**Introduction**

Emicizumab
- Emicizumab is a drug with a unique mechanism of action, and is administered through subcutaneous injection in persons with HA.  
- Studies established emicizumab's efficacy and safety for routine prophylaxis, leading to approval in persons with inherited HA without factor (F) VIII inhibitors. Through 2019, more than 6,100 persons have received emicizumab across the globe.  
- Thrombosis
  - Studies identified a risk of thrombosis (i.e. blood clotting) and thrombotic microangiopathy (TMA; a clinical syndrome due to damage caused by microscopic blood clots in small blood vessels) when emicizumab was used with aPCC dosed on average >100 U/kg/24hrs for ≥24 hours.  
  - While thrombotic events (TEs) have been observed in persons with coagulation disorders, further studies on their occurrence in HA are needed.  
  - Myocardial infarction (MI; heart attack) is a complication that can be caused by thrombosis. A previous study found its occurrence in persons with inherited HA, similar to that in an age- and sex-matched population without HA.  
  - Cardiovascular risk factors (such as hypertension) are common in inherited HA, but report incidence varies.  

**Methods**

**Sources**
- Clinical trials, expanded-access programs, compassionate use, registries, and post-marketing reports.  

**Search terms**
- Thrombosis, prophylaxis, acquired hemophilia (AHA), hemophilia, and emicizumab.  

**Legend**
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**Types of excluded events**
- Indirect case review was used to exclude non-thrombotic events that were misidentified, and duplicated reports.  

**Guidance on use of emicizumab alongside aPCC**  
- Since guidance on use of emicizumab + aPCC together was issued, one TMA occurred in congenital HA.  

**Clinical trials of emicizumab prophylaxis for HA**
- 20 events were identified, including 16 thrombotic events and four TMA events (Figure 2).  
- Following individual case review, only one event was excluded: a case of hemiparesis (i.e. weakness of one side of the body caused by a brain bleed rather than a clot) with no described thrombosis.  

**Figure 1.** Approach to identify thrombotic and TMA events in persons treated with emicizumab.

**Figure 2.** Summary of thrombotic and TMA events across all persons treated with emicizumab.  

**Table 1.** Thrombotic and TMA events in persons treated with emicizumab.

<table>
<thead>
<tr>
<th>Type of event</th>
<th>n</th>
<th>TMA</th>
<th>TE</th>
<th>Total TE (n = 16)</th>
<th>TMA (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPCC-related TE</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-aPCC-related TE</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related TE</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congruent</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboses</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Guidance on use of emicizumab alongside aPCC**
- Since guidance on use of emicizumab + aPCC together was issued, one TMA occurred in congenital HA.  

**Figure 3.** Thrombotic and TMA events associated with emicizumab + aPCC >100 U/kg/24hrs for ≥24 hours.  

**Conclusions**

Experience with emicizumab is growing. Thrombotic and TMA events when emicizumab is used with aPCC >100 U/kg/24hrs for ≥24 hours are known risks being managed with boxed warnings and risk minimization measures.  

All other thrombotic events in persons treated with emicizumab were associated with other known medical problems or pre-existing risk factors.  

Roche continues to carefully evaluate thrombotic and TMA events in post-marketing studies and registries.  

**Reference**
- KM: 2013;8:e57479; >100 U/kg/24hrs for ≥24 hours  
- 11. Gardner-Caldwell Communications and was funded by F. Hoffmann-La Roche Ltd.

**All available sources of information**
- (i.e. clinical trials, post-marketing reports) on thromboses and TMA events in persons treated with emicizumab were searched through December 31, 2019.  
- Then individual cases were reviewed to ensure only relevant events were included (Figure 1).  

**Figure 4.** Thrombotic events in congenital HA (8 events in 7 persons).

**Figure 5.** Number of myocardial infarction (heart attack) events categorized by number of reported risk factors (n = 6).

**Post-market setting**
- • The majority of TEs resolved, and few were reported as related to emicizumab. One fatal outcome occurred consistent to other the threatening events and critical.  

**Outputs**
Number of events and clinical factors (indication, age, FVIII inhibitor status, other medical problems) aggregated from individual reports.