# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761235Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW of BLA 761235

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|---|---|
| **Application Type** | BLA |
| **Application Number** | 761235 |
| **Priority or Standard** | Priority |
| **Submit Date** | May 28, 2021 |
| **Received Date** | May 28, 2021 |
| **PDUFA Goal Date** | January 28, 2022 |
| **Division/Office** | DO/OND/OSM |
| **Reviewer Name** | Lucious Lim, MD, MPH |
| **Review Completion Date** | November 13, 2021 |
| **Established/Proper Name** | faricimab-xxxx |
| **(Proposed) Trade Name** | Vabysmo |
| **Applicant** | Genentech, Inc. |
| **Dosage Form(s)** | Intravitreal injection |
| **Applicant Proposed Dosing Regimen(s)** | Neovascular (wet) age-related macular degeneration: Faricimab 6 mg (0.05 mL) is recommended to be administered by intravitreal injection. The initial treatment is 1 injection every 4 weeks (approximately 28 days, monthly) for four doses, followed by additional injection (b) (4)<br><br>Diabetic macular edema: Faricimab 6 mg (0.05 mL) is recommended to be administered by intravitreal injection. The initial treatment is 1 injection every 4 weeks (approximately 28 days, monthly) for four doses, followed by additional injection (b) (4) |
| **Applicant Proposed Indication** | Treatment of patients with:<br>• Neovascular (wet) age-related macular degeneration (nAMD)<br>• Diabetic macular edema (DME)<br>• Diabetic retinopathy (DR) |
| **Recommended Regulatory Action** | Recommend approval for treatment of patients with:<br>• Neovascular (wet) age-related macular degeneration (nAMD)<br>• Diabetic macular edema (DME) |
| **Recommended Indication** | Treatment of patients with:<br>• nAMD<br>• DME |

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## Glossary

| | |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| AH | aqueous humor |
| AMD | age-related macular degeneration |
| ANCOVA | analysis of covariance |
| Ang-2 | angiopoietin-2 (protein) |
| anti-VEGF | anti-vascular endothelial growth factor |
| APTC | Anti-Platelet Trialist's Collaboration |
| ATE | arterial-thromboembolic event |
| BARs | Bioanalytical Report |
| BCVA | best-corrected visual acuity |
| BLQ | below the limit of quantitation |
| BM | Bruch's membrane |
| CEC | Clinical Events Committee |
| CFP | color fundus photograph |
| CMH | Cochran-Mantel-Haenszel |
| CNV | choroidal neovascularization |
| COVID-19 | Coronavirus Disease 2019 |
| CRC | central reading center |
| CSR | clinical study report |
| CST | central subfield thickness |
| CV | coefficient of variation |
| EC | Ethics Committee |
| eCRF | electronic case report form |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| FFA | fundus fluorescein angiography |
| ICGA | indocyanine green angiography |
| ICH | International Council for Harmonization |
| iDDC | independent Data Coordination Center |
| iDMC | independent Data Monitoring Committee |
| ILM | internal limiting membrane |
| IMP | investigational medicinal product |
| IOI | intraocular inflammation |
| IOP | intraocular pressure |
| IRB | institutional review board |
| ITT | intent-to-treat |
| IxRS | interactive web-response system |
| LLD | low luminance deficit |
| LLOQ | lower limit of quantification |

| | |
|---|---|
| LOCF | last observation carried forward |
| LPLV | last patient, last visit |
| MAR | missing at random |
| MMRM | mixed-effect model for repeated measures |
| nAMD | neovascular age-related macular degeneration |
| NEI-VFQ-25 | National Eye Institute 25-Item Visual Functioning Questionnaire |
| OCT | optical coherence tomography |
| OCT-A | optical coherence tomography-angiography |
| PCV | polypoidal choroidal vasculopathy |
| PD | pharmacodynamic |
| PDMS | Protocol Deviation Management System |
| PK | pharmacokinetic |
| PP | per-protocol |
| PT | Preferred Term |
| PTI | personalized treatment interval |
| Q4W | every 4 weeks |
| Q8W | every 8 weeks |
| Q12W | every 12 weeks |
| Q16W | every 16 weeks |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD-OCT | spectral-domain optical coherence tomography |
| SOC | System Organ Class |
| SS-OCT | swept-source optical coherence tomography |
| UWP | ultra-wide photography |
| VA | visual acuity |
| VEGF--A | vascular endothelial growth factor-A |
| YAG | yttrium aluminum garnet |

# 1. Executive Summary

## 1.1. Product Introduction

Faricimab is a humanized antibody of the CrossMAb format that binds vascular endothelial growth factor A (VEGF) and angiopoietin-2 (Ang-2).

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

BLA 761235 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of BEOVU for the treatment of neovascular (wet) age-related macular degeneration and diabetic macular edema (b) (4)

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Integrated Assessment**

The adequate and well controlled studies (GR40306 [TENAYA] and GR40844 [LUCERNE]) contained in this submission establish the efficacy of Vabysmo (faricimab (b) (4)-xxxx) injection, 6 mg (0.05 mL) for the treatment of neovascular (wet) age-related macular degeneration (nAMD) when the product is administered intravitreally every 4 weeks (approximately every 28 days, monthly) for the first four doses, and then administered at intervals (b) (4). This demonstration of efficacy is based on non-inferiority in mean change from baseline in BCVA at Week 40 with a 4-letter noninferiority margin.

The adequate and well controlled studies (GR40349 [YOSEMITE] and GR40398 [RHINE]) contained in this submission establish the efficacy of Vabysmo (faricimab (b) (4)-xxxx) injection, 6 mg (0.05 mL) for the treatment of diabetic macular edema (DME) when the product is administered intravitreally every 4 weeks (approximately every 28 days, monthly) for the first four doses, and then administered at intervals of (b) (4). This demonstration of efficacy is based on non-inferiority in mean change from baseline in BCVA at Week 40 with a 4-letter noninferiority margin.

(b) (4)

The most common ocular adverse events after treatment with faricimab for nAMD were conjunctival hemorrhage and worsening nAMD. The most common ocular adverse events after treatment with faricimab for DME were cataract and conjunctival hemorrhage.

There is a favorable benefit-risk ratio of faricimab 6 mg (0.05 mL) in the treatment of neovascular (wet) age-related macular degeneration (nAMD) and DME with some of the proposed dosing regimens.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide.<br>• The neovascular form of AMD makes up about 10% of all AMD cases, but accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.<br>• The natural history of untreated wet AMD is that most eyes lose a letter of visual acuity each month.<br>• Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus (DM). The pathology includes microvascular leakage followed by proliferation of abnormal vessels (PDR).<br>• The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by edema and retinal thickening. | The goal of treatment of wet AMD is the preservation of the central retina (macula) and the preservation of central visual acuity.<br><br>The goal of treatment of DR and DME is to prevent or stop progression of DR and DME. |
| **Current Treatment Options** | • Lucentis, Eylea and Beovu have been shown to be safe and effective and are approved for the treatment of nAMD. The use of Avastin is supported by adequate and well controlled studies, but a BLA for its use intravitreal use has never been submitted.<br>• Lucentis and Eylea have been shown to be safe and effective and are approved to treat DME and DR in patients with and without DME. | Faricimab was non-inferior to aflibercept in the treatment of nAMD and DME. Faricimab would provide practitioners with an additional treatment option. |
| **Benefit** | • Studies TENAYA and LUCERNE demonstrate that faricimab was non-inferior to aflibercept in change from baseline in best-corrected visual acuity (BCVA) averaged over Weeks 40/44/48 in patients with nAMD.<br>• Studies YOSEMITE and RHINE demonstrate that faricimab was non-inferior to aflibercept in change from baseline in best-corrected visual acuity (BCVA) averaged over Weeks 48/52/56 in patients with DME. | Adequate and well controlled studies support the efficacy of faricimab in patients with nAMD and DME. Use of the product led to patients maintaining stable vision (losing less than 15 letters in BCVA). |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Risk and Risk Management** | • The impact of faricimab on corneal endothelial health has not been evaluated. The safety profile of Vabysmo was otherwise similar to the safety profile of the approved anti-VEGF products. | The following phase 4 commitment is recommended: conduct a study to examine endothelial cell count in a minimum of 100 eyes treated with faricimab at baseline and at the end of a trial of at least 12 months. |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide. Ten to thirteen percent of individuals over age 65 in North America, Europe and Australia are affected. Genetic, environmental, and health factors are strongly associated with development of AMD. AMD is classified into two different forms: the non-neovascular or atrophic (dry) form and the neovascular or exudative (wet) form.

