expected to achieve haemostasis, with the initial dose being ≤50 U/kg
- Perform local laboratory assessments to monitor for the risk of TMA or TEś; a central laboratory will analyse samples post hoc, for confirmation

aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; rFVIIa, recombinant activated factor VII; TE, thrombotic event; TMA, thrombotic microangiopathy

Guidance on the management of surgical procedures

- Investigators for the STASEY study were given the following guidance relating to the use of BPAs for surgical management:\(^1\)
  - If BPAs are required, rFVIIa should be administered at the **lowest dose** expected to achieve haemostasis (≤90 µg/kg)
  - Given that circulating emicizumab may increase the patients’ coagulation potential, doses required to achieve haemostasis may be lower than doses used prior to starting emicizumab treatment
  - Use of aPCC for short-term prophylaxis is **prohibited** in patients receiving emicizumab
  - **Repeated dosing** of BPAs should be **medically supervised**
    - Plasma samples should be collected for both local and central laboratory analyses every 24–48 hours until 24–48 hours after the last dose of BPA used to treat a bleed

- During the HAVEN 1 and HAVEN 2 trials, a number of minor and major surgical procedures* were performed. A post-hoc analysis of these events showed 19 of 29 (66%) procedures were managed without prophylactic BPAs\(^2\)
  - Of these procedures, five (26%) resulted in post-operative bleeds
  - Two of five (40%) post-operative bleeds were treated, while the remaining three (60%) were not

---

*Participants expected to receive planned / elective surgery during the course of the study (excluding minor procedures such as tooth extraction; CVAD removal, incision or drainage; and emergency surgery) were excluded.
aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; CVAD, central venous access device; rFVIIa, recombinant activated factor VII

1. F. Hoffmann-La Roche Ltd. STASEY MO39129 protocol v3;
Severe adverse events of interest in haemophilia A
Adverse events and haemophilia A

• With appropriate management of their condition, PwHA can expect to have a near-normal lifespan\(^1\)

• However, a number of complications can arise, which vary from mild to serious or even life-threatening in severity\(^2\)
  – these complications may be disease-related or treatment-related

• The risk of life-threatening adverse events, such as ICH, TEs and TMA requires close monitoring and management to reduce the danger posed to the patient\(^2,3\)

ICH, intracranial hemorrhage; PwHA, people with haemophilia A; TE, thrombotic event; TMA, thrombotic microangiopathy

Intracranial haemorrhage and haemophilia

ICH is the most serious bleeding symptom in PwHA, characterised by high morbidity and mortality.

ICH is 20–50 times more frequent in PwHA compared with those without haemophilia, affecting 3–10% of the haemophilia A population.

The mortality rate of ICH is around 20%, and most survivors of ICH experience some form of neurological sequelae.

ICH is affected by many risk factors, including severity of disease and inhibitor status.

ICH is more common in PwHA receiving on-demand treatment than in those receiving prophylaxis.

ICH is most common in the neonatal period, with a mean age at diagnosis of 4–5 days. After this period, risk is reduced but then increases again with age, especially in the elderly.

Common symptoms at presentation include headache, coma and vomiting.

Most instances of ICH in PwHA are spontaneous (non-traumatic).

Many PwHA require increased treatment and long-term support after suffering an ICH, which can have an impact on healthcare system resources.

ICH, intracranial haemorrhage; PwHA, people with haemophilia A

Risk factors for ICH in haemophilia

**Age**
- During the neonatal period, ICH affects 3.5–4% of PwHA (40–80 times higher than the general population)[1,2,4]
- Following the neonatal period (age <3 years), there is a gradual reduction in the incidence of ICH until the age of 40, when the incidence rate increases[2,3]

**Inhibitor status**
- PwHA with FVIII inhibitors have a 2.5-fold increase in risk of ICH[3], and high-titre FVIII inhibitors are one of the most common risk factors for ICH[1]
- PwHA with FVIII inhibitors also have a 50% higher ICH mortality rate[3]

**Concomitant disease**
- Particularly HIV, hepatitis C, and hypertension[1,3]
- The increased risk in this group may be due to HIV-related thrombocytopenia[1,2]
- PwHA with severe disease and HIV have a 48% greater risk of experiencing ICH[5]
- Hypertension is the most frequent comorbidity in adult PwHA[3]

**Severity of disease**
- ICH is more common in PwHA with severe disease. Although rare, ICH can occur in PwHA with mild or moderate forms of the disease[2]

**Prior ICH**
- Previous ICH is a risk factor for subsequent episodes[3]
- Following an ICH, treatment is intensified to reduce the risk of future events[1,4]

**Treatment regimen**
- ICH is most commonly seen in patients receiving on-demand treatment[3]
- Prophylactic treatment is associated with a reduction of ICH in PwHA with severe disease[2,3]

**Concomitant disease**
- Particularly HIV, hepatitis C, and hypertension[1,3]
- The increased risk in this group may be due to HIV-related thrombocytopenia[1,2]
- PwHA with severe disease and HIV have a 48% greater risk of experiencing ICH[5]
- Hypertension is the most frequent comorbidity in adult PwHA[3]

