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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Novartis sponsored the SRC; The SRC was solely responsible for the findings

The Safety Review Committee

 **Purpose**	• 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 • While the report of the SRC will be shared with Novartis, its ultimate release is solely under the direction of the SRC

SRC, Safety Review Committee.

Members of the Safety Review Committee

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** Harvard Medical School, Boston, MA, USA	**Christian Pruente, MD** Augenklinik Universitätsspital Basel, Switzerland
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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

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

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%])

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

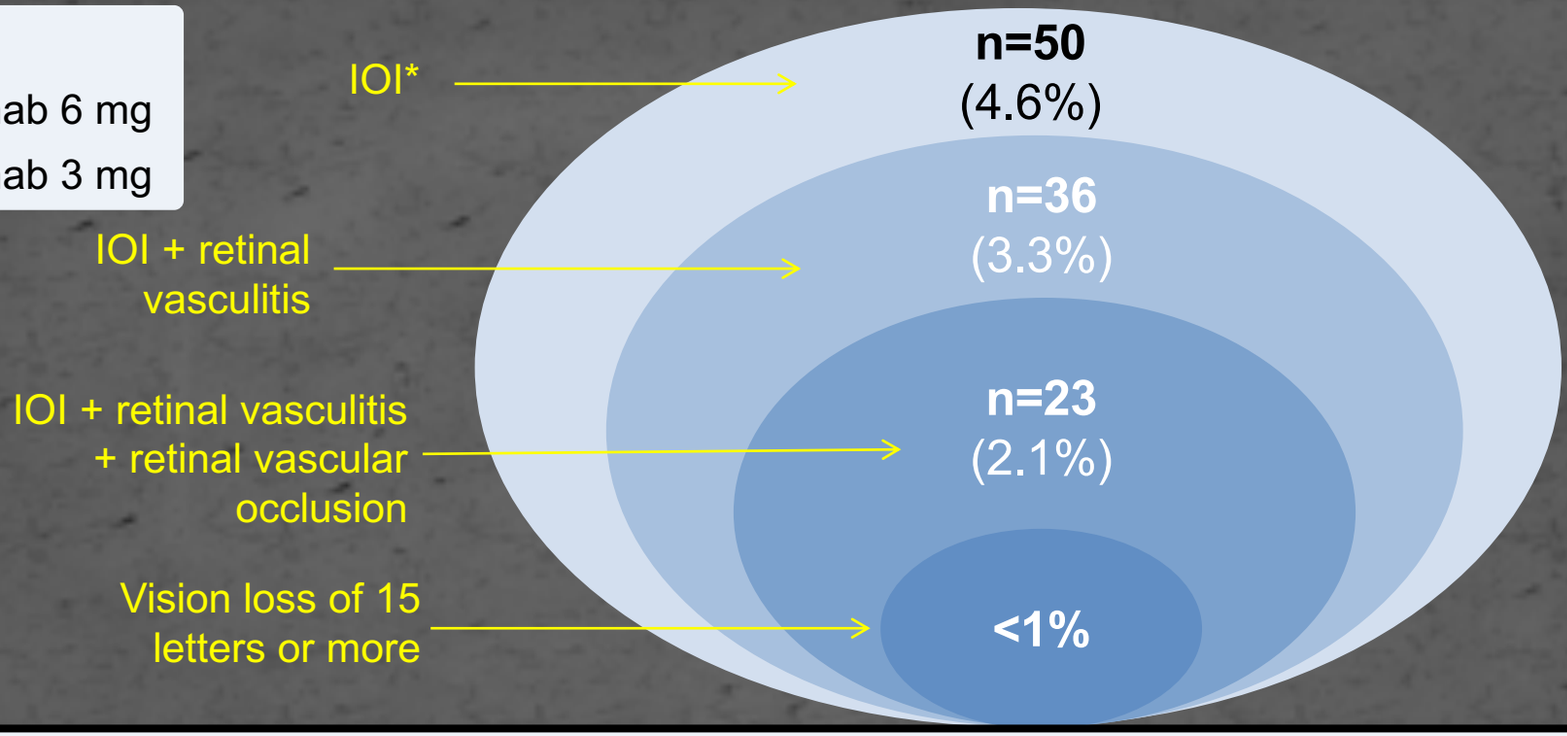
* 8 patients with vasculitis developed moderate vision loss; 7 of the 8 also had retinal vascular occlusion
** 5 patients with vasculitis and retinal vascular occlusion developed severe vision loss

ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation; SRC, Safety Review Committee.

