Intraocular Inflammation, Vasculitis, and Retinal Vascular Occlusion in HAWK & HARRIER: Findings of the Safety Review Committee

Jeffrey S Heier, MD on behalf of the Safety Review Committee
## Financial Disclosures

- Consultant/Scientific Advisory Board

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<th>4DMT</th>
<th>Daiichi Sankyo</th>
<th>Novartis</th>
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<td>Adverum</td>
<td>Eloxx</td>
<td>Ocular Therapeutix</td>
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<td>Aerie</td>
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<td>Alkahest</td>
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Novartis sponsored the SRC; The SRC was solely responsible for the findings
## The Safety Review Committee

<table>
<thead>
<tr>
<th>Purpose</th>
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| • To provide an independent and standardized assessment of **post-marketing reports** of patients treated with brolucizumab  
| • To compare these cases with those observed in the **Phase III HAWK and HARRIER trials** to determine whether they represent a new safety signal  
| **Members** |  
| • **Global retina and uveitis specialists and imaging experts** (5 US, 3 EU) plus an observer from the ASRS  
| • Ophthalmology experts from two distinct external Data Monitoring Committees (DMCs) of ongoing studies  
| **Autonomy** |  
| • The SRC had **full autonomy** with respect to the analysis and assessment of the cases and conclusions formed  
<p>| • While the report of the SRC will be shared with Novartis, its ultimate release is solely under the direction of the SRC |</p>
<table>
<thead>
<tr>
<th>Members of the Safety Review Committee</th>
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| **Thomas Albini, MD**  
Bascom Palmer Eye Institute  
Miami, FL, USA |
| **Peter Kaiser, MD**  
Cleveland Clinic  
Cleveland, OH, USA |
| **Tim Murray, MD (ASRS observer)**  
Murray Ocular Oncology and Retina  
Miami, FL, USA |
| **Frederick L. Ferris, MD**  
Ophthalmic Research Consultants  
Waxhaw, NC, USA |
| **Ivana Kim, MD**  
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Boston, MA, USA |
| **Christian Pruente, MD**  
Augenklinik Universitätsspital Basel,  
Switzerland |
| **Jeff Heier, MD (Chair)**  
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Boston, MA, USA |
| **Jean Francois Korobelnik, MD**  
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Bordeaux, France |
| **Ingrid.U. Scott, MD**  
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Hershey, PA, USA |
| **Frank Holz, MD**  
Universitäts-Augenklinik Bonn  
Bonn, Germany |
| **Jordi Mones, MD**  
Institut de la Màcula,  
Barcelona, Spain |
| **Sunil K. Srivastava, MD**  
Cleveland Clinic  
Cleveland, OH, USA |
| **Glenn Jaffe, MD**  
Duke University  
Durham, NC, USA |
| **Darius Moshfeghi, MD**  
Stanford University  
Stanford, CA, USA |
| **Ramin Tadayoni, MD**  
Hôpital Lariboisière  
Paris, France |
**Process flow**

**Sunday 15th March**
- First SRC meeting (Webinar) to review the Charter, orient members to the data portal and case formats, and explain the process.

**Sunday 22nd March**
- Second SRC meeting to review post-marketing cases.

**Sunday 29th March**
- Third SRC meeting to review HAWK and HARRIER cases.

**Friday 3rd April**
- Fourth SRC meeting to review HAWK and HARRIER cases.

**Sunday 5th April**
- Fifth SRC meeting to review remaining cases in the initial phase.
- Joint discussion of the cases to align on clinical interpretation.
- SRC confirmed a safety signal of rare adverse event.

**Week of 6th April**
- Internal Novartis meetings to decide on action plans.
- Health Authorities informed.
- Investigators of ongoing trials informed.

**Sunday 16th April**
- Review of additional HAWK & HARRIER cases.
- Discussion of next steps.

**Ongoing**
- June 4: ASRS members updated of initial findings; pdf version included on the brolucizumab.info website on June 5, with additional societies to distribute the report.
- SRC to also publish their review in a peer-reviewed publication.
- Novartis establishes taskforce to look into root cause, patient characteristics, mitigation and treatment of these events.

ASRS, American Society of Retina Specialists; SRC, Safety Review Committee.
### SRC classification of the 60 cases in the Core studies

<table>
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<th>Consensus diagnosis</th>
<th>Number of cases (N=60), n (%)</th>
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<tr>
<td><strong>Group 1</strong> Definately drug related; within spectrum of IOI +/- vasculitis +/- vascular occlusion</td>
<td>28 (46.7%)</td>
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<tr>
<td><strong>Group 2</strong> Probably drug-related; not clear whether in the spectrum</td>
<td>22 (36.7%)</td>
</tr>
<tr>
<td><strong>Group 3</strong> Not drug-related, not in spectrum</td>
<td>10 (16.7%)</td>
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</table>

50 cases considered by SRC as having IOI; (28 definite and 22 probable)

IOI, intraocular inflammation; SRC, Safety Review Committee.
2-year incidence of inflammatory events and vision loss

- Incidence of IOI observed by the SRC (4.6%); similar to the IOI incidence reported in HAWK & HARRIER (4.4%)
- Overall incidence of at least moderate vision loss due to IOI remains <1%
- However, the SRC found that their observed incidences of both retinal vasculitis and retinal vascular occlusion were higher than that reported by the investigators

The SRC classified the observations of interest as definite (28 out of a total of 50 patients with IOI [56%]) or probable (22/50 [44%])

