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## **Faricimab Treat-and-Extend for Diabetic Macular Edema: 2-Year Results from the Randomized Phase 3 YOSEMITE and RHINE Trials**

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## 1 Faricimab Treat-and-Extend for Diabetic Macular Edema: 2-Year 2 Results from the Randomized Phase 3 YOSEMITE and RHINE Trials

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124 **Running Head:** 2-Year Efficacy, Durability, and Safety of Faricimab in DME

125  
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132 **Abbreviations and Acronyms:**

133 **AE** = adverse event; **Ang** = angiopoietin; **BCVA** = best-corrected visual acuity; **CMH** =  
134 Cochran-Mantel-Haenszel; **CI** = confidence interval; **CST** = central subfield thickness; **DME** =  
135 diabetic macular edema; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early  
136 Treatment Diabetic Retinopathy Study; **IRF** = intraretinal fluid; **ITT** = intention-to-treat; **MMRM** =  
137 mixed model for repeated measures; **OCT** = optical coherence tomography; **Q4W** = every 4  
138 weeks; **Q8W** = every 8 weeks; **Q12W** = every 12 weeks; **Q16W** = every 16 weeks; **SD** =  
139 standard deviation; **VEGF** = vascular endothelial growth factor.

140 This article contains additional online-only material. The following should appear online-only:  
141 Figures S4, S6, S8, S10, S12, and S14 and Tables S1, S2, S3, S5, S6, S7, and S8.

142

143 **Keywords:** Angiopoietin-2, Diabetic macular edema, Faricimab, Vascular endothelial growth  
144 factor-A, Vascular stability.

Journal Pre-proof

145 **Abstract**

146 **Purpose:** To evaluate the 2-year efficacy, durability, and safety of dual angiopoietin-  
147 2/vascular endothelial growth factor (VEGF)-A pathway inhibition with intravitreal faricimab  
148 according to a personalized treat-and-extend–based regimen (T&E) with up to every-16-week  
149 (Q16W) dosing in the YOSEMITE/RHINE (NCT03622580/NCT03622593) phase 3 trials of  
150 diabetic macular edema (DME).

151 **Design:** Randomized, double-masked, noninferiority phase 3 trials.

152 **Participants:** Adults with visual acuity loss due to center-involving DME.

153 **Methods:** Patients were randomized 1:1:1 to faricimab 6.0 mg Q8W, faricimab 6.0 mg  
154 T&E (previously referred to as personalized treatment interval), or aflibercept 2.0 mg Q8W. The  
155 T&E up to Q16W dosing regimen was based on central subfield thickness (CST) and best-  
156 corrected visual acuity (BCVA) change.

157 **Main Outcome Measures:** Included changes from baseline in BCVA and CST, number  
158 of injections, durability, absence of fluid, and safety through week 100.

159 **Results:** In YOSEMITE/RHINE (N=940/951), noninferior year 1 visual acuity gains were  
160 maintained through year 2; mean BCVA change from baseline at 2 years (weeks 92/96/100  
161 average) with faricimab Q8W (YOSEMITE/RHINE, +10.7/+10.9 letters) or T&E (+10.7/+10.1  
162 letters) were comparable with aflibercept Q8W (+11.4/+9.4 letters). The median number of study  
163 drug injections was lower with faricimab T&E (YOSEMITE/RHINE, 10/11 injections) versus  
164 faricimab Q8W (15 injections) and aflibercept Q8W (14 injections) across both trials during the  
165 entire study. In the faricimab T&E arms, durability was further improved during year 2, with  
166 >60% of patients on Q16W dosing and ~80% on  $\geq$ Q12W dosing at week 96. Almost 80% of  
167 patients who achieved Q16W dosing at week 52 maintained Q16W dosing without an interval  
168 reduction through week 96. Mean CST reductions were greater, and more patients achieved  
169 absence of DME (CST <325 $\mu$ m) and absence of intraretinal fluid with faricimab Q8W or T&E

170 versus aflibercept Q8W through year 2. Overall, faricimab was well tolerated, with a safety  
171 profile comparable to aflibercept.

172 **Conclusions:** Clinically meaningful visual acuity gains from baseline, anatomic  
173 improvements, and extended durability with intravitreal faricimab up to Q16W were maintained  
174 through year 2. Faricimab given as a personalized T&E-based dosing regimen supports the role  
175 of dual angiopoietin-2/VEGF-A inhibition to promote vascular stability and provide durable  
176 efficacy for patients with DME.

Journal Pre-proof

177 Over the past decade, intravitreal anti-vascular endothelial growth factor (VEGF) therapy  
178 has become the standard of care for patients with center-involving diabetic macular edema  
179 (DME) with visual impairment.<sup>1-3</sup> However, studies frequently show that the efficacy associated  
180 with anti-VEGF therapies in clinical trials are not achieved nor maintained in real-world clinical  
181 practices.<sup>4-9</sup> Suboptimal real-world outcomes may be attributed to undertreatment associated  
182 with the burden of frequent monitoring visits and injections, and heterogeneity in anti-VEGF  
183 treatment response across patient populations.<sup>9, 10</sup> Concurrently, it is increasingly clear that the  
184 pathophysiology of DME involves multiple biologic pathways<sup>3, 11</sup>; therefore, multi-targeted  
185 treatment strategies may address additional sequela that can develop in patients treated with  
186 anti-VEGF therapy, and have the potential to improve durability and outcomes beyond targeting  
187 the VEGF pathway alone.

188 The angiotensin (Ang)-1/Tie2 signaling pathway is a key regulator of vascular stability and  
189 controls vessel permeability, inflammation, and angiogenic responses.<sup>12, 13</sup> Under homeostatic  
190 conditions, the agonistic ligand Ang-1 binds to and activates Tie2, leading to downstream  
191 signaling that maintains vascular stability by promoting endothelial cell survival, pericyte  
192 recruitment, and improved endothelial barrier function.<sup>12, 13</sup> In DME and other retinal vascular  
193 diseases, Ang-2 is upregulated and acts as a competitive antagonist of Ang-1, binding to Tie2  
194 and disrupting the vascular stabilization effects of Ang-1/Tie2 signaling, resulting in vascular  
195 permeability, instability, and remodeling.<sup>12-15</sup> Elevated levels of Ang-2 promotes retinal vessel  
196 sensitivity to proinflammatory mediators and the angiogenic effects of VEGF,<sup>15-19</sup> and drives  
197 inflammation by inducing expression of intercellular adhesion molecule-1 and vascular cell  
198 adhesion molecule-1, which leads to leukocyte adhesion and transmigration.<sup>20</sup> Independently of  
199 Tie2, Ang-2 can have direct proangiogenic effects by signaling through integrins to promote  
200 vascular destabilization and apoptosis of pericytes and astrocytes.<sup>21-24</sup> Faricimab was designed  
201 as a novel bispecific antibody for intraocular use that binds and neutralizes both Ang-2 and  
202 VEGF-A.<sup>25</sup> Data from proof of concept phase 2 and confirmatory phase 3 clinical trials across 3



203 retinal indications (DME, neovascular age-related macular degeneration, and retinal vein  
204 occlusion) supported the hypothesis that dual Ang-2/VEGF-A pathway inhibition with faricimab  
205 may promote vascular stability, extend treatment durability (yet to be confirmed for retinal vein  
206 occlusion), and optimize outcomes for these retinal diseases.<sup>26-31</sup>

207 The phase 3 YOSEMITE and RHINE randomized active-controlled trials evaluated faricimab  
208 treatment for DME (N=1891). Patients with DME received intravitreal faricimab every 8 weeks  
209 (Q8W), faricimab according to a personalized treat-and-extend-based regimen (T&E) with  
210 dosing extended up to every 16 weeks (Q16W), or aflibercept 2.0 mg Q8W over 2 years.<sup>31, 32</sup> At  
211 1 year, YOSEMITE and RHINE each met their primary endpoint; adjusted mean best-corrected  
212 visual acuity (BCVA) changes from baseline with faricimab Q8W and T&E up to Q16W dosing  
213 ranged between 10.8 and 11.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters  
214 and were noninferior to aflibercept Q8W.<sup>31</sup> Secondary endpoints at year 1 also showed greater  
215 anatomical benefits with faricimab Q8W and faricimab T&E compared with aflibercept Q8W;  
216 central subfield thickness (CST) reductions were greater with faricimab versus aflibercept at 1  
217 year, and more faricimab-treated patients achieved absence of protocol-defined DME (CST  
218 <325 µm) and absence of intraretinal fluid (IRF) compared with aflibercept over time.<sup>31</sup>  
219 Importantly, in the faricimab T&E up to Q16W dosing arms, clinically significant visual acuity  
220 gains and anatomic improvements were achieved with extended dosing; >70% of patients were  
221 extended to every-12-week (Q12W) or longer dosing and >50% were extended to Q16W dosing  
222 at week 52.<sup>31</sup> Faricimab was well tolerated through year 1 with a safety profile comparable to  
223 aflibercept, and no cases of retinal vasculitis or occlusive retinal vasculitis reported.<sup>31</sup>

224 The year 1 data from YOSEMITE and RHINE, the largest DME program ever conducted,  
225 suggest that dual Ang-2/VEGF-A pathway inhibition with faricimab in DME may confer anatomic  
226 and durability advantages over VEGF inhibition alone.<sup>31</sup> To evaluate the longer-term efficacy,  
227 durability, and safety of faricimab in patients with DME, we herein report 2-year results from the  
228 phase 3 YOSEMITE and RHINE trials.

229

## 230 **Methods**

### 231 **YOSEMITE and RHINE**

232 The study design, rationale, and primary 1-year results of YOSEMITE and RHINE are described  
233 in detail elsewhere.<sup>31, 32</sup> In brief, YOSEMITE (Clinicaltrials.gov identifier NCT03622580) and  
234 RHINE (NCT03622593) were identically designed, randomized, double-masked, active  
235 comparator-controlled, phase 3 trials conducted across 353 study sites in 31 participating  
236 countries. YOSEMITE and RHINE adhered to the International Council for Harmonization E6  
237 Guideline for Good Clinical Practice, tenets of the Declaration of Helsinki, US Food and Drug  
238 Administration regulations, European Union Clinical Trials Directive (2001/20/EC), and  
239 applicable local, state, and federal laws. Institutional Review Board (IRB)/Ethics Committee  
240 approval was obtained for study protocols as appropriate, and all patients provided written  
241 informed consent to participate.

242 Patients eligible for inclusion were aged  $\geq 18$  years and had center-involving DME  
243 secondary to diabetes (Type 1 or 2), defined as CST  $\geq 325$   $\mu\text{m}$  (measured as the average  
244 thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm  
245 diameter of the ETDRS grid) and BCVA 25–73 ETDRS letters (approximate Snellen equivalent,  
246 20/320–20/40). Full eligibility criteria for YOSEMITE and RHINE are reported in the primary trial  
247 publication.<sup>31</sup> One eye per patient was designated the study eye; if both eyes were eligible, the  
248 eye with worse BCVA at screening was selected. Previously anti-VEGF–treated eyes (last  
249 treated  $\geq 3$  months before day 1) were eligible for inclusion but limited to 25% of total enrolment.