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**Prior ICH**
- Previous ICH is a risk factor for subsequent episodes[3]
- Following an ICH, treatment is intensified to reduce the risk of future events[1,4]

HIV, human immunodeficiency virus; ICH, intracranial haemorrhage; PwHA, people with haemophilia A

TEs and TMAs

TEs1,2

• Thrombus formation is an appropriate response to blood vessel wall injury

• However, there are three factors that can lead to inappropriately high levels of thrombus formation
  – endothelial damage / abnormal vessel walls
  – abnormal flow / blood stasis or turbulence
  – altered coagulability / abnormal blood components

• Thromboembolism occurs when a thrombus breaks loose into the bloodstream and creates a blockage in another vessel

• Venous thromboembolic events are associated with significant levels of mortality in the general population (as high as 14% within 30 days of a confirmed event, with rates being 20-fold higher in those ≥80 years versus those <40 years2)

TMA3–5

• TMA is characterised by damage to endothelial cells in the capillaries and arterioles that causes them to become thickened, swollen or detached

• The vascular damage associated with TMAs can manifest as arteriolar and capillary thrombosis, and abnormalities in the endothelium and vessel cell wall

• Diagnosis of TMA is confirmed by the presence of schistocytes, microangiopathic haemolytic anaemia, thrombocytopenia, and organ injury

• TMA is a rare condition associated with high morbidity and mortality, particularly if left unmanaged

Baseline risk of TEs in PwHA is not clearly established

- TEs occur in persons with coagulation disorders, however, the true incidence of TEs in congenital HA is unknown\(^1\)
  - further studies on the occurrence of TEs in PwHA are needed
  - while reported incidence varies in the literature, CV risks are common in congenital HA\(^2\)
  - a recent analysis indicated that MI risk for congenital HA is similar to that of an age/sex-matched population without HA\(^3\)

- Thrombosis is a known risk of high plasma levels of FVIII (FVIII > ~200%)\(^4\)

- Emicizumab is thought to confer a mild-to-moderate phenotype in persons with severe HA\(^5\)

### No evidence of a different risk of MI in PwHA relative to non-HA counterparts in a RWD study\(^3\)

<table>
<thead>
<tr>
<th>People with congenital HA ((n = 3,144))</th>
<th>Matched cohort of individuals without HA ((n = 15,673))</th>
<th>Adjusted incidence rate ratio ((aIRR)^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 ((0.15–0.34))</td>
<td>0.22 ((0.18–0.27))</td>
<td>1.31 ((0.85–2.00))</td>
</tr>
</tbody>
</table>

*\(^*\)A Poisson regression model was fitted to estimate the aIRR; the model was adjusted for all baseline covariates as well as HIV and hepatitis C status, with age as a time-varying covariate.

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TEs and TMA events with emicizumab
Summary of TMA events and TEs reported across >6,100 persons treated with emicizumab through 31 December 2019\(^\dagger\)

- **Total TMA (n = 4)/TE (n = 16)**
  - \(n = 20^{\ast\dagger}\)
- **aPCC-associated TMA/TE**
  - \(n = 6\)
  - **TMA**
    - \(n = 4\)
  - **TE**
    - \(n = 2\)
- **Non-aPCC-associated TE**
  - \(n = 13^{\dagger}\)
  - **Non-device related**
    - \(n = 10^{\dagger}\)
  - **Device-related**
    - \(n = 3\)
  - **AHA***
    - \(n = 2\)
  - **Congenital**
    - \(n = 8^{\dagger}\)
  - **Thromboses**
    - \(n = 2\)
  - **Oclusion\(^\dagger\)**
    - \(n = 1\)
- **Excluded**
  - [hemiparesis]
  - \(n = 1\)

\(*\)includes off-label use; \(^\dagger\)Two events occurred in one person; \(^\dagger\)Captured TE event through SMQ review, however does not fit the clinical definition of TE.

AHA, acquired haemophilia A; aPCC, activated prothrombin complex concentrate; SMQ, standardised MedDRA queries; MedDRA, Medical Dictionary for Regulatory Activities; TE, thrombotic event; TMA, thrombotic microangiopathy

Only one additional TMA\textsuperscript{1} associated with the known risk\textsuperscript{2} of concomitant aPCC has been reported since guidance was issued\textsuperscript{*}

\begin{itemize}
  \item Education for HCPs, patients and caregivers
  \item Warnings and precautions (i.e. boxed warning in US; black triangle in EU)
\end{itemize}

\begin{itemize}
  \item Ongoing safety monitoring in all clinical studies
  \item Studies designed specifically to look at frequency of TEs/TMA events
\end{itemize}


\textsuperscript{*}>6,100 people treated with emicizumab at time of reporting.

aPCC, activated prothrombin complex concentrate; HCP, healthcare professional; TE, thrombotic event; TMA, thrombotic microangiopathy

TMA and TEs associated with emicizumab + aPCC >100 U/kg/24hrs for ≥24 hours\textsuperscript{1}