Neovascular age-related macular degeneration (nAMD) is characterized by the new growth of abnormal blood vessels (neovascularization) emanating from the subjacent choroid in the subretinal pigment epithelium (RPE) space and the subretinal space. These growths are termed choroidal neovascular membranes (CNV or CNVM). These newly formed vessels have an increased likelihood to leak blood and serum causing separation of Bruch's membrane, RPE and retina from each other and resulting in the accumulation of sub-RPE, sub-retinal or intra-retinal fluid. Fluid accumulation leads to a generalized thickening of the retina and/or the formation of cystic spaces. These pathological manifestations of the retina cause the photoreceptors to become misaligned and eventually degenerative changes occur with cell loss and eventual fibrosis and scar tissue formation. This damage to the retina results in progressive, severe vision loss, metamorphopsia, scotoma, photopsia, and impaired dark adaptation. Without treatment, most affected eyes will have poor central vision (20/200) within 12 months. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it has accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.

Diabetic retinopathy (DR) and diabetic macular edema (DME) are complications of both Type 1 and Type 2 diabetes mellitus (DM). The pathology includes microvascular leakage followed by proliferation of abnormal vessels (PDR). The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by edema and retinal thickening in the macula.

## 2.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection) was approved for the treatment of neovascular AMD in 2006 for DME in 2012, DR with DME in 2015 and DR without DME in 2017.

Eylea (aflibercept) was approved for the treatment of neovascular AMD in 2011, DME in 2014, and DR with and without DME in 2019.

Beovu (brolucizumab) was approved for the treatment of neovascular AMD in 2019.

Avastin (bevacizumab) is prescribed off-label for the indication.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Faricimab has not been marketed in the U.S.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

- IND received August 29, 2013
- Chemistry, manufacturing, and controls (CMC) Type C meeting held April 3, 2017
- Clinical Type C meeting for nAMD, and DME/DR programs held November 17, 2017
- End-of-Phase 2 (EOP2) meeting for DME/DR program held April 24, 2018
- End-of-Phase 2 (EOP2) meeting for nAMD program held August 30, 2018
- Statistical Type C WRO for nAMD, and DME/DR programs January 15, 2020
- CMC Type C WRO March 17, 2020
- Pre-BLA meeting scheduled for July 7, 2020 and cancelled after receiving preliminary comments.

## 3.3. Foreign Regulatory Actions and Marketing History

Faricimab has not been approved for marketing in any other countries.

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

Four clinical sites (one each from TENAYA, LUCERNE, YOSEMITE, and RHINE) were selected for inspection. The final OSI review is pending. See CDTL review for complete findings.

## 4.2. Product Quality

Faricimab (6 mg/0.05 mL) drug product is a sterile, colorless to brownish-yellow solution in a sterile single-use 2 mL vial. It contains no preservatives. Each single-use, 2 mL vial contains 6 mg (nominal) of faricimab at target pH 5.5. The drug product is formulated as 120 mg/mL faricimab.

**Components and Quantitative Composition of Faricimab Drug Product- 6 mg/0.05 mL**

| Component | Nominal Amount per Vial | Concentration | Function | Specification |
|---|---|---|---|---|
| Faricimab | 600 mg | 120 mg/mL | Active ingredient | See Product Quality review |
| L-Histidine | 155 µg | 20 mmol/L | (b) (4) | USP-NF/Ph. Eur./JP |
| Acetic acid (b) (4) | QS to pH 5.5 | - | | Ph. Helv.[a] |
| L-Methionine | 52.2 µg | 7 mmol/L | | USP-NF/Ph. Eur./JP |
| Sodium chloride | 73.1 µg | 25 mmol/L | | USP-NF/Ph. Eur./JP |
| D-Sucrose | 2.74 mg | 160 mmol/L | | USP-NF/Ph. Eur./JP |
| Polysorbate 20 | 20.00 µg | 0.4 mg/mL | | USP-NF/Ph. Eur./JPE |
| Water for injection | QS to 0.05 mL | - | | USP-NF/Ph. Eur./JP |

[a] Manufactured by supplier (b) (4) acid USP-NF/Ph. Eur./JP.

Refer to the Product Quality review for further details.

### 4.3. Clinical Microbiology

This product is not an anti-infective.

### 4.4. Nonclinical Pharmacology/Toxicology

See CDTL review for complete findings.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

| **Study Name / Phase** | **Study Design** | **Number of Patients Enrolled** | **Study Drug Treatment Groups**<br><br>**Duration of Follow-up** | **Primary Efficacy Analysis / Outcome Measures** |
|---|---|---|---|---|
| **Efficacy and Safety Studies (nAMD)** | | | | |
| TENAYA (GR40306)<br><br>Module 5.3.5.1 | Phase 3, multicenter, randomized, double-masked, active-controlled, parallel-group study to evaluate safety, efficacy, and PK of faricimab in patients with nAMD | Total randomized=671<br><br>Faricimab=334<br>Aflibercept=337 | • Faricimab: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108<br>• Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to Week 108 | **Primary Endpoint:** Change from baseline in BCVA (as measured on the ETDRS chart) averaged over Weeks 40, 44, and 48 |

| Study Name / Phase | Study Design | Number of Patients Enrolled | Study Drug Treatment Groups<br><br>Duration of Follow-up | Primary Efficacy Analysis / Outcome Measures |
|---|---|---|---|---|
| | | | Patients will return for a final visit at Week 112<br><br>48 weeks for the primary Analysis and 108 weeks for the study | |
| LUCERNE (GR40844)<br><br>Module 5.3.5.1 | Same as TENAYA | Total randomized=658<br><br>Faricimab=331<br>Aflibercept=327 | Same as TENAYA | Same as TENAYA |
| STAIRWAY (CR39521)<br><br>Module 5.3.5.1. | **Study Design:**<br>Phase 2, multicenter, randomized, active-controlled, double-masked, parallel group (three treatment arms) study to evaluate safety, efficacy, and PK in treatment-naïve patients with nAMD | Total randomized=76<br><br>Faricimab Q12W= 29<br>Faricimab Q16W= 31<br>Ranibizumab Q4W = 16 | • 6 mg faricimab Q12W<br>• 6 mg faricimab Q16W<br>• 0.5 mg ranibizumab Q4W<br><br>40 weeks for the primary Analysis and 52 weeks for the study | **Primary Endpoint:**<br>Mean change from baseline best corrected visual acuity (BCVA) at Week 40 |
| AVENUE (BP29647)<br><br>Module 5.3.5.1 | **Study Design:**<br>Phase 2, multicenter, randomized, active-controlled, double-masked, parallel group (five treatment arms) study to evaluate safety, efficacy, and PK in treatment-naïve patients with nAMD | Total randomized = 273<br><br>1.5 mg faricimab Q4W=47<br>6 mg faricimab Q4W=42<br>6 mg faricimab Q8W=47<br>0.5 mg ranibizumab Q4W=68<br>0.5 mg ranibizumab Q4W + 6 mg faricimab Q4W=69 | Intravitreal injections<br>• 1.5 mg faricimab Q4W: 1.5 mg faricimab Q4W for 32 weeks<br><br>• 6 mg faricimab Q4W: 6 mg faricimab Q4W for 32 weeks<br><br>• 6 mg faricimab Q8W: 6 mg faricimab Q4W up to Week 12, followed by Q8W (i.e., on Weeks 20 and 28)<br><br>• 0.5 mg ranibizumab Q4W: 0.5 mg ranibizumab Q4W for 32 weeks<br><br>• 0.5 mg ranibizumab Q4W + 6 mg faricimab Q4W: 0.5 mg ranibizumab Q4W up to Week 8, followed by 6 mg faricimab intravitreal injections Q4W to Week 32<br><br>36 weeks for the primary | **Primary Endpoint:**<br>Mean change from baseline best corrected visual acuity (BCVA) at Week 36 |

| **Study Name / Phase** | **Study Design** | **Number of Patients Enrolled** | **Study Drug Treatment Groups**<br><br>**Duration of Follow-up** | **Primary Efficacy Analysis / Outcome Measures** |
|---|---|---|---|---|
| | | | Analysis and up to 40 weeks for the study | |