250 Patients were randomized 1:1:1 to intravitreal faricimab 6.0 mg Q8W after 6 initial every-  
251 4-week (Q4W) doses, intravitreal faricimab 6.0 mg T&E with up to Q16W dosing intervals after  
252  $\geq 4$  initial Q4W doses, or intravitreal aflibercept Q8W after 5 initial Q4W doses. Aflibercept Q8W  
253 dosing was selected to align with the approved aflibercept label, in the absence of a globally

254 accepted extended dosing regimen.<sup>33-35</sup> The T&E regimen is a personalized treat-and-extend–  
255 based dosing regimen that allowed adjustable dosing (from Q4W up to Q16W) based on  
256 protocol prespecified CST and BCVA criteria at active dosing visits.<sup>31, 32</sup> The personalized T&E  
257 regimen is commonly used clinically,<sup>36</sup> but in the registrational phase 3 trial setting was referred  
258 to as “personalized treatment interval”, as the regimen used an automated treatment algorithm  
259 driven by an interactive voice or web-based response system to determine whether a patient’s  
260 treatment interval should be reduced, maintained, or extended based on protocol pre-specified  
261 criteria.<sup>32</sup> Patients randomized to the faricimab T&E arms initially received faricimab at Q4W  
262 intervals until they first reached CST <325  $\mu\text{m}$  at or after week 12. Once achieved, treatment  
263 intervals were extended to an initial Q8W dosing, then could be maintained, extended by 4  
264 weeks (up to Q16W), or reduced by 4 weeks or 8 weeks (as low as Q4W) based on  
265 prespecified CST and BCVA criteria at active dosing visits (Fig 1). To maintain masking, all  
266 patients attended Q4W study visits where they received active treatment or sham up to week  
267 96; the final study visit was at week 100. For patients that received faricimab T&E, dosing  
268 interval decisions were made at active treatment visits only.

269 Key ocular assessments throughout the study period included BCVA, intraocular  
270 pressure, slit-lamp examination, indirect ophthalmoscopy, and retina imaging (spectral-domain  
271 optical coherence tomography [OCT], OCT-angiography [OCT-A] where available, color fundus  
272 photography [CFP], and fundus fluorescein angiography [FFA]) that were independently  
273 assessed at central reading centers (OCT and OCT-A: Duke Reading Center, Durham, NC;  
274 Vienna Reading Center, Austria; CFP and FFA: Wisconsin Reading Center, Madison, WI).

275

## 276 **Outcome Measures**

277 The primary efficacy endpoint of YOSEMITE and RHINE was change in BCVA from baseline at  
278 1 year, averaged over weeks 48, 52, and 56.<sup>31</sup> Two-year trial outcomes reported herein were  
279 consistent with prespecified endpoints in the primary analysis,<sup>31</sup> and included change in BCVA

280 from baseline at 2 years (defined as the average of weeks 92, 96, and 100) and over time; the  
281 proportion of patients in the faricimab T&E dosing arms on Q4W, Q8W, Q12W, or Q16W dosing  
282 intervals at week 96 and over time; change in CST from baseline at 2 years and over time; the  
283 proportion of patients with absence of DME (CST <325  $\mu\text{m}$  based on protocol-defined DME at  
284 screening) over time; the proportion of patients with absence of IRF over time (measured in the  
285 central 1 mm ETDRS circle); and the incidence and severity of ocular and nonocular adverse  
286 events (AEs) through study end. Other 2-year efficacy endpoints included the proportion of  
287 patients that gained BCVA ( $\geq 15$ ,  $\geq 10$ ,  $\geq 5$ , or  $\geq 0$  ETDRS letters) or avoided BCVA loss ( $\geq 15$ ,  $\geq 10$ ,  
288 or  $\geq 5$  ETDRS letters) at 2 years; patients that gained  $\geq 15$  ETDRS letters or achieved Snellen  
289 BCVA 20/20 or better ( $\geq 84$  ETDRS letters) at 2 years; patients with Snellen BCVA 20/40 or  
290 better ( $\geq 69$  ETDRS letters) at 2 years; and the proportion of patients with  $\geq 2$ -step improvement  
291 on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) at week 96.

292

### 293 **Statistical Analysis**

294 Two-year efficacy and safety analyses were performed as described in the primary 1-year trial  
295 publication.<sup>31</sup> Efficacy analyses were based on the intent-to-treat (ITT) population, grouped by  
296 treatment arm at randomization. Adjusted means for continuous endpoints were assessed using  
297 a mixed model for repeated measures (MMRM), with the same analysis method and data  
298 handling rules as described previously for the primary endpoint. In brief, the MMRM included  
299 change from baseline as the response variable, and categorical covariates of treatment group,  
300 visit, visit-by-treatment group interaction, baseline value for the response variable (continuous),  
301 study (YOSEMITE vs. RHINE; for the pooled cohort data only), and randomization stratification  
302 factors as fixed effects. The model assumed an unstructured covariance structure; missing data  
303 were implicitly imputed assuming a missing at random mechanism. For binary secondary  
304 endpoints, weighted proportions were estimated using the Cochran-Mantel-Haenszel (CMH)  
305 method stratified by baseline BCVA score (<64 letters vs.  $\geq 64$  letters), prior intravitreal anti-

306 VEGF therapy (yes vs. no), region (US and Canada, Asia, and the rest of the world), and study  
307 (YOSEMITE vs. RHINE; for the pooled cohort data only). For all MMRM and CMH analyses,  
308 intercurrent events related to the COVID-19 pandemic were handled using a hypothetical  
309 strategy where all values were censored after the intercurrent event, and non-COVID-19-  
310 related intercurrent events were handled using a treatment policy strategy where all observed  
311 values were used regardless of the intercurrent event. Adjusted means and weighted  
312 proportions are reported with 95.04% confidence intervals (CIs) for the individual trial data, to  
313 adjust for interim safety assessments conducted through to the completion of the primary  
314 analysis, and as 95% CIs for the pooled cohort data.<sup>31</sup> Post hoc hypothesis tests were  
315 performed to detect differences between faricimab and aflibercept treatment arms, with *P*-  
316 values presented for reference. The YOSEMITE/RHINE safety analysis population included all  
317 patients who received  $\geq 1$  dose of faricimab or aflibercept, grouped by actual treatment regimen  
318 received. Safety and tolerability were assessed through descriptive summaries of ocular and  
319 nonocular AEs (coded using Medical Dictionary for Regulatory Activities thesaurus terms),  
320 deaths, and ocular assessments through study end.

321

## 322 **Results**

### 323 **Patient Disposition**

324 A total of 940 and 951 patients were enrolled in YOSEMITE (September 2018 to September  
325 2019) and RHINE (October 2018 to September 2019), respectively.<sup>31</sup> One eye per patient was  
326 designated as the study eye. The ITT population of YOSEMITE included 315 patients  
327 randomized to faricimab Q8W, 313 patients randomized to faricimab T&E, and 312 patients  
328 randomized to aflibercept Q8W (Fig 2A). The ITT population of RHINE included 317 patients  
329 randomized to faricimab Q8W, 319 patients randomized to faricimab T&E, and 315 patients  
330 randomized to aflibercept Q8W (Fig 2B).

331 Overall, 84% of patients who received  $\geq 1$  dose of faricimab or aflibercept in YOSEMITE and  
332 87% of those in RHINE completed study treatment through week 100. The proportion of patients  
333 who discontinued study treatment and the reasons for discontinuation were generally balanced  
334 across treatment arms and trials (Fig 2). Major protocol deviations through study end were  
335 reported for 563 (60%) patients in YOSEMITE and 602 (63%) patients in RHINE (Table S1,  
336 available at [www.aaajournal.org](http://www.aaajournal.org)). The number, proportion of patients, and type of major protocol  
337 deviations through study end were consistent across treatment arms and trials. The majority of  
338 the major protocol deviations were procedural, such as selected missed visits (YOSEMITE: 308  
339 [33.0%] patients; RHINE: 328 [35.0%] patients) and issues with images of the study eye  
340 (YOSEMITE: 94 [10.0%] patients; RHINE: 139 [15.0%] patients). Among patients with major  
341 protocol deviations, 191 (20%) in YOSEMITE and 279 (29%) in RHINE reported  $\geq 1$  major  
342 protocol deviation related to COVID-19, most of whom missed  $\geq 1$  study visit around the primary  
343 endpoint and/or final study visits (167 [18%] and 210 [22%] patients, respectively). Of these,  
344 only 63 (6.7%) patients in YOSEMITE and 76 (8.0%) in RHINE missed  $\geq 1$  dose of study  
345 treatment around the primary endpoint visits, and 15 (1.6%) and 48 (5.0%) patients,  
346 respectively, missed  $\geq 1$  dose of study treatment around the final study visits.

347 As reported in the primary trial publication,<sup>31</sup> baseline patient characteristics in YOSEMITE  
348 and RHINE were generally well balanced across treatment arms and trials.

349

### 350 **Visual Acuity Outcomes**

351 YOSEMITE and RHINE reproducibly demonstrated visual gains with faricimab Q8W and T&E  
352 that were maintained over time through year 2 and were comparable with aflibercept Q8W,  
353 despite fewer treatment doses administered in the faricimab T&E arm (Fig 3). In YOSEMITE,  
354 adjusted mean BCVA change from baseline at 2 years (averaged over weeks 92, 96, and 100)  
355 was +10.7 ETDRS letters (95.04% CI, +9.4 to +12.1) in the faricimab Q8W arm and +10.7  
356 ETDRS letters (+9.4 to +12.1) in the faricimab T&E arm versus +11.4 ETDRS letters (+10.0 to

357 +12.7) in the aflibercept Q8W arm (mean difference vs. aflibercept Q8W, -0.7 ETDRS letters  
358 [-2.6 to +1.2] and -0.7 ETDRS letters [-2.5 to +1.2], respectively; nominal  $P > 0.05$  for both).  
359 Corresponding 2-year BCVA gains in RHINE were +10.9 ETDRS letters (+9.5 to +12.3) and  
360 +10.1 ETDRS letters (+8.7 to +11.5) versus +9.4 ETDRS letters (+7.9 to +10.8), respectively  
361 (mean difference vs. aflibercept Q8W, +1.5 ETDRS letters [-0.5 to +3.6] and +0.7 ETDRS  
362 letters [-1.3 to +2.7]; nominal  $P > 0.05$  for both). In the pooled YOSEMITE/RHINE cohort, 2-  
363 year BCVA gains were +10.8 ETDRS letters (+9.8 to +11.8) and +10.4 ETDRS letters (+9.4 to  
364 +11.4) in the faricimab Q8W and faricimab PTI arms, respectively, versus +10.3 ETDRS letters  
365 (+9.3 to +11.3) in the aflibercept Q8W arm (mean difference vs. aflibercept Q8W, +0.5 ETDRS  
366 letters [-0.9 to +1.8] and +0.1 ETDRS letters [-1.3 to +1.5]; nominal  $P > 0.05$  for both [Fig S4,  
367 available at [www.aaojournal.org](http://www.aaojournal.org)]). Sensitivity and supplemental analyses to test the robustness  
368 of these results were consistent across different methods for handling missing data and  
369 intercurrent events (Table S2, available at [www.aaojournal.org](http://www.aaojournal.org)). Additional 2-year BCVA  
370 endpoints were similarly consistent across treatment arms and reproducible across trials (Table  
371 S3, available at [www.aaojournal.org](http://www.aaojournal.org)).