2-year incidence of inflammatory events

Observations of interest: IOI, retinal vasculitis and/or retinal vascular occlusion

N=1088
730 = Brolucizumab 6 mg
358 = Brolucizumab 3 mg

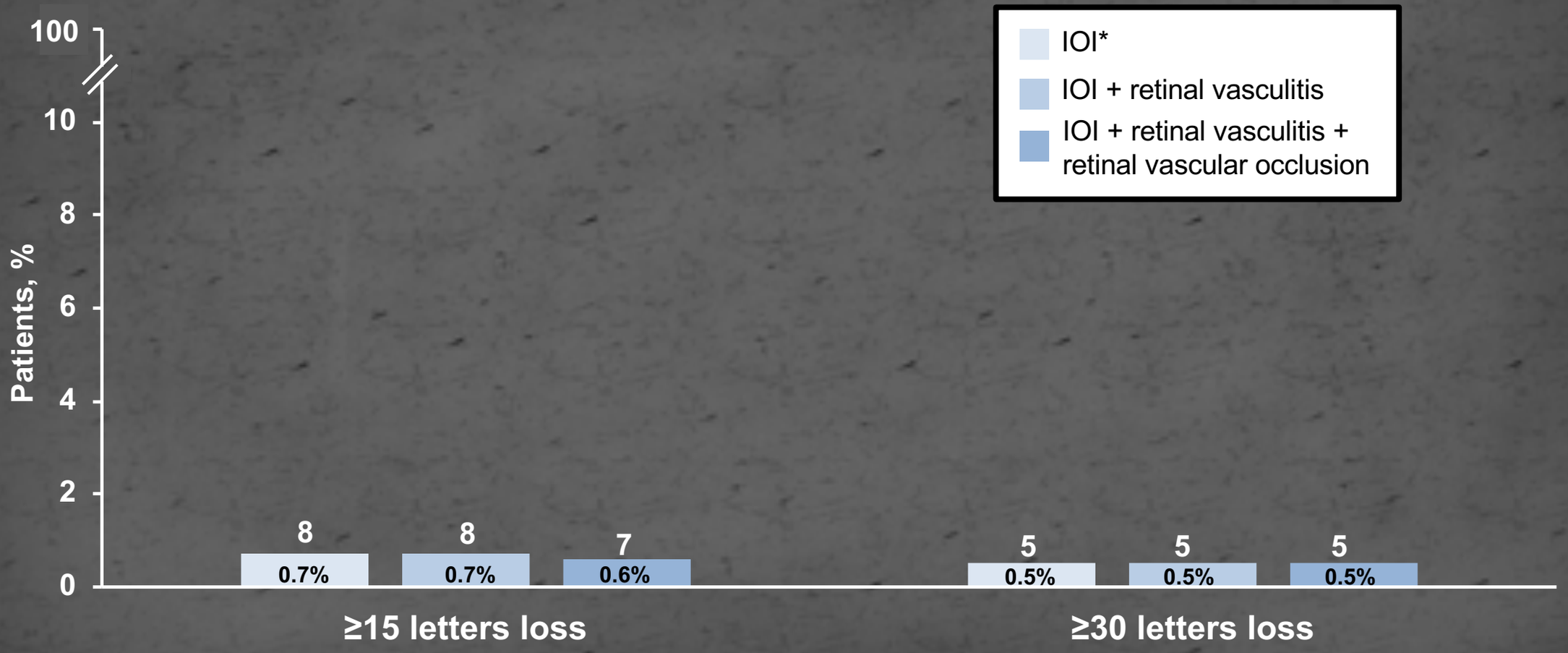


- Incidence of IOI observed by the SRC (4.6%); **similar to** the IOI incidence reported in HAWK & HARRIER (4.4%)
- However, the SRC found that their observed incidences of both retinal vasculitis and retinal vascular occlusion were **higher** than that reported by the investigators
- Overall incidence 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.

SRC Report: Timing of the inflammatory events

- 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:

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

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

	Brolucizumab n/N (%)	Aflibercept n/N (%)
Moderate or severe vision loss (≥15 ETDRS letter loss)	81/1088 (7.4%)	56/729 (7.7%)

ETDRS, Early Treatment Diabetic Retinopathy Study.

SRC Report: Rates in aflibercept patients

- 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

Observations of interest	Overall risk of developing IOI, vasculitis or retinal vascular occlusion Total N = 729	Overall risk of developing at least moderate vision loss (≥15 ETDRS letter loss) Total N = 729	Sub-population risk of developing at least moderate vision loss (≥15 ETDRS letter loss) Subgroup N=8
IOI, retinal vasculitis and/or retinal vascular occlusion)	8/729 (1.1%)	1/729 (0.13%)	1/8 (12.5%)

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.