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

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Summary

Background To reduce treatment burden and optimise patient outcomes in diabetic macular oedema, we present 1-year results from two phase 3 trials of faricimab, a novel angiopoietin-2 and vascular endothelial growth factor-A bispecific antibody.

Methods YOSEMITE and RHINE were randomised, double-masked, non-inferiority trials across 353 sites worldwide. Adults with vision loss due to centre-involving diabetic macular oedema were randomly assigned (1:1:1) to intravitreal faricimab 6·0 mg every 8 weeks, faricimab 6·0 mg per personalised treatment interval (PTI), or aflibercept 2·0 mg every 8 weeks up to week 100. PTI dosing intervals were extended, maintained, or reduced (every 4 weeks up to every 16 weeks) based on disease activity at active dosing visits. The primary endpoint was mean change in best-corrected visual acuity at 1 year, averaged over weeks 48, 52, and 56. Efficacy analyses included the intention-to-treat population (non-inferiority margin 4 Early Treatment Diabetic Retinopathy Study [ETDRS] letters); safety analyses included patients with at least one dose of study treatment. These trials are registered with ClinicalTrials.gov (YOSEMITE NCT03622580 and RHINE NCT03622593).

Findings 3247 patients were screened for eligibility in YOSEMITE (n=1532) and RHINE (n=1715). After exclusions, 940 patients were enrolled into YOSEMITE between Sept 5, 2018, and Sept 19, 2019, and 951 patients were enrolled into RHINE between Oct 9, 2018, and Sept 20, 2019. These 1891 patients were randomly assigned to faricimab every 8 weeks (YOSEMITE n=315, RHINE n=317), faricimab PTI (n=313, n=319), or aflibercept every 8 weeks (n=312, n=315). Non-inferiority for the primary endpoint was achieved with faricimab every 8 weeks (adjusted mean *vs* aflibercept every 8 weeks in YOSEMITE 10·7 ETDRS letters [97·52% CI 9·4 to 12·0] *vs* 10·9 ETDRS letters [9·6 to 12·2], difference –0·2 ETDRS letters [–2·0 to 1·6]; RHINE 11·8 ETDRS letters [10·6 to 13·0] *vs* 10·3 ETDRS letters [9·1 to 11·4] letters, difference 1·5 ETDRS letters [–0·1 to 3·2]) and faricimab PTI (YOSEMITE 11·6 ETDRS letters [10·3 to 12·9], difference 0·7 ETDRS letters [–1·1 to 2·5]; RHINE 10·8 ETDRS letters [9·6 to 11·9], difference 0·5 ETDRS letters [–1·1 to 2·1]). Incidence of ocular adverse events was comparable between faricimab every 8 weeks (YOSEMITE n=98 [31%], RHINE n=137 [43%]), faricimab PTI (n=106 [34%], n=119 [37%]), and aflibercept every 8 weeks (n=102 [33%], n=113 [36%]).

Interpretation Robust vision gains and anatomical improvements with faricimab were achieved with adjustable dosing up to every 16 weeks, demonstrating the potential for faricimab to extend the durability of treatment for patients with diabetic macular oedema.

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*YOSEMITE and RHINE investigators and study sites are listed in the appendix (pp 2–7)

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Introduction

Diabetic retinopathy is a leading cause of avoidable vision impairment and blindness worldwide.[1] Vision loss associated with diabetic retinopathy is commonly attributed to diabetic macular oedema, characterised by increased permeability of the retinal vasculature and fluid accumulation in the macula.[2] Upregulation of vascular endothelial growth factor (VEGF)-A is a key driver of vascular leakage in diabetic macular oedema,[2–4] and vision and anatomical improvements have been shown with intravitreal anti-VEGF agents.[5–8] These data have established anti-VEGF therapy as the standard of care for patients with centre-involving diabetic macular oedema.[9]

Despite the efficacy of anti-VEGF therapy in clinical trials, optimal outcomes are difficult to achieve and maintain in clinical practice.[10–12] Best-achievable responses to anti-VEGF therapy often require close monitoring and

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See Online for appendix

Research in context

Evidence before this study

For the past decade, intravitreal anti-vascular endothelial growth factor (VEGF) therapy has been the mainstay of treatment for patients with diabetic macular oedema. Landmark trials have demonstrated the visual and anatomical benefits achievable with VEGF pathway inhibition; however, real-world studies show that treatment outcomes in clinical practice are frequently suboptimal. Adherence to injections every 4–8 weeks and frequent monitoring visits are burdensome for patients, their caregivers, and eye care providers, and are major barriers to achieving optimal outcomes with current anti-VEGF therapies.

Diabetic macular oedema is a multifactorial disease characterised by increased permeability of the retinal vasculature; therefore, novel targets beyond the VEGF pathway might promote vascular stability, extend treatment durability, and improve patient outcomes. The angiopoietin (Ang) and tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Tie) signalling pathway is a key regulator of vascular stability, and Ang-2 upregulation has been implicated in the pathogeneses of diabetic macular oedema and other retinal vascular diseases. As such, dual pathway inhibition via Ang-2 and VEGF-A blockade is a novel therapeutic strategy for the treatment of patients with diabetic macular oedema.

In preclinical studies, dual Ang-2 and VEGF-A inhibition demonstrated the potential for increased vascular stability, with greater reductions in vascular leakage, neovascularisation, and inflammation versus VEGF-A inhibition alone. Subsequently, the phase 2 BOULEVARD trial examined dual pathway inhibition with faricimab in patients with diabetic macular oedema, and reported superior vision gains versus ranibizumab, improvements in secondary visual and anatomical outcomes, and the potential for extended durability.

We conducted a PubMed search on July 7, 2021, using the terms ("diabetic retinopathy") AND ("macular edema") AND ("vascular endothelial growth factor A") AND ("angiogenesis inhibitors") AND ("monoclonal antibodies") AND ("intravitreal injections"), which identified 139 clinical trial reports (filters: "Clinical Trial" OR "Clinical Trial, Phase III") evaluating intravitreal therapies for diabetic macular oedema. Adding the terms ("angiopoietin-2") OR ("bispecific") OR ("dual inhibition") identified one report describing the phase 2 BOULEVARD trial of faricimab in diabetic macular oedema. Filtering our search by "Clinical Trial, Phase III" only returned no phase 3 clinical trial reports of dual Ang-2 and VEGF-A inhibition in patients with diabetic macular oedema.

Added value of this study

Faricimab is the first bispecific antibody designed for intraocular use, and YOSEMITE and RHINE are the first phase 3 clinical trials to evaluate dual Ang-2 and VEGF-A pathway inhibition for the treatment of diabetic macular oedema. The personalised treatment interval (PTI) algorithm, with adjustable dosing up to every 16 weeks, was designed to test the durability of faricimab using methods similar to those common in clinical practice, and is the first individualised treatment regimen to be examined in a double-masked manner. Year 1 data from YOSEMITE and RHINE showed that faricimab offered non-inferior vision gains compared with aflibercept, while demonstrating anatomical improvements that exceeded a commonly used and effective anti-VEGF agent for retinal fluid resolution. These outcomes were achieved by patients receiving faricimab either every 8 weeks or per PTI, a group in which more than 50% achieved dosing every 16 weeks at week 52, and more than 70% achieved dosing every 12 weeks or longer. This level of durability in the first year of treatment has not previously been reported in a phase 3 diabetic macular oedema trial.

Implications of all the available evidence

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 diabetic macular oedema. Data from the PTI groups also demonstrate the potential for individualised 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 diabetic macular oedema.

injections every 4–8 weeks; however, real-world injection frequencies are consistently lower than clinical trial protocols and labelled dosing schedules.[10–13] Moreover, patient responses to anti-VEGF therapy are heterogeneous and long-term efficacy can be difficult to achieve, even in those adherent to close monitoring and frequent injections.[14]

To reduce the burden of anti-VEGF therapy and optimise patient outcomes, personalised regimens, including pro re nata (ie, injections are administered as needed based on anatomical or vision outcomes at regular monitoring visits), and treat and extend (ie, dosing intervals are determined by clinical findings at the last dosing visit) have been studied and adopted in clinical practice.[8,15–18] However, the success of pro re nata treatment remains reliant on frequent monitoring, and treat-and-extend protocols often lead to a higher number of injections versus pro re nata regimens.[15–18] Newer agents and drug delivery systems are under investigation to extend the durability of anti-VEGF therapy for patients with diabetic macular oedema.[19,20] Alternatively, novel targets beyond the VEGF pathway might address the multifactorial cause of diabetic macular oedema,[2] improve

efficacy and durability, enhance personalised therapy, reduce treatment burden, and optimise outcomes in clinical practice.