372 In the safety analysis population, the median (mean [standard deviation (SD)]) number  
373 of study drug injections in each of the YOSEMITE and RHINE faricimab T&E arms was 8  
374 injections (YOSEMITE 8.4 [2.45], RHINE 8.7 [2.50]) in year 1 (baseline to week 56), compared  
375 with 10 injections in each of the faricimab Q8W (YOSEMITE 9.5 [1.41], RHINE 9.3 [1.52]) and  
376 aflibercept Q8W (YOSEMITE 9.2 [1.47], RHINE 9.3 [1.36]) arms. During year 2 (week 60 to  
377 week 96), the faricimab T&E arms received a median (mean [SD]) of 3 study drug injections  
378 (YOSEMITE 3.5 [1.76], RHINE 3.6 [1.98]), versus 5 injections in each of the faricimab Q8W  
379 (YOSEMITE 4.7 [0.74], RHINE 4.7 [0.82]) and aflibercept Q8W (YOSEMITE 4.5 [0.92], RHINE  
380 4.5 [0.99]) arms. From baseline during the entire study, the median (mean [SD]) number of  
381 study drug injections in the T&E arms was 10 (11.5 [3.98]) in YOSEMITE and 11 (12.1 [4.12]) in

382 RHINE, compared with 15 (YOSEMITE 13.6 [2.87], RHINE 13.5 [2.87]) in the faricimab Q8W  
383 arms and 14 (YOSEMITE 13.3 [2.75], RHINE 13.4 [2.66]) in the aflibercept Q8W arms.

384

### 385 **Durability Outcomes**

386 The durability of faricimab reported in the 1-year primary analysis<sup>31</sup> was further improved during  
387 year 2 of YOSEMITE and RHINE, with greater proportions of patients in the T&E arm extending  
388 their dosing while maintaining comparable visual acuity gains and greater anatomical benefits  
389 versus aflibercept (Fig 5). At week 96, 211 (78%) patients in the faricimab T&E arm of  
390 YOSEMITE and 224 (78%) patients in RHINE achieved  $\geq$ Q12W dosing intervals (557 patients  
391 [78%] in the pooled YOSEMITE/RHINE cohort), which included 162 (60%) and 185 (64%)  
392 patients, respectively, who achieved Q16W dosing (Fig 5A; pooled YOSEMITE/RHINE cohort,  
393 347 patients [62%] [Fig S6A, available at [www.aaajournal.org](http://www.aaajournal.org)]). Patient ability to achieve and/or  
394 maintain extended faricimab dosing intervals up to Q16W through week 96 is shown in the  
395 dosing interval schematic, which shows that in most patients who achieved Q12W or Q16W  
396 dosing at 1 year, it was possible to maintain and/or extend their dosing interval through year 2  
397 (Fig 5B; Fig S6B for the pooled YOSEMITE/RHINE cohort, available at [www.aaajournal.org](http://www.aaajournal.org)).  
398 Approximately 79% of patients who achieved  $\geq$ Q12W dosing at week 52 maintained  $\geq$ Q12W  
399 dosing without an interval reduction below Q12W through week 96 (YOSEMITE, 150 [75%]  
400 patients; RHINE, 172 [83%] patients). Similarly, 76% of patients that achieved Q16W dosing at  
401 week 52 maintained Q16W dosing without an interval reduction through week 96 (YOSEMITE,  
402 100 [70%] patients; RHINE, 121 [82%] patients). Approximately 18% of patients rapidly  
403 achieved Q16W dosing at week 32 (i.e., the earliest time point that Q16W dosing was possible  
404 due to the study design) and subsequently maintained Q16W dosing through week 96  
405 (YOSEMITE, 44 [16%] patients; RHINE, 58 [20%] patients). Conversely, <5% of patients  
406 extended to Q8W dosing at or after week 12, and then remained on Q8W or Q4W dosing  
407 through week 96 (YOSEMITE, 10 [4%] patients; RHINE, 16 [6%] patients). In approximately 4%



408 of patients it was not possible to extend the dosing interval beyond Q4W from baseline through  
409 week 96 (YOSEMITE, 7 [3%] patients; RHINE, 15 [5%] patients).

410

#### 411 **Anatomic Outcomes**

412 Overall, improved anatomic outcomes achieved with faricimab versus aflibercept at 1 year<sup>31</sup>  
413 were maintained through year 2. In YOSEMITE, adjusted mean CST change from baseline at  
414 year 2 (averaged over weeks 92, 96, and 100) was  $-216.0 \mu\text{m}$  (95.04% CI,  $-224.0$  to  $-208.0$ ) in  
415 the faricimab Q8W arm, which was greater than that in the aflibercept Q8W arm ( $-196.3 \mu\text{m}$   
416  $[-204.3$  to  $-188.2]$ ; nominal  $P = 0.0007$ ) (Fig 7). In RHINE, mean 2-year CST reductions were  
417 also greater with faricimab Q8W versus aflibercept Q8W ( $-202.6 \mu\text{m}$   $[-211.1$  to  $-194.2]$  vs.  
418  $-185.6 \mu\text{m}$   $[-194.1$  to  $-177.1]$ ; nominal  $P = 0.0052$ ) (Fig 7). In the faricimab T&E arms, adjusted  
419 mean CST change at 2 years was comparable with aflibercept Q8W in YOSEMITE ( $-204.5 \mu\text{m}$   
420  $[-212.4$  to  $-196.5]$ ; nominal  $P > 0.05$ ) and RHINE ( $-197.1 \mu\text{m}$   $[-205.3$  to  $-188.9]$ ; nominal  $P >$   
421  $0.05$ ), but was achieved with most patients on Q16W dosing (Fig 7). In the pooled  
422 YOSEMITE/RHINE cohort, mean 2-year CST reductions were greater in both the faricimab  
423 Q8W arm ( $-209.4 \mu\text{m}$   $[-215.2$  to  $-203.6]$ ) and the faricimab T&E arm ( $-201.0 \mu\text{m}$   $[-206.7$  to  
424  $-195.3]$ ) compared with the aflibercept Q8W arm ( $-190.9 \mu\text{m}$   $[-196.7$  to  $-185.0]$ ; nominal  $P <$   
425  $0.0001$  and  $P = 0.0150$  vs aflibercept Q8W, respectively [Fig S8]).

426 Consistent with the 1-year primary analysis,<sup>31</sup> the proportion of patients who achieved  
427 absence of protocol-defined DME was higher for faricimab compared with aflibercept through  
428 year 2 (Fig 9). The proportion of patients in YOSEMITE who achieved absence of DME at  
429 weeks 92–100 was 87%–92% in the faricimab Q8W arm and 78%–86% in the faricimab T&E  
430 arm, compared with 77%–81% in the aflibercept Q8W arm. Corresponding proportions in  
431 RHINE were 88%–93% and 85%–88% versus 80%–84%, respectively (Fig 9). In the pooled  
432 YOSEMITE/RHINE cohort, the proportion of patients who achieved absence of DME at weeks

433 92–100 was 88%–92% in the faricimab Q8W arm, 81%–86% in the faricimab T&E arm, and  
434 79%–83% in the aflibercept Q8W arm (Fig S10, available at [www.aaojournal.org](http://www.aaojournal.org)).

435 Absence of IRF was also achieved by more patients treated with faricimab when compared  
436 to those treated with aflibercept through year 2 (Fig 11). At weeks 92–100 of YOSEMITE, the  
437 proportion of patients who achieved absence of IRF was 59%–63% in the faricimab Q8W arm  
438 and 43%–48% in the faricimab T&E arm, compared with 33%–38% in the aflibercept Q8W arm.  
439 Proportions were similar in RHINE (56%–62% and 45%–52% vs. 39%–45%, respectively).  
440 Corresponding proportions for the pooled YOSEMITE/RHINE cohort were 57%–63% and 44%–  
441 48% in the faricimab Q8W and faricimab T&E arms, respectively, vs. 36%–41% in the  
442 aflibercept Q8W arm (Fig S12, available at [www.aaojournal.org](http://www.aaojournal.org)).

443 The proportion of patients that had  $\geq 2$ -step ETDRS-DRSS improvement from baseline at  
444 week 96 was similar across treatment arms and trials (Fig 13). In YOSEMITE, 51.4% (95.04%  
445 CI, 44.8–57.9) of patients in the faricimab Q8W arm had  $\geq 2$ -step ETDRS-DRSS improvement at  
446 week 96 compared with 42.2% (35.9–48.5) in the aflibercept Q8W arm (nominal  $P > 0.05$ ). In  
447 RHINE, the corresponding estimate was 53.5% (46.9–60.1) in the faricimab Q8W dosing arm,  
448 which was greater than that in the aflibercept Q8W arm (43.8% [37.2–50.4]; nominal  $P =$   
449 0.0475). In the faricimab T&E arms, the proportion of patients that had  $\geq 2$ -step ETDRS-DRSS  
450 improvement at week 96 was comparable with aflibercept Q8W in YOSEMITE (42.8% [36.6–  
451 49.0]; nominal  $P > 0.05$ ) and RHINE (44.3% [37.9–50.7]; nominal  $P > 0.05$ ) (Fig 13).

452 Corresponding proportions in the YOSEMITE/RHINE pooled cohort were 52.4% (47.8–57.0) in  
453 the faricimab Q8W arm and 43.5% (39.1–48.0) in the faricimab T&E arms versus 43.0% (38.4–  
454 47.5) in the aflibercept Q8W arm (nominal  $P = 0.0058$  and  $P > 0.05$  vs. aflibercept Q8W,  
455 respectively [Fig S14, available at [www.aaojournal.org](http://www.aaojournal.org)]). These findings were achieved in the  
456 T&E arms with 60% (3 injections) of the median number of injections received in the faricimab  
457 Q8W and aflibercept Q8W arms (5 injections) in year 2.

458

459 **Safety Outcomes**

460 Consistent with the 1-year primary analysis,<sup>31</sup> faricimab was well tolerated with a safety profile  
461 that remained comparable to aflibercept through study end (Table 4 and Tables S5–S8  
462 [available at [www.aaojournal.org](http://www.aaojournal.org)]). The incidence of ocular AEs in the study eye through study  
463 end was similar between the faricimab Q8W (YOSEMITE, 147 [47%] patients; RHINE, 166  
464 [52%] patients), faricimab T&E (146 [47%] patients; 165 [52%] patients), and aflibercept Q8W  
465 arms (144 [46%] patients; 140 [45%] patients). Most ocular AEs were mild or moderate in  
466 severity, and common ocular AEs reported were generally balanced across faricimab and  
467 aflibercept treatment arms. The incidence of serious ocular AEs through study end was low and  
468 comparable between patients receiving faricimab Q8W (YOSEMITE, 12 [4%] patients; RHINE,  
469 14 [4%] patients), faricimab T&E (14 [4%] patients; 20 [6%] patients), and aflibercept Q8W (7  
470 [2%] patients; 13 [4%] patients). Nonocular AEs and Anti-Platelet Trialists' Collaboration events  
471 were also similar across treatment arms and trials. The incidence of intraocular inflammation  
472 (IOI) events through study end was low and similar among patients receiving faricimab Q8W  
473 (YOSEMITE, 6 [2%] patients; RHINE, 3 [1%] patients), faricimab T&E (7 [2%] patients; 4 [1%]  
474 patients), and aflibercept Q8W (5 [2%] patients; 2 [1%] patients). All IOI events were considered  
475 by the investigator to be mild or moderate in severity with the exception of 4 events in  
476 YOSEMITE. There was 1 case of severe vitritis reported in the faricimab Q8W arm, which led to  
477 treatment withdrawal; this event was treated and not associated with BCVA loss and had  
478 recovered/resolved by end of study. Three cases of severe uveitis were reported in the  
479 faricimab T&E arm and led to treatment withdrawal: 1 patient with moderate chorioretinitis and  
480 severe uveitis associated with BCVA loss of 11 ETDRS letters (treated with topical steroids), 1  
481 patient with severe uveitis associated with BCVA loss of 31 ETDRS letters (treated with topical  
482 steroids), and one patient with mild keratic precipitates and severe uveitis associated with BCVA  
483 loss of 37 ETDRS letters (treated with topical antibiotics and non-steroidal anti-inflammatory

484 drugs). There were no severe IOI events in the aflibercept Q8W arms of YOSEMITE or RHINE.  
485 All IOI events except 1 in YOSEMITE (mild iritis in the faricimab up to Q16W dosing arm) had  
486 recovered/resolved or were recovering/resolving by end of study. No IOI events were  
487 associated with retinal occlusive events, and there were no cases of retinal vasculitis or  
488 occlusive retinal vasculitis reported through study end.

