Effect of Dual Angiopoietin-2/VEGF-A Inhibition With Faricimab on Macular Anatomy in the STAIRWAY Phase 2 Study of Neovascular Age-Related Macular Degeneration

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STAIRWAY

Disclosures

Financial Disclosures

- EML: Consultant: Allegro Ophthalmics, Apellis, Galimedix, Gemini, Genentech, Inc./Roche, Novartis, Retrotope; Financial Support: Apellis, LumiThera, Novartis, Roche (through Duke University)
- HL, CQR, ZH: Employee: Genentech, Inc.
- DS: Employee: Roche Products Ltd., UK
- KB: Employee: Roche Products Ltd., Ireland

Study Disclosures

- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
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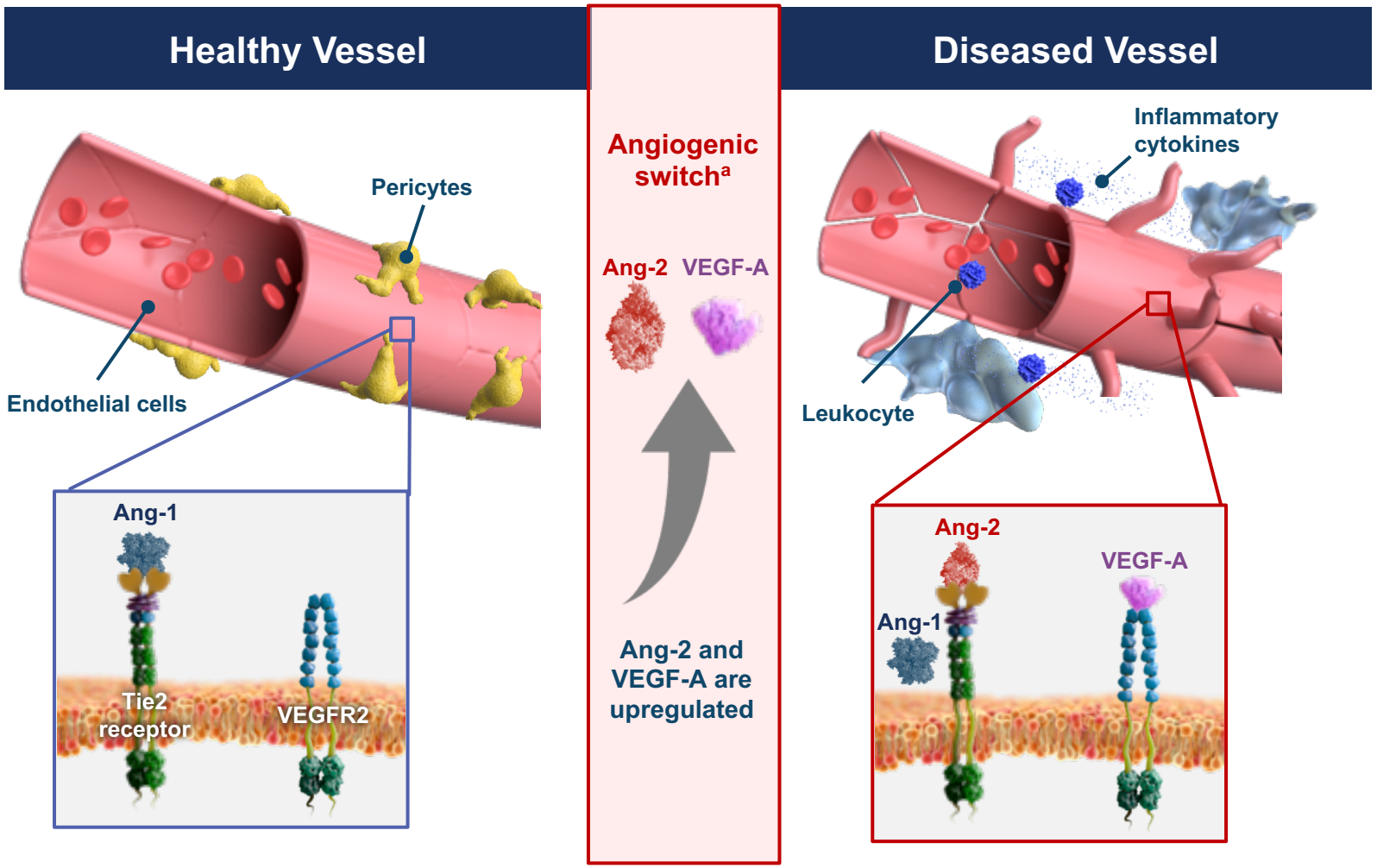
Summary

- Faricimab is a bispecific antibody that independently binds and neutralizes Ang-2 and VEGF-A, the key drivers of retinal and choroidal diseases, with high specificity and potency and without steric hindrance
- In preclinical in vivo models, compared with the inhibition of either Ang-2 or VEGF-A alone, dual inhibition showed synergistic benefits, reducing:
  - Vascular leakage
  - CNV lesion activity
  - Microvascular inflammation
- Dual Ang-2 and VEGF-A inhibition using faricimab may lead to a more sustained vessel stabilization compared with VEGF-A inhibition alone
- **STAIRWAY**, a phase 2 trial, showed the potential for extended durability for faricimab in nAMD
  - BCVA gains and anatomic improvements observed in patients treated with faricimab Q12W/Q16W were comparable with ranibizumab Q4W
  - 2/3 (65%) of faricimab-treated patients had no active disease 12 weeks after the last initiation dose
- Phase 3 trials investigating faricimab in nAMD are currently underway

Ang-2, angiopoietin-2; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; nAMD, neovascular age-related macular degeneration; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; VEGF-A, vascular endothelial growth factor-A.

