Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular edema (YOSEMITE and RHINE): two randomized, double-masked, phase 3 trials

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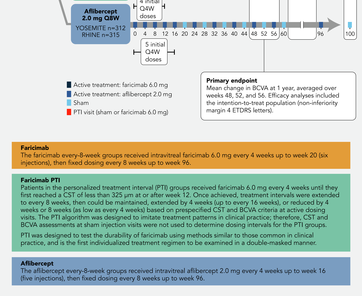
One-year results from two phase 3 trials of faricimab, a novel angiopoietin (Ang)-2 and vascular endothelial growth factor (VEGF)-A bispecific antibody, were presented with the goals of reducing treatment burden and optimizing outcomes in diabetic macular edema (DME). The trials, YOSEMITE and RHINE, represent the first phase 3 clinical trials to evaluate dual Ang-2 and VEGF-A pathway inhibition for the treatment of DME.

Adults with vision loss due to center-involving DME were randomized, double-masked, and assigned to non-inferiority trials across 353 sites worldwide.



Faricimab
The faricimab every-8-week groups received intravitreal faricimab 6.0 mg every 4 weeks up to week 20 (six injections), then fixed dosing every 8 weeks up to week 96.

Faricimab PTI
Patients in the personalized treatment interval (PTI) groups received faricimab 6.0 mg every 4 weeks until they first reached a CST of less than 325 µm at or after week 12. Once achieved, treatment intervals were extended to every 8 weeks, then could be maintained, extended by 4 weeks (up to every 16 weeks), or reduced by 4 weeks or 8 weeks (as low as every 4 weeks) based on prespecified CST and BCVA criteria at active dosing visits. The PTI algorithm was designed to imitate treatment patterns in clinical practice; therefore, CST and BCVA assessments at sham injection visits were not used to determine dosing intervals for the PTI groups.
PTI was designed to test the durability of faricimab using methods similar to those common in clinical practice, and a the first individualized treatment regimen to be examined in a double-masked manner.

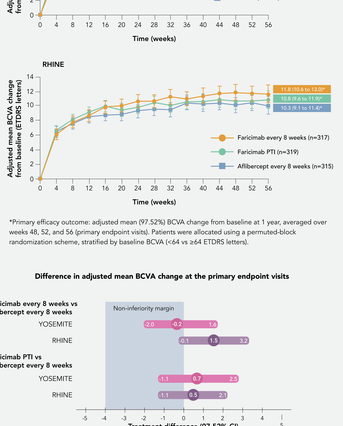
Aflibercept
The aflibercept every-8-week groups received intravitreal aflibercept 2.0 mg every 4 weeks up to week 16 (five injections), then fixed dosing every 8 weeks up to week 96.

To maintain masking, all patients attended study visits every 4 weeks and received sham injections at non-active dosing visits.

BVCA = best-corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study

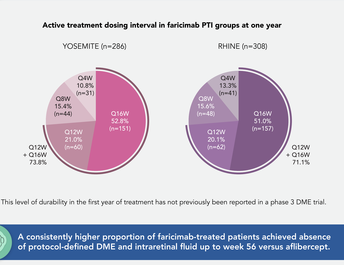
YOSEMITE and RHINE met their primary efficacy endpoint, each showing non-inferior 1-year vision gains with faricimab compared to aflibercept, while demonstrating improved anatomical outcomes. These outcomes were achieved by patients receiving faricimab either every 8 weeks or per PTI.

Adjusted mean change in BCVA from baseline over 1 year in YOSEMITE AND RHINE



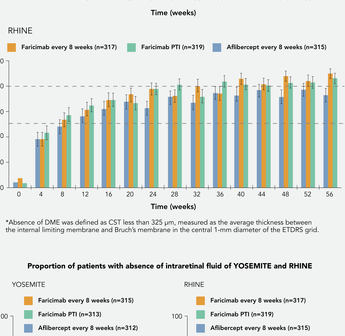
*Primary efficacy outcome: adjusted mean (97.52%) BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56 (primary endpoint visits). Patients were allocated using a permuted-block randomization scheme, stratified by baseline BCVA (<64 vs ≥64 ETDRS letters).

Difference in adjusted mean BCVA change at the primary endpoint visits



Faricimab demonstrated strong durability in YOSEMITE and RHINE. In the PTI group, more than 50% of patients achieved dosing every 16 weeks and 70% of achieved dosing every-12-week or longer at 1 year.

Active treatment dosing interval in faricimab PTI groups at one year



This level of durability in the first year of treatment has not previously been reported in a phase 3 DME trial.

A consistently higher proportion of faricimab-treated patients achieved absence of protocol-defined DME and intraretinal fluid up to week 56 versus aflibercept.

Proportion of patients with absence of DME of YOSEMITE and RHINE

*Absence of DME was defined as CST less than 325 µm, measured as the average thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm diameter of the ETDRS grid.

Proportion of patients with absence of intraretinal fluid of YOSEMITE and RHINE

†Intraretinal fluid was measured in the central 1-mm diameter of the ETDRS grid.
Weeks 48, 52, and 56 were defined as the primary endpoint visits.

Conclusions

Primary results from YOSEMITE and RHINE support the hypothesis that dual Ang-2 and VEGF-A pathway inhibition with faricimab might promote vascular stability beyond current anti-VEGF therapies for DME. Data from the PTI groups also demonstrate the potential for individualized faricimab therapy to maintain vision gains and improve anatomical outcomes with extended dosing intervals, which might help to reduce treatment burden and close the patient outcome gap between clinical trials and current clinical practice. In light of these results and its novel mechanism of action, faricimab might herald an important shift towards multitargeted treatment strategies for patients with DME.