489

## 490 **Discussion**

491 Building on the year 1 primary outcome analysis,<sup>31</sup> we report the 2-year data from the phase 3  
492 YOSEMITE and RHINE trials. We demonstrated consistency of results across 2 years;  
493 comparable clinically meaningful BCVA gains and greater anatomic improvements with  
494 faricimab versus aflibercept were maintained through study end at year 2. In the faricimab T&E  
495 arms, the year 1 durability findings were further improved and extended in year 2. These  
496 findings further support the role of Ang/Tie signalling in vascular stability and the potential for  
497 dual Ang-2/VEGF-A inhibition to promote vascular stability and extend treatment durability  
498 beyond targeting VEGF inhibition alone for DME.

499 The current standard of care for DME using available anti-VEGF agents is limited by the  
500 considerable burden of frequent visits, which can lead to undertreatment and, as a result, real-  
501 world clinical practice outcomes often appear to not match those achieved in trial participants.<sup>4-9</sup>  
502 In YOSEMITE and RHINE, patients randomized to faricimab T&E received fewer injections per  
503 year (a median of 8 and 3 injections during year 1 and 2, respectively) compared with patients in  
504 the faricimab Q8W arm (a median of 10 and 5 injections, respectively). Furthermore, the median  
505 number of faricimab T&E injections received during the 2-year YOSEMITE and RHINE trials  
506 was less than those reported in previous clinical trials of anti-VEGF treatments administered  
507 using as-needed (pro re nata) dosing regimens. In the Diabetic Retinopathy Clinical Research  
508 Network (DRCR.Net) Protocol T study, where patients with DME received intravitreal aflibercept

509 2.0 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg as needed based on protocol-specified  
510 BCVA and CST retreatment criteria, a median of 9–10 anti-VEGF injections were given across  
511 treatment arms in year 1, and 5–6 injections during year 2.<sup>37, 38</sup> As patients in the active  
512 comparator arms of YOSEMITE and RHINE received aflibercept Q8W, it was not possible to  
513 assess whether the median number of aflibercept injections received during the 2-year trials  
514 differed to that reported in the DRCR.Net Protocol T study, where as-needed dosing regimens  
515 were used. Overall, these findings highlight the potential for T&E dosing with faricimab to extend  
516 treatment durability and reduce the burden of frequent visits and injections for patients with  
517 DME over 2 years.

518 Year 2 data from YOSEMITE and RHINE showed that initial 1-year visual acuity gains  
519 achieved with faricimab Q8W and faricimab T&E were maintained through year 2 and remained  
520 comparable with aflibercept Q8W. In the year 1 primary analysis, faricimab Q8W and faricimab  
521 T&E demonstrated greater anatomic improvements over aflibercept Q8W through year 1<sup>31</sup>; this  
522 faricimab-associated benefit was maintained through year 2. The adjusted mean CST change  
523 from baseline at 2 years was greater with faricimab Q8W and faricimab T&E dosing versus  
524 aflibercept Q8W, and greater proportions of patients achieved absence of DME and absence of  
525 IRF with faricimab Q8W and faricimab T&E versus aflibercept Q8W at most time points across  
526 both trials. Together, these data suggest that dual Ang-2/VEGF-A inhibition with faricimab may  
527 improve resolution of retinal fluid compared with VEGF inhibition alone and that fewer faricimab  
528 injections may be needed to reach this outcome. In clinical practice, retinal drying is important to  
529 assess treatment effectiveness and to guide treatment decisions; however, the clinical  
530 implications of the observed difference remain to be determined as visual acuity was similar  
531 between the faricimab and aflibercept arms through the trial. Guidance from future studies is  
532 needed to definitively answer remaining questions about whether there are differences in BCVA  
533 efficacy between these treatments over the course of more long-term follow up. Similar to the  
534 anatomical findings of YOSEMITE/RHINE, the phase 2 RUBY (NCT02712008) study of

535 nesvacumab (anti-Ang-2 antibody) and aflibercept combination treatment for DME showed  
536 greater anatomical improvements with aflibercept plus high-dose nesvacumab compared with  
537 aflibercept alone at week 12 of the trial, including greater CST changes from baseline and  
538 increased proportions of eyes with complete resolution of fluid at the foveal center and  
539 normalization of macular thickness.<sup>39</sup> Although direct comparisons are limited by differences  
540 between the trials, including different treatment regimens and patient populations, overall, the  
541 results of RUBY further support the potential for improved anatomical outcomes when both Ang-  
542 2 and VEGF are inhibited in patients with DME.

543 In the faricimab T&E arms, it was possible to extend the dosing intervals by the end of year  
544 2 compared with the end of year 1,<sup>31</sup> while maintaining durable visual acuity gains and anatomic  
545 improvements through year 2. Overall, the proportion of patients on Q16W dosing increased  
546 from 52% to 62% between week 52 and week 96, and the proportion of patients on Q12W  
547 dosing or longer increased from 72% to 78% over the same period. Furthermore, for the  
548 majority of patients on Q12W or Q16W dosing at 1 year, it was possible to maintain the  
549 extended dosing regimen without an interval reduction through year 2. Only approximately 4%  
550 of patients required continued Q4W dosing throughout the entire period of both studies, and  
551 these patients never qualified for interval extension because the CST did not drop below 325  
552  $\mu\text{m}$ . These results demonstrate the potential for faricimab to extend treatment durability for  
553 patients with DME when given in a real-world treatment scenario.

554 The T&E regimen in YOSEMITE and RHINE was designed specifically to test the durability  
555 of faricimab using a T&E-based regimen commonly used in clinical practice to reduce the  
556 burden of frequent clinic visits.<sup>32</sup> In the setting of the registrational clinical trials, we used the  
557 term “personalized treatment interval” as patients were required to undergo monthly visits to  
558 maintain masking and to enable collection of monthly efficacy and safety data. Of note, dosing  
559 interval decisions in the T&E arms were dependent on BCVA and CST values from active  
560 dosing visits only, and as such, the criteria for treatment interval reductions, maintenance, or

561 extensions were based on standard routine criteria in clinical practice. In YOSEMITE and  
562 RHINE, the faricimab T&E arms were designed with treatment intervals that could be extended  
563 by 4-week increments following the 4 initial monthly loading doses (and when CST of  $<325 \mu\text{m}$   
564 was met). Although physicians across global real-world clinical practices may follow variable  
565 patterns, including T&E extensions and reductions of ~2-week increments (dependent on the  
566 individual patient's situation and scheduling availability),<sup>36</sup> the objective in a clinical trial setting  
567 is to ensure a feasible schedule with minimal variability to minimize potential bias. Our results of  
568 visual acuity stability and anatomical improvements achieved over 2 years with faricimab dosed  
569 up to Q16W support extension of faricimab dosing intervals by up to 4-week increments in the  
570 real world, and the potential to decrease both the number of injections and frequency of clinic  
571 visits for patients with DME.

572 Consistent with the year 1 primary analysis,<sup>31</sup> faricimab remained well tolerated through  
573 study end and no new safety signals were identified. Ocular AEs in the study eye were mostly  
574 mild or moderate in severity, and the incidence of these events was similar across faricimab and  
575 aflibercept treatment arms. The incidence of IOI events through study end was low (1.6% and  
576 1.1% for faricimab- and aflibercept-treated patients, respectively); most IOI events were mild or  
577 moderate in severity, and none were associated with retinal vasculitis or retinal occlusive  
578 events.

579 Our study has some limitations that warrant discussion. First, the fixed dosing faricimab  
580 Q8W arms of YOSEMITE and RHINE were designed to evaluate the maximal efficacy of  
581 faricimab, whereas the faricimab T&E arms were designed to test optimal durability. However,  
582 following the 5 initial Q4W does, the active comparator arms received aflibercept Q8W per the  
583 globally aligned aflibercept label,<sup>35</sup> which precluded a head-to-head comparison of durability  
584 between faricimab and aflibercept. The number of injections across treatment arms was not  
585 compared statistically as only patients in the faricimab T&E arms could receive a variable  
586 number of injections. The globally aligned and accepted aflibercept posology was selected due

587 to the registrational nature of the YOSEMITE and RHINE trials, and because no extended  
588 dosing regimen exists for aflibercept that is globally approved or uniformly practiced.<sup>33-35</sup>  
589 Second, the YOSEMITE and RHINE trials were conducted throughout the COVID-19 pandemic,  
590 which affected patient participation at some sites and had an impact on the rate of major  
591 protocol deviations; however, sensitivity and supplemental analyses showed that the pandemic  
592 had limited impact on data integrity and study outcomes. Third, and as discussed in more detail  
593 above, although the faricimab T&E arms were designed with treatment intervals that could be  
594 extended by 4-week increments and may differ from variable patterns followed by physicians in  
595 real-world clinical practice,<sup>32, 36</sup> we believe the criteria used in our T&E regimen for treatment  
596 interval extension, maintenance, or reduction can be readily applied in clinical settings.

597 The substantial potential of dual Ang-2/VEGF-A inhibition for DME should be confirmed with  
598 further studies. The YOSEMITE and RHINE trials enrolled a large cohort of 1891 patients  
599 across 353 study sites worldwide, which to our knowledge, is the largest study in patients with  
600 DME. Patients who completed YOSEMITE and RHINE were eligible to enter the RHONE-X  
601 long-term extension study (NCT04432831), which will continue to provide data on the safety  
602 and tolerability of faricimab, administered open label and T&E, for a further 2 years, and will  
603 provide data on the effects of switching from bimonthly aflibercept to faricimab T&E. The  
604 majority of patients in YOSEMITE and RHINE were of white race or ethnicity; the treatment  
605 response to faricimab in underrepresented patients with DME will be evaluated in the phase 4  
606 ELEVATUM trial (NCT05224102). Additionally, VOYAGER (NCT05476926), an observational,  
607 prospective, multinational, multicenter study, will offer real-world insights for both faricimab and  
608 the Port Delivery System with ranibizumab among patients with DME and neovascular age-  
609 related macular degeneration in routine clinical practice globally. Furthermore, the phase 2b  
610 ALTIMETER (NCT04597918) biomarker hypothesis-generating study will explore the  
611 associations between clinical endpoints, multimodal imaging assessments, and aqueous humor  
612 biomarker patterns in patients with DME treated with faricimab. Previous studies have explored



613 associations between specific characteristics on OCT with outcomes of patients with DME in an  
614 effort to identify OCT imaging biomarkers predictive of treatment response to anti-VEGF  
615 therapy.<sup>40, 41</sup> In ALTIMETER, exploratory endpoints will evaluate changes from baseline over  
616 time in multimodal imaging, including CST and absence of IRF and subretinal fluid, and  
617 aqueous humor protein/metabolite composition to identify potential biomarkers of the Ang-2  
618 effect of faricimab.