Ang-2 and VEGF-A Are Key Drivers of Vascular Instability: Vascular Leakage, Neovascularization, and Inflammation



- **Ang-1** binds to Tie2 on endothelial cells, leading to Tie2 activation and vascular stability
- **Ang-2** levels are increased in the vitreous of patients with nAMD, DR, and RVO[1]
- **Ang-2** competes with Ang-1 for binding to Tie2 and inactivates the Tie2 receptor
- **Ang-2** and **VEGF** synergistically drive vascular instability, characterized by:
  - Vascular leakage
  - Neovascularization
  - Inflammation

[a] Conditions of stress, such as irregular glucose concentration, ischemia, hypoxia, growth factors, and inflammatory cytokines, can induce an angiogenic switch (shift in the balance of pro- and antiangiogenic factors).

1. Regula JT et al. *EMBO Mol Med.* 2016;8(11):1265-1288, with correction in Regula JT et al. *EMBO Mol Med.* 2019;11(5):e10666.

Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; DR, diabetic retinopathy; nAMD, neovascular age-related macular degeneration; RVO, retinal vein occlusion; Tie2, tyrosine kinase with immunoglobulin-like domains-2; VEGF-A, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor-2.

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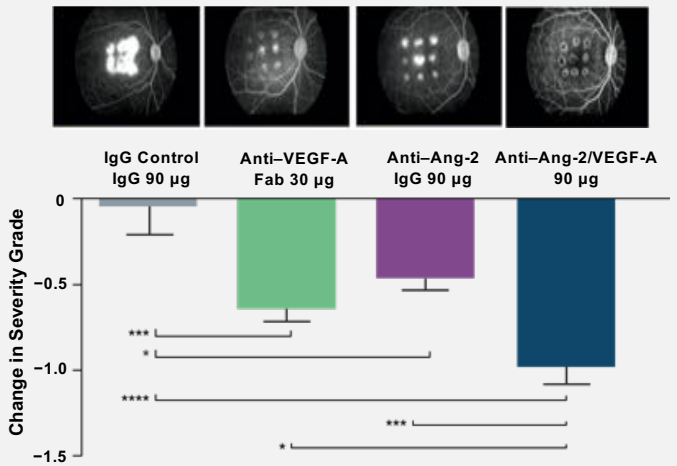
Preclinical Evidence Suggests a Role for Ang-2 in Vascular Instability

Vascular Leakage[1]

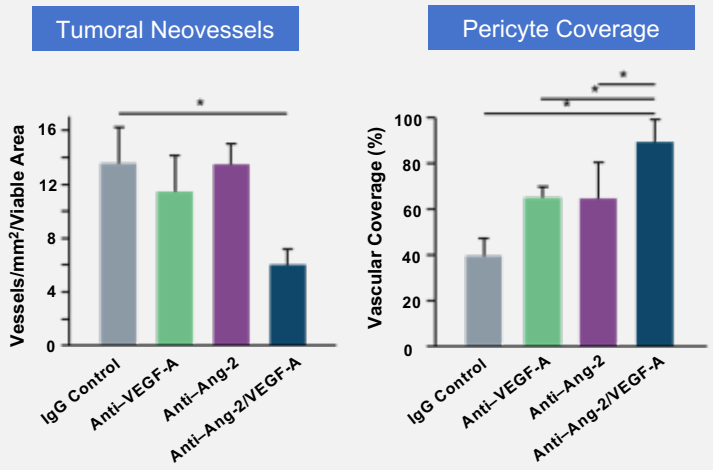
CNV Cynomolgus Monkey Model



- Dual Ang-2/VEGF-A inhibition significantly reduced the severity of vessel leakage

Neovascularization[2]

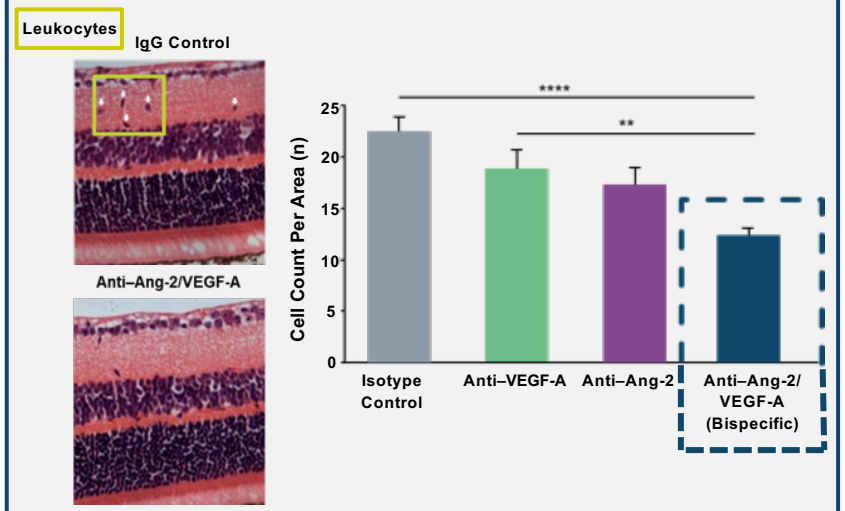
Human Breast Tumor-Bearing Mouse Model



- Dual Ang-2/VEGF-A inhibition promoted vessel stability by synergistically reducing angiogenesis and enhancing pericyte coverage

Inflammation[1]

Mouse Endotoxin-Induced Uveitis Model



- Dual Ang-2/VEGF-A inhibition synergistically reduced leukocyte transmigration in the retina

1. Regula JT et al. *EMBO Mol Med*. 2016;8(11):1265-1288, with correction in Regula JT et al. *EMBO Mol Med*. 2019;11(5):e10666. 2. Kienast Y et al. *Clin Cancer Res.* 2013;19(24):6730-6740.
Error bars show standard error of the mean. Significance by analysis of variance and Tukey's multiple *t* test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$. * $P \leq 0.04$.
Ang-2, angiopoietin-2; CNV, choroidal neovascularization; Fab, fragment antigen binding; IgG, immunoglobulin G; VEGF-A, vascular endothelial growth factor-A.

