Post-marketing reports have highlighted the occurrence of intraocular inflammation (IOI) in association with retinal vasculitis and retinal vascular occlusion with brolucizumab, 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 brolucizumab 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 brolucizumab, the overall rates of at least moderate vision loss (≥15 ETDRS letter loss) are similar between the brolucizumab and aflibercept treatment arms: 7.4% or 81/1088 in brolucizumab 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 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

We would like to recognize the collaboration that Novartis has demonstrated throughout this process. The SRC was given unrestricted access to the brolucizumab 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 brolucizumab on www.brolucizumab.info.

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