619 In conclusion, the 2-year results from the phase 3 YOSEMITE and RHINE trials demonstrate  
620 and confirm the durability, efficacy, and safety of faricimab in patients with DME. Clinically  
621 significant 1-year visual acuity gains with faricimab Q8W and T&E were maintained through  
622 year 2 and remained comparable to aflibercept Q8W, while anatomic improvements remained  
623 greater with faricimab over aflibercept Q8W. The impact of the anatomical improvements with  
624 faricimab on long-term visual acuity outcomes will be further evaluated in the RHONE-X  
625 extension study. The durability of faricimab was further extended in year 2, with more patients in  
626 the faricimab T&E arms achieving and maintaining dosing intervals of up to Q16W. During year  
627 2, the median number of faricimab T&E injections was 3 (vs. 5–6 for the DRCR.Net Protocol T  
628 study)<sup>38</sup>, which may translate into fewer clinic visits and might reduce treatment burden with  
629 real-world faricimab use. These data reinforce the potential of dual inhibition of Ang-2 and  
630 VEGF-A with faricimab as a novel, multitargeted strategy that may extend DME treatment  
631 durability and improve outcomes beyond VEGF inhibition alone.

632

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637 provided by Ellen M. Ross, PhD, and Karina D. Hamilton-Peel, PhD, CMPP, of Envision Pharma  
638 Group.

639

640 **Roche Data Sharing Statement**

641 For eligible studies, qualified researchers may request access to individual patient level clinical

642 data through a data request platform. At the time of writing, this request platform is Vivli

643 (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the

644 Sharing of Clinical Information and how to request access to related clinical study documents,

645 see here ([https://go.roche.com/data\\_sharing](https://go.roche.com/data_sharing)). Anonymized records for individual patients across

646 more than one data source external to Roche cannot, and should not, be linked due to a

647 potential increase in risk of patient re-identification

## 648 References

- 649 1. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern®.  
650 Ophthalmology 2020;127(1):P66-P145.
- 651 2. Tan GS, Cheung N, Simo R, et al. Diabetic macular oedema. Lancet Diabetes  
652 Endocrinol 2017;5(2):143-55.
- 653 3. Wong TY, Cheung CM, Larsen M, et al. Diabetic retinopathy. Nat Rev Dis Primers  
654 2016;2:16012.
- 655 4. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular  
656 endothelial growth factor therapy in diabetic macular edema in the United States. Ophthalmol  
657 Retina 2018;2(12):1179-87.
- 658 5. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy  
659 intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. Br J  
660 Ophthalmol 2021;105(2):216-21.
- 661 6. Massin P, Creuzot-Garcher C, Kodjikian L, et al. Real-world outcomes after 36-month  
662 treatment with ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular  
663 edema (BOREAL-DME). Ophthalmic Res 2021;64(4):577-86.
- 664 7. Shimura M, Kitano S, Muramatsu D, et al. Real-world management of treatment-naive  
665 diabetic macular oedema in Japan: two-year visual outcomes with and without anti-VEGF  
666 therapy in the STREAT-DME study. Br J Ophthalmol 2020;104(9):1209-15.
- 667 8. Sugimoto M, Handa C, Hirano K, et al. Intravitreal aflibercept for diabetic macular edema  
668 in real-world clinical practice in Japan: 24-month outcomes. Graefes Arch Clin Exp Ophthalmol  
669 2022;260(11):3489-98.
- 670 9. Van Aken E, Favreau M, Ramboer E, et al. Real-world outcomes in patients with diabetic  
671 macular edema treated long term with ranibizumab (VISION study). Clin Ophthalmol  
672 2020;14:4173-85.

- 673 10. Ashraf M, Souka A, Adelman R. Predicting outcomes to anti-vascular endothelial growth  
674 factor (VEGF) therapy in diabetic macular oedema: a review of the literature. *Br J Ophthalmol*  
675 2016;100(12):1596-604.
- 676 11. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface.  
677 *Prog Retin Eye Res* 2018;63:20-68.
- 678 12. Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/Tie pathway in retinal vascular  
679 diseases: a review. *Retina* 2021;41(1):1-19.
- 680 13. Jousseaume AM, Ricci F, Paris LP, et al. Angiopoietin/Tie2 signalling and its role in retinal  
681 and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)* 2021;35(5):1305-16.
- 682 14. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway.  
683 *Nat Rev Drug Discov* 2017;16(9):635-61.
- 684 15. Yancopoulos GD, Davis S, Gale NW, et al. Vascular-specific growth factors and blood  
685 vessel formation. *Nature* 2000;407(6801):242-8.
- 686 16. Benest AV, Kruse K, Savant S, et al. Angiopoietin-2 is critical for cytokine-induced  
687 vascular leakage. *PLoS One* 2013;8(8):e70459.
- 688 17. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in  
689 hyperpermeability of diabetic retinal vessels. *Ophthalmic Res* 1995;27(1):48-52.
- 690 18. Murata T, Nakagawa K, Khalil A, et al. The relation between expression of vascular  
691 endothelial growth factor and breakdown of the blood-retinal barrier in diabetic rat retinas. *Lab*  
692 *Invest* 1996;74(4):819-25.
- 693 19. Oshima Y, Deering T, Oshima S, et al. Angiopoietin-2 enhances retinal vessel sensitivity  
694 to vascular endothelial growth factor. *J Cell Physiol* 2004;199(3):412-7.
- 695 20. Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells  
696 to TNF-alpha and has a crucial role in the induction of inflammation. *Nat Med* 2006;12(2):235-9.
- 697 21. Felcht M, Luck R, Schering A, et al. Angiopoietin-2 differentially regulates angiogenesis  
698 through TIE2 and integrin signaling. *J Clin Invest* 2012;122(6):1991-2005.

- 699 22. Hakanpaa L, Sipila T, Leppanen VM, et al. Endothelial destabilization by angiotensin-2  
700 via integrin  $\beta 1$  activation. *Nat Commun* 2015;6:5962.
- 701 23. Park SW, Yun JH, Kim JH, et al. Angiotensin 2 induces pericyte apoptosis via  $\alpha 3\beta 1$   
702 integrin signaling in diabetic retinopathy. *Diabetes* 2014;63(9):3057-68.
- 703 24. Yun JH, Park SW, Kim JH, et al. Angiotensin 2 induces astrocyte apoptosis via  $\alpha v\beta 5$ -  
704 integrin signaling in diabetic retinopathy. *Cell Death Dis* 2016;7(2):e2101.
- 705 25. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways  
706 with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*  
707 2016;8(11):1265-88.
- 708 26. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of  
709 intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration  
710 (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials.  
711 *Lancet* 2022;399(10326):729-40.
- 712 27. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly  
713 dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the  
714 STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol* 2020;138(9):964-72.
- 715 28. Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens  
716 of faricimab vs ranibizumab in neovascular age-related macular degeneration: the AVENUE  
717 phase 2 randomized clinical trial. *JAMA Ophthalmol* 2020;138(9):955-63.
- 718 29. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiotensin-2 and  
719 vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD  
720 phase 2 randomized trial. *Ophthalmology* 2019;126(8):1155-70.
- 721 30. Tadayoni R, Paris LP, Abreu F, et al. Faricimab in RVO: results from the BALATON and  
722 COMINO phase 3 studies. *Angiogenesis, Exudation, and Degeneration Virtual Congress*.  
723 February 11, 2023.

- 724 31. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal  
725 faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema  
726 (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*  
727 2022;399(10326):741-55.
- 728 32. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical  
729 trials of faricimab for diabetic macular edema: study design and rationale. *Ophthalmol Sci*  
730 2021;2(1):100111.
- 731 33. Medicines.org.uk. 2012. Eylea 40mg/ml solution for injection in a vial. Summary of  
732 product characteristics. Available at: [medicines.org.uk/emc/product/2879/smcp#](https://www.medicines.org.uk/emc/product/2879/smcp#).
- 733 34. Eylea [package insert]. Osaka, Japan: Bayer Yakuhin, 2015.
- 734 35. Eylea [package insert]. Tarrytown, NY,: Regeneron Pharmaceuticals, Inc., 2021.
- 735 36. Rezaei KA, Stone TW. 2015 Global Trends in Retina Survey. Chicago, IL: American  
736 Society of Retina Specialists, 2015.
- 737 37. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for  
738 diabetic macular edema. *N Engl J Med* 2015;372(13):1193-203.
- 739 38. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for  
740 diabetic macular edema: two-year results from a comparative effectiveness randomized clinical  
741 trial. *Ophthalmology* 2016;123(6):1351-9.
- 742 39. Brown DM, Boyer DS, Csaky K, et al. Intravitreal nesvacumab (antiangiopoietin 2) plus  
743 aflibercept in diabetic macular edema: phase 2 RUBY randomized trial. *Retina* 2022;42(6):1111-  
744 20.
- 745 40. Hui VWK, Szeto SKH, Tang F, et al. Optical coherence tomography classification  
746 systems for diabetic macular edema and their associations with visual outcome and treatment  
747 responses - an updated review. *Asia Pac J Ophthalmol (Phila)* 2022;11(3):247-57.

- 748 41. Szeto SK, Hui VWK, Tang FY, et al. OCT-based biomarkers for predicting treatment  
749 response in eyes with centre-involved diabetic macular oedema treated with anti-VEGF  
750 injections: a real-life retina clinic-based study. Br J Ophthalmol 2023;107(4):525-33.

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## 751 **Figure Legends**

752 **Figure 1.** Faricimab T&E algorithm in YOSEMITE/RHINE. Reference CST was defined as  
753 the CST value when the initial CST threshold criteria were met (CST <325  $\mu\text{m}$  at or after the  
754 week 12 study visit). The reference CST was adjusted if CST decreased by >10% from the  
755 previous reference CST for two consecutive study drug dosing visits and the values obtained  
756 were within 30  $\mu\text{m}$ . The CST value obtained at the latter visit served as the new reference  
757 CST. Reference BCVA was defined as the mean of the three best BCVA scores obtained at  
758 any previous active dosing visit. BCVA = best-corrected visual acuity; CST = central subfield  
759 thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; Q4W = every 4 weeks;  
760 Q16W = every 16 weeks; T&E = treat-and-extend. Reprinted from The Lancet, Vol. 399,  
761 Wykoff CC et al, Efficacy, durability, and safety of intravitreal faricimab with extended dosing  
762 up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE):  
763 two randomised, double-masked, phase 3 trials, Pages 741–755, Copyright (2022), with  
764 permission from Elsevier.

765

766 **Figure 2.** CONSORT flow diagram for YOSEMITE (A) and RHINE (B). Q8W = every 8  
767 weeks; T&E = treat-and-extend.