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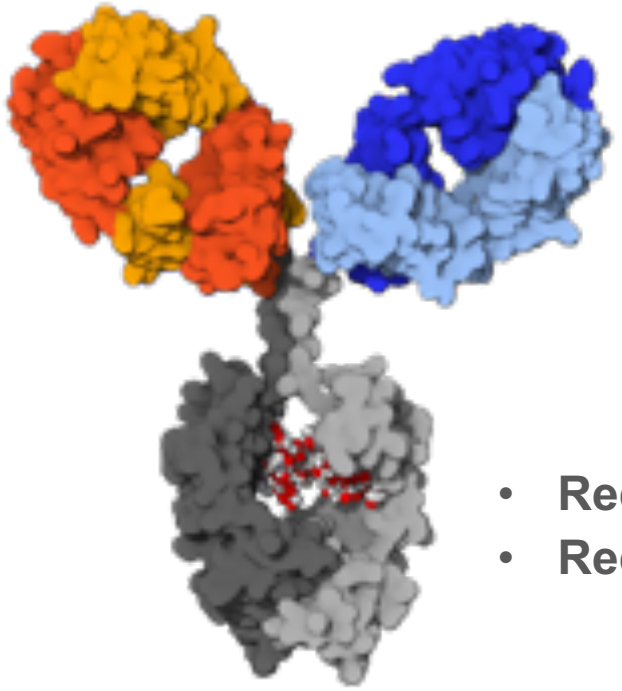
Faricimab: First Bispecific Antibody Designed for Intraocular Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

1 molecule, 2 targets

Anti–Ang-2 Fab

Enhances vessel stabilization



Anti–VEGF-A Fab

Inhibits vascular leakage and neovascularization

Modified Fc

- **Reduced systemic exposure**
- **Reduced inflammatory potential**

CrossMAb molecule representative of faricimab.

Regula JT et al. *EMBO Mol Med*. 2016;8(11):1265-1288, with correction in Regula JT et al. *EMBO Mol Med*. 2019;11(5):e10666.

Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.

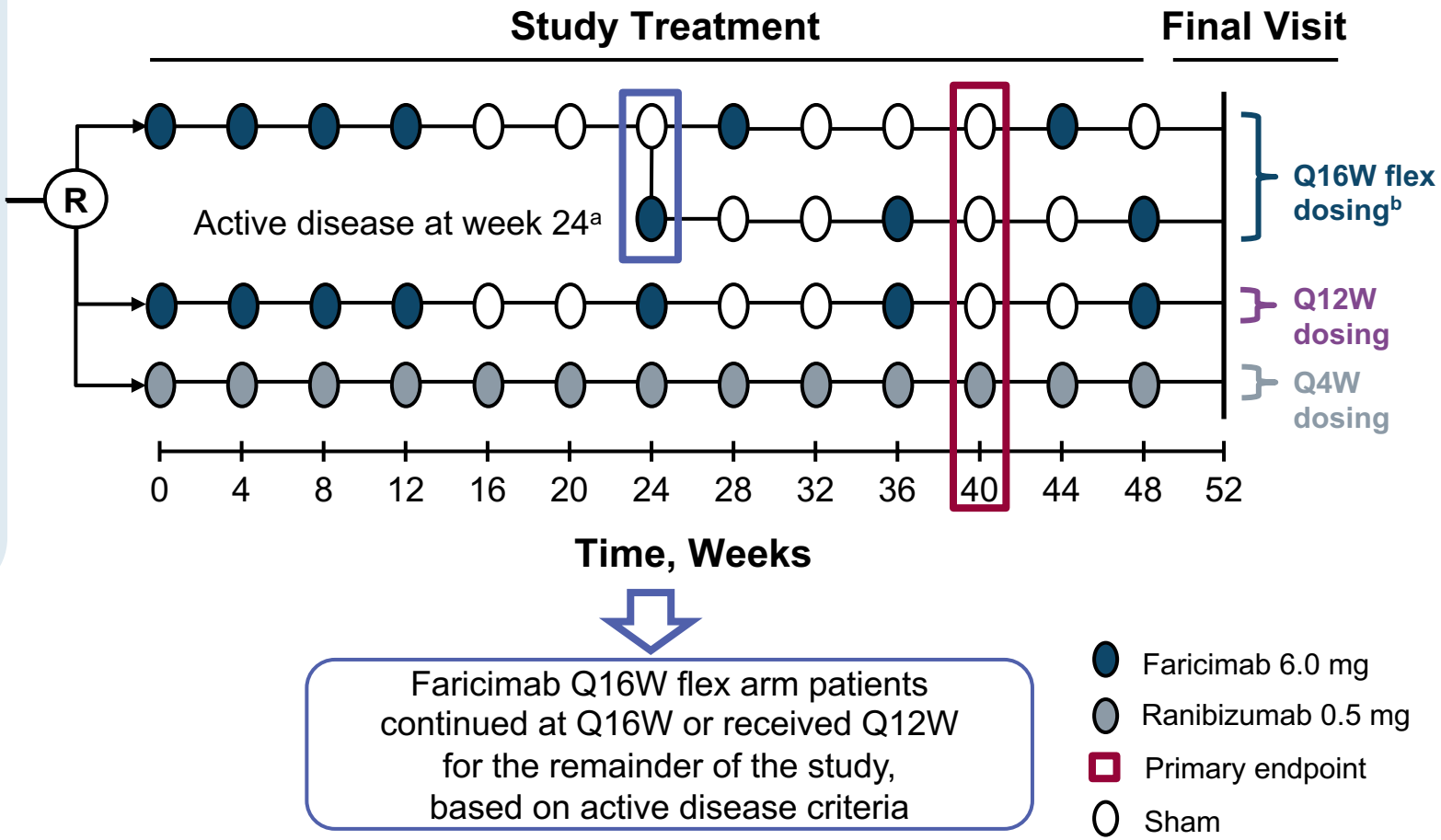
STAIRWAY Was a Phase 2, Multicenter, Randomized, Controlled Clinical Trial of Faricimab in Patients With nAMD

