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Member Update: Novartis-Appointed Safety Review Committee Reports Initial Brolocizumab Findings

Following the recent FDA-approval of brolocizumab for the treatment of neovascular AMD, the ASRS received reports of associated intraocular inflammation (IOI) including occlusive retinal vasculitis. Findings from analysis of these vasculitis events by the ASRS ReST Committee have been reported in real time with serial communications to the retina community ([see Retina Times article](#)).

Parallel to these ReST investigations, Novartis commissioned a Safety Review Committee (SRC) to analyze these events independent and autonomous to Novartis oversight. An initial SRC report based on a critical review of the Phase 3 data from HAWK and HARRIER is below.

A crucial contribution from the SRC analysis is an identification of the rate of these events, which cannot be accurately determined based on voluntarily submitted post-marketing reports. IOI of any form was identified in 4.6% (50/1088) of study patients. Of those, 36 subjects had concomitant retinal vasculitis for an overall rate of 3.3% (36/1088). Of the 36 subjects with IOI and vasculitis, 23 subjects had concomitant vascular occlusion for an overall rate of 2.1% (23/1088).

The absolute risk of developing IOI of any form and losing 15 or more letters was 0.7% (8/1088). Risk of ≥ 3 line vision loss and ≥ 6 line vision loss over 2 years in patients with retinal vasculitis (36/1088) was 22% (8/36) and 14% (5/36), respectively, and in those with occlusive retinal vasculitis (23/1088) was 30% (7/23) and 22% (5/23), respectively. In our ReST analysis, with short-term follow-up of 26 eyes from 25 patients with retinal vasculitis (of which 85% were designated as occlusive), ≥ 3 line vision loss and ≥ 6 line vision loss was seen in 46% and 35%, respectively.

Of note, although the SRC identified that the majority of inflammation events presented within the first 6 months of brolocizumab initiation (74%, 37/50), some events presented between 12-18 months (12%, 6/50).

Interestingly, despite the risk of vision loss associated with retinal vasculitis following brolocizumab injection, the overall rate of vision loss in the study population was not different when comparing the brolocizumab to aflibercept arms in HAWK and HARRIER.

With all therapeutics, the risk of adverse events and their visual consequences need to be balanced with potential benefits. The ReST Committee believes that this risk-benefit assessment at the individual patient level is best determined by the judgment of the treating provider. Safety data from this SRC analysis provides an important complement

to existing data from the ASRS ReST Committee analysis and from other reports. These data contribute to appropriate, informed decisions by practitioners. The ASRS will continue to analyze these cases and will continue to communicate any updates to the retina community. As always, we strongly encourage active surveillance and reporting by all retina specialists.

Safety Review Committee (SRC) Report

Post-marketing reports have highlighted the occurrence of intraocular inflammation (IOI) in association with retinal vasculitis and retinal vascular occlusion with brolocizumab, which differs from the common experience with other approved anti-VEGF agents. A Safety Review Committee (SRC) consisting of clinical trial, imaging, and uveitis experts as well as Data Monitoring Committee members was established by Novartis to independently review these post-marketing cases.

Based upon its review, the SRC felt it was important to perform an unmasked post-hoc review of all cases of investigator-reported IOI, retinal vascular occlusions and endophthalmitis in the phase 3 neovascular AMD HAWK and HARRIER studies (NCT02307682 and NCT02434328). Such a review would result in more accurate evaluation of the incidence of the observations of interest (i.e., IOI, retinal vasculitis and/or retinal vascular occlusion) and contribute to the benefit/risk analysis.

While the incidence of IOI observed by the SRC (4.6%) remains close to the IOI incidence reported by the investigators in the HAWK and HARRIER studies (4.4%) and the overall incidence of at least moderate vision loss due to IOI remains <1%, the SRC found that their observed incidences of both retinal vasculitis and retinal vascular occlusion were higher than the incidences reported by the investigators. The SRC classified the observations of interest as definite (28 out of a total of 50 patients with IOI or 56%) or probable (22/50 or 44%). The 2-year risk of definite or probable IOI, retinal vasculitis and/or retinal vascular occlusion for the combined brolocizumab 3mg and 6mg (HAWK) and 6mg group (HARRIER) are reported and represent a per patient risk as opposed to per injection risk:

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 IOI and retinal 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

The overall incidence of the observations of interest (i.e., IOI, retinal vasculitis and/or retinal vascular occlusion) in the aflibercept arm of the HAWK and HARRIER trials 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.

Of note, despite the vision loss associated with increased incidences of IOI, retinal vasculitis and/or retinal vascular occlusion associated with brolocizumab, the overall rates of at least moderate vision loss (≥ 15 ETDRS letter loss) are similar between the brolocizumab and aflibercept treatment arms: 7.4% or 81/1088 in brolocizumab and 7.7% or 56/729 in aflibercept.

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

Time interval after the first IVT dose of brolocizumab	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

We would like to recognize the collaboration that Novartis has demonstrated throughout this process. The SRC was given unrestricted access to the brolocizumab post-marketing case reports as well as the Hawk and Harrier database. The selection of cases, analysis of data, and determination of how and when such data would be conveyed was determined solely by the SRC. Detailed SRC results will be published in forthcoming peer-reviewed publications however both the SRC and Novartis believe it is important for the retina community to be made aware of the above information immediately.

Novartis is updating the latest information pertaining to the safety of brolocizumab on www.brolocizumab.info.

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