768

769 **Figure 3.** Adjusted mean change in BCVA from baseline through week 100. <sup>a</sup>Adjusted mean  
770 BCVA change from baseline at 2 years, averaged over weeks 92, 96, and 100. Results are  
771 based on a MMRM analysis of the intention-to-treat population. Treatment policy strategy  
772 and hypothetical strategy were applied to non-COVID-19-related and COVID-19-related  
773 intercurrent events, respectively. Missing data were implicitly imputed by the MMRM. Error  
774 bars represent 95.04% CI. BCVA = best-corrected visual acuity; CI = confidence interval;  
775 ETDRS = Early Treatment Diabetic Retinopathy Study; MMRM = mixed model for repeated  
776 measures; Q8W = every 8 weeks; T&E = treat-and-extend.

777



778 **Figure 5.** Proportion of patients in the faricimab T&E arms who achieved Q4W, Q8W,  
779 Q12W, or Q16W dosing at week 96 (**A**), and dosing intervals in the faricimab T&E arms  
780 through week 96 (**B**). Analyses included patients in the faricimab T&E arms who had not  
781 discontinued the study at the week 96 visit (YOSEMITE, n = 270; RHINE, n = 287).  
782 Treatment interval at week 96 was defined as the treatment interval decision made at that  
783 visit in (**A**), and treatment interval at a given visit is shown as the interval at the start of the  
784 visit in (**B**). The week 96 decision (calculated/recorded at week 96) is shown in the last  
785 column. Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W =  
786 every 16 weeks; T&E = treat-and-extend.

787

788 **Figure 7.** Adjusted mean change in CST from baseline through week 100. \*Nominal  $P <$   
789 0.05 vs. aflibercept Q8W for adjusted mean CST change from baseline at 2 years, averaged  
790 over weeks 92, 96, and 100. Results are based on a MMRM analysis of the intention-to-treat  
791 population. Treatment policy strategy and hypothetical strategy were applied to non-COVID-  
792 19-related and COVID-19-related intercurrent events, respectively. Missing data were  
793 implicitly imputed by the MMRM. Error bars represent 95.04% CI. CST was defined as the  
794 average thickness between the internal limiting membrane and Bruch's membrane in the  
795 central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. CI =  
796 confidence interval; CST = central subfield thickness; MMRM = mixed model for repeated  
797 measures; Q8W = every 8 weeks; T&E = treat-and-extend.

798

799 **Figure 9.** Proportion of patients with absence of DME through week 100. \*Nominal  $P <$  0.05  
800 vs. aflibercept Q8W; nominal  $P >$  0.05 where no asterisk is shown. Weighted proportions  
801 were estimated for the intention-to-treat population using the CMH method; weighted  
802 proportions for the aflibercept Q8W arms are presented for the faricimab Q8W vs. aflibercept  
803 Q8W comparison. Baseline values (defined as the last available measurement obtained on  
804 or before randomization) are based on observed data. Treatment policy strategy and  
805 hypothetical strategy were applied to non-COVID-19-related and COVID-19-related

806 intercurrent events, respectively. Missing data were not imputed. Error bars represent  
807 95.04% CI; CI estimates <0% and >100% were imputed as 0% and 100%, respectively.  
808 <sup>a</sup>Absence of DME was defined as CST <325  $\mu\text{m}$ , measured as the average thickness  
809 between the internal limiting membrane and Bruch's membrane in the central 1-mm  
810 diameter of the Early Treatment Diabetic Retinopathy Study grid. CMH = Cochran-Mantel-  
811 Haenszel; CI = confidence interval; CST = central subfield thickness; DME = diabetic  
812 macular edema; Q8W = every 8 weeks; T&E = treat-and-extend.

813

814 **Figure 11.** Proportion of patients with absence of IRF through week 100. \*Nominal  $P < 0.05$   
815 vs. aflibercept Q8W; nominal  $P > 0.05$  where no asterisk is shown. Weighted proportions  
816 were estimated for the intention-to-treat population using the CMH method; weighted  
817 proportions for the aflibercept Q8W arms are presented for the faricimab Q8W vs. aflibercept  
818 Q8W comparison. Baseline values (defined as the last available measurement obtained on  
819 or before randomization) are based on observed data. Treatment policy strategy and  
820 hypothetical strategy were applied to non-COVID-19-related and COVID-19-related  
821 intercurrent events, respectively. Missing data were not imputed. Error bars represent  
822 95.04% CI; CI estimates <0% and >100% were imputed as 0% and 100%, respectively. <sup>a</sup>IRF  
823 was measured in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy  
824 Study grid. CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IRF = intraretinal  
825 fluid; Q8W = every 8 weeks; T&E = treat-and-extend.

826

827 **Figure 13.** Proportion of patients with  $\geq 2$ -step ETDRS-DRSS improvement from baseline at  
828 week 96. \*Nominal  $P < 0.05$  vs. aflibercept Q8W; nominal  $P > 0.05$  where no asterisk is  
829 shown. Analyses included patients with evaluable color fundus photographs at baseline and  
830 week 96. Weighted proportions were estimated for the intention-to-treat population using the  
831 CMH method; weighted proportions for the aflibercept Q8W arms are presented for the  
832 faricimab Q8W vs. aflibercept Q8W comparison. Treatment policy strategy and hypothetical  
833 strategy were applied to non-COVID-19-related and COVID-19-related intercurrent events,

834 respectively. Missing data were not imputed. Error bars represent 95.04% CI; CI estimates  
835 <0% and >100% were imputed as 0% and 100%, respectively. CI = confidence interval;  
836 CMH = Cochran-Mantel-Haenszel; DRSS = Diabetic Retinopathy Severity Scale; ETDRS =  
837 Early Treatment Diabetic Retinopathy Study; Q8W = every 8 weeks; T&E = treat-and-  
838 extend.

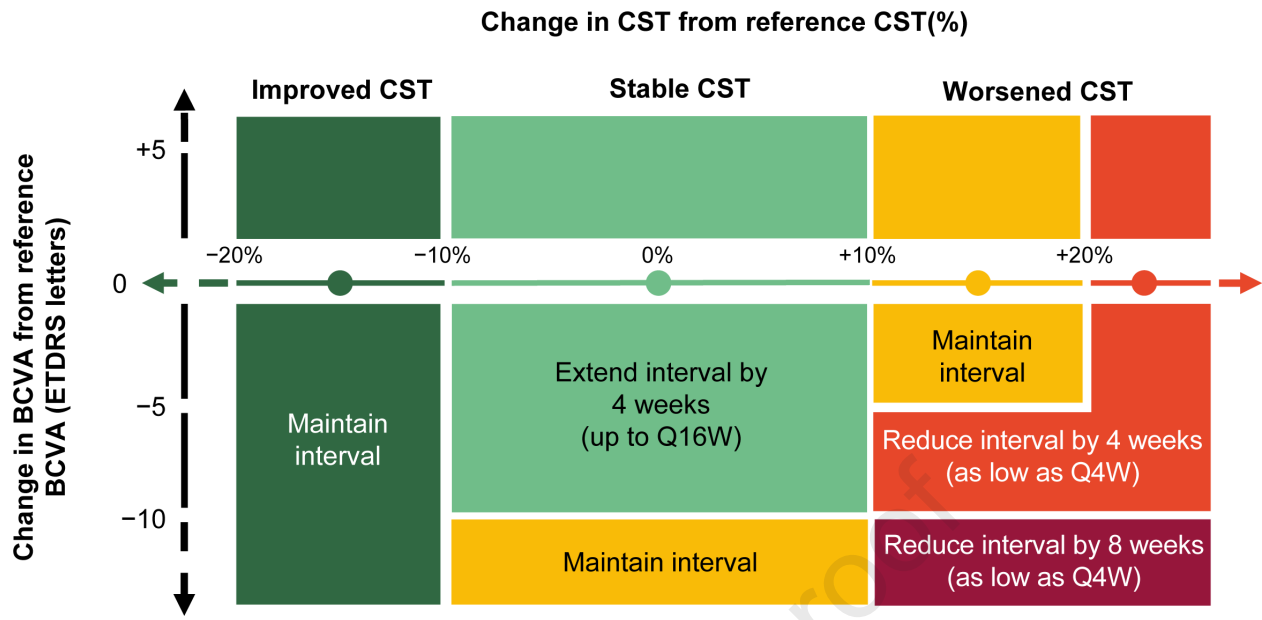
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1 **Table 4.** Summary of Key Adverse Events Through Study End (Safety Analysis Population)

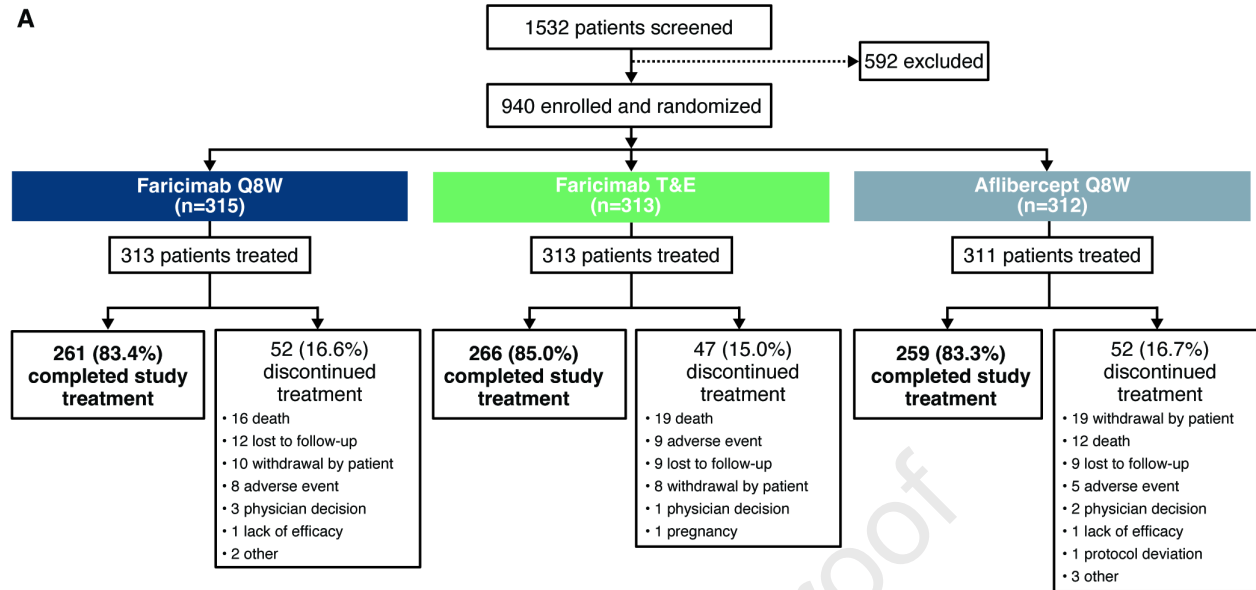
	YOSEMITE (N = 937)			RHINE (N = 950)		
	Faricimab Q8W (n = 313)	Faricimab T&E (n = 313)	Aflibercept Q8W (n = 311)	Faricimab Q8W (n = 317)	Faricimab T&E (n = 319)	Aflibercept Q8W (n = 314)
<b>Summary of AEs, n (%)</b>						
Total number of AEs*	1621	1632	1476	1658	1420	1386
Total number of SAEs*	234	201	174	173	152	189
Patients with ≥1 ocular AE†	147 (47.0)	146 (46.6)	144 (46.3)	166 (52.4)	165 (51.7)	140 (44.6)
Patients with ≥1 ocular SAE†	12 (3.8)	14 (4.5)	7 (2.3)	14 (4.4)	20 (6.3)	13 (4.1)
Patients with ≥1 nonocular AE	240 (76.7)	251 (80.2)	242 (77.8)	220 (69.4)	218 (68.3)	231 (73.6)
Patients with ≥1 nonocular SAE	99 (31.6)	97 (31.0)	84 (27.0)	76 (24.0)	64 (20.1)	89 (28.3)
Patients with ≥1 treatment-related ocular AE†	10 (3.2)	7 (2.2)	6 (1.9)	10 (3.2)	14 (4.4)	15 (4.8)
Patients with ≥1 treatment-related ocular SAE†	0	4 (1.3)	0	0	3 (0.9)	0
Patients with ≥1 ocular AE of special interest†,‡	11 (3.5)	13 (4.2)	8 (2.6)	14 (4.4)	20 (6.3)	12 (3.8)
<b>IOI events, n (%)†,§</b>						
Patients with ≥1 IOI event	6 (1.9)	7 (2.2)	5 (1.6)	3 (0.9)	4 (1.3)	2 (0.6)
Uveitis	3 (1.0)	3 (1.0)	0	0	1 (0.3)	0
Iritis	1 (0.3)	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)
Iridocyclitis	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.6)	1 (0.3)
Vitreitis	1 (0.3)	0	2 (0.6)	1 (0.3)	0	0
Postprocedural inflammation	0	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Chorioretinitis	0	1 (0.3)	0	0	0	0
Keratic precipitates	0	1 (0.3)	0	0	0	0
Keratouveitis	0	1 (0.3)	0	0	0	0
<b>Ocular SAEs associated with intravitreal anti-VEGF therapy, n (%)†,¶</b>						
Endophthalmitis	0	3 (1.0)	0	2 (0.6)	1 (0.3)	1 (0.3)
Intraocular pressure increased	0	0	0	1 (0.3)	0	0
Retinal tear	0	1 (0.3)	0	0	2 (0.6)	0
Rhegmatogenous retinal detachment	1 (0.3)	0	0	0	0	0
Traumatic cataract	0	0	0	0	0	0
<b>Retinal vasculitis and noninflammatory occlusive events, n (%)†</b>						
Retinal vasculitis	0	0	0	0	0	0
Retinal artery occlusion	0	0	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Retinal vein occlusion	1 (0.3)	2 (0.6)	0	0	2 (0.6)	0
Arterial occlusive disease	0	0	0	0	0	1 (0.3)
Retinal artery embolism	0	0	0	0	0	1 (0.3)
<b>APTC events, n (%)  </b>						
Patients with ≥1 APTC event	23 (7.3)	22 (7.0)	18 (5.8)	11 (3.5)	8 (2.5)	14 (4.5)
Nonfatal myocardial infarction	4 (1.3)	4 (1.3)	4 (1.3)	3 (0.9)	1 (0.3)	3 (1.0)
Nonfatal stroke	8 (2.6)	6 (1.9)	7 (2.3)	3 (0.9)	4 (1.3)	4 (1.3)