Primary Efficacy Objective:

- To evaluate the efficacy of faricimab administered at 16- and 12-week intervals, as assessed by BCVA

Key Inclusion Criteria:

- Treatment-naïve nAMD
- Subfoveal CNV
- Age ≥ 50 years
- BCVA 20/40–20/320 (73–24 ETDRS letters)



Patients were randomized 2:2:1 into the 3 treatment arms. Data from 1 site are excluded from the analyses owing to Good Clinical Practice noncompliance. N = 76; only 1 eye was chosen as the study eye. [a] Protocol-defined assessment of disease activity at week 24 required Q16W patients with active disease to switch to a Q12W dosing regimen of faricimab 6.0 mg for the remainder of the study, with injections commencing at week 24 and repeated at weeks 36 and 48. [b] The Q16W flex group included faricimab Q16W patients and those required to "drop down" to a faricimab Q12W dosing regimen at week 24 due to active disease. Patients with no week 24 visit assessment are not considered to have active disease at week 24. STAIRWAY clinical trial (NCT03038880). BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; R, randomized.

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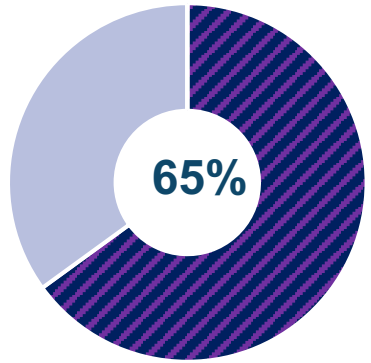
At 12 Weeks After Last Faricimab Loading Dose, 65% of Patients Had No Disease Activity, and Could Potentially Benefit From Q16W Dosing

Disease Activity Was Assessed Using 6 Strict Protocol-Defined Criteria

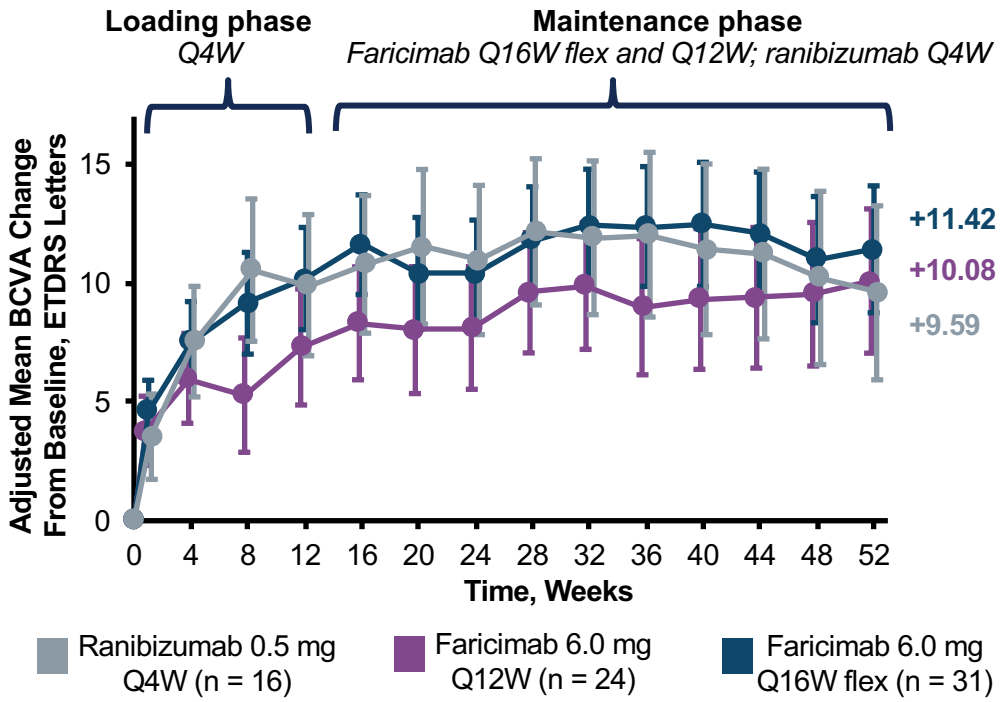
CST ↑	> 50 µm vs **average** CST over last 2 visits on SD-OCT
CST ↑	≥ 75 µm **over lowest** CST over last 2 visits on SD-OCT
BCVA ↓	≥ 5 letters of BCVA vs **average** BCVA over last 2 visits
BCVA ↓	≥ 10 letters of BCVA vs **highest** BCVA over last 2 visits, due to nAMD
Fundus Exam	Presence of new macular hemorrhage
Other Disease Activity	Investigator opinion of significant nAMD disease activity at week 24 that requires immediate treatment

~ $^2/_3$ could be suitable for Q16W dosing

% of faricimab-treated patients free from disease activity 12 weeks after the last initiation dose (36/55 patients)



Maintenance of BCVA Gains With Faricimab Q16W Flex and Q12W Comparable With Ranibizumab Q4W



Vision gains and maintenance with faricimab Q16W flex and Q12W were comparable with ranibizumab Q4W at week 52

Least squares means from linear model analysis of study eye BCVA change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline BCVA. Error bars represent 80% CIs. STAIRWAY clinical trial (NCT03038880). Baseline BCVA, mean (SD), ETDRS letters: ranibizumab Q4W: 55.3 (12.1); faricimab Q12W: 57.8 (10.5); faricimab Q16W flex: 60.4 (10.8).
BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; SD-OCT, spectral-domain optical coherence tomography.

