### Background

Heredity angioedema (HAE) is characterized by recurrent and unpredictable episodes of edema or swelling affecting the abdomen, extremities, genitalia, face, and larynx.

- Results from clinical trials suggest that currently available on-demand treatments for HAE are associated with adverse events such as hypersensitivity reactions, thromboembolic events, injection site reactions, and headache.

### Methods

- We searched FAERS data from 10/1/2009 to 7/16/2014 for HAE treatments.
- The FAERS database contains information on adverse events and medication error reports submitted to FDA by healthcare professionals (such as physicians, nurses, and others) and consumers (such as patients, family members, lawyers, and others).
- Cases were only included if the HAE drug was listed as the 'primary suspect' potentially leading to an ADR.
- The ADRs of interest to this study included those from clinical trials denoted on approved HAE drug US package inserts.
- Analysis was conducted on a single ADR (headache) and four ADR composites.

### Results

- For each drug-event pair, the Reporting Odds Ratio (ROR) and the Empirical Bayesian Geometric Mean (EBGM) were calculated.
- The FAERS database contains information on adverse events and spontaneous reporting and, thus, cannot be used to estimate incidence rates typically in the first two years of commercial availability.

### Discussion

- Although adverse events are underestimated in spontaneous reporting systems, reporting estimated to represent just 6% of actual events.

### Limitations

- Adverse events reported in clinical trials and subsequently in the FAERS database may reveal clinically important associations to help guide clinical decision-making.

### Conclusions

- The FAERS database contains information on adverse events and spontaneous reporting and, thus, cannot be used to estimate incidence rates typically in the first two years of commercial availability.

### Acknowledgments

The authors thank Travis J. Miller, PhD of Generativity Health Outcomes for his work. KalVista Pharmaceuticals Cambridge, MA, USA provided the authors with data.

### References


### Table 1. ADR composites and associated preferred terms

<table>
<thead>
<tr>
<th>ADR Composite</th>
<th>Preferred Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>Venous thrombosis, arterial thrombosis, embolism, thromboembolic event</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Reaction, urticaria, rash, angioedema, wheal, erythema, flushing</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>Pain, erythema, numbness, coldness, burning, swelling, induration</td>
</tr>
</tbody>
</table>

### Table 2. Reporting odds ratio and empirical Bayesian geometric mean values for HAE on-demand parenteral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>ROR</th>
<th>CI</th>
<th>P-value</th>
<th>EBGM</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE Drug</td>
<td>n=4,790 ADRs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icatibant</td>
<td>1.10</td>
<td>(0.85, 1.41)</td>
<td>0.37</td>
<td>1.14</td>
<td>(0.93, 1.41)</td>
</tr>
<tr>
<td>Ecallantide</td>
<td>1.20</td>
<td>(0.94, 1.53)</td>
<td>0.14</td>
<td>1.24</td>
<td>(1.00, 1.53)</td>
</tr>
<tr>
<td>Ruconest</td>
<td>1.01</td>
<td>(0.82, 1.24)</td>
<td>0.86</td>
<td>1.04</td>
<td>(0.85, 1.27)</td>
</tr>
<tr>
<td>Firazyr</td>
<td>1.23</td>
<td>(1.00, 1.50)</td>
<td>0.05</td>
<td>1.29</td>
<td>(1.06, 1.56)</td>
</tr>
</tbody>
</table>

### Figure 1. Sex distribution by ADR for each HAE drug

- The majority of ADRs were reported by females (Figure 1a-1d).
- A nominal increased reporting rate in males was observed for:
  - Hypersensitivity in pC1-Inh (33% vs 24%)
  - Thromboembolic events in icatibant (41% vs 22%)
  - Injection site reactions in icatibant (53% vs 35%)

### Conclusions

- The analysis suggests the currently approved on-demand treatments for HAE are associated with an elevated risk of specific ADRs similar to those reported in clinical trials and FDA-approved labels.

- The increased rates of reporting were found for hypersensitivity, injection site reactions, and injection site reactions.

- Overall, ADR reporting was more frequent for women. In addition, male patients were at a greater risk for hypersensitivity and thromboembolic events.