Death	11 (3.5)	12 (3.8)	7 (2.3)	5 (1.6)	3 (0.9)	7 (2.2)
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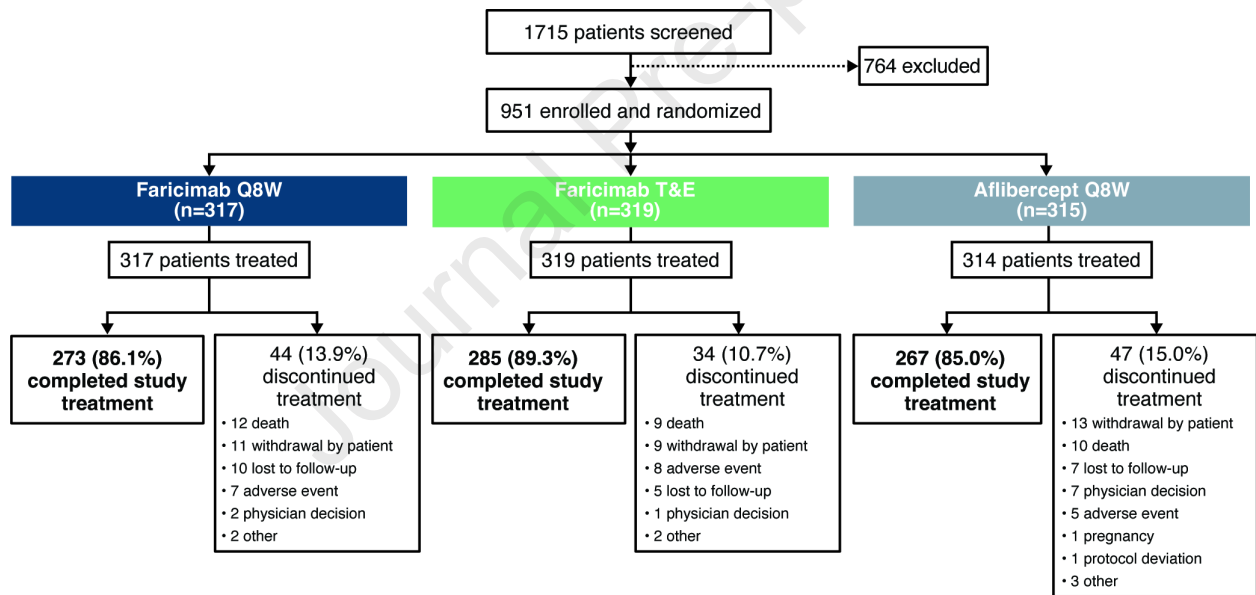
- 2 \*Total number of AEs and SAEs includes nonocular events and ocular events in the study or fellow eye.
- 3 †Ocular AEs in the study eye only are presented.
- 4 ‡Ocular AEs of special interest were defined as events associated with severe IOI, events requiring surgical or medical intervention to  
5 prevent permanent loss of sight, or events associated with BCVA loss of  $\geq 30$  ETDRS letters for  $>1$  hour. A full list of ocular AEs of  
6 special interest is provided in Table S6 (available at [www.aaojournal.org](http://www.aaojournal.org)).
- 7 §Includes serious and nonserious IOI events; excludes endophthalmitis events.
- 8 ¶A full list of ocular SAEs is provided in Table S5 (available at [www.aaojournal.org](http://www.aaojournal.org)).
- 9 ||APTIC events were externally adjudicated; all other events were investigator reported.
- 10 Includes AEs with onset from the first dose of study drug through study end; percentages are based on n values in the column  
11 headings. Multiple occurrences of the same AE in 1 individual are counted only once, except for the “Total number of events” rows, in  
12 which multiple occurrences of the same AE are counted separately.
- 13 AE = adverse event; APTC = Anti-Platelet Trialists’ Collaboration; BCVA = best-corrected visual acuity; ETDRS = Early Treatment  
14 Diabetic Retinopathy Study; IOI = intraocular inflammation; Q8W = every 8 weeks; SAE = serious adverse event; T&E = treat-and-  
15 extend; VEGF = vascular endothelial growth factor

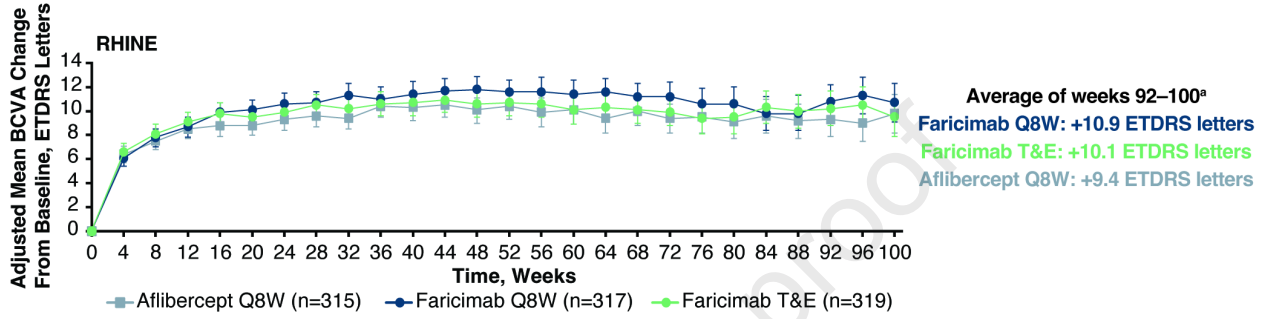
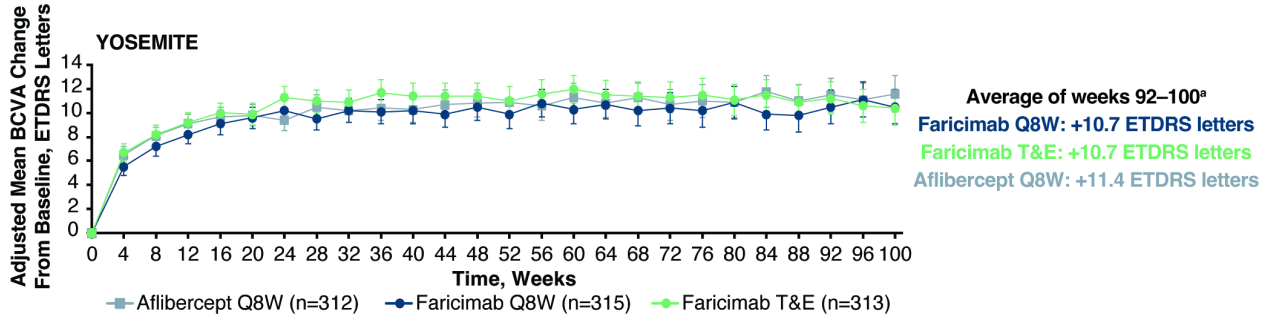