The angiopoietin (Ang) and tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Tie) signalling pathway is a key regulator of vascular stability in the retinal vasculature.[2,21–23] Under physiological conditions, Ang-1 mediates endothelial cell survival and cell junction integrity via Tie2 receptors. In retinal vascular diseases, Ang-2 upregulation competitively inhibits Ang-1 binding to Tie2, thereby neutralising the vasoprotective effects of the Ang-1 and Tie2 signalling pathway. Binding of Ang-2 to Tie2 also stimulates pericyte apoptosis and promotes leukocyte adhesion and transmigration, both of which sensitise the endothelium to other proinflammatory and angiogenic cytokines, including VEGF-A. Therefore, Ang-2 and VEGF-A synergistically drive vascular leakage and inflammation in diabetic macular oedema, and dual pathway inhibition might promote vascular stability and improve outcomes beyond current anti-VEGF therapies. In support of this hypothesis, preclinical models have demonstrated greater improvements in vascular leakage, inflammation, and neovascularisation with dual Ang-2 and VEGF-A inhibition versus VEGF-A inhibition alone.[23,24]

Faricimab is the first bispecific antibody designed for intraocular use. Its antigen-binding fragments independently inhibit Ang-2 and VEGF-A with high affinity and specificity, while its fragment crystallisable (Fc) region was engineered to reduce Fc-mediated effector functions and systemic half-life.[24] The safety and efficacy of faricimab in diabetic macular oedema were evaluated in the phase 2 BOULEVARD trial,[25] which compared intravitreal faricimab with ranibizumab in anti-VEGF treatment-naive and previously treated patients. BOULEVARD demonstrated statistically superior vision gains at week 24 in treatment-naive patients randomly assigned to faricimab 6·0 mg every 4 weeks versus ranibizumab 0·3 mg every 4 weeks. In both treatment-naive and previously treated patients, secondary visual and anatomical outcomes favoured faricimab, and time to retreatment after week 20 was longer with faricimab versus ranibizumab. Faricimab was well tolerated, with no new or unexpected safety signals identified.[25]

In light of these findings, two identically designed, multicentre, global, randomised, double-masked, active comparator-controlled, phase 3, non-inferiority trials further investigated faricimab for diabetic macular oedema. Herein we present 1-year data describing the efficacy, safety, and durability of faricimab in the YOSEMITE and RHINE trials.

Methods

Study design

The study design and rationale for YOSEMITE and RHINE have been previously described.[26] In brief, patients were enrolled at 353 hospitals and specialist retina clinics worldwide (YOSEMITE, 179 study sites in 16 countries; RHINE, 174 study sites in 24 countries; appendix pp 2–7). Both trials were conducted in accordance with the International Council for Harmonisation E6 Guideline for Good Clinical Practice, tenets of the Declaration of Helsinki, US Food and Drug Administration regulations, and the European Union Clinical Trials Directive (2001/20/EC) as appropriate; and all applicable local, state, and federal laws. Study protocols were approved by applicable institutional review boards and ethics committees before trial commencement (appendix pp 28–29).

Participants

Adults aged 18 years or older with centre-involving macular oedema secondary to diabetes (type 1 or 2) were eligible, with one eye per patient designated the study eye. Key ocular inclusion criteria were central subfield thickness (CST) 325 µm or more (defined as the average thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study [ETDRS] grid), and best-corrected visual acuity (BCVA) of 25–73 ETDRS letters (approximate Snellen equivalent 20/320–20/40). If both eyes were eligible, the eye with worse BCVA at screening was selected. Study eyes were spermitted to be anti-VEGF treatment naive or previously treated (provided that the last treatment was 3 months or more before the day 1 study visit). Previously treated study eyes were limited to 25% of the total enrolment, given the heterogeneity of this population and the potential for limited BCVA improvement in chronic diabetic macular oedema. Additional eligibility criteria are provided in the appendix (pp 8–9) and all patients provided written informed consent to participate.

Randomisation and masking

Patients were randomly assigned (1:1:1) into three treatment groups through an interactive voice or web-based response system: intravitreal faricimab 6·0 mg every 8 weeks; intravitreal faricimab 6·0 mg per personalised treatment interval (PTI; with adjustable dosing up to every 16 weeks); or intravitreal aflibercept 2·0 mg every 8 weeks. To maintain masking, all patients attended study visits every 4 weeks and received sham injections at non-active dosing visits. Further details on randomisation and masking are provided in the appendix (p 10).

Procedures

YOSEMITE and RHINE each consisted of a screening period of up to 28 days, a 96-week treatment period, and a final study visit at week 100 (appendix p 11). 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. The faricimab PTI groups received intravitreal

faricimab 6·0 mg every 4 weeks up to week 12 (four injections), then adjustable dosing up to every 16 weeks until week 96 (described below). 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. Dosing protocols in YOSEMITE and RHINE were informed by the phase 2 BOULEVARD trial for faricimab,[25] and globally aligned posology for aflibercept.[27]

Patients were monitored every 4 weeks from day 1 up to study end. Key ocular assessments at prespecified timepoints included BCVA (using the ETDRS chart at a starting distance of 4 m), intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, spectral-domain optical coherence tomography (OCT), OCT-angiography where available, colour fundus photography, and fundus fluorescein angiography. Ocular images were independently assessed by masked evaluators at a central reading centre.

The PTI algorithm is an automated, protocol-driven dosing regimen based on treat and extend. Patients in the 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 (appendix p 12). 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.

Outcomes

The primary efficacy outcome was change in BCVA from baseline at 1 year, averaged over weeks 48, 52, and 56 (defined as the primary endpoint visits). This outcome was averaged over three timepoints to account for BCVA variability over time and differences in time from last treatment between patients. Secondary endpoints reported herein include the proportion of patients in the faricimab PTI groups receiving dosing every 4 weeks, every 8 weeks, every 12 weeks, or every 16 weeks at week 52 and over time; change in CST at the primary endpoint visits and over time; patients with absence of protocol-defined diabetic macular oedema (CST <325 µm) over time; and patients with absence of intraretinal fluid over time. Other secondary endpoints included change in BCVA over time; patients who gained BCVA (≥15, ≥10, ≥5, or ≥0 ETDRS letters) or avoided BCVA loss (≥15, ≥10, or ≥5 ETDRS letters) over time; patients who gained 15 ETDRS letters or more or achieved Snellen BCVA 20/20 or better (≥84 ETDRS letters) over time; patients with Snellen BCVA 20/40 or better (≥69 ETDRS letters) over time; patients with absence of subretinal fluid over time; and patients with at least two-step improvement on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) at week 52. Prespecified safety endpoints included incidence and severity of ocular and non-ocular adverse events; additional endpoints are listed in the appendix (p 13).

Statistical analysis

Unless otherwise specified, efficacy analyses were based on the intention-to-treat (ITT) population and anti-VEGF treatment-naive populations, grouped by treatment group at randomisation. Safety analyses included all patients who received at least one dose of faricimab or aflibercept, grouped by actual treatment regimen received.

Sample size calculations were based on the primary endpoint of mean BCVA change from baseline at 1 year. A sample size of 300 patients per group (ie, N=900 per trial) was estimated to provide more than 90% power to detect non-inferiority of faricimab every 8 weeks or PTI in pairwise comparisons with aflibercept every 8 weeks in the ITT population for each trial. This was calculated using a non-inferiority margin of 4 ETDRS letters and assuming an SD of 11 ETDRS letters, two-sample *t* test, 1·25% one-sided type I error rate, and 10% dropout rate.

The primary outcome was assessed using a mixed model for repeated measures (MMRM). The MMRM included change from baseline at weeks 4–56 as the response variable, and categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), and randomisation stratification factors as fixed effects. The model assumed an unstructured covariance structure; missing data were implicitly imputed assuming a missing at random mechanism. Three hypotheses were tested at an overall significance level of α=0·0496 using a graph-based testing procedure[28] to control for overall type I error rate: non-inferiority of faricimab versus aflibercept every 8 weeks in the ITT population, superiority of faricimab versus aflibercept every 8 weeks in the treatment-naive population, and superiority of faricimab versus aflibercept every 8 weeks in the ITT population.

