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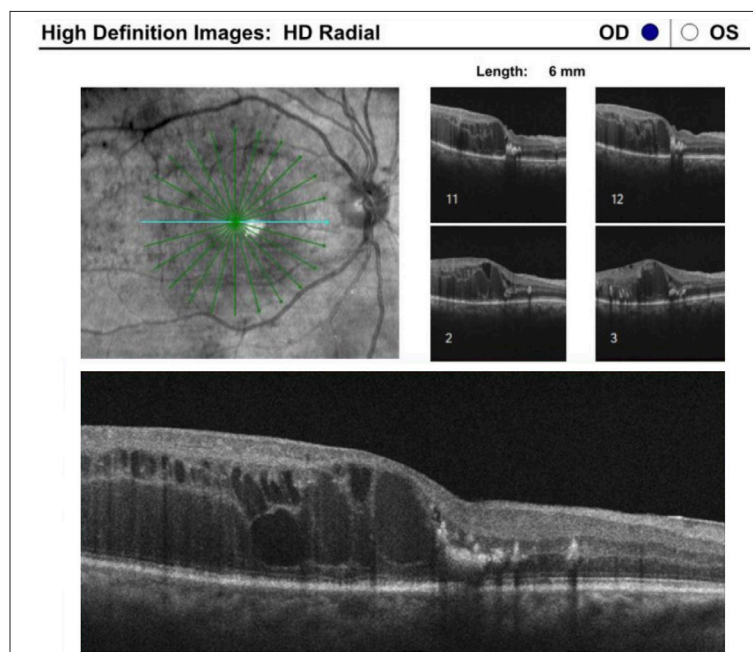
# Two antibodies are better than one?— Faricimab, a newly approved therapy for DME and nAMD

### Introduction:

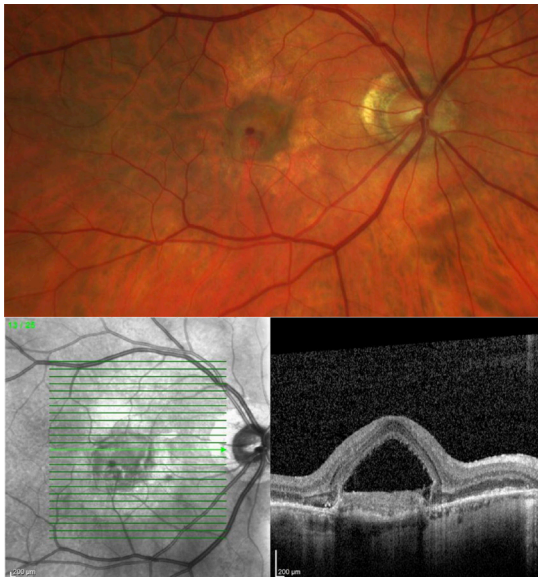
Intravitreal injections of anti VEGF (vascular endothelial growth factor) medications have revolutionized the treatment of macular and retinovascular disease. Despite the success of anti-VEGF therapy, there remain important gaps and room for improvement upon current treatments. As retina specialists, one of the most frequent questions that we receive from patients is a variation of “how often and how long will I need to get these injections?”

A majority of patients and treating physicians would welcome the opportunity for more durable, less frequent treatment without sacrificing visual acuity or structural outcomes. Current medications and dosing regimens have allowed many patients to move beyond fixed monthly dosing, but there remains an unmet need for patients who have persistent edema despite monthly injections and patients who are unable to extend to an acceptable interval with current medications. The need for frequent office visits and injections remains a significant barrier to therapy for many patients. More durable therapies would help minimize the overall treatment burden by decreasing the frequency and total number of visits and injections.

In recent months, the FDA has approved two new therapies for neovascular macular degeneration (nAMD) which promise more durable and consistent treatment than current medications. The first, the ranibizumab port-delivery-system (Susvimo®) was detailed in the March 2022 newsletter and requires the surgical implantation of a refillable reservoir of ranibizumab which can then be re-filled as needed in the office. The second therapy, faricimab (Vabysmo®) is a new intravitreal injection medication which was approved for both nAMD and diabetic macular edema (DME). Faricimab is a bispecific antibody that inhibits both the VEGF-A receptor as well as a new target, angiopoietin-2.<sup>1</sup> Because Faricimab is administered in the office with the same intravitreal injection procedure as existing medications, there may be fewer barriers to adoption for both patients and providers.