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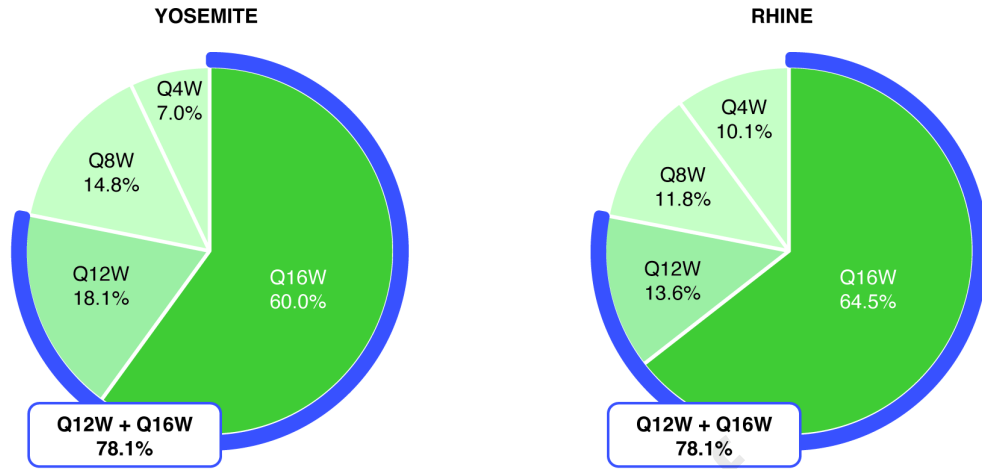
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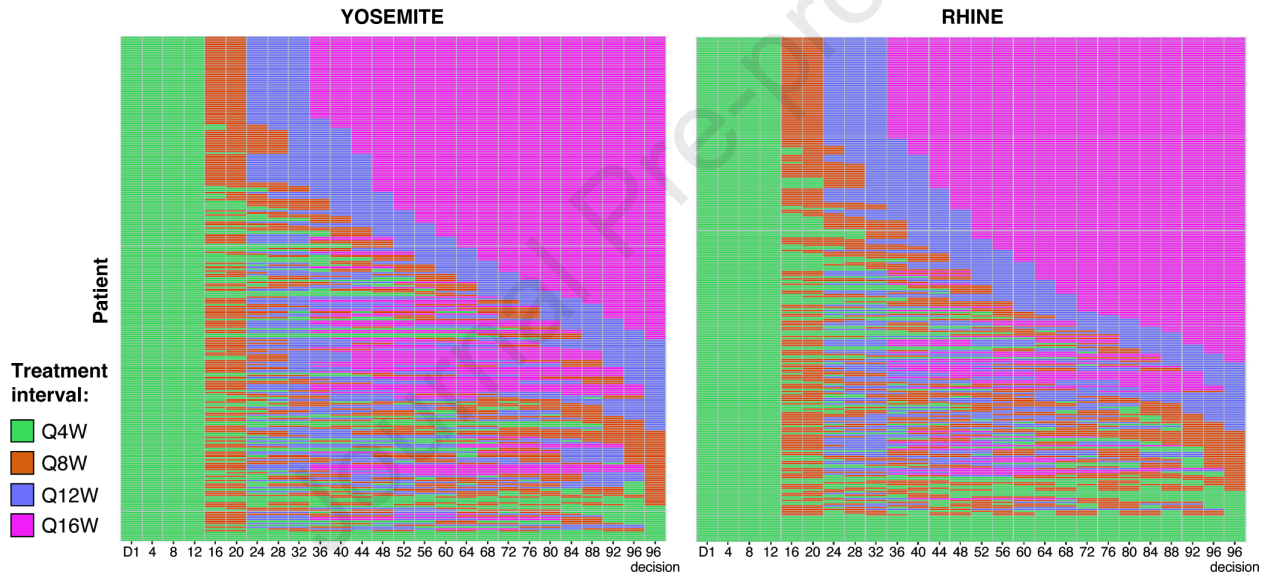


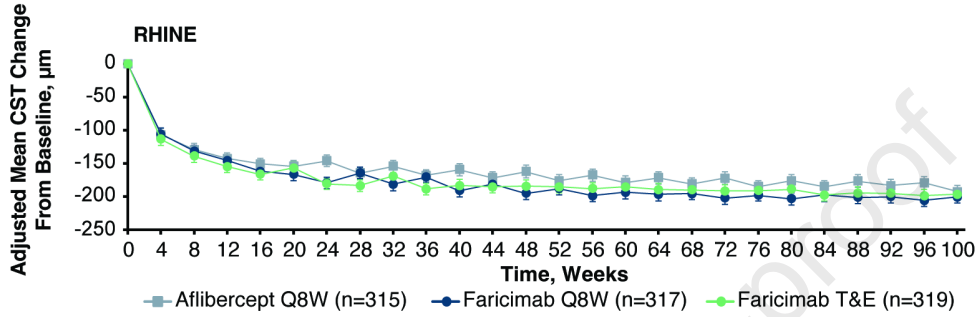
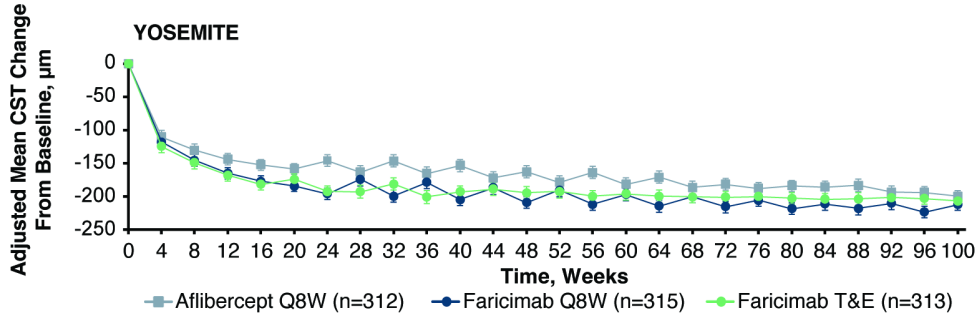


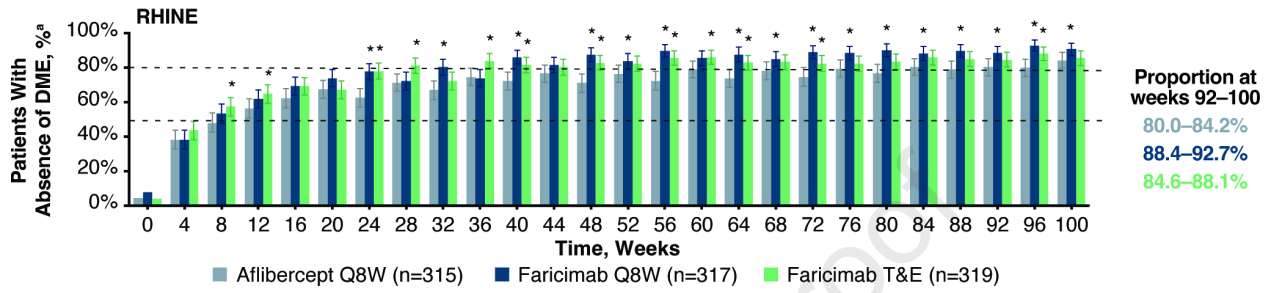
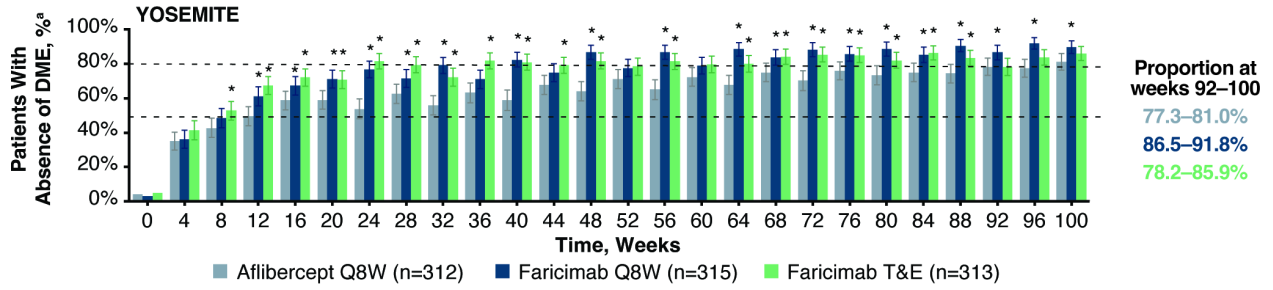
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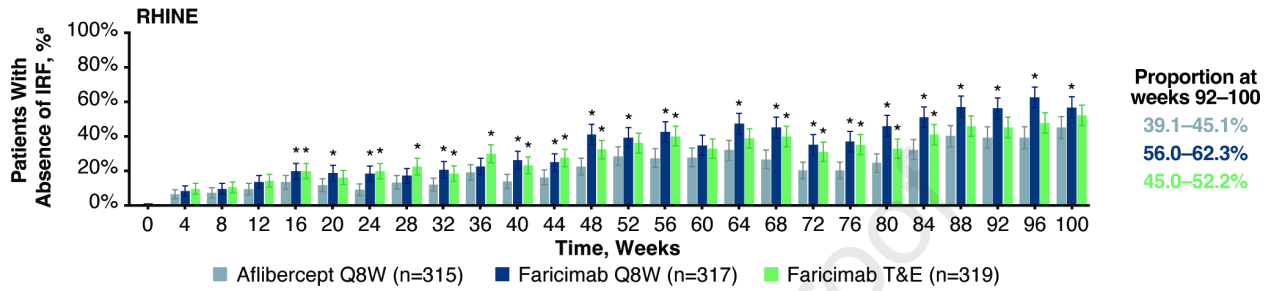
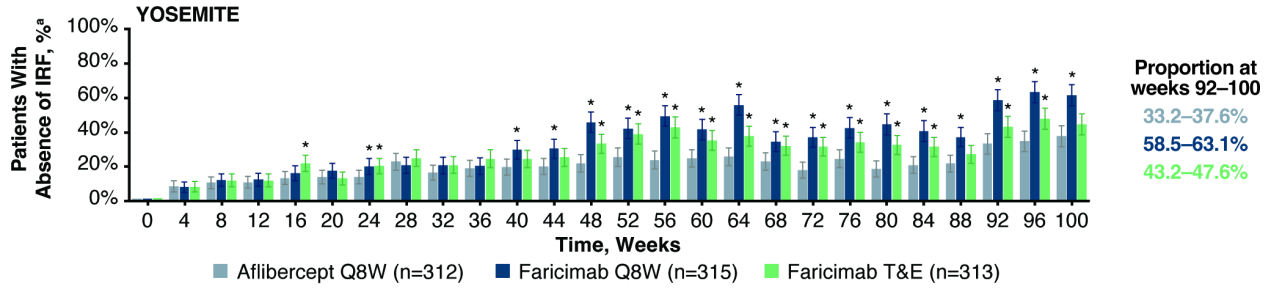


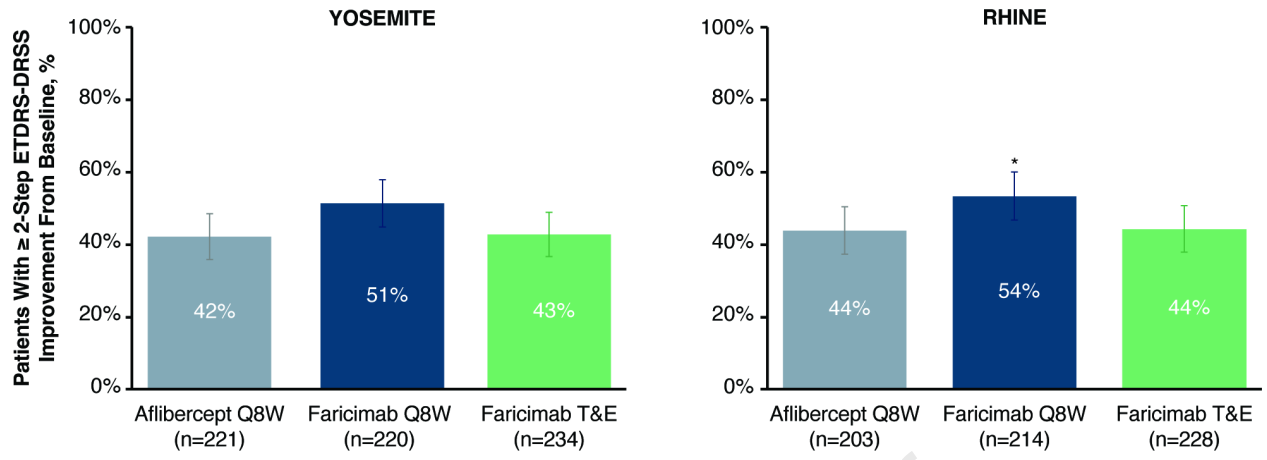
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Journal Pre-proof

1 **Précis**

2 Over 2 years, faricimab offered comparable visual acuity gains and improved anatomic  
3 outcomes compared with aflibercept. In the faricimab treat-and-extend arms, durable visual  
4 acuity gains, and anatomic improvements were maintained with up to every-16-week dosing.

5

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