For the primary analysis, intercurrent events due to the COVID-19 pandemic (ie, study treatment discontinuation; use of prohibited systemic treatment or prohibited therapy in the study eye; missed doses with potential impact on efficacy [ie, weeks 44, 48, or 52]; or death) were handled using a hypothetical strategy where all values were censored after the intercurrent event. For intercurrent events not due to COVID-19 (ie, study treatment discontinuation due to adverse events or lack of efficacy; or use of prohibited systemic treatment or prohibited therapy in the study eye), a treatment policy strategy was applied where all observed values were used regardless of the intercurrent event. To test the robustness of these assumptions, sensitivity and supplemental analyses were performed using alternative

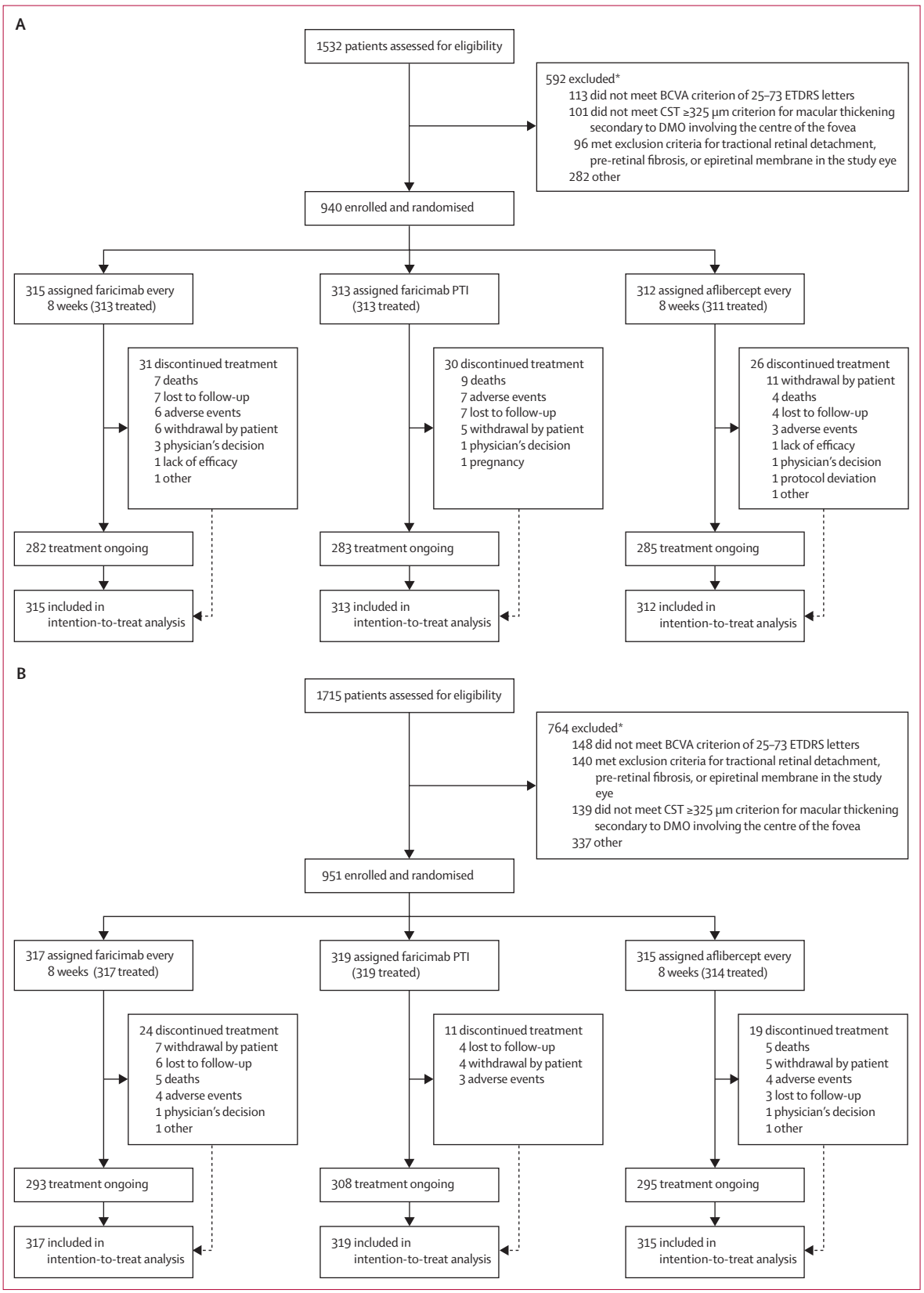


Figure 1: **Trial profile for YOSEMITE (A) and RHINE (B)**
BCVA=best-corrected visual acuity. CST=central subfield thickness. DMO=diabetic macular oedema. ETDRS=Early Treatment Diabetic Retinopathy Study. PTI=personalised treatment interval. *Primary reason for exclusion; some patients were excluded for more than one reason.

	YOSEMITE (N=940)			RHINE (N=951)		
	Faricimab every 8 weeks (n=315)	Faricimab PTI (n=313)	Aflibercept every 8 weeks (n=312)	Faricimab every 8 weeks (n=317)	Faricimab PTI (n=319)	Aflibercept every 8 weeks (n=315)
Age, years*	61·6 (9·5)	62·8 (10·0)	62·2 (9·6)	62·5 (10·1)	61·6 (10·1)	62·3 (10·1)
Sex						
Female	128 (41%)	116 (37%)	134 (43%)	123 (39%)	120 (38%)	129 (41%)
Male	187 (59%)	197 (63%)	178 (57%)	194 (61%)	199 (62%)	186 (59%)
Geographical region						
USA and Canada	167 (53%)	168 (54%)	168 (54%)	110 (35%)	111 (35%)	109 (35%)
Asia†	21 (7%)	19 (6%)	20 (6%)	29 (9%)	29 (9%)	26 (8%)
Rest of the world‡	127 (40%)	126 (40%)	124 (40%)	178 (56%)	179 (56%)	180 (57%)
Race or ethnicity§						
White	241 (77%)	240 (77%)	253 (81%)	250 (79%)	249 (78%)	253 (80%)
Asian	31 (10%)	26 (8%)	27 (9%)	34 (11%)	36 (11%)	32 (10%)
Black or African American	22 (7%)	25 (8%)	12 (4%)	18 (6%)	23 (7%)	24 (8%)
American Indian or Alaska Native	6 (1%)	5 (2%)	7 (2%)	0	0	1 (<1%)
Native Hawaiian or other Pacific Islander	2 (1%)	0	3 (1%)	2 (1%)	0	0
Hispanic or Latinx	37 (12%)	40 (13%)	37 (12%)	56 (18%)	78 (24%)	67 (21%)
Non-ocular characteristics						
Body-mass index, kg/m^2	30·9 (6·9)	30·9 (6·9)	31·0 (6·7)	30·5 (6·1)	29·9 (5·7)	30·1 (6·1)
HbA_{1c}, %, mmol/mol	7·6 (1·1), 59 (12·2)	7·6 (1·1), 60 (12·5)	7·6 (1·1), 60 (12·4)	7·6 (1·2), 60 (12·6)	7·7 (1·2), 61 (12·8)	7·7 (1·2), 60 (13·1)
Type 2 diabetes	291 (92·4%)	299 (96%)	299 (96%)	297 (94%)	300 (94%)	298 (95%)
Systolic blood pressure, mm Hg	136·9 (15·9)	137·7 (16·0)	136·1 (14·8)	137·0 (15·6)	138·1 (15·6)	137·6 (17·3)
Ocular characteristics						
BCVA, ETDRS letters	62·0 (9·9)	61·9 (10·2)	62·2 (9·5)	61·9 (10·1)	62·5 (9·3)	62·1 (9·4)
CST, µm	492·3 (135·8)	485·8 (130·8)	484·5 (131·1)	466·2 (119·4)	471·3 (127·0)	477·3 (129·4)
Macular ischaemic non-perfusion	127 (40%)	117 (37%)	122 (39%)	126 (40%)	138 (43%)	132 (42%)
Macular leakage	305 (97%)	301 (96%)	293 (94%)	300 (95%)	309 (97%)	299 (95%)
Time since DMO diagnosis, months	14·0 (21·7)	17·6 (36·2)	17·5 (27·6)	18·9 (32·2)	20·7 (33·0)	20·3 (37·1)
Anti-VEGF treatment naive	238 (76%)	245 (78%)	242 (78%)	254 (80%)	255 (80%)	248 (79%)
Previously anti-VEGF treated	77 (24%)	68 (22%)	70 (22%)	63 (20%)	64 (20%)	67 (21%)
Time since last anti-VEGF treatment, months	20·5 (20·5)	17·6 (17·2)	16·6 (12·6)	20·7 (20·8)	15·5 (19·5)	19·9 (17·4)
Phakic	242 (77%)	230 (74%)	229 (73%)	234 (74%)	244 (77%)	239 (76%)
ETDRS-DRSS status						
Diabetic retinopathy absent or questionable; mild to moderate NPDR (ETDRS-DRSS level 10/12, 14/20, 35, 43)	174 (55%)	187 (60%)	182 (58%)	183 (58%)	178 (56%)	180 (57%)
Moderately severe to severe NPDR (ETDRS-DRSS level 47, 53)	113 (36%)	99 (32%)	103 (33%)	109 (34%)	99 (31%)	105 (33%)
PDR (ETDRS-DRSS level 61, 65, 71/75)	22 (7%)	21 (7%)	18 (6%)	20 (6%)	37 (12%)	20 (6%)
Cannot grade (ETDRS-DRSS level 90)	4 (1%)	5 (2%)	7 (2%)	2 (1%)	5 (2%)	5 (2%)
Missing	2 (1%)	1 (<1%)	2 (1%)	3 (1%)	0	5 (2%)

Data are mean (SD) or n (%). BCVA=best-corrected visual acuity. CST=central subfield thickness. DMO=diabetic macular oedema. DRSS=Diabetic Retinopathy Severity Scale. ETDRS=Early Treatment Diabetic Retinopathy Study. HbA_{1c}=glycated haemoglobin. NPDR=non-proliferative diabetic retinopathy. PDR=proliferative diabetic retinopathy. PTI=personalised treatment interval. VEGF=vascular endothelial growth factor. *Age at randomisation. †Asia includes China, Hong Kong, Japan, Singapore, South Korea, Taiwan, and Thailand. ‡Rest of the world includes Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Mexico, the Netherlands, New Zealand, Peru, Poland, Portugal, Russia, Slovakia, South Africa, Spain, Switzerland, Turkey, Ukraine, and the UK. §Not all race categories are listed; therefore, the sum of proportions shown do not equal 100%.