<table>
<thead>
<tr>
<th>Type of study</th>
<th>No. of events</th>
</tr>
</thead>
</table>
| Clinical study | \begin{itemize}
  \item 3 TMA
  \item 2 TE
\end{itemize} \textsuperscript{n = 5} |
| Post-market setting | \begin{itemize}
  \item 1 TMA
\end{itemize} \textsuperscript{n = 1} |
Non-aPCC-related TEs in congenital HA were associated with a history of CV disease or other risk factors for thrombosis\(^1\)

*Seven PwHA, but 8 TEs, as 2 events occurred in 1 person. CV risk factors included: hypertension, hyperlipidaemia, ischaemic heart disease, smoking, and advanced age.\(^2,3\) Risk factors did not include family history of CV disease in a first degree relative.

aPCC, activated prothrombin complex concentrate; CV, cardiovascular; HA, haemophilia A; MI, myocardial infarction; PwHA, people with haemophilia A; TE, thrombotic event; TMA, thrombotic microangiopathy

Most people who experienced TEs recovered and continued to receive emicizumab prophylaxis¹

Reported event outcomes of non-device associated TEs, n = 10 events (9 PwHA)∗

Outcome

- Recovered/resolved
- Recovering/resolving
- Recovered with sequelae
- Fatal†
- Not reported

No. of events

0 1 2 3 4 5

Related, n = 1
Possibly related, n = 1
Unlikely to be related, n = 1
Not related, n = 3
Not reported, n = 4

Reported assessment of causality of non-device-related TEs, n = 10 events (9 PwHA)

*2 events occurred in 1 person; in addition, 2 events occurred in individuals receiving emicizumab off-label for acquired haemophilia A; †TE occurred concurrent to other life-threatening events, critical illnesses, and/or critical conditions.

In 7/9 people who had TEs, there was no reported change to their emicizumab treatment as a result of the event

PwHA, people with haemophilia A; TE, thrombotic event

Summary (I)

• In the Phase I–III clinical trials, emicizumab was shown to be well tolerated in adult and paediatric PwHA with FVIII inhibitors, and in adult PwHA without FVIII inhibitors

• During the early-phase emicizumab trials, no SAEs were reported\(^1,2\)
  – the Phase Ib study reported that emicizumab-related AEs were more common in the cohort receiving the largest dose of emicizumab (3 mg/kg)\(^2\)
  – over an extended 33-month treatment period, 4 SAEs were reported; none were considered related to emicizumab

• Guidance is available for managing breakthrough bleeding and minimizing the risk of TEs and TMA in PwHA receiving emicizumab\(^3\)

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AE, adverse event; aPCC, activated prothrombin complex concentrate; F, factor; PwHA, people with haemophilia A; SAE, serious adverse event; TMA, thrombotic microangiopathy

Summary (II)

• In HAVEN 1, 85.7% of participants have experienced an AE\(^1\)
  – of these, 32 (28.6%) participants experienced an emicizumab-related AE
  – at the time of the updated analysis, 19 SAEs had been reported
  – one participant died in HAVEN 1; this death was considered unrelated to emicizumab by the investigator
  – the occurrence of thrombotic events and TMAs in HAVEN 1 was associated with the concomitant use of aPCC averaging >100 U/kg daily for ≥24 hours

• In HAVEN 2, 30 participants reported an emicizumab-related AE\(^2\)
  – the most common emicizumab-related event was injection-site reaction
  – SAEs were reported in 17 participants (19.3%) and no TE, TMA or fatalities were reported

• In HAVEN 3, 543 AEs were reported in 127 (84.7%) participants\(^3\)
  – 14 serious adverse events were reported, but none were considered related to emicizumab
  – no TE, TMA or fatalities were reported at the time of the primary analysis; one TE has subsequently been reported\(^6\)

• Emicizumab was found to be well tolerated when administered every 4 weeks in HAVEN 4\(^4\)
  – one SAE was reported; no TE or TMA was observed
  – consistent with earlier findings, the most common emicizumab-related AE was injection-site reaction

• The interim results from the STASEY study were consistent with the results from HAVEN 1–4\(^5\)

AE, adverse event; aPCC, activated prothrombin complex concentrate; PwHA, people with haemophilia A; SAE, serious adverse event; TE, thrombotic event; TMA, thrombotic microangiopathy

Summary (III)

- Safety continues to be a key issue for all PwHA, with several events that may pose a threat to life, e.g. intracranial haemorrhage and thrombotic events, being of particular concern\(^1\)–\(^3\)

- The baseline risk of many of these events for PwHA is unknown and can be difficult to gauge in such a heterogeneous population\(^3\)

- TMA events and TEs with concomitant emicizumab and aPCC >100 U/kg/24hrs for ≥24 hours are known risks being managed with boxed warnings and risk minimisation measures\(^4\)

- All other TEs in persons treated with emicizumab were associated with known co-morbidities or pre-existing risk factors\(^5\)

- The incidence rate of arterial and venous TEs in the current HA population needs to be established, regardless of therapeutic approach\(^3\)

Doing now what patients need next