Correspondence

Comment on: Is this a 737 Max Moment for Brolucizumab

EDITOR:

WE READ WITH INTEREST THE EDITORIAL TITLED "IS THIS A 737 Max Moment for Brolucizumab."[1] At Novartis, providing safe and effective treatments for patients is our highest priority. Working closely with health authorities around the world, including FDA, we continuously monitor the benefit-risk profile of our medicines. Although other anti–vascular endothelial growth factor (anti-VEGF) agents are available, there are current unmet needs with neovascular AMD (nAMD) treatment that we believe brolucizumab addresses. Moreover, we believe the choice of treatment should ultimately be left to individual treating physicians and their patients, after appropriate evaluation of the benefit-risk profile of the product.

As a greater number of patients were exposed to brolucizumab following FDA approval, Novartis received reports of retinal vasculitis, including retinal occlusive vasculitis. Novartis initiated its own internal review of these postmarketing safety case reports, including the establishment of an external safety review committee (SRC) to provide an independent review of these cases and compare them to events seen in the brolucizumab Phase III trials. Using the terminology defined by the SRC, Novartis concluded a confirmed safety signal of rare adverse events termed "retinal vasculitis" and/or "retinal vascular occlusion" that may result in severe vision loss.

Additionally, Novartis has established a fully dedicated research, drug development, and medical task force who are working with top external global specialists with the goal of examining the following key questions: (1) root cause; (2) identifying at-risk patient characteristics; (3) risk mitigation strategies; and (4) treatment algorithms for these rare events.

Since the launch of brolucizumab, transparency and communication with the retina community have been first and foremost in our minds. In addition to the commissioning of the SRC and the task force, Novartis worked closely with the American Society of Retina Specialists (ASRS) ReST Committee to provide access to postmarketing data to ensure physicians and patients fully understood the risks and benefits associated with brolucizumab. We have also created a global safety website, brolucizumab.info, to provide the latest information and guidance. Other actions included (1) working with health authorities to update the prescribing information worldwide; (2) informing investigators of ongoing clinical trials and asking them to reconsent patients; (3) amending the protocols, informed consent forms, and investigator brochures of all Novartis-sponsored trials; and (4) informing all physicians who request brolucizumab through our Managed Access Program.

Physicians are advised to carefully monitor each patient treated with brolucizumab for evidence of inflammation or other adverse events. It is advised they follow recommendations set forth in/by the brolucizumab label, and specialty societies and organizations, such as the ASRS, regarding management and timing of repeated administrations of anti-VEGF agents. Brolucizumab is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to brolucizumab.

Brolucizumab represents an important treatment option for patients with nAMD. At Novartis, we support individual physicians, who we believe, whether or not they choose to use brolucizumab, are able to make the best treatment choices for their patients.

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REFERENCE

1. Rosenfeld PJ, Browning DJ. Is this a 737 Max moment for brolucizumab? *Am J Ophthalmol* 2020;216:A7–A8https://www.ajo.com/article/S0002-9394(20)30242-7/fulltext.

Reply to Comment on: Is this a 737 Max Moment for Brolucizumab?

EDITOR:

WE READ THE CORRESPONDENCE BY KAYATH AND SAUER[1] from Novartis Pharmaceuticals with interest. Their letter fails to disclose the recent clarifications in the HAWK and HARRIER trial data, and by doing so they fail to reveal the true risks and benefits for the patients who might be given brolucizumab.

The American Society of Retina Specialists (ASRS) safety review committee (SRC) reviewed the postmarketing cases of intraocular inflammation, retinal vasculitis,

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and retinal vascular occlusion associated with brolucizumab and was concerned enough to perform a post hoc review of the data from the HAWK and HARRIER trials regarding these relevant adverse events. Novartis is to be commended for providing all the data to review. The SRC report is only available to ASRS members, but the results were emailed to members of our specialty societies, so we will take this opportunity to discuss these recent findings (Table 1).

The SRC found that the observed incidences of both retinal vasculitis and retinal vascular occlusion in these trials were higher than reported previously in the HAWK and HARRIER trials. These data, and the discrepancy from the previously released results, in addition to the cases arising from the community use of brolucizumab, raise red flags.

In response to our call for a moratorium, Kayath and Sauer[1] recommend that physicians carefully monitor each patient for evidence of inflammation and respond according to the current recommendations set forth by the revised package insert and the ASRS. But once inflammation develops, it is too late. While they state that "brolucizumab represents an important treatment option for patients with neovascular age-related macular degeneration," we believe that the benefits of brolucizumab are not worth the risks compared with similarly effective therapies that do not have the same risk of an occlusive vasculitis. Novartis suggests that physicians follow the advice from the ASRS, but the most recent SRC report from June 4th made no recommendations other than to monitor patients.

While brolucizumab had a greater rate of inflammation, vasculitis, and occlusion, Novartis argues that the overall rates of vision loss (≥15 Early Treatment of Diabetic Retinopathy Study letters) in the studies were comparable between brolucizumab (81/1088; 7.4%) and aflibercept (56/729; 7.7%). However, this comparison is flawed. Patients with neovascular age-related macular degeneration lose vision even when managed properly, so the most meaningful comparison is not based on the total study population but based on the risk of vision loss from the drug and not from the natural history of disease progression after anti–vascular endothelial growth factor injections. The denominators for these comparisons should not include all of the patients in the study but instead should include only those patients who develop inflammation and related complications because of our choice of drugs. Of the 23 patients who developed inflammation, vasculitis, and vascular occlusion from brolucizumab, 7 eyes (30.4%) lost ≥15 Early Treatment of Diabetic Retinopathy Study letters compared with the 1 eye treated with aflibercept that had probable, not definite, inflammation, vasculitis, and occlusion resulting in lost vision.

While we encourage continued vigilance on the part of Novartis and the retinal community in reporting and investigating the causes of inflammation, vasculitis, and occlusion caused by brolucizumab, we reiterate our recommendation that a moratorium be imposed on the use of brolucizumab until the cause is discovered for these inflammatory side effects and until remedies are devised. It comes down to a simple question for Novartis and the vitreoretinal community: how many more patients need to lose vision before this moratorium is implemented?

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TABLE 1. Risk of Intraocular Inflammation, Retinal Vasculitis, Vascular Occlusion, and Vision Loss in the HAWK and HARRIER Trials

Condition	Brolucizumab	Aflibercept
Sample size, N	1088	729
IOI ± vasculitis ± vascular occlusion, n (%)	50 (4.6)	8 (1.1)
IOI + retinal vasculitis, n (%)	36 (3.3)	0
IOI + retinal vasculitis + vascular occlusion, n (%)	23 (2.1)	1 (0.1)
ETDRS letters lost, n (%)		
≥15	8 (0.7)	1 (0.1)
≥30	5 (0.5)	Not given

ETDRS = Early Treatment of Diabetic Retinopathy Study; IOI = intraocular inflammation.

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REFERENCE

1. Kayath M, Sauer D. Comment on: "Is this a 737 Max Moment for Brolucizumab?". *Am J Ophthalmol* 2020; https://doi.org/10.1016/j.ajo.2020.06.035.

Comment on: Posterior Capsule Opacification With Two Hydrophobic Acrylic Intraocular Lenses: 3-Year Results of a Randomized Trial

EDITOR:

WE READ WITH GREAT INTEREST THE ARTICLE BY LEYDOLT and associates, which set out to compare the incidence