Table 1: **Baseline patient characteristics in YOSEMITE and RHINE (intention-to-treat population)**

handling strategies for missing data and intercurrent events (appendix pp 14–15).

Secondary endpoints measured on a continuous scale were assessed using the same analysis method and data handling rules described above. For binary endpoints, proportions and overall differences between groups were estimated using the weighted average of observed proportions and differences in observed proportions over

the strata defined by randomisation factors using Cochran-Mantel-Haenszel (CMH) weights. CIs were calculated using normal approximation to weighted proportions.

Safety and tolerability were assessed through descriptive summaries of ocular and systemic adverse events, deaths, and ocular assessments up to week 56. Adverse events were coded using Medical Dictionary for Regulatory Activities thesaurus terms and summarised by treatment group and System Organ Class.

An independent data monitoring committee evaluated safety and study conduct until completion of the primary analysis. A nominal type I error penalty of 0·0001 was taken for each unmasked safety review performed, such that efficacy analyses were performed with a family-wise significance level of α=0·0496. Statistical analyses were performed using SAS version 9·4. The YOSEMITE and RHINE trials are registered with ClinicalTrials.gov (YOSEMITE NCT03622580 and RHINE NCT03622593).

Role of the funding source

F Hoffmann-La Roche participated in the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the paper for publication. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

3247 patients were screened for eligibility in YOSEMITE (n=1532) and RHINE (n=1715). After exclusions, 940 patients were enrolled into YOSEMITE between Sept 5, 2018, and Sept 19, 2019, and 951 patients were enrolled into RHINE between Oct 9, 2018, and Sept 20, 2019. In YOSEMITE, patients were randomly assigned to faricimab every 8 weeks (ITT n=315, including 238 anti-VEGF treatment-naive eyes), faricimab PTI (ITT n=313, treatment naive n=245), or aflibercept every 8 weeks (ITT n=312, treatment naive n=242). In RHINE, patients were randomly assigned to faricimab every 8 weeks (ITT n=317, treatment naive n=254), faricimab PTI (ITT n=319, treatment naive n=255), or aflibercept every 8 weeks (ITT n=315, treatment naive n=248). Overall, 937 (99·7%) patients in YOSEMITE and 950 (99·9%) in RHINE received at least one dose of study treatment and were included in the safety analysis population (figure 1).

Major protocol deviations up to week 56 were reported for 451 (48%) patients in YOSEMITE and 475 (50%) in RHINE, and were generally balanced across treatment groups (appendix pp 16–17). 244 (32%) of 766 major protocol deviations in YOSEMITE and 319 (39%) of 819 major protocol deviations in RHINE were related to COVID-19, which were reported for 156 (17%) patients in YOSEMITE and 195 (21%) patients in RHINE. Most of these patients missed at least one study visit at weeks 44, 48, 52, or 56 (YOSEMITE n=139 [15%], RHINE n=160 [17%]), and were equally distributed across treatment groups. However, not all missed visits resulted in missed doses with a potential impact on efficacy; 63 (7%) patients in YOSEMITE and 76 (8%) patients in RHINE missed at least one dose at weeks 44, 48, or 52.

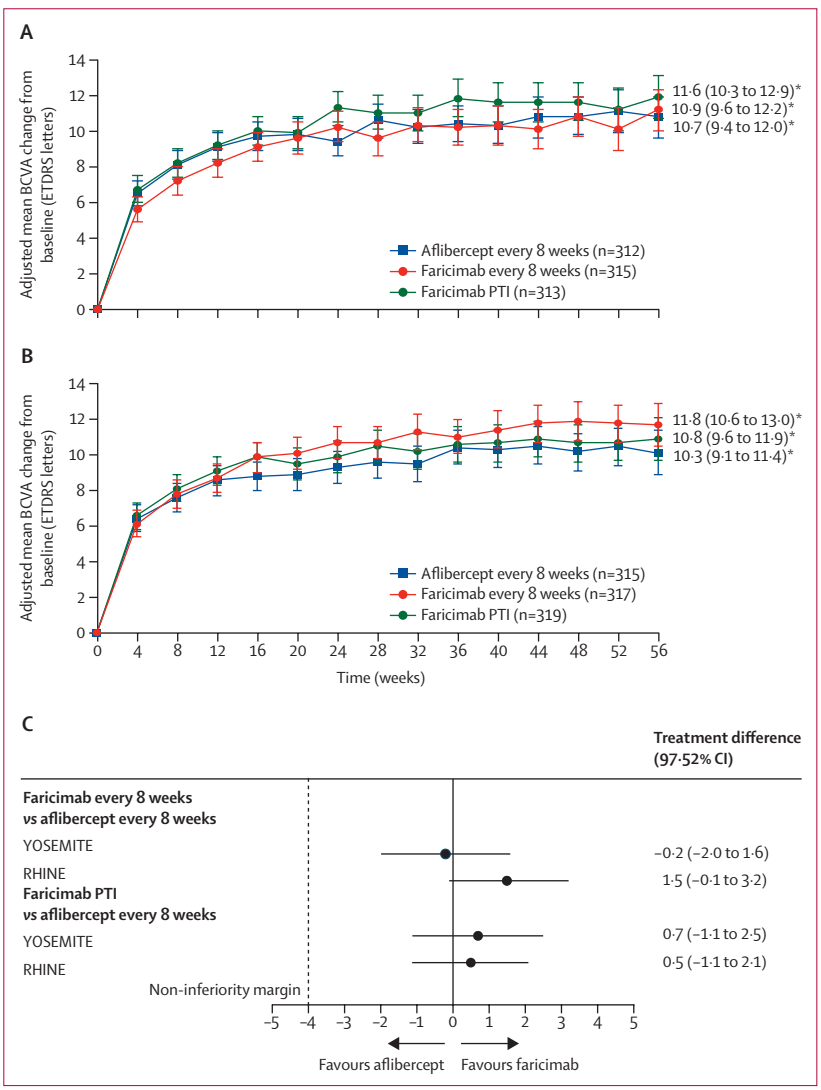
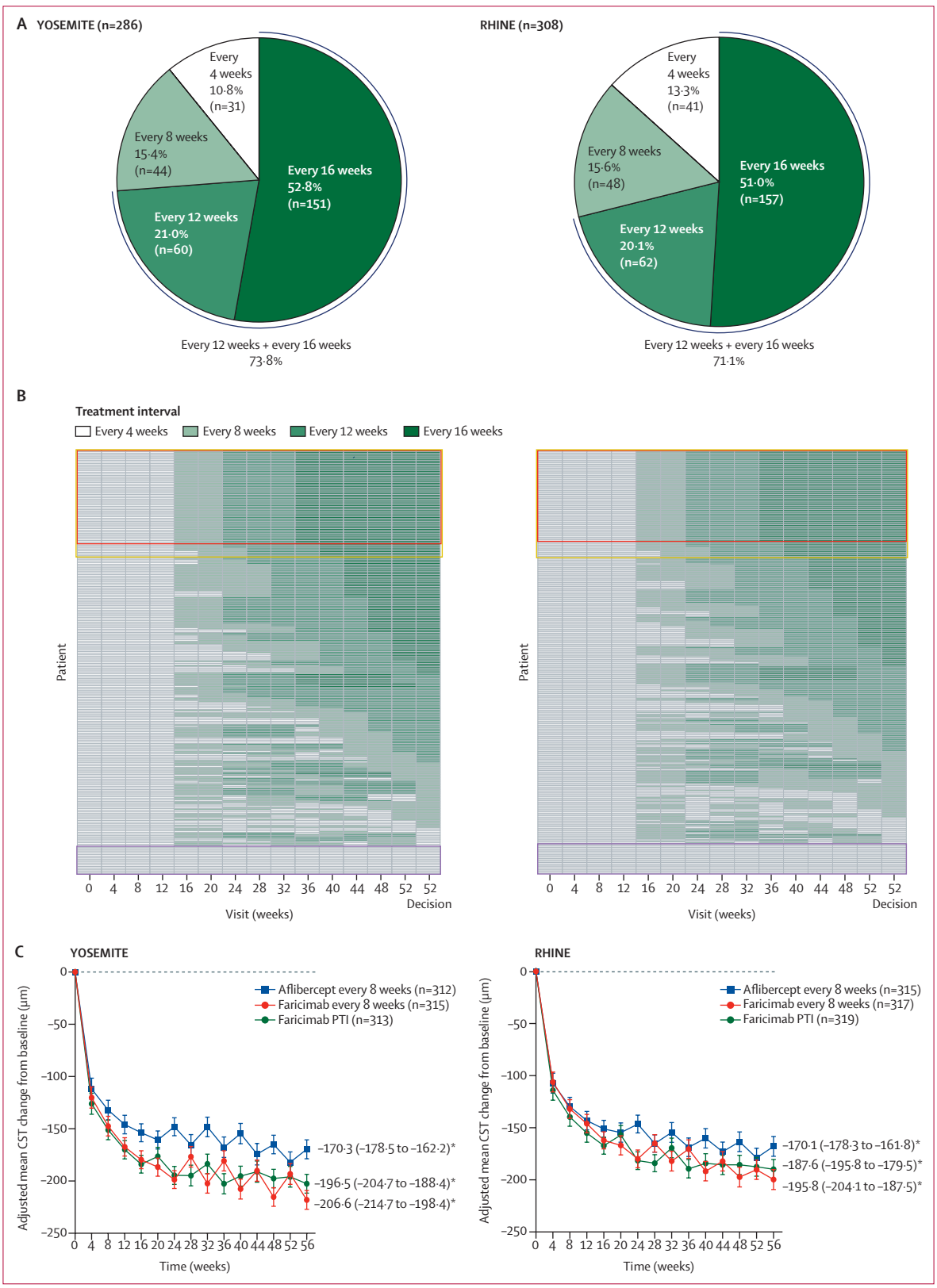