<table>
<thead>
<tr>
<th>Observations of interest (IOI, retinal vasculitis and/or retinal vascular occlusion)</th>
<th>Overall risk of developing IOI, vasculitis or retinal vascular occlusion</th>
<th>Overall risk of developing at least moderate vision loss (≥15 ETDRS letter loss)*</th>
<th>Sub-population risk of developing at least moderate vision loss (≥15 ETDRS letter loss)*</th>
<th>Overall risk of developing severe vision loss (≥30 ETDRS letter loss)**</th>
<th>Sub-population risk of developing severe vision loss (≥30 ETDRS letter loss)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 patients developed IOI with or without vasculitis and with or without retinal vascular occlusion</td>
<td>50/1088 (4.6%)</td>
<td>8/1088 (0.7%)</td>
<td>8/50 (16.0%)</td>
<td>5/1088 (0.5%)</td>
<td>5/50 (10.0%)</td>
</tr>
<tr>
<td>36 of the 50 patients with IOI had retinal vasculitis</td>
<td>36/1088 (3.3%)</td>
<td>8/1088 (0.7%)</td>
<td>8/36 (22.2%)</td>
<td>5/1088 (0.5%)</td>
<td>5/36 (13.9%)</td>
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<tr>
<td>23 of the 36 patients with vasculitis had retinal vascular occlusion</td>
<td>23/1088 (2.1%)</td>
<td>7/1088 (0.6%)</td>
<td>7/23 (30.4%)</td>
<td>5/1088 (0.5%)</td>
<td>5/23 (21.7%)</td>
</tr>
</tbody>
</table>

* 8 patients with vasculitis developed moderate vision loss; 7 of the 8 also had retinal vascular occlusion
** 5 patients with vasculitis and retinal vascular occlusion developed severe vision loss

ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation; SRC, Safety Review Committee.
Incidence of IOI observed by the SRC (4.6%); similar to the IOI incidence reported in HAWK & HARRIER (4.4%)

However, the SRC found that their observed incidences of both retinal vasculitis and retinal vascular occlusion were higher than that reported by the investigators

Overall incidence of at least moderate vision loss due to IOI remains <1%

* ‘IOI’ category includes patients who developed IOI with or without vasculitis and with or without retinal vascular occlusion. IOI, intraocular inflammation; SRC, Safety Review Committee.
2-year incidence of inflammatory events and vision loss

Overall risk of vision loss (N=1088):

* ‘IOI’ category includes patients who developed IOI with or without vasculitis and with or without retinal vascular occlusion. IOI, intraocular inflammation; SRC, Safety Review Committee.
The SRC found that the inflammatory events occurred more frequently in the first 6 months following the first dose; Earlier events were associated more frequently with moderate or severe vision loss:

<table>
<thead>
<tr>
<th>Time interval after the first IVT dose of brolucizumab</th>
<th>0−3 months</th>
<th>0−6 months</th>
<th>&gt;6−12 months</th>
<th>&gt;12−18 months</th>
<th>&gt;18−24 months</th>
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<tr>
<td>50 patients developed IOI with or without vasculitis and with or without retinal vascular occlusion with initial event in the following intervals</td>
<td>24/50 (48.0%)</td>
<td>37/50 (74.0%)</td>
<td>7/50 (14.0%)</td>
<td>6/50 (12.0%)</td>
<td>0/50 (0.0%)</td>
</tr>
<tr>
<td>8 of the 50 patients with IOI developed at least moderate vision loss (≥15 ETDRS letter loss)</td>
<td>5/8</td>
<td>7/8</td>
<td>1/8</td>
<td>0/8</td>
<td>0/8</td>
</tr>
<tr>
<td>5 of the 8 patients in row two developed severe vision loss (≥30 ETDRS letter loss)</td>
<td>3/5</td>
<td>4/5</td>
<td>1/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
</tbody>
</table>

ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation; IVT, intravitreal; SRC, Safety Review Committee.
SRC Report: Overall rates of vision loss of ≥15 letters were similar with aflibercept and brolucizumab

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<th>Brolucizumab n/N (%)</th>
<th>Aflibercept n/N (%)</th>
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<tr>
<td>Moderate or severe vision loss (≥15 ETDRS letter loss)</td>
<td>81/1088 (7.4%)</td>
<td>56/729 (7.7%)</td>
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</table>

ETDRS, Early Treatment Diabetic Retinopathy Study.
The overall incidence of the observations of interest (i.e., IOI, retinal vasculitis and/or retinal vascular occlusion) was 1.1% (8/729).

The overall risk of moderate vision loss (≥15 ETDRS letters) in eyes with IOI, retinal vasculitis and/or retinal vascular occlusion in the aflibercept arms of the HAWK and HARRIER trials was <1% (1/729), with a risk of 12.5% (1/8) in the affected sub-population.

A similarly careful review of these patients revealed one case of probable IOI with retinal vasculitis and retinal vascular occlusion.

### SRC Report: Rates in aflibercept patients

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<tbody>
<tr>
<td>IOI, retinal vasculitis and/or retinal vascular occlusion</td>
<td>8/729 (1.1%)</td>
<td>1/729 (0.13%)</td>
<td>1/8 (12.5%)</td>
</tr>
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</table>

ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation.
Overall summary

- Incidence of IOI observed by the SRC (4.6%); similar to the IOI incidence reported in HAWK & HARRIER (4.4%)

- Overall incidence of at least moderate vision loss due to IOI remains <1%

- However, the SRC found that their observed incidences of both retinal vasculitis and retinal vascular occlusion were higher than that reported by the investigators.

- The inflammatory events occurred more frequently in the first 6 months following the first dose; Earlier events were associated more frequently with moderate or severe vision loss.

IOI, intraocular inflammation; SRC, Safety Review Committee.