**Figure 1:** Patient with persistent center-involving DME despite monthly anti-VEGF injections. Patients like this may benefit from the added inhibition of angiopoietin-2 by faricimab.



**Figure 2:** Patient with nAMD presenting with subretinal fluid and subretinal hemorrhage.

### Faricimab (Vabysmo) Background

Vascular endothelial growth factor (VEGF) is upregulated in nearly all retinal vascular disease, and inhibition of VEGF with intravitreal injections has proven beneficial in conditions as varied as retinopathy of prematurity, diabetic retinopathy, vein occlusion, radiation retinopathy and neovascular macular degeneration. However, VEGF is far from the only signal molecule involved in these conditions. When blood flow is interrupted through hyperglycemia, hypoxia or ischemia, numerous cytokines are released. Angiopoietin 2 is one such cell-signal molecule and therapeutic target that is upregulated in ischemic tissue and is implicated in both vasculogenesis and increased vascular permeability.<sup>1</sup> In both nAMD and diabetic retinopathy, the elevated levels of Ang-2 competitively inhibit angiopoietin 1, which normally stabilizes vessels, leading to increased inflammation, vascular permeability and leakage.<sup>2</sup>

While current treatments such as ranibizumab, aflibercept, bevacizumab and brolucizumab target only the VEGF receptor, faricimab aims to achieve a greater magnitude and duration of action than VEGF inhibition alone.

NJRetina has been selected to participate as investigator sites for all of the clinical trials of faricimab. Successful phase II trials, AVENUE and BOULEVARD, demonstrated the safety and efficacy of faricimab compared to ranibizumab in the treatment of nAMD and DME, and the STAIRWAY trial demonstrated the feasibility of extended interval dosing of 12 to 16 weeks in nAMD.<sup>3</sup>

Following the successful phase II trials, phase III trials were undertaken to compare the efficacy and safety of faricimab to aflibercept, and also to determine the durability of treatment in nAMD (TENAYA and LUCERNE) and DME (YOSEMITE and RHINE).<sup>4,5</sup> The studies compared faricimab 6.0mg at treat-and-extend intervals of 8, 12 or 16 weeks to aflibercept 2.0mg at fixed 8 week intervals. Subjects in the faricimab treat-and-extend arms were able to be extended to a longer interval if the central subfield thickness was maintained at < 325 microns.

Across the four phase III trials, faricimab achieved vision gains that were identical to aflibercept q8weeks for both nAMD and DME.

Furthermore, nearly half of participants were able to be successfully maintained on 16 week dosing intervals, and nearly 80% were able to be maintained at 12 week or greater intervals with similar results (Table 1).

Dual inhibition of VEGF-A and Ang2 by faricimab may result in greater drying of the macula than with current treatments. In the YOSEMITE trial, patients on faricimab had a decrease in central subfield thickness of 206.6 microns and 196.5 microns for fixed q8week and treat-and-extend dosing respectively, compared to a decrease of only 170.3 microns for aflibercept q8weeks.<sup>5</sup>

Adverse events, such as endophthalmitis and significant intraocular inflammation did not differ significantly between the two groups, and there were no cases of retinal vasculitis such as those reported with brolucizumab injection.<sup>4,5</sup>

These favorable two-year results of the phase III trials of nAMD and DME were recently published and led to subsequent FDA approval of faricimab (Vabysmo®, Roche-Genentech) on January 31<sup>st</sup>, 2022 as the first bi-specific antibody approved for use in the eye.

### Discussion:

The approval of Vabysmo is exciting both for the introduction of a new therapeutic target and in the opportunity to offer patients a potentially more effective and more durable treatment. However, as with any new therapy, there are important caveats to consider. It should be noted that visual outcomes with faricimab were non-inferior to those with aflibercept – in short, Vabysmo was equivalent (but not better than) current treatment for primary visual outcomes. With regard to the extended dosing, the study criteria allowed patients to be continued on the longer interval even with persistent fluid as long as central thickness remained < 325 microns, a criteria more permissive in the clinical trial design than in real world clinical practice. Finally, there was only a treat-and-extend arm for Vabysmo, but not aflibercept, so we do not have a direct comparison to know whether a similar number of patients could have safely been extended on aflibercept. In clinical practice, some patients with nAMD can be extended beyond 8 weeks with current therapies, and further phase IV research is required to determine whether faricimab is truly more durable than currently available therapies.