Figure 2: **Adjusted mean change in BCVA from baseline over 1 year in YOSEMITE (A) and RHINE (B), and difference in adjusted mean BCVA change at the primary endpoint visits (C)**

Results are based on a MMRM analysis of the intention-to-treat population, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<64 *vs* ≥64 ETDRS letters), previous intravitreal anti-VEGF therapy (yes *vs* no), and region (USA and Canada, Asia, and rest of the world). Treatment policy strategy was applied to non-COVID-19-related intercurrent events and hypothetical strategy was applied to COVID-19-related intercurrent events. Missing data were implicitly imputed by the MMRM. Error bars represent 95·04% CI. BCVA=best-corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. MMRM=mixed model for repeated measures. PTI=personalised treatment interval. VEGF=vascular endothelial growth factor. *Primary efficacy outcome was adjusted mean (97·52% CI) BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56 (primary endpoint visits).

Baseline patient characteristics were generally well balanced across treatment groups and trials (table 1). At baseline, mean age ranged between 61·6–62·8 years and mean BCVA was 61·9–62·5 ETDRS letters, whereas mean CST in YOSEMITE (485–492 μm) was slightly greater than



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in RHINE (466–477 µm). Approximately 31–36% of patients had moderately severe to severe non-proliferative diabetic retinopathy at baseline (ETDRS-DRSS level 47–53), and 6–12% had proliferative diabetic retinopathy (ETDRS-DRSS level 61–75). The proportion of previously anti-VEGF-treated patients ranged from 20% to 24% across groups, and baseline characteristics for anti-VEGF treatment-naive subgroups were similarly well balanced (appendix p 18).

YOSEMITE and RHINE met their primary efficacy endpoint, each demonstrating non-inferior 1-year vision gains with faricimab every 8 weeks or PTI versus aflibercept every 8 weeks in the ITT population (figure 2). In YOSEMITE, adjusted mean BCVA change from baseline at the primary endpoint visits was 10·7 ETDRS letters (97·52% CI 9·4 to 12·0) in the faricimab every-8-week group and 11·6 ETDRS letters (10·3 to 12·9) in the faricimab PTI group versus 10·9 ETDRS letters (9·6 to 12·2) in the aflibercept every-8-week group (mean difference *vs* aflibercept every 8 weeks –0·2 ETDRS letters [–2·0 to 1·6] in the faricimab every-8-week group and 0·7 ETDRS letters [–1·1 to 2·5] in the faricimab PTI group). Corresponding mean BCVA gains in RHINE were 11·8 ETDRS letters (10·6 to 13·0) in the faricimab every-8-week group and 10·8 ETDRS letters (9·6 to 11·9) in the faricimab PTI group versus 10·3 ETDRS letters (9·1 to 11·4) in the aflibercept every-8-week group (mean difference *vs* aflibercept every 8 weeks 1·5 ETDRS letters [–0·1 to 3·2] in the faricimab every-8-week group and 0·5 ETDRS letters [–1·1 to 2·1] in the faricimab PTI group). Because the lower bounds of the 97·52% CIs for the adjusted mean differences were greater than –4 ETDRS letters, non-inferiority of faricimab every 8 weeks and PTI versus aflibercept every 8 weeks was established (figure 2). Sensitivity and supplemental analyses showed that these results were consistent across various methods for handling missing data and intercurrent events (appendix pp 14–15). 1-year vision gains among anti-VEGF treatment-naive patients were consistent with the ITT population, and no faricimab group demonstrated superiority versus aflibercept (appendix p 19). Secondary BCVA endpoints in the ITT population were also comparable across treatment groups and reproducible across trials (appendix p 20).

Faricimab demonstrated strong durability in YOSEMITE and RHINE, with more than 70% of patients in the PTI groups achieving every-12-week dosing or longer at 1 year (figure 3). At the week 52 visit, 151 (53%) patients in YOSEMITE and 157 (51%) patients in RHINE achieved dosing every 16 weeks, and a further 60 (21%) patients in YOSEMITE and 62 (20%) patients in RHINE achieved dosing every 12 weeks. Approximately two-thirds of patients reached every-12-week or every-16-week dosing at week 52 without an interval reduction below every 12 weeks during year 1 (YOSEMITE n=194 [68%], RHINE n=198 [64%]).

Among the patients on every-16-week dosing at week 52, 70 (46%) in YOSEMITE and 71 (45%) in RHINE had already successfully completed a full 16-week dosing cycle (figure 3). Approximately one-quarter of the faricimab PTI groups in YOSEMITE (n=72 [24%]) and RHINE (n=80 [26%]) rapidly achieved dosing every 16 weeks by week 32 (ie, the first timepoint that patients could be extended to every-16-week dosing); most of these patients subsequently completed a full 16-week dosing cycle and remained on every-16-week dosing at week 52 (YOSEMITE n=61 [85%], RHINE n=61 [77%]). At the week 52 visit, 31 (11%) patients in YOSEMITE and 41 (13%) patients in RHINE received dosing every 4 weeks; of these patients, 19 (61%) in YOSEMITE and 22 (54%) in RHINE never had their dosing interval extended beyond every 4 weeks during year 1.

Reductions in CST over 1 year consistently favoured faricimab over aflibercept (figure 3). In YOSEMITE, adjusted mean CST change from baseline at the primary endpoint visits was –206·6 µm (95·04% CI –214·7 to –198·4) in the faricimab every-8-week group and –196·5 µm (–204·7 to –188·4) in the faricimab PTI group. These reductions were greater than in the aflibercept every-8-week group (–170·3 µm [–178·5 to –162·2]). Similarly in RHINE, adjusted mean CST change at the primary endpoint visits was greater with faricimab every 8 weeks (–195·8 µm [–204·1 to –187·5]) and PTI (–187·6 µm [–195·8 to –179·5]) versus aflibercept every 8 weeks (–170·1 µm [–178·3 to –161·8]).