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| | | | | |
|---|---|---|---|---|
| **Efficacy and Safety Studies (DME and DR)** | | | | |
| YOSEMITE (GR40349)<br><br>Module 5.3.5.1 | **Study Design:** Phase 3, multicenter, randomized, double-masked, active-controlled, parallel-group study to evaluate safety, efficacy, and PK of faricimab in patients with DME | Total randomized=940<br><br>Faricimab Q8W =315<br>Faricimab PTI =313<br>Aflibercept Q8W=312 | • Faricimab Q8W: 6 mg intravitreal faricimab injections Q4W to Week 20 followed by Q8W to Week 96<br>• Faricimab PTI b: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96<br>• Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96<br><br>56 weeks for the primary analysis and 96 weeks for the study | **Primary Endpoint:** Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at 1 year (averaged over Weeks 48, 52, and 56)<br>**Key Secondary Endpoint:** Proportion of patients with a ≥ 2-step diabetic retinopathy severity (DRS) improvement from baseline on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) at Week 52 |
| RHINE (GR40398)<br><br>Module 5.3.5.1 | Same as YOSEMITE | Total randomized=951<br><br>Faricimab Q8W = 317<br>Faricimab PTI = 319<br>Aflibercept Q8W =315 | Same as YOSEMITE | Same as YOSEMITE |
| BOULEVARD (BP30099))<br><br>Module 5.3.5.1 | **Study Design:** Phase 2, multicenter, randomized, double-masked, active-controlled, parallel-group study to evaluate safety, tolerability, efficacy, and PK of faricimab in patients with DME | Total randomized=229<br><br>Faricimab 1.5 mg= 55<br>Faricimab 6.0 mg= 84<br>Ranibizumab 0.3 mg =90 | • Faricimab 1.5 mg Q4W<br>• Faricimab 6.0 mg Q4W<br>• Ranibizumab 0.3 mg Q4W<br><br>24 weeks for the primary analysis and 40 weeks for the study | **Primary Endpoint:** Mean change in BCVA (ETDRS letters) from baseline at Week 24 |
| **Safety Study (nAMD and DME)** | | | | |
| JP39844 | **Study Design:** Phase 1, multicenter, open-label, ascending dose study to evaluate safety, tolerability, PK, and PD of faricimab in Japanese patients with nAMD and DME | Total enrolled =12<br><br>nAMD = 4<br>DME = 8 | Faricimab 1.5 mg or 6 mg Q4W (3 doses) | Safety, tolerability, PK, and PD |

## 5.2. Review Strategy

Clinical data for Studies TENAYA and LUCERNE listed in Section 5.1 were reviewed to support safety and efficacy for the indication nAMD. Clinical data for Studies YOSEMITE and RHINE listed in Section 5.1 were reviewed to support safety and efficacy for the indications DME and DR. Clinical data from the additional studies in Section 5.1 were reviewed as appropriate to support safety.

# 6. Review of Relevant Individual Trials Used to Support Efficacy

## 6.1. Study GR40306 (TENAYA)– A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients with Neovascular Age-related Macular Degeneration (nAMD)

### 6.1.1. Study Design

**Primary Objective:** To evaluate the efficacy of intravitreal injections of the 6 mg dose of faricimab on best corrected visual acuity (BCVA).

**List of Investigators**
There were 149 study center(s) in 15 countries: United States (53), United Kingdom (15), Japan (29), Canada (9), Poland (7), Spain (8), Israel (5), Hungary (4), Russia (3), Italy (3), Turkey (3), Germany (3), Mexico (3), Netherlands (2), and Switzerland (2).

**Table 6.1.1-1 Investigator(s) Who Randomized 10 or more Subjects**

| Site Number | Principal Investigator Site Address | Number of Subjects Randomized |
|---|---|---|
| 319088 | Goldstein,Michaella<br>Tel Aviv Sourasky MC; Ophthalmology<br>6 weizman st<br>Tel Aviv,6423906,<br>ISRAEL | 10 |
| 320820 | Escobar, Joan Josep<br>Hospital dos de maig; servicio de oftalmologia<br>carrer del dos de maig 301<br>Barcelona,BARCELONA,08025,<br>SPAIN | 16 |
| 319411 | Huddleston, Stephen<br>(Calzada, Jorge)<br>Charles Retina Institute<br>1432 Kimbrough Rd.<br>Germantown,TN,38138,<br>UNITED STATES | 17 |
| 319418 | Chang, Emmanuel<br>Retina & Vitreous of Texas<br>2727 Gramercy St.<br>Houston,TX,77025,<br>UNITED STATES | 10 |
| 319471 | Rich, Ryan (Chittum, Mark)<br>Retina Consultants of Southern<br>2770 North Union Blvd., Suite 140<br>Colorado Springs | 15 |
| 319558 | Eichenbaum, David<br>Retina Vitreous Assoc of FL<br>4344 Central Avenue<br>Saint Petersburg,FL,33711,<br>UNITED STATES | 11 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 319587 | Amini, Payam<br>California Eye Specialists<br>2619 East Colorado Blvd Suite 150<br>PASADENA,CA,91107,<br>UNITED STATES | 14 |
| 319602 | Khanani, Arshad*<br>Sierra Eye Associates<br>950 Ryland Street<br>Reno, NV,89502,<br>UNITED STATES | 22 |
| 319612 | Patel, Apurva<br>(Dreyer, Richard)<br>Retina Northwest<br>2525 NW Lovejoy Street, Suite 100<br>Portland, OR, 97210,<br>UNITED STATES | 12 |
| 319613 | London, Nikolas<br>Retina Consultants, San Diego<br>12630 Monte Vista Road, Suite 104 & 209<br>POWAY,PA,92064,<br>UNITED STATES | 15 |
| 319624 | Brown, David M.<br>Retina Consultants of Houston<br>6560 Fannin St., Suite 750<br>Houston, TX,77030,<br>UNITED STATES | 14 |

* Routine site inspection of this site was performed by the Office of Scientific Investigations.

**Overall Design:**
This was a Phase 3, prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of faricimab 6 mg with aflibercept 2 mg in treatment-naïve subjects with neovascular age-related macular degeneration (nAMD). Approximately 640 subjects were planned for randomization with a 1:1 allocation ratio to receive:

**Treatment Arm A**: 6 mg faricimab every 4 weeks (Q4W) up to Week 12 (four injections). At Week 20, following a protocol-defined assessment of disease activity, patients with active disease received faricimab at that visit and continued on a fixed-Q8W dosing regimen until Week 60. At Week 24, patients with active disease received faricimab at that visit and continued on a fixed-Q12W dosing regimen until Week 60. The remaining patients who did not have active disease at Week 20 or Week 24 were treated with a fixed Q16W dosing regimen of faricimab until Week 60.

**Weeks 20 and 24 Disease Activity Criteria**
For patients randomized to receive faricimab (Arm A), determination of active disease at Weeks 20 and 24 were made if any of the following criteria were met:

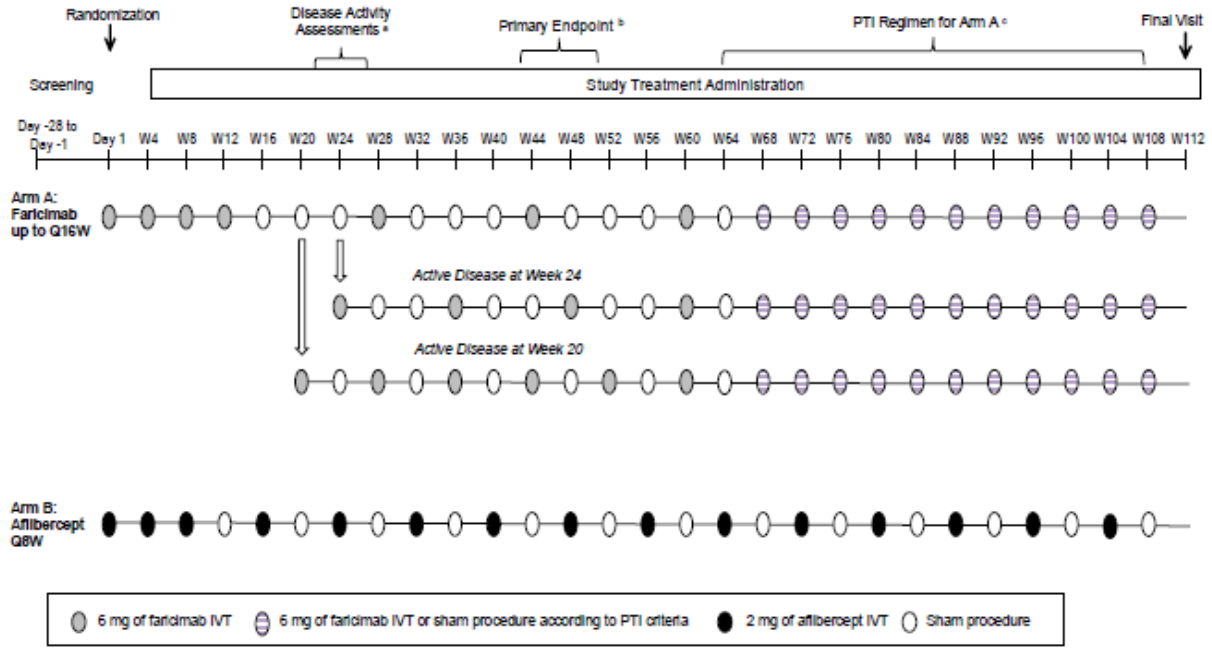
- Increase > 50 µm in central subfield thickness (CST) compared with the average CST value over the previous two scheduled visits (Weeks 12 and 16 for the Week 20 assessment and Weeks 16 and 20 for the Week 24 assessment)
  **Or**
- Increase ≥ 75 µm in CST compared with the lowest CST value recorded at either of the previous two scheduled visits
  **Or**
- Decrease ≥ 5 letters in BCVA compared with average BCVA value over the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)
  **Or**
- Decrease ≥ 10 letters in BCVA compared with the highest BCVA value recorded at either of the previous two scheduled visits, owing to nAMD disease activity (as determined by the investigator)
  **Or**
- Presence of new macular hemorrhage (as determined by the investigator), owing to nAMD activity

From Week 60, all patients were treated according to a personalized treatment interval (PTI) dosing regimen up to Week 108. (PTI dosing criteria were defined in the protocol).