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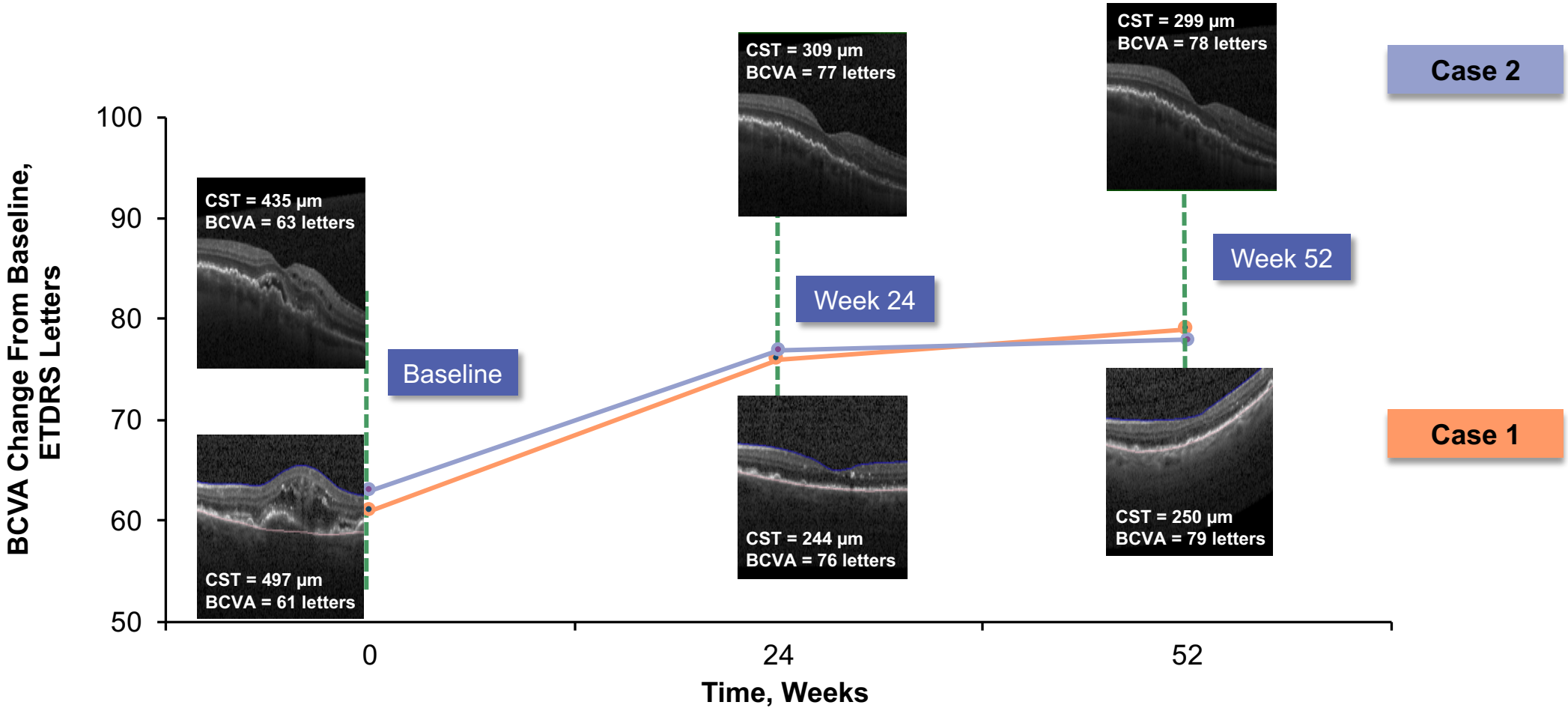
Faricimab Dosed at Extended Q16W Intervals Showed Sustained Anatomic and Visual Improvements

Case Images of Patients From Q16W Flex Arm With No Active Disease at Week 24; Treated With Q16W Dosing Through Study End



Least squares means from linear model analysis of study eye change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline [a] BCVA or [b] CST. STAIRWAY clinical trial (NCT03038880).
BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q16W, every 16 weeks.