A consistently higher proportion of faricimab-treated patients achieved absence of protocol-defined diabetic

Figure 3: **Proportion of patients in the faricimab PTI groups who achieved dosing every 4 weeks, every 8 weeks, every 12 weeks, or every 16 weeks at week 52 (A), dosing intervals in the faricimab PTI groups over 1 year (B), and adjusted mean change in CST from baseline over 1 year (C) in YOSEMITE and RHINE**

(A, B) Analyses included patients in the faricimab PTI groups who had not discontinued the study at the week 52 visit. Treatment interval at week 52 was defined as the treatment interval decision made at that visit in (A), and treatment interval at a given visit is shown as the interval at the start of the visit in (B). The week 52 decision (calculated and recorded at week 56) is shown in the last column. Blue lines in (A) indicate the proportion of patients who achieved every-12-week or every-16-week dosing at week 52. Red boxes in (B) indicate patients who rapidly achieved dosing every 16 weeks at week 32 and were maintained on this interval at week 52; yellow boxes indicate patients who had already successfully completed a full 16-week dosing cycle at week 52; purple boxes indicate patients who never had their dosing interval extended beyond every 4 weeks up to week 52. (C) Results are based on a MMRM analysis of the intention-to-treat population, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (<64 *vs* ≥64 ETDRS letters), previous intravitreal anti-VEGF therapy (yes *vs* no), and region (USA and Canada, Asia, and rest of the world). Treatment policy strategy was applied to non-COVID-19-related intercurrent events and hypothetical strategy was applied to COVID-19-related intercurrent events. Missing data were implicitly imputed by the MMRM. Error bars represent 95·04% CI. BCVA=best-corrected visual acuity. CST=central subfield thickness. ETDRS=Early Treatment Diabetic Retinopathy Study. MMRM=mixed model for repeated measures. PTI=personalised treatment interval. VEGF=vascular endothelial growth factor. *Adjusted mean (95·04% CI) CST change from baseline at 1 year, averaged over weeks 48, 52, and 56 (primary endpoint visits).

macular oedema (CST <325 µm) up to week 56 versus aflibercept (figure 4). In CMH-weighted estimates, 77–87% of the faricimab every-8-week group and 80–82% of the faricimab PTI group in YOSEMITE achieved absence of diabetic macular oedema at weeks 48–56, versus 64–71% of the aflibercept every-8-week group. Corresponding proportions in RHINE were 85–90% in the faricimab every-8-week group and 83–87% in the faricimab PTI group versus 71–77% in the aflibercept every-8-week group.

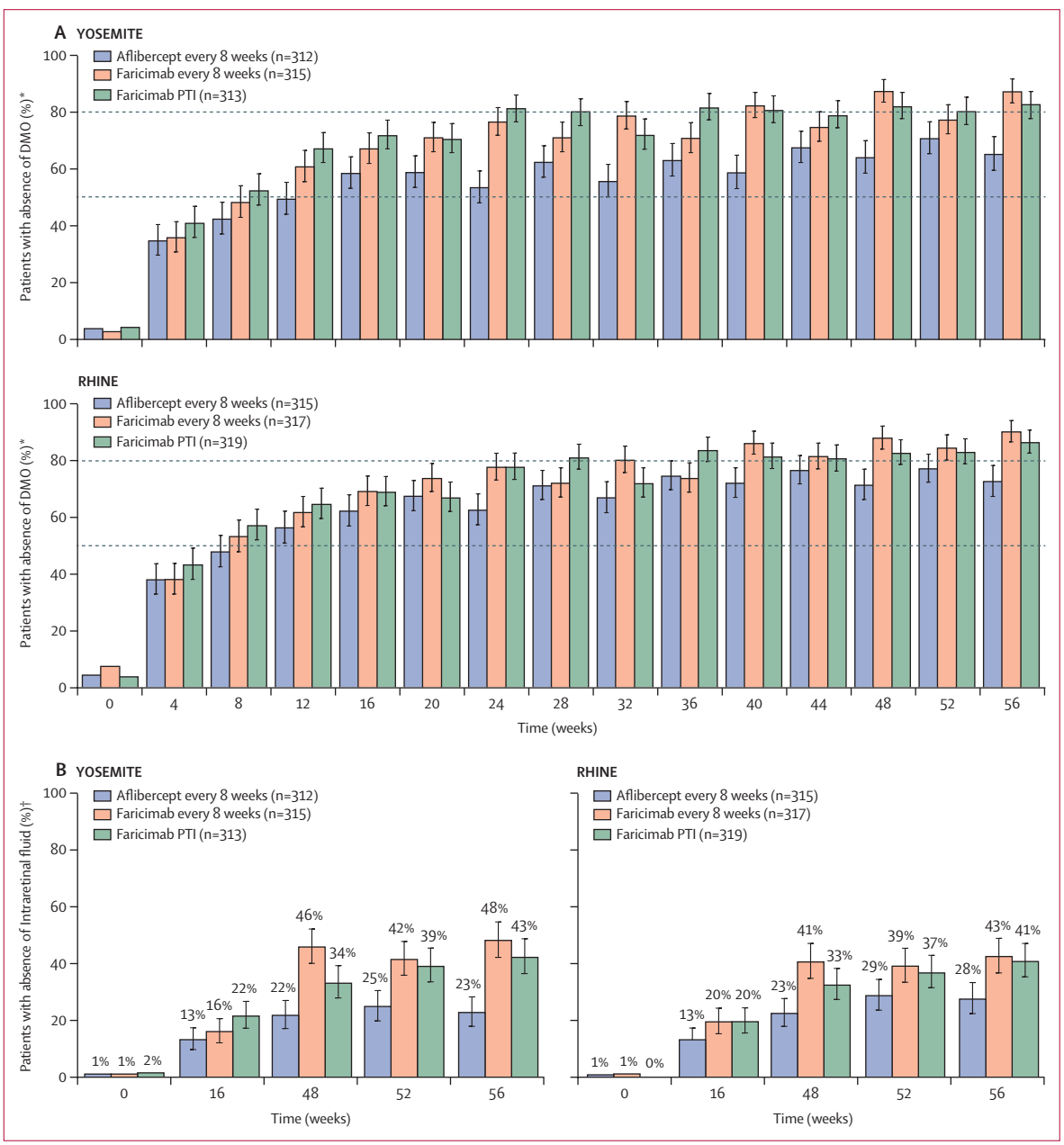

Figure 4: **Proportion of patients with absence of DMO (A) and intraretinal fluid (B) up to week 56 of YOSEMITE and RHINE**
Weighted proportions were estimated for the intention-to-treat population using the CMH method, stratified by baseline BCVA (<64 *vs* ≥64 ETDRS letters), previous intravitreal anti-VEGF therapy (yes *vs* no), and region (USA and Canada *vs* Asia and rest of the world combined). Weighted proportions for the aflibercept every-8-weeks groups are presented for the faricimab every 8 weeks versus aflibercept every 8 weeks comparison. Baseline values (defined as the last available measurement obtained on or before randomisation) are based on observed data. Treatment policy strategy was applied to non-COVID-19-related intercurrent events and hypothetical strategy was applied to COVID-19-related intercurrent events. Missing data were not imputed. Error bars represent 95·04% CI; estimates less than 0% were imputed as 0% and estimates more than 100% were imputed as 100%. BCVA=best-corrected visual acuity. CMH=Cochran-Mantel-Haenszel. CST=central subfield thickness. DMO=diabetic macular oedema. ETDRS=Early Treatment Diabetic Retinopathy Study. PTI=personalised treatment interval. VEGF=vascular endothelial growth factor. *Absence of DMO 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. †Intraretinal fluid was measured in the central 1-mm diameter of the ETDRS grid.

	YOSEMITE (N=937)			RHINE (N=950)		
	Faricimab every 8 weeks (n=313)	Faricimab PTI (n=313)	Aflibercept every 8 weeks (n=311)	Faricimab every 8 weeks (n=317)	Faricimab PTI (n=319)	Aflibercept every 8 weeks (n=314)
Summary of adverse events						
Total number of adverse events*	1062	1016	938	1107	875	914
Total number of serious adverse events*	171	114	96	101	79	95
Patients with ≥1 ocular adverse event†	98 (31%)	106 (34%)	102 (33%)	137 (43%)	119 (37%)	113 (36%)
Patients with ≥1 ocular serious adverse event†	6 (2%)	9 (3%)	2 (1%)	9 (3%)	10 (3%)	6 (2%)
Patients with ≥1 non-ocular adverse event	204 (65%)	210 (67%)	203 (65%)	189 (60%)	175 (55%)	187 (60%)
Patients with ≥1 non-ocular serious adverse event	75 (24%)	64 (20%)	50 (16%)	52 (16%)	39 (12%)	52 (17%)
Patients with ≥1 treatment-related ocular adverse event†	11 (4%)	8 (3%)	5 (2%)	8 (3%)	8 (3%)	14 (4%)
Patients with ≥1 treatment-related ocular serious adverse event†	0	4 (1%)	0	0	1 (<1%)	0
Patients with ≥1 ocular adverse event of special interest†‡	6 (2%)	8 (3%)	1 (<1%)	9 (3%)	9 (3%)	5 (2%)
Intraocular inflammation events†§						
Patients with ≥1 intraocular inflammation event	5 (2%)	7 (2%)	3 (1%)	3 (1%)	2 (1%)	1 (<1%)
Anterior chamber inflammation	0	1 (<1%)	0	0	0	0
Chorioretinitis	0	1 (<1%)	0	0	0	0
Iridocyclitis	2 (1%)	1 (<1%)	0	0	1 (<1%)	0
Iritis	0	3 (1%)	1 (<1%)	2 (1%)	0	1 (<1%)
Keratic precipitates	0	1 (<1%)	0	0	0	0
Keratouveitis	0	1 (<1%)	0	0	0	0
Uveitis	2 (1%)	3 (1%)	0	0	1 (<1%)	0
Vitritis	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	0	0
Ocular serious adverse events associated with intravitreal anti-VEGF therapy†¶						
Endophthalmitis	0	2 (1%)	0	2 (1%)	0	1 (<1%)
Intraocular pressure increased	0	0	0	0	1 (<1%)	0
Retinal tear	0	1 (<1%)	0	0	1 (<1%)	0
Rhegmatogenous retinal detachment	1 (<1%)	0	0	0	0	0
Traumatic cataract	0	0	0	0	0	0
Retinal vasculitis or occlusive events†						
Retinal vasculitis	0	0	0	0	0	0
Retinal vein occlusion	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Retinal artery occlusion	0	0	1 (<1%)	0	0	0
Retinal artery embolism	0	0	0	0	0	1 (<1%)
APTC events‖						
Patients with ≥1 APTC event	9 (3%)	10 (3%)	9 (3%)	4 (1%)	2 (1%)	5 (2%)
Non-fatal myocardial infarction	4 (1%)	2 (1%)	4 (1%)	0	0	2 (1%)
Non-fatal stroke	3 (1%)	2 (1%)	3 (1%)	1 (<1%)	2 (1%)	1 (<1%)
Death	2 (1%)	6 (2%)	2 (1%)	3 (1%)	0	2 (1%)