Finally, despite the rigors of understanding drug safety through a pharmaceutically sponsored multiphase clinical trial program leading up to FDA approval, one must continue to independently monitor the safety of any new to market therapy following FDA approval. One must remain selective and cautious in their initial utilization of faricimab until phase IV safety data are available. Enthusiasm for any new anti-VEGF therapy is necessarily tempered by our recent experience with brolucizumab (Beovu®) which was introduced with similar hopes for greater durability. Unfortunately, in the case of brolucizumab, the risk of severe intraocular inflammation and retinal vasculitis has limited its clinical use and was not fully known until post-marketing studies. In the phase III studies of faricimab, there was a slightly greater rate of intraocular inflammation with faricimab than with aflibercept, and more data will be required to establish the safety of Vabysmo in clinical practice.

NJRetina physicians have been involved with all of the trials of faricimab, including the ongoing BALATON trial of faricimab for the treatment of macular edema secondary to branch retinal vein occlusion. As further evidence of safety and efficacy are established, we look forward to having an additional treatment option for our patients with DME and nAMD.

	nAMD (TENAYA & LUCERNE)	DME (YOSEMITE & RHINE)
Participants	1329	1891
Protocol	4 monthly doses of faricimab followed by t/e or aflibercept at fixed intervals	Faricimab at fixed 8 week intervals, faricimab t/e or aflibercept at fixed intervals
Mean VA Gains Vabysmo (ETDRS Letters)	+6.2 letters	+11.2 Letters
Mean VA Gains Aflibercept (ETDRS Letters)	+5.8 letters	+10.6 letters
Extended Intervals	Q12 weeks: 32.9-34.0% Q16 weeks: 44.9-45.7% Total > q12 weeks: ~80%	Q12 weeks: 20.1-21.0% Q16 weeks: 51.0-52.8% Total > q12 weeks: ~ 70%
Intraocular inflammation	1.5-2.4% for faricimab 0.6-1.8% for aflibercept No cases of retinal vasculitis.	1.3% of faricimab patients vs 0.6% of aflibercept patients No cases of retinal vasculitis

Table 1: Summary of phase III trials of faricimab.

**References:**

1. Khan M, Aziz AA, Shafi NA, et al. Targeting Angiopoietin in Retinal Vascular Diseases: A Literature Review and Summary of Clinical Trials Involving Faricimab. *Cells* 2020;9:E1869.
2. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration: The STAIRWAY Phase 2 Randomized Clinical Trial. *JAMA Ophthalmol* 2020;138:964–972.
3. Khanani AM, Guymer RH, Basu K, et al. TENAYA and LUCERNE. *Ophthalmol Sci* 2021;1:100076.
4. Nicolò M, Ferro Desideri L, Vagge A, Traverso CE. Faricimab: an investigational agent targeting the Tie-2/angiopoietin pathway and VEGF-A for the treatment of retinal diseases. *Expert Opin Investig Drugs* 2021;30:193–200.
5. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *The Lancet* 2022;399:741–755.



# At the forefront of clinical research

NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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## Enrolling Studies:

### Dry AMD

#### Teaneck and Toms River

Gallego: A Phase II, Multicenter, Randomized, Single-masked, Sham-controlled Study to Assess Safety, Tolerability, and Efficacy of Intravitreal Injections of FHTR2163 in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration (Gallego)

### Diabetic Retinopathy

#### Teaneck

Altitude: A Phase 2, Randomized, Dose-escalation, Observation-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of RGX-314 Gene Therapy Delivered Via One or Two Suprachoroidal Space (SCS) Injections in Participants with Diabetic Retinopathy (DR) without Center Involved-diabetic Macular Edema (CI-DME) (ALTITUDE)

### Wet AMD

#### Edison

Opthea Coast: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Aflibercept, Compared with Aflibercept Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

#### Toms River

Opthea Shore: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

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