**Treatment Arm B**: 2 mg aflibercept Q4W up to Week 8 (three injections), followed by 2 mg aflibercept Q8W up to Week 108

The total study duration was 112 weeks.

## Study Schema




BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; IVT=intravitreal; PTI=personalized treatment interval; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; W=Week.

[a] At Weeks 20 and 24, patients will undergo a disease activity assessment. Patients with anatomic or functional signs of disease activity at these timepoints will receive Q8W or Q12W dosing, respectively, rather than Q16W dosing.

[b] The primary endpoint is the change from baseline in BCVA (as assessed on the ETDRS chart at a starting distance of 4 meters) based on an average at Weeks 40, 44, and 48.

[c] From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W).

Patients in both treatment arms completed scheduled study visits at Q4W intervals up to the primary endpoint and will continue for the entire study duration (112 weeks).

**Inclusion Criteria**

Patients must meet the following criteria for study entry:

### General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent
  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization, and in other countries, as applicable according to national laws.
- Age ≥ 50 years on Day 1
- Ability to comply with the study protocol, in the investigator's judgment

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive measures that result in failure rate <1% per year during the treatment period and for at least 3 months after the final dose of study treatment. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. Examples of acceptable contraceptive methods include bilateral tubal ligation, male sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices. Contraception methods that do not result in a failure rate of < 1% per year such as male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide are not acceptable. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For patients enrolled in the *Japan* extension at *Japanese* sites: current residents of *Japan*

**Ocular Inclusion Criteria for Study Eye**

Patients must meet the following ocular criteria for study entry:

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or juxtafoveal*/extrafoveal* CNV with a subfoveal component related to the CNV activity *identified* by FFA or OCT (*where CNV activity is defined as showing evidence of* subretinal fluid, subretinal hyper-reflective material, *or* leakage)
- CNV lesion of any type (i.e., predominantly classic, minimally classic, or occult [including polypoidal choroidal vasculopathy and retinal angiomatous proliferation]) that exhibits **all** of the following characteristics:
  - A total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤ 9 disc areas on FFA
  - A CNV component area of ≥ 50% of the total lesion size on FFA
  - Active CNV confirmed on FFA (evidence of leakage)
  - CNV exudation confirmed on OCT (presence of fluid)
- BCVA of 78 to 24 letters, inclusive (20/32 to 20/320 approximate Snellen equivalent), using the ETDRS protocol and assessed at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

**Exclusion Criteria**

Patients who meet any of the following criteria will be excluded from study entry:

**General Exclusion Criteria**

Patients who meet any of the following general exclusion criteria will be excluded from study entry:

- Any major illness or major surgical procedure within 1 month before screening

- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for > 12 months
- Requirement for continuous use of any medications and treatments indicated in, Prohibited Therapy
- Systemic treatment for suspected or active systemic infection on Day 1 Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor
- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure > 100 mmHg while a patient is at rest on Day 1 If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or *historical or current* clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Pregnancy or breastfeeding, or intention to become pregnant during the study
- Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study-related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1

**Ocular Exclusion Criteria for Study Eye**

Patients who meet any of the following ocular exclusion criteria for the study eye will be excluded from study entry:

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid
- Presence at screening of central serous chorioretinopathy
- Retinal pigment epithelial tear involving the macula on Day 1
- On FFA/CFP:
  – Subretinal hemorrhage of > 50% of the total lesion area and/or that involves the fovea
  – Fibrosis or atrophy of > 50% of the total lesion area and/or that involves the fovea
- Any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction)

that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study
- Current vitreous hemorrhage on Day 1
- Uncontrolled glaucoma
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded -8 diopters of myopia.
- Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (e.g., anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, $C_3F_8$, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (*e.g.*, pars plana vitrectomy, glaucoma surgery, corneal transplant, or radiotherapy)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

**Ocular Exclusion Criteria for Fellow (Non-Study) Eye**
Patients who meet the following exclusion criterion for the fellow eye (non-study eye) *at both the screening and Day 1 visits* will be excluded from study entry:
- Non-functioning non-study eye, defined as either:
  – BCVA of hand motion or worse
  – No physical presence of non-study eye (i.e., monocular)

**Exclusion Criteria for Both Eyes**
Patients who meet the following exclusion criteria for either eye will be excluded from study entry:
- Prior IVT administration of faricimab in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

**Test and Reference Therapies**
Faricimab and aflibercept were supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials. The sham vial was empty and remained empty throughout the sham treatment.

**Treatment masking**
Both treatment arms (faricimab up to Q16W and aflibercept Q8W) maintained Q4W study visits for the duration of the study. To preserve masking of the randomized treatment arm, patients had the sham procedure performed at study treatment visits when they were not treated with either faricimab or aflibercept as applicable per their treatment arm schedule. The sham was a

procedure that mimicked an IVT injection and involved the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

**Reviewer's Comments:** *Patients can often tell that they are receiving a sham injection instead of an actual injection.*

**Prohibited Medications/Treatments**
Use of the following medications were prohibited during the study:

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
- IVT anti-VEGF agents (other than study-assigned aflibercept or faricimab) in the study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex®, Illuvien®), or chronic topical (ocular) corticosteroids in the study eye
- Concurrent use of any macular photocoagulation or photodynamic therapy with verteporfin in the study eye
- Other experimental therapies (except those comprising vitamins and minerals)

**Pharmacokinetics**
Plasma samples to determine concentrations of faricimab or aflibercept, free VEGF-A, free Ang-2, anti-drug (faricimab) antibodies (ADAs), and additional biomarkers (PD sample) were collected.

**Safety Assessments** consisted of collecting all adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments (hematology, serum chemistry, urinalysis, and coagulation), measuring protocol-specified vital signs (temperature, pulse rate, respiratory rate, pulse rate, and BP), and performing protocol-specified ocular assessments (such as detailed ocular examinations, including indirect ophthalmoscopy, slit-lamp examination, and IOP).

**Statistical Methods**

**Primary Efficacy Endpoint -** Change from baseline in BCVA averaged over Weeks 40, 44, and 48

**Analysis Populations**

- Intent-to treat (ITT) population – all randomized patients
- Per protocol (PP) population – all patients randomized in the study who receive at least one dose of study treatment and who do not have a major protocol violation.
- Safety population – all patients who receive at least one injection of active study drug (faricimab or aflibercept).

**Noninferiority Margin**
The FDA Clinical Review team agreed to a non-inferiority margin of 4 letters.

**Safety Analyses**
The safety analyses were conducted on the safety population. Safety evaluations through Week 48 included adverse events, clinical laboratory tests, and vital signs and the 4-month safety update.

**Compliance with Good Clinical Practices**
This study was conducted per the principles of Good Clinical Practices (GCP).