Data are n or n (%). Includes adverse events with onset up to day 405 (last day of week 56 analysis visit window); percentages are based on n values in the column headings. Multiple occurrences of the same adverse event in one individual are counted only once, except for the "Total number of events" rows, in which multiple occurrences of the same adverse event are counted separately. APTC=Anti-Platelet Trialists' Collaboration. BCVA=best-corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. PTI=personalised treatment interval. VEGF=vascular endothelial growth factor. *Total number of adverse events and serious adverse events includes non-ocular events and ocular events in the study or fellow eye. †Ocular adverse events in the study eye only are presented. ‡Ocular adverse events of special interest were defined as events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with BCVA loss of 30 ETDRS letters or more for more than 1 h. A full list of ocular adverse events of special interest is provided in the appendix (p 25). §Includes serious and non-serious intraocular inflammation events; excludes endophthalmitis events. Most intraocular inflammation events occurred after the initial every-4-week dosing phase for each treatment group, and approximately 4–6 weeks after the most recent dose of faricimab or aflibercept. ¶A full list of ocular serious adverse events is provided in the appendix (pp 23–24). ‖APTC events were externally adjudicated; all other events were investigator reported.

Table 2: **Summary of key adverse events up to week 56 of YOSEMITE and RHINE (safety analysis population)**

More faricimab-treated versus aflibercept-treated patients in YOSEMITE and RHINE achieved absence of intraretinal fluid up to week 56 (figure 4). In YOSEMITE, weighted proportions of patients with absence of intraretinal fluid at weeks 48–56 were greater for those receiving faricimab every 8 weeks (42–48%) and PTI (34–43%) versus aflibercept every 8 weeks (22–25%). These results were reproducible in RHINE (39–43% in the faricimab every-8-week group and 33–41% in the faricimab PTI group *vs* 23–29% in the aflibercept every-8-week group). Absence of subretinal fluid was observed in 61–69% of patients across treatment groups and trials at baseline; weighted proportions increased to near 100% for all groups at week 16 and were maintained up to week 56 (appendix p 21).

Rates of at least two-step ETDRS-DRSS improvement from baseline at week 52 were consistent across faricimab treatment groups and reproducible across trials (appendix p 22). In CMH-weighted estimates, the proportion of patients who achieved at least two-step ETDRS-DRSS improvement at week 52 of YOSEMITE was 46·0% (97·52% CI 38·8–53·1) with faricimab every 8 weeks, 42·5% (35·5–49·5) with faricimab PTI, and 35·8% (29·1–42·5) with aflibercept every 8 weeks. Corresponding estimates in RHINE were 44·2% (37·1–51·4) in the faricimab every-8-week group, 43·7% (36·8–50·7) in the faricimab PTI group, and 46·8% (39·8–53·8) in the aflibercept every-8-week group.

Key ocular and non-ocular adverse events reported up to week 56 are summarised in table 2 and the appendix (pp 23–27). Overall, faricimab was well tolerated, with an acceptable safety profile comparable with aflibercept. Incidence of ocular events in the study eye was similar between patients receiving faricimab every 8 weeks (YOSEMITE n=98 [31%], RHINE n=137 [43%]), faricimab PTI (n=106 [34%], n=119 [37%]), and aflibercept every 8 weeks (n=102 [33%], n=113 [36%]); most of these events were mild or moderate in severity, and common ocular events (>2% in any group) were generally balanced across treatment groups. Serious ocular events were also comparable between patients receiving faricimab every 8 weeks (YOSEMITE n=6 [1·9%], RHINE n=9 [2·8%]), faricimab PTI (n=9 [2·9%], n=10 [3·1%]), and aflibercept every 8 weeks (n=2 [0·6%], n=6 [1·9%]), and numerical differences across treatment groups do not appear to be clinically meaningful (appendix pp 23–24). Non-ocular and Anti-Platelet Trialists' Collaboration events were generally similar between trials and treatment groups.

Rates of intraocular inflammation events were low across both trials (table 2). Incidence of intraocular inflammation was numerically greater among patients receiving faricimab every 8 weeks (YOSEMITE n=5 [1·6%], RHINE n=3 [0·9%]) and faricimab PTI (n=7 [2·2%], n=2 [0·6%]) versus aflibercept every 8 weeks (n=3 [1·0%], n=1 [0·3%]). All events except three in YOSEMITE were mild or moderate in severity. Two cases of severe uveitis were reported in the faricimab PTI group and led to treatment withdrawal: one patient with uveitis and keratic precipitates associated with BCVA loss of 30 ETDRS or more letters, and one patient with uveitis and chorioretinitis associated with BCVA loss of 15 ETDRS or more letters. One case of severe vitritis was reported in the faricimab every-8-week group and led to treatment withdrawal; this event was not associated with BCVA loss and had resolved by week 56. All intraocular inflammation events except two in YOSEMITE (iridocyclitis in the faricimab every-8-week group; keratic precipitates in the faricimab PTI group described above) had resolved or were resolving at week 56.

Discussion

Primary 1-year data from YOSEMITE and RHINE showed that faricimab every 8 weeks or PTI offered non-inferior vision gains versus aflibercept every 8 weeks, improved anatomical outcomes, and extended durability with dosing up to every 16 weeks. These findings highlight the potential for faricimab, via its novel mechanism of dual Ang-2 and VEGF-A pathway inhibition, to address a significant unmet need for durable therapies that optimise real-world outcomes.[29]

YOSEMITE and RHINE each met their primary efficacy endpoint of non-inferiority, reproducibly demonstrating rapid and sustained vision gains with faricimab every 8 weeks or PTI that were comparable with aflibercept every 8 weeks at 1 year. For the PTI groups, non-inferiority was achieved with fewer interval-determining visits (ie, dosing visits from which CST and BCVA were used to inform treatment intervals) and extended dosing, with more than 50% of patients receiving faricimab every 16 weeks at week 52 and more than 70% receiving faricimab every 12 weeks or longer. This durability of treatment effect has not previously been reported in a phase 3 diabetic macular oedema trial. Furthermore, the PTI algorithm is the first individualised treatment regimen for diabetic macular oedema to be assessed in a prespecified, double-masked manner, and was designed to test the durability of faricimab using a standardised method based on anti-VEGF treatment patterns in clinical practice. Overall, data from the PTI groups highlight the potential for faricimab, with individualised dosing up to every 16 weeks, to reduce treatment burden while maintaining efficacy, and to close the patient outcome gap between clinical trials and current clinical practice.[11–13]

Findings from the American Society of Retina Specialists 2020 Preferences and Trends survey[29] indicate that aflibercept is a commonly used and effective anti-VEGF agent for retinal fluid resolution. In YOSEMITE and RHINE, non-inferior vision gains with faricimab every 8 weeks or PTI coincided with CST reductions that

exceeded aflibercept every 8 weeks at 1 year. Moreover, absence of diabetic macular oedema and absence of intraretinal fluid up to week 56 were achieved by a greater proportion of faricimab-treated patients versus aflibercept. Together, these data support the hypothesis that dual pathway inhibition via Ang-2 and VEGF-A blockade promotes vascular stability beyond VEGF inhibition alone. Robust fluid resolution with faricimab likely enabled extended dosing in the PTI groups, given that individualised treatment decisions in YOSEMITE and RHINE were primarily guided by CST findings.

The proportion of patients with at least two-step ETDRS-DRSS improvement at week 52 was consistent and reproducible across faricimab groups in YOSEMITE and RHINE (43–46%), whereas results for the aflibercept every-8-week groups differed numerically between trials (YOSEMITE 36%, RHINE 47%). Year 2 of YOSEMITE and RHINE will further explore whether dual Ang-2 and VEGF-A pathway inhibition with faricimab might improve diabetic retinopathy severity beyond what is achievable with VEGF inhibition alone.