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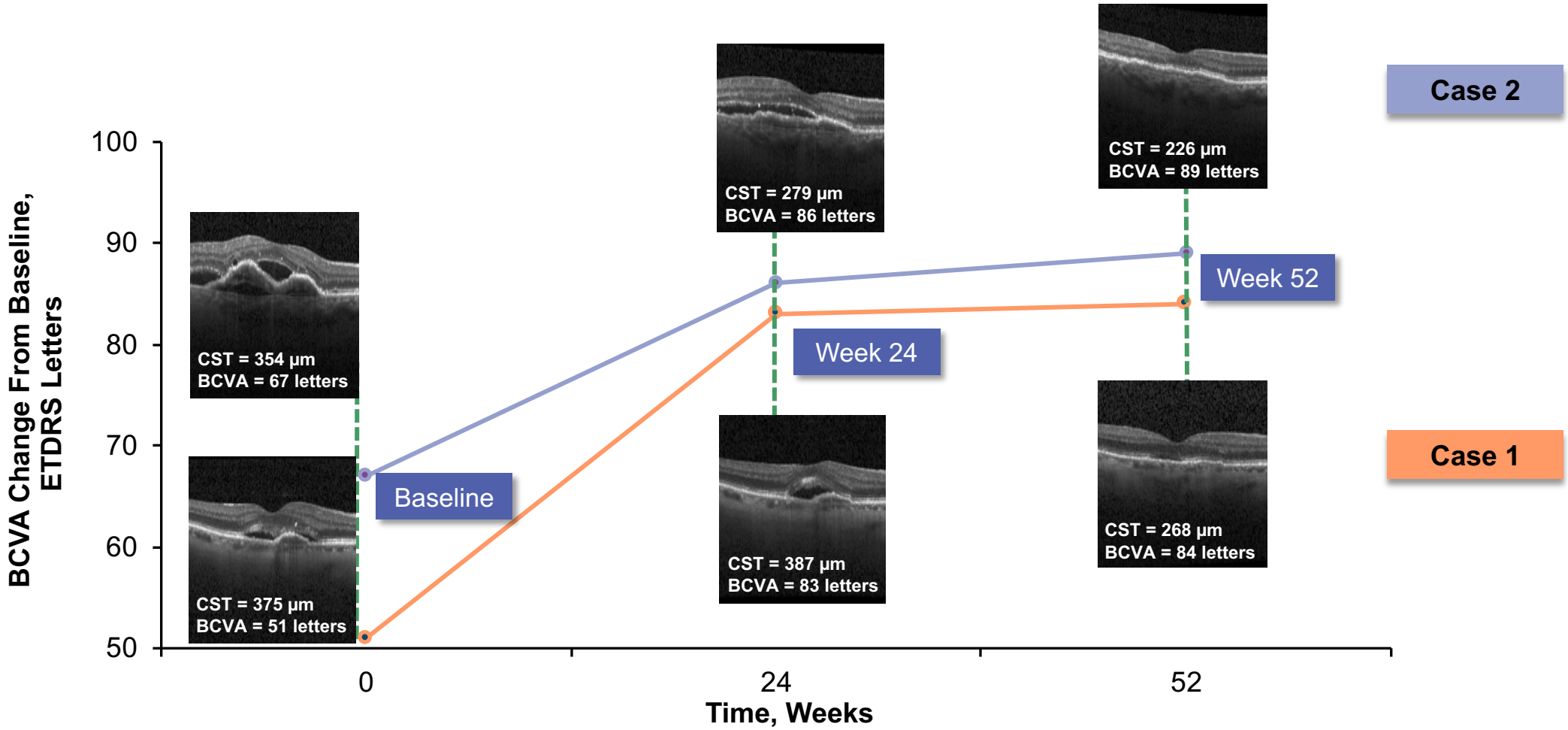
Faricimab Dosed at Extended Q12W Intervals Showed Sustained Anatomic and Visual Improvements

Case Images of Patients From Q16W Flex Arm With Active Disease at Week 24; Treated With Q12W Dosing Through Study End



Least squares means from linear model analysis of study eye change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline [a] BCVA or [b] CST. STAIRWAY clinical trial (NCT03038880).

BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q12W, every 12 weeks; Q16W, every 16 weeks.

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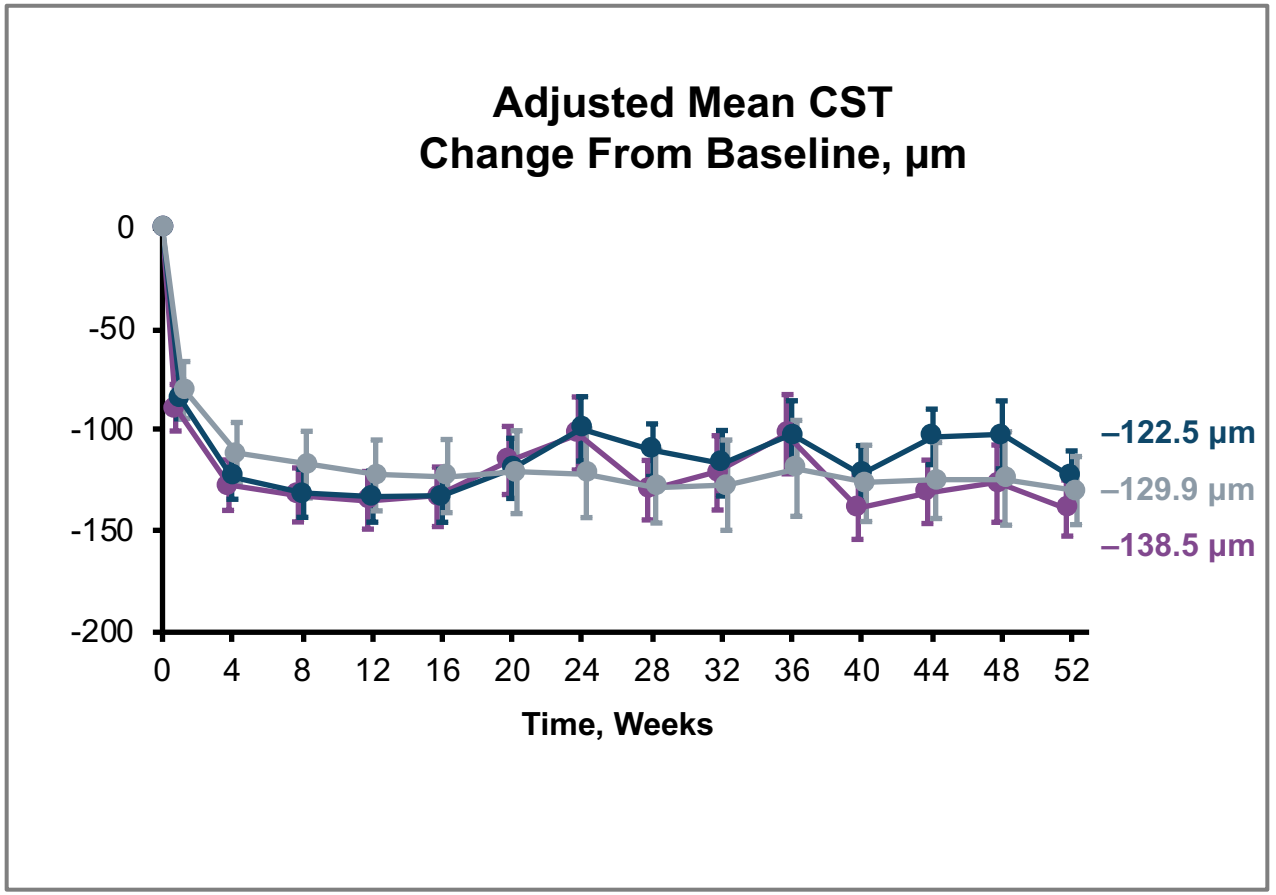
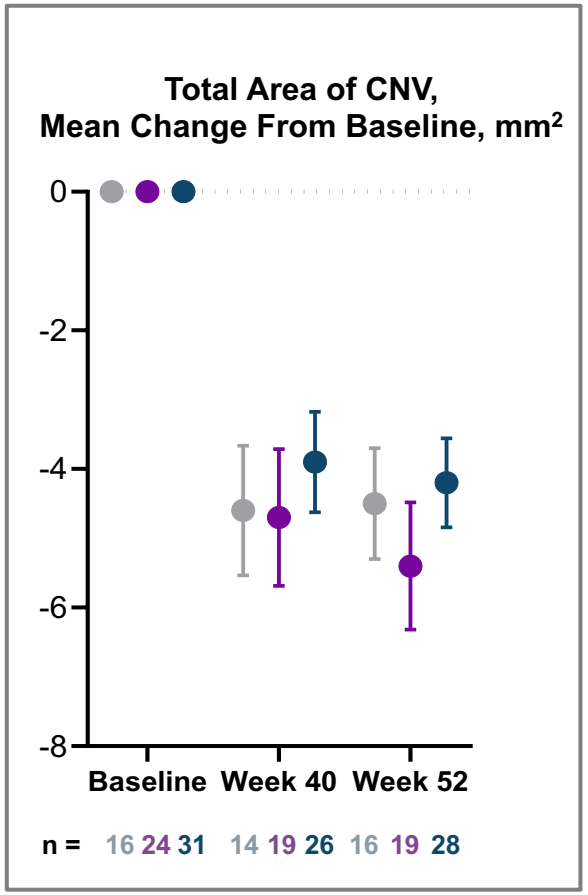
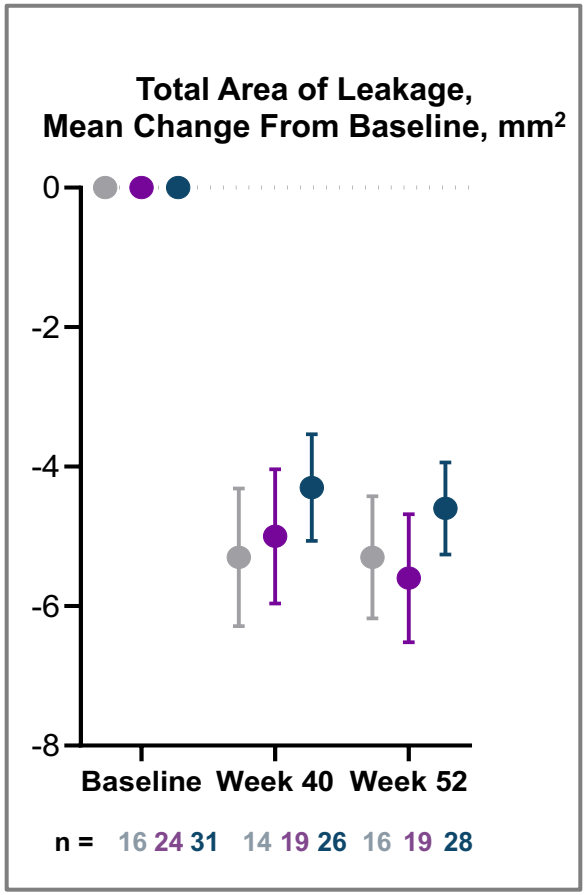
Anatomic Outcomes With Faricimab Q16W Flex and Q12W Were Comparable With Ranibizumab Q4W







Ranibizumab 0.5 mg Q4W (n = 16)

Faricimab 6.0 mg Q12W (n = 24)

Faricimab 6.0 mg Q16W flex (n = 31)

CST (SD-OCT): least squares means from linear model analysis of study eye CST change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline CST. Error bars represent 80% CIs. STAIRWAY clinical trial (NCT03038880). Lesion area and area of leakage (FFA). Error bars represent SE. Baseline sample size: ranibizumab Q4W: 16; faricimab Q12W: 24; faricimab Q16W flex: 31. Baseline CST, mean (SD), µm: ranibizumab Q4W: 443.1 (125.0); faricimab Q12W: 417.9 (84.3); faricimab Q16W flex: 382.2 (80.9). Baseline area of choroidal neovascularization, mean (SD), mm^2: ranibizumab Q4W: 7.3 (2.9); faricimab Q12W: 7.1 (3.9); faricimab Q16W flex: 5.9 (3.8). CST, central subfield thickness; CNV, choroidal neovascularization; FFA, fundus fluorescein angiography; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; SD-OCT, spectral-domain optical coherence tomography.

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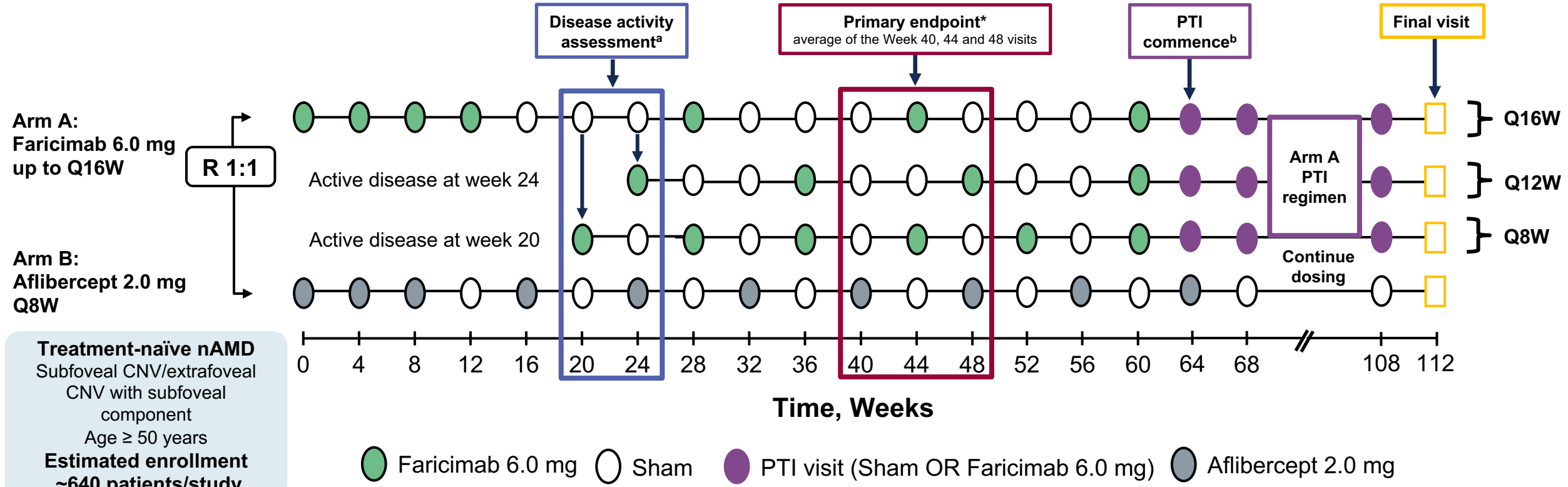
TENAYA and LUCERNE: 2 Global, Randomized, Multicenter, Phase 3 Trials, Designed Based on Phase 2 STAIRWAY, to Assess Efficacy Safety, and Durability of Faricimab in nAMD



Treatment-naïve nAMD
Subfoveal CNV/extrafoveal CNV with subfoveal component
Age ≥ 50 years
Estimated enrollment ~640 patients/study

Primary Study Objective: Mean BCVA change from baseline at Week 48 as an average of Weeks 40, 44 and 48

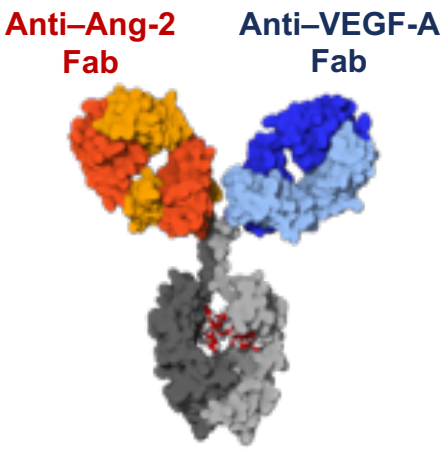
Key Secondary Objective: Proportion of patients on a Q8W, Q12W, or Q16W treatment interval

*Change from baseline in BCVA, as measured on the ETDRS chart at a starting distance of 4 meters, based on an average of the Week 40, 44 and 48 visits. [a]Protocol-defined assessment of disease activity at week 20 and 24. Patients with anatomic or functional signs of disease activity at these timepoints will receive Q8W or Q12W, respectively. [b]PTI: IxRS-guided flexible dosing in faricimab arms starting at Week 60. From Week 60 onward, patients in Arm A will be treated according to a PTI dosing regimen between Q8W and Q16W.
ClinicalTrials.gov. TENAYA study information. https://clinicaltrials.gov/ct2/show/NCT03823287 [last accessed Feb 2020]; ClinicalTrials.gov. LUCERNE study information. https://clinicaltrials.gov/ct2/show/NCT03823300 [last accessed Feb 2020].
BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PTI, personalized treatment interval as specified in study protocol; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; R, randomized.

TENAYA LUCERNE

Conclusions

- In preclinical in vivo models, compared with the inhibition of either Ang-2 or VEGF-A alone, dual inhibition showed synergistic benefits, reducing:
  - Vascular leakage
  - CNV lesion activity
  - Microvascular inflammation
- **STAIRWAY**, a phase 2 trial, showed the potential for extended durability of faricimab in nAMD
  - BCVA gains and anatomic improvements observed in patients treated with faricimab Q12W/Q16W were comparable with ranibizumab Q4W
  - 2/3 (65%) of faricimab-treated patients had no active disease 12 weeks after the last initiation dose
  - Faricimab was well tolerated, with no new safety signals identified
- 2 large global phase 3 trials, TENAYA and LUCERNE, are investigating the efficacy, safety, and durability of faricimab in patients with nAMD



Ang-2, angiopoietin-2; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; Fab, fragment antigen binding; nAMD, neovascular age-related macular degeneration; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; VEGF-A, vascular endothelial growth factor-A.