**Figure 6.1.1-2 Evaluation and Visit Schedule**

| | | Visit Day | | Visit Week | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening [a] | 1 [a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | ET [b] |
| Day(s) (Visit window) | –28 to –1 | N/A | (±3) | 28 (±7) | 56 (±7) | 84 (±7) | 112 (±7) | 140 (±7) | 168 (±7) | 196 (±7) | 224 (±7) | 252 (±7) | 280 (±7) | 308 (±7) | 336 (±7) | (≥28) |
| Informed consent [c] | x | | | | | | | | | | | | | | | |
| Sample informed consent [c] for optional aqueous, vitreous, and blood samples | x | | | | | | | | | | | | | | | |
| Optional (RBR) residual samples and DNA whole blood sample informed consent [c] | x | | | | | | | | | | | | | | | |
| Review of inclusion and exclusion criteria | x | x | | | | | | | | | | | | | | |
| Demographic data | x | | | | | | | | | | | | | | | |
| Medical history [d] | x | | | | | | | | | | | | | | | |
| Targeted physical examination [e] | x | | | | | | | | | | | | | | | x |
| Body weight and height | x | | | | | | | | | | | | | | | |
| Vital signs [f] | x | x | | | | | | | | | | | | | x | x |
| NEI VFQ-25 [g] | | x | | | | | | | x | | | | | | x | x |
| BCVA [h] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Low-luminance BCVA | | x | | | | | | | | | | | | | x | |
| Pre-treatment IOP [i] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

**Figure 6.1.1-2 Evaluation and Visit Schedule (continued)**

| | | Visit Day | | Visit Week | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening [a] | 1 [a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | |
| Day(s)<br>(Visit window) | –28 to –1 | N/A | (±3) | 28<br>(±7) | 56<br>(±7) | 84<br>(±7) | 112<br>(±7) | 140<br>(±7) | 168<br>(±7) | 196<br>(±7) | 224<br>(±7) | 252<br>(±7) | 280<br>(±7) | 308<br>(±7) | 336<br>(±7) | ET [b]<br>(≥28) |
| Pregnancy test [j] | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| *Whole blood sample* (hematology, chemistry panel, coagulation), and urinalysis [k] | x | | | | | | | | | | | | | | x | |
| Optional aqueous humor sample [l] | | x | x | | | | x | x | x | x | | | | | | x |
| Optional vitreous humor sample [m] | | If elective vitrectomy is performed [m] | | | | | | | | | | | | | | |
| *Optional PK plasma sample (if vitreous humor sample collected)* [m] | | *If elective vitrectomy is performed and vitreous humor sample collected* [m] | | | | | | | | | | | | | | |
| Optional blood sample for RBR [n] | | x | | | | | | | | | | | | | | |
| *Mandatory* plasma PK sample [o] | | x | | x | | | x | x | | | | | | | x | x |
| Optional PK plasma sample (if aqueous humor sample is collected) | | | x [p] | | | | | | | | | | | | | |
| *Mandatory* plasma PD sample [o] | | x | | x | | | x | x | | | | | | | x | x |
| Optional PD plasma sample (if aqueous humor sample is collected) | | | x [p] | | | | | | | | | | | | | |
| *Mandatory* plasma sample for ADAs [o] | | x | | x | | | | x | | | | | | | x | x |
| Slitlamp examination | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

**Figure 6.1.1-2 Evaluation and Visit Schedule (continued)**

| | | Visit Day | | Visit Week | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening [a] | 1 [a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | |
| Day(s)<br>(Visit window) | –28 to –1 | N/A | (±3) | 28<br>(±7) | 56<br>(±7) | 84<br>(±7) | 112<br>(±7) | 140<br>(±7) | 168<br>(±7) | 196<br>(±7) | 224<br>(±7) | 252<br>(±7) | 280<br>(±7) | 308<br>(±7) | 336<br>(±7) | ET [b]<br>(≥28) |
| Indirect ophthalmoscopy | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| OCT [q] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Optional OCT-A [q, r] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| FFA [q] | x | | | | | | | | | | | | | | x | x |
| CFP [q] | x | | | | | | | | | | | | | | x | x |
| Optional ICGA [q, s] | x | | | | | | | | | | | | | | x | |
| Disease activity assessment [t] | | | | | | | | x | x | | | | | | | |
| Administration of study treatment | | x | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Finger counting test [u] | | x | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Post-treatment IOP [v] | | x | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Adverse events [w] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications [x] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concurrent ocular procedures [y] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

ADA=anti-drug antibody; BCVA=best-corrected visual acuity; CFP=color fundus photograph; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; ICGA=indocyanine green angiography; IOP=intraocular pressure; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; OCT=optical coherence tomography; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; RBR=Research Biosample Repository; VA=visual acuity.

### 6.1.2. Study Results

**Table 6.1.2-1 Subject Disposition - ITT Population**

| | Faricimab 6 mg n (%) | Aflibercept 2 mg n (%) |
|---|---|---|
| **Week 48 Analysis** | | |
| **All randomized** | 334 (100) | 337 (100) |
| **Randomized and treated** | 333 (99.7) | 336 (99.7) |
| **Discontinued treatment prior to Week 48*** | | |
| Total | 26 (7.8) | 15 (4.5) |
| **Reason for Discontinuation** | | |
| Adverse event | 2 (0.6) | 3 (0.9) |
| Death | 4 (1.2) | 1 (0.3) |
| Lack of efficacy | 1 (0.3) | 0 |
| Lost to follow-up | 4 (1.2) | 3 (0.9) |
| Protocol deviation | 1 (0.3) | 0 |
| Withdrawal by subject | 10 (3.0) | 8 (2.4) |
| Physician decision | 2 (0.6) | 0 |
| Other reason | 2 (0.6) | 0 |
| **Discontinued study prior to Week 48**** | | |
| Total | 15 (4.5) | 14 (4.2) |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

Source: Study TENAYA CSR, Table 2
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Over 90% of subjects in both the faricimab and aflibercept treatment groups completed Week 48. The number of subjects who discontinued the study prior to Week 48 were 15 (4.5%) for faricimab and 14 (4.2%) for aflibercept. Withdrawal by the subject, was the most common reason for discontinuation (~3%) for both treatment groups.*

**Table 6.1.2-2 Summary of Major Protocol Deviations (ITT) – Week 48 Analysis**

| Type of Deviation | Faricimab 6 mg (N=334) n (%) | Aflibercept 2 mg (N=337) n (%) |
|---|---|---|
| Total # patients with at least one major protocol deviation | 143 (42.8) | 160 (47.5) |
| Total # Major Protocol Deviations | 289 | 269 |
| Total # patients with at least one procedural major protocol deviation | 141 (42.2) | 151 (44.8) |
| Total Procedural Major Protocol Deviations | 274 | 251 |
| Selected missed visits | 71 (21.3) | 85 (25.2) |
| SE: Major issues with images | 31 (9.3) | 24 (7.1) |
| Optional samples collected from a patient who did not provide consent | 26 (7.8) | 26 (7.7) |
| Study treatment inadvertently not administered at an attended visit | 14 (4.2) | 11 (3.3) |
| SE: ETDRS, BCVA assessment not done or testing stopped too early | 13 (3.9) | 10 (3.0) |
| Incorrect BCVA/LL-BCVA entered in IxRS leading to incorrect stratification | 7 (2.1) | 11 (1.6) |
| Unmasked MD performed masked MD task | 6 (1.8) | 6 (1.8) |
| Other significant procedural deviation issues | 3 (0.9) | 5 (1.5) |
| SAE/AESI not reported in timely manner | 2 (0.6) | 6 (1.8) |
| Incorrect IXRS data entry impacting treatment interval assuming subject is in Arm A | 3 (0.9) | 4 (1.2) |
| Masked MD performed unmasked MD task | 4 (1.2) | 1 (0.3) |
| ICF not signed by patient in timely manner | 1 (0.3) | 1 (0.3) |
| Patient treatment inadvertently unmasked | 2 (0.6) | 0 |
| VA examiner unmasked to the patient's study eye | 0 | 2 (0.6) |

Source: Study TENAYA CSR, Table 4
AESI = Adverse Event of Special Interest; BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IxRS = Interactive Voice Response System; LL-BCVA = Low-luminance BCVA; MD = Doctor of Medicine; SAE = Serious Adverse Event; SE = Study Eye; tx = Treatment; VA = Visual acuity.
Table includes major protocol deviations related and not related to COVID-19 and occurred on or prior to Day 349 (last day of Week 48 analysis visit window). Selected missed visits are weeks 4, 8, 12, 20, 24, 36, 40, 44, and 48. Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Arm A = Faricimab 6 mg.
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.

**Reviewer's Comment:** *A total of 303 subjects, 143 (42.8%) in the faricimab arm and 160 (47.5%) in the aflibercept arm had major protocol deviations during the study. There were no significant differences between treatment groups.*

**Table 6.1.2-3 Analysis Populations – Week 48 Analysis**

| Analysis Population | Faricimab 6 mg (N=334) n (%) | Aflibercept 2 mg (N=337) n (%) |
|---|---|---|
| Intent-to-Treat (ITT) (as Randomized) | 334 (100) | 337 (100) |
| Safety (as Treated) | 333 (99.7) | 336 (99.7) |
| Per-Protocol (PP) (as Treated) | 284 (85.0) | 295(87.5) |

Source: Study TENAYA CSR, Table 3

**Table 6.1.2-4 Subject Demographics (ITT) – Week 48 Analysis**

| | Faricimab 6 mg (N=334) n (%) | Aflibercept 2 mg (N=337) n (%) |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 75.9 (8.6) | 76.7 (8.8) |
| Min, Median, Max | 50, 77, 99 | 51, 77, 95 |
| **Age group, n (%)** | | |
| < 75years | 130 (38.9) | 124 (36.8) |
| ≥ 75years | 204 (61.1) | 213 (63.2) |
| **Sex, n (%)** | | |
| Female | 191 (57.2) | 211 (62.6) |
| Male | 143 (42.8) | 126 (37.4) |
| **Race, n (%)** | | |
| White | 303 (90.7) | 302 (89.6) |
| Asian | 26 (7.8) | 28 (8.3) |
| American Indian or Alaska Native | 1 (0.3) | 2 (0.6) |
| Black or African American | 0 | 3 (0.9) |
| Unknown | 3 (0.9) | 2 (0.6) |
| Multiple | 1 (0.3) | 0 |

Source: Study TENAYA CSR Table 5

**Reviewer's Comment:** *Overall, the study population had a mean age of 77 years, was majority female (60%), and white (90%) which is consistent with the disease population.*

**Table 6.1.2-5 Baseline Ocular Characteristics (ITT) – Week 48 Analysis**

| Baseline Characteristic | Faricimab 6 mg (N=334) n (%) | Aflibercept 2 mg (N=337) n (%) |
|---|---|---|
| **CNV Lesion type by FFA, n (%)** | | |
| n | 334 | 337 |
| Occult | 177 (53.0) | 174 (51.6) |
| Classic | 84 (25.1) | 73 (21.7) |
| Minimally classic | 32 (9.6) | 30 (8.9) |
| RAP | 14 (4.2) | 27 (8.0) |
| Predominantly classic | 17 (5.1) | 19 (5.6) |
| Missing///No Done | 4 (1.2) | 8 (2.4) |
| PCV | 6 (1.8) | 6 (1.8) |
| **Total Area of CNV Lesion by FFA, $mm^2$** | | |
| n | 330 | 330 |
| Mean (SD) | 4.7 (4.8) | 4.5 (4.1) |
| Min, Median, Max | 0, 3.2, 35 | 0, 3.4, 21 |
| Missing/Not Done | 4 | 7 |
| **CNV Location by FFA** | | |
| n | 334 | 337 |
| Subfoveal | 201 (60.2) | 186 (55.2) |
| Juxafoveal | 88 (26.3) | 88 (26.1) |
| Extrafoveal | 41 (12.3) | 55 (16.3) |
| Missing/Not Done | 4 (1.2) | 8 (2.4) |
| **BCVA, number of letters, n (%)** | | |
| n | 334 | 337 |
| Mean (SD) | 61.3 (12.5) | 61.5 (12.9) |
| Min, Median, Max | 26, 65, 78 | 24, 65, 78 |
| ≥ 74 letters (20/32 or better) | 47 (14.1) | 52 (15.4) |
| 73 – 55 letters (between 20/40 and 20/80) | 200 (59.9) | 201 (59.6) |
| ≤ 54 letters (20/80 or worse) | 87 (26.0) | 84 (24.9) |
| Missing/Invalid | 0 | 0 |
| **CST (ILM-BM), microns** | | |
| n | 328 | 333 |
| Mean (SD) | 486.4 (178.6) | 473.9 (166.8) |
| Min, Median, Max | 199, 437, 1170 | 223, 431, 1226 |
| Missing/Not Done | 6 | 4 |
| **CST (ILM-RPE), microns** | | |

| Baseline Characteristic | Faricimab 6 mg (N=334) n (%) | Aflibercept 2 mg (N=337) n (%) |
|---|---|---|
| n | 328 | 332 |
| Mean (SD) | 360.5 (124.1) | 356.1 (107.0) |
| Min, Median, Max | 124, 331.5, 987 | 148, 333.5, 879 |
| Missing/Not Done | 6 | 5 |
| **Absence of IRF, n (%)** | | |
| n | 327 | 334 |
| Yes | 181 (54.2) | 177 (52.5) |
| No | 146 (43.7) | 157 (46.6) |
| **Absence of SRF, n (%)** | | |
| n | 329 | 332 |
| Yes | 113 (33.8) | 107 (31.8) |
| No | 216 (64.7) | 225 (66.8) |
| **Absence of PED, n (%)** | | |
| n | 329 | 334 |
| Yes | 29 (8.7) | 26 (7.7) |
| No | 300 (89.8) | 308 (91.4) |
| **PCV Status by ICGA, n (%)** | | |
| n | 82 | 36 |
| Yes | 4 (4.9) | 3 (4.2) |
| No | 78 (95.1) | 68 (95.8) |
| **Lens status, n (%)** | | |
| n | 334 | 337 |
| Pseudophakic | 141 (42.2) | 153 (45.4) |
| Phakic | 193 (57.8) | 184 (54.6) |

Source: Study TENAYA CSR, Table 6
BCVA-best corrected visual acuity; BM-Bruch's membrane; CST-central subfield thickness; CNV-choroidal neovascularization; FFA -Fundus fluorescein angiography; ICGA -Indocyanine green angiography; ILM-internal limiting membrane; IRF-intraretinal fluid; PCV-polypoidal choroidal vasculopathy; PED-pigment epithelia detachment; RAP-retinal angiomatous proliferation; RPE-retinal pigment epithelium; SRF-subretinal fluid.

**Reviewer's Comment:** *The baseline ocular characteristics were comparable between treatment groups.*

## Primary Efficacy Results

### Table 6.1.2-6 Change in Baseline in BCVA in the Study Eye Averaged over Week 40/44/48 – MMRM Method*

| | Faricimab 6 mg N=334 | Aflibercept 2 mg N=337 | Difference (faricimab – aflibercept) |
|---|---|---|---|
| **ITT Population[1]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 5.8 (4.6, 7.1) | 5.1 (3.9, 6.4) | |
| Difference (95% CI) | | | 0.7 (-1.1, 2.5) |
| **PP Population[2]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 5.9 (4.5, 7.2) | 5.6 (-4.2, 6.9) | |
| Difference (95% CI) | | | 0.3 (-1.6, 2.2) |

Source: Study TENAYA CSR, Tables 8
* MMRM - mixed-model repeated measurement
1 Primary analysis – MMRM Method
2 Supplementary analysis – MMRM Method

**Reviewer's Comment:** *For the ITT population, the difference between the faricimab and aflibercept arms was 0.7 with a lower limit of the 95% confidence interval = -1.1.*

*For the PP population, the difference between the faricimab and aflibercept arms was 0.3 with a lower limit of the 95% confidence interval = -1.6.*

*The lower limit of the 95% confidence interval for the treatment differences between the faricimab arm and the aflibercept arm met the non-inferiority margin of 4 letters for both the ITT and PP populations (-1.1 and -1.6, respectively).*

## Key Primary Efficacy Sensitivity Analysis

### Table 6.1.2-7 Change in Baseline in BCVA in the Study Eye Averaged over Week 40/44/48 – LOCF: MMRM Method*

| | Faricimab 6 mg N=334 | Aflibercept 2 mg N=337 | Difference (faricimab – aflibercept) |
|---|---|---|---|
| **ITT Population[1]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 5.9 (4.6, 7.1) | 5.1 (3.9, 6.3) | |
| Difference (95% CI) | | | 0.7 (-1.0, 2.5) |

Source: Study TENAYA CSR, Tables 8
* MMRM - mixed-model repeated measurement

**Reviewer's Comment:** *The results of the primary and sensitivity analyses are similar*

## 6.2. Study GR40844 (LUCERNE) – A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients with Neovascular Age-related Macular Degeneration (nAMD)

### 6.2.1. Study Design – Identical to Study GR40306 (TENAYA)

**List of Investigators**

There were 122 study center(s) in the following countries: United States (41), Australia (9), France (9), Republic of Korea (8), Argentina (7), Italy (6), Spain (6), Germany (4), Poland (4), Russia (4), Turkey (4), Hungary (3), Taiwan (3), Austria (2), Brazil (2), Bulgaria (2), Denmark (2), Hong Kong (2), Portugal (2), Singapore (2).

**Table 6.2.1-1 Investigator(s) Who Randomized 10 or More Subjects**

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 320030 | Schlottmann, Patricio<br>ORGANIZACION MEDICA DE INVESTIGACION<br>Uruguay 725 PB<br>Capital Federal,C1015ABO,<br>ARGENTINA | 10 |
| 320031 | Alezzandrini, Arturo<br>Oftalmos<br>Av. Cordoba 1830<br>Capital Federal,C1120AAN,<br>ARGENTINA | 12 |
| 320032 | Furno Sola, Federico<br>Grupo Laser Vision<br>Mariano Moreno 1397<br>Rosario,S2000DLA,<br>ARGENTINA | 19 |
| 320034 | Zeolite, Carlos<br>Oftar<br>Montevideo 513<br>Mendoza,M5500GGK,<br>ARGENTINA | 10 |
| 319551 | Sacu, Stefan<br>Medizinische Universität Wien;<br>Universitätsklinik für Augenheilkunde und Optometrie<br>Währinger Gürtel 18-20,Abteilung A<br>Wien,1090,<br>AUSTRIA | 10 |
| 320481 | Cornut, Pierre Loic<br>Pole Vision Val d'Ouest; Ophtalmologie<br>39 Chemin de la Vernique<br>ECULLY,69130,<br>FRANCE | 10 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 319671 | Toth-Molnar, Edit<br>Szegedi Tudományegyetem ÁOK;<br>Department of Ophtalmology<br>Korányi fasor 10-11<br>Szeged,6720,<br>HUNGARY | 11 |
| 319673 | Vogt, Gábor<br>Magyar Honvedseg Egeszsegugyi Kozpont;<br>Szemészeti Osztály<br>Róbert Károly krt. 44<br>Budapest,1134,<br>HUNGARY | 15 |
| 319678 | Zatorska, Barbara<br>Caminomed<br>Wyszynskiego 3a<br>Tarnowskie Góry,42-600,<br>POLAND | 26 |
| 319488 | Parke, D. Wilkin<br>Vitreoretinal Surgery<br>3601 76th Street West,Suite 300<br>Minneapolis,MN,55435,<br>UNITED STATES | 13 |
| 319489 | Patel, Sunil<br>Retina Res Institute of Texas<br>5441 Health Center Dr.<br>Abilene,TX,79606,<br>UNITED STATES | 20 |
| 319492 | Pearlman, Joel<br>Retinal Consultants Med Group<br>3939 J Street, Suite 106<br>Sacramento,CA,95819,<br>UNITED STATES | 10 |
| 319516 | Sheth, Veeral<br>University Retina and Macula Associates, PC<br>6320 W. 159th St., Suite A<br>Oak Forest,IL,60452,<br>UNITED STATES | 13 |
| 319532 | Warrow, David (Hu,Allen)<br>Cumberland Valley Retina PC<br>1150 Opal Court<br>Hagerstown,MD,21740,<br>UNITED STATES | 21 |
| 319534 | Wells, John A.<br>Palmetto Retina Center<br>124 Sunset Court<br>West Columbia,SC,29169,<br>UNITED STATES | 23 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 319537 | Wykoff, Charles C.<br>Retina Consultants of Houston<br>17350 St. Luke's Way, Ste. 120<br>The Woodlands,TX,77384,<br>UNITED STATES | 23 |
| 319590 | Liu, Mimi<br>Colorado Retina Associates, PC<br>400 Indiana St,Suite 250<br>Golden,CO,80401,<br>UNITED STATES | 11 |
| 319597 | Nielsen, Jared<br>Wolfe Eye Clinic<br>6200 Westown Parkway<br>West Des Moines,IA,50266,<br>UNITED STATES | 10 |

*Routine site inspection was performed by the Office of Scientific Investigations.

### 6.2.2. Study Results

**Table 6.2.2-1 Subject Disposition - ITT Population**

| | Faricimab 6 mg n (%) | Aflibercept 2 mg n (%) |
|---|---|---|
| **Week 48 Analysis** | | |
| **All randomized** | 331 (100) | 327 (100) |
| **Randomized and treated** | 331 (100) | 326 (99.7) |
| **Discontinued treatment prior to Week 48*** | | |
| Total | 18 (5.4) | 22 (6.7) |
| **Reason for Discontinuation** | | |
| Adverse event | 7 (2.1) | 1 (0.3) |
| Death | 2 (0.6) | 5 (1.5) |
| Lack of efficacy | 0 | 2 (0.6) |
| Lost to follow-up | 1 (0.3) | 1 (0.3) |
| Protocol deviation | 1 (0.3) | 1 (0.3) |
| Withdrawal by subject | 6 (1.8) | 8 (2.5) |
| Physician decision | 0 | 4 (1.2) |
| Other reason | 1 (0.3) | 0 |

Source: Study LUCERNE CSR, Table 2
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Over 90% of subjects in both the faricimab and aflibercept treatment groups completed Week 48. The number of subjects who discontinued the study prior to Week 48*

*were 10 (3.0%) for faricimab and 18 (5.5%) for aflibercept. Withdrawal by the subject, was the most common reason for discontinuation (2%) for both treatment groups.*

**Table 6.2.2-2 Summary of Major Protocol Deviations (ITT) – Week 48 Analysis**

| Type of Deviation | Faricimab 6 mg (N=331) n (%) | Aflibercept 2 mg (N=327) n (%) |
|---|---|---|
| Total # patients with at least one major protocol deviation | 123 (37.2) | 131 (40.1) |
| Total # Major Protocol Deviations | 212 | 221 |
| Total # patients with at least one procedural major protocol deviation | 112 (33.8) | 122 (37.3) |
| Total Procedural Major Protocol Deviations | 274 | 251 |
| Selected missed visits | 69 (20.8) | 63 (19.3) |
| SE: Major issues with images | 25 (7.6) | 28 (8.6) |
| Optional samples collected from a patient who did not provide consent | 15 (4.5) | 8 (2.4) |
| Incorrect BCVA/LL-BCVA entered in IxRS leading to incorrect stratification | 7 (2.1) | 8 (2.4) |
| Incorrect IXRS data entry impacting treatment interval assuming subject is in Arm A | 7 (2.1) | 7 (2.1) |
| Study treatment inadvertently not administered at an attended visit | 6 (1.8) | 6 (1.8) |
| SE: ETDRS, BCVA assessment not done or testing stopped too early | 3 (0.9) | 8 (2.4) |
| Other significant procedural deviation issues | 3 (0.9) | 7 (2.1) |
| SAE/AESI not reported in timely manner | 2 (0.6) | 5 (1.5) |
| Non-study staff performed assessment(s) at scheduled study visit | 2 (0.6) | 4 (1.2) |
| ICF not signed by patient in timely manner | 4 (1.2) | 1 (0.3) |
| Unmasked MD performed masked MD task | 2 (0.6) | 3 (0.9) |
| VA examiner unmasked to the patient's study eye | 0 | 3 (0.9) |
| Masked MD performed unmasked MD task | 1 (0.3) | 1 (0.3) |
| Pt randomized without CRC confirmation of eligibility | 1 (0.3) | 0 |

Source: Study LUCERNE CSR, Table 4
AESI = Adverse Event of Special Interest; BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IxRS = Interactive Voice Response System; LL-BCVA = Low-luminance BCVA; MD = Doctor of Medicine; SAE = Serious Adverse Event; SE = Study Eye; tx = Treatment; VA = Visual acuity.
Table includes major protocol deviations related and not related to COVID-19 and occurred on or prior to Day 349 (last day of Week 48 analysis visit window). Selected missed visits are weeks 4, 8, 12, 20, 24, 36, 40, 44, and 48. Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Arm A = Faricimab 6 mg.
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.

**Reviewer's Comment:** *A total of 254 subjects, 123 (37%) in the faricimab arm and 123 (40%) in the ranibizumab arm had major protocol deviations during the study.*

**Table 6.2.2-3 Analysis Populations – Week 48 Analysis**

| Analysis Population | Faricimab 6 mg (N=331) n (%) | Aflibercept 2 mg (N=327) n (%) |
|---|---|---|
| Intent-to-Treat (ITT) (as Randomized) | 331 (100) | 327 (100) |
| Safety (as Treated) | 331 (100) | 326 (99.7) |
| Per-Protocol (PP) (as Treated) | 286 (86.4) | 291 (87.5) |

Source: Study LUCERNE CSR, Table 3

**Table 6.2.2-4 Subject Demographics (ITT) – Week 48 Analysis**

| | Faricimab 6 mg (N=331) n (%) | Aflibercept 2 mg (N=327) n (%) |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 74.8 (8.4) | 76.1 (8.6) |
| Min, Median, Max | 50, 75, 95 | 50, 76, 95 |
| **Age group, n (%)** | | |
| < 75years | 156 (47.1) | 131 (40.1) |
| ≥ 75years | 175 (52.9) | 196 (59.9) |
| **Sex, n (%)** | | |
| Female | 203 (61.3) | 188 (57.5) |
| Male | 128 (38.7) | 139 (42.5) |
| **Race, n (%)** | | |
| White | 278 (84.0) | 270 (82.6) |
| Asian | 38 (11.5) | 34 (10.4) |
| Unknown | 12 (3.6) | 17 (5.2) |
| Black or African American | 2 (0.6) | 5 (1.5) |
| American Indian or Alaska Native | 1 (0.3) | 0 |
| Multiple | 0 | 1 (0.3) |

Source: Study LUCERNE CSR Table 5

**Reviewer's Comment:** *Overall, the study population had a mean age of 76 years, was majority female (59%), and white (83%) which is consistent with the disease population.*

**Table 6.2.2-5 Baseline Ocular Characteristics (ITT) – Week 48 Analysis**

| Baseline Characteristic | Faricimab 6 mg (N=331) n (%) | Aflibercept 2 mg (N=327) n (%) |
|---|---|---|
| **CNV Lesion type by FFA, n (%)** | | |
| n | 331 | 327 |
| Occult | 171 (51.7) | 140 (42.8) |
| Classic | 98 (29.6) | 109 (33.3) |
| Minimally classic | 30 (9.1) | 31 (9.5) |
| RAP | 14 (4.2) | 15 (4.6) |
| Predominantly classic | 6 (1.8) | 16 (4.9) |
| Missing///No Done | 7 (2.1) | 8 (2.4) |
| PCV | 5 (1.5) | 8 (2.4) |
| **Total Area of CNV Lesion by FFA, $mm^2$** | | |
| n | 328 | 320 |
| Mean (SD) | 4.7 (4.7) | 4.3 (4.3) |
| Min, Median, Max | 0, 3.2, 28 | 0, 2.9, 24 |
| Missing/Not Done | 3 | 7 |
| **CNV Location by FFA** | | |
| n | 331 | 327 |
| Subfoveal | 209 (63.1) | 191 (58.4) |
| Juxafoveal | 73 (22.1) | 84 (25.7) |
| Extrafoveal | 42 (12.7) | 44 (13.5) |
| Missing/Not Done | 7 (2.1) | 8 (2.4) |
| **BCVA, number of letters, n (%)** | | |
| n | 331 | 327 |
| Mean (SD) | 58.7 (14.0) | 58.9 (13.3) |
| Min, Median, Max | 24, 61, 78 | 24, 61, 78 |
| ≥ 74 letters (20/32 or better) | 45 (13.6) | 39 (11.9) |
| 73 – 55 letters (between 20/40 and 20/80) | 181 (54.7) | 183 (56.0) |
| ≤ 54 letters (20/80 or worse) | 105 (31.7) | 105 (32.1) |
| Missing/Invalid | 0 | 0 |
| **CST (ILM-BM), microns** | | |
| n | 327 | 324 |
| Mean (SD) | 490.3 (194.9) | 469.6 (176.4) |
| Min, Median, Max | 175, 433.0, 1335 | 201, 428.0, 1225 |

| Baseline Characteristic | Faricimab 6 mg (N=331) n (%) | Aflibercept 2 mg (N=327) n (%) |
|---|---|---|
| Missing/Not Done | 4 | 3 |
| **CST (ILM-RPE), microns** | | |
| n | 327 | 323 |
| Mean (SD) | 353.1 (120.1) | 359.0 (131.1) |
| Min, Median, Max | 133, 323.0, 1011 | 161, 329.0, 1158 |
| Missing/Not Done | 4 | 4 |
| **Absence of IRF, n (%)** | | |
| n | 326 | 325 |
| Yes | 184 (55.6) | 171 (52.3) |
| No | 142 (42.9) | 154 (47.1) |
| **Absence of SRF, n (%)** | | |
| n | 328 | 325 |
| Yes | 107 (32.3) | 103 (31.5) |
| No | 221 (66.8) | 222 (67.9) |
| **Absence of PED, n (%)** | | |
| n | 327 | 325 |
| Yes | 23 (6.9) | 27 (8.3) |
| No | 304 (91.8) | 298 (91.1) |
| **PCV Status by ICGA, n (%)** | | |
| n | 82 | 36 |
| Yes | 4 (4.9) | 3 (4.2) |
| No | 78 (95.1) | 68 (95.8) |
| **Lens status, n (%)** | | |
| n | 331 | 327 |
| Pseudophakic | 141 (42.6) | 142 (43.4) |
| Phakic | 190 (57.4) | 185 (56.6) |

Source: Study LUCERNE CSR, Table 6
BCVA-best corrected visual acuity; BM-Bruch's membrane; CST-central subfield thickness; CNV-choroidal neovascularization; FFA -Fundus fluorescein angiography; ICGA -Indocyanine green angiography; ILM-internal limiting membrane; IRF-intraretinal fluid; PCV-polypoidal choroidal vasculopathy; PED-pigment epithelia detachment; RAP-retinal angiomatous proliferation; RPE-retinal pigment epithelium; SRF-subretinal fluid.

**Reviewer's Comment:** *The baseline ocular characteristics were comparable between treatment groups.*

## Primary Efficacy Results

### Table 6.2.2-6 Change in Baseline in BCVA in the Study Eye Averaged over Week 40/44/48 – MMRM Method*

| | Faricimab 6 mg N=334 | Aflibercept 2 mg N=337 | Difference (faricimab – aflibercept) |
|---|---|---|---|
| **ITT Population[1]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 6.6 (5.3, 7.8) | 6.6 (5.3, 7.8) | |
| Difference (95% CI) | | | 0.0 (-1.7, 1.8) |
| **PP Population[2]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 6.6 (5.2, 7.9) | 6.7 (5.3, 8.0) | |
| Difference (95% CI) | | | -0.1 (-2.0, 1.8) |

Source: Study LUCERNE CSR, Tables 8
* MMRM - mixed-model repeated measurement
[1] Primary analysis – MMRM Method
[2] Supplementary analysis – MMRM Method

**Reviewer's Comment:** *For the ITT population, the difference between the faricimab and aflibercept arms was 0.0 with a lower limit of the 95% confidence interval = -1.7.*

*For the PP population, the difference between the faricimab and aflibercept arms was -0.1 with a lower limit of the 95% confidence interval = -2.0.*

*The lower limit of the 95% confidence interval for the treatment differences between the faricimab arm and the aflibercept arm met the non-inferiority margin of 4 letters for both the ITT and PP populations (-1.7 and -2.0, respectively).*

## Key Primary Efficacy Sensitivity Analysis

### Table 6.2.2-7 Change in Baseline in BCVA in the Study Eye Averaged over Week 40/44/48 – LOCF: MMRM Method*

| | Faricimab 6 mg N=334 | Aflibercept 2 mg N=337 | Difference (faricimab – aflibercept) |
|---|---|---|---|
| **ITT Population[1]** | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 40/44/48 (95% CI) | 6.8 (5.0, 8.0) | 6.6 (5.4, 7.9) | |
| Difference (95% CI) | | | 0.2 (-1.6, 1.9) |

Source: Study LUCERNE CSR, Tables 8
* MMRM - mixed-model repeated measurement
[1] Sensitivity analysis

**Reviewer's Comment:** *The results of the primary and sensitivity analyses are similar.*

## 6.3. Study GR40349 (YOSEMITE) – A Phase II, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients with Diabetic Macular Edema

### 6.3.1. Study Design

**Primary Objective:** Evaluate the efficacy of intravitreal injections of the 6 mg dose of faricimab on best corrected visual acuity (BCVA) outcomes

**List of Investigators**
There were 179 study center(s) in 16 countries: United States (83), Poland (8), Hungary (6), Israel (5), Spain (9), Bulgaria (5), Slovakia (3), Mexico (4), Italy (6), Peru (4), Russian Federation (3), Austria (4), France (4), Germany (5), Turkey (3), and Japan (27).

**Table 6.3.1-1 Investigator(s) Who Randomized 10 or more Subjects**

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 313161 | Daskalov, Vesselin<br>Pentagram Eye Hospital (Medical Center "Pentagram")<br>"Vranya" 109,g k. Sveta Troitsa<br>SOFIA,1309,<br>BULGARIA | 10 |
| 312242 | Seres, András<br>Budapest Retina Associates Kft.<br>Váci út 76. (Capital Square), II. torony, 3. emelet<br>Budapest,1133,<br>HUNGARY | 13 |
| 313038 | Varsanyi, Balazs<br>Ganglion Medial Center<br>Váradi A. u. 10/A.<br>Pécs,7621,<br>HUNGARY | 10 |
| 313212 | Toth-Molnar, Edit<br>