Overall, faricimab was well tolerated, with an acceptable safety profile comparable with aflibercept. The incidence of adverse events up to week 56 was comparable across treatment groups, and ocular events in the study eye were mostly mild or moderate in severity and consistent with intravitreal anti-VEGF therapy for diabetic macular oedema.[27,30] Rates of intraocular inflammation were low (1·3% for faricimab-treated patients and 0·6% for aflibercept-treated patients), most of these events were mild or moderate in severity, and the majority had resolved or were resolving at week 56.

YOSEMITE and RHINE compared the efficacy of faricimab every 8 weeks or PTI with aflibercept every 8 weeks per its globally aligned label,[27] representing a well established and effective comparator against which to test non-inferiority. Due to the registrational nature of the trials and no globally approved nor uniformly practiced extended dosing regimen for aflibercept, one limitation is that YOSEMITE and RHINE were not designed to assess the head-to-head durability of faricimab versus aflibercept. Although this article presents clinically relevant outcomes at the time of the primary endpoint analysis, another limitation is the relatively short follow-up period of 1 year. For example, the earliest timepoint that the faricimab PTI groups could achieve dosing every 16 weeks was week 32, which consequently limited the number of 16-week dosing cycles possible up to week 52. Although 1-year outcomes should be interpreted with appropriate caution, long-term data from YOSEMITE and RHINE and the RHONE-X open-label extension study (NCT04432831) will be available to elucidate the ongoing efficacy, durability, and safety of faricimab in patients with diabetic macular oedema.

To our knowledge, YOSEMITE and RHINE represent the largest registrational study programme conducted to date in diabetic macular oedema; however, the COVID-19 pandemic threatened to negatively impact trial participants, study conduct, and data integrity. In response, several mitigation strategies were implemented to minimise risks to data collection (eg, prioritising assessment of critical safety and primary endpoints to ensure continuity of care), and sensitivity and supplemental analyses were done to test the robustness of the primary results. Collectively, these measures ensured that efficacy and safety data were interpretable amid the COVID-19 pandemic, and the benefit–risk profile of faricimab could be conclusively established.

In conclusion, primary 1-year results from the phase 3 YOSEMITE and RHINE trials showed that dual Ang-2 and VEGF-A pathway inhibition with faricimab, the first bispecific antibody designed for intraocular use, offered non-inferior vision gains and improved anatomical outcomes versus aflibercept, which were achievable with adjustable dosing up to every 16 weeks. The PTI algorithm was designed to address the need for a standardised approach to individualised therapy in clinical practice, and showed the potential for faricimab to achieve and maintain optimal treatment outcomes with extended dosing intervals. Year 2 of YOSEMITE and RHINE and the RHONE-X extension study will allow the efficacy, durability, and safety of faricimab to be studied over 4 years in total, and might elucidate differential roles of Ang-2 and VEGF-A pathway inhibition on long-term vascular stability. In light of the present data and its novel mechanism of action, faricimab might herald an important shift towards multitargeted treatment strategies for patients with diabetic macular oedema.

Contributors

FA, KB, ZH, HL, DS, and JRW participated in the design of the study. CCW, DAE, AL, IAP, TS, PGS, JKS, JAW, and RT participated in advisory committees and as study investigators. FA, APA, KB, ZH, HL, SM, DS, and JRW provided study oversight. CCW, FA, KB, DAE, ZH, HL, AL, SM, IAP, TS, PGS, DS, JKS, JAW, JRW, and RT participated in data acquisition or research execution, or both. All authors participated in the analysis or interpretation of the data, or both. FA, KB, ZH, HL, SM, DS, and JRW vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. All authors participated in the drafting and critical review of the study manuscript. All authors had full access to the study data and accept responsibility to submit the manuscript for publication.

Declaration of interests

CCW reports research support from Adverum, Aerie, Aldeyra, Alimera, Allergan, Amgen, Apellis, AsclepiX, Bayer, Boehringer Ingelheim, Chengdu Kanghong, Clearside, Gemini, Genentech, Graybug Vision, Gyroscope, Ionis, iRenix Medical, Iveric Bio, Kodiak, Lowy Medical Research Institute, Neurotech, NGM Bio, Novartis, Oxurion, RecensMedical, Regeneron, Regenxbio, Roche, SamChunDang Pharm, Samsung Bioepis, Taiwan Liposome Company, and Xbrane BioPharma, outside the submitted work. CCW reports consulting fees from Adverum, Aerie, Aerpio, Allergan, Allgenesis, Apellis, Arrowhead, Bausch and Lomb, Bayer, Bionic Vision Technologies, Chengdu Kanghong, Clearside, EyePoint, Genentech, Gyroscope, Iveric Bio, Janssen, Kato, Kodiak, Long Bridge Medical, NGM Bio, Novartis, OccuRx, Ocular Therapeutix, ONL Therapeutics, Opthea, Oxurion, Palatin, PolyPhotonix, RecensMedical, Regeneron, Regenxbio, Roche, Santen, Surrozen, Takeda, Verana Health, and Vitranu, outside the

submitted work. CCW reports other personal fees from Regeneron, stock or stock options from ONL Therapeutics, PolyPhotonix, RecensMedical, and Visgenx, and has served on advisory boards for Kato, outside the submitted work. CCW has served as a board member of the American Society of Retina Specialists and the Vit-Buckle Society, outside the submitted work. FA is an employee of Genentech. APA was an employee of Genentech during the course of this study and reports stock or stock options from Roche. KB was an employee of Genentech during the course of this study and is a current employee of Roche Products (Ireland). DAE reports research support from Alkahest, AsclepiX, Bayer, Chengdu Kanghong, EyePoint, Gemini, Genentech, Gyroscope, Ionis, Iveric Bio, Kodiak, Mylan, NGM Bio, Novartis, Ocular Therapeutix, Opthea, RecensMedical, Regeneron, and Regenxbio, outside the submitted work. DAE reports consulting fees from Alimera, Allergan, Apellis, Bausch and Lomb, Dutch Ophthalmic, EyePoint, Genentech, Gyroscope, Iveric Bio, KKR, Kodiak, Notal Vision, Novartis, RecensMedical, Regeneron, and Regenxbio, outside the submitted work. DAE reports other personal fees from Allergan, Apellis, Bayer, Dutch Ophthalmic, EyePoint, Genentech, and Novartis; stock or stock options from Boston Image Reading Center, Clearside, Hemera, and Network Eye; and has served on advisory boards for Genentech, Iveric Bio, and RecensMedical, outside the submitted work. DAE has served as a board member of the Florida Society of Ophthalmology, outside the submitted work. ZH is an employee of Genentech, and reports stock or stock options from Genentech. HL is an employee of Genentech, reports personal fees and stock or stock options from Roche/Genentech, and is a coauthor on patent application WO202123804 involving the PTI algorithm. AL reports research support from Notal Vision and Novartis, and consulting fees from Allergan, Bayer, Beyeonics Surgical, and Syneos Health, outside the submitted work. SM is an employee of Genentech, and reports stock or stock options from Genentech. IAP reports consulting and other personal fees from Allergan, Bayer, Novartis, and Roche, and has served on advisory boards for Bayer, Novartis, and Roche, outside the submitted work. TS reports research support from Bayer, Chugai, Novartis, Santen, and Senju; consulting and other personal fees from Bayer, Novartis, and Senju; and has served on advisory boards for Bayer, Novartis, and Roche, outside the submitted work. PGS reports personal fees and has served on advisory boards for Roche, outside the submitted work. DS is an employee of Roche Products, reports personal fees and stock or stock options from Roche, and is a coauthor on patent application WO202123804 involving the PTI algorithm. JKS reports research support from Boehringer Ingelheim, Jaeb Center for Health Research, Juvenile Diabetes Research Foundation, KalVista, Novartis, Optovue, and Physical Sciences; personal fees from Merck, Novartis, and Novo Nordisk; and equipment loans from Adaptive Sensory Technology, Boston Micromachines, and Optovue, outside the submitted work. JAW reports research support from Adverum, Alimera, Bayer, Clover Therapeutics, Genentech, Iveric Bio, Kodiak, Lowy Medical Research Institute, NIH National Eye Institute, Neurotech, Opthea, and Regeneron, and consulting fees from Genentech, outside the submitted work. JRW is an employee of Genentech, reports stock or stock options from Genentech, and is a coauthor on patent application WO202123804 involving the PTI algorithm. RT reports consulting and personal fees and has served on advisory boards for AbbVie, Alcon, Allergan, Apellis, Bayer, Chengdu Kanghong, Genentech, Iveric Bio, Novartis, Oculis, Roche, and Thea, and reports equipment from Zeiss, outside the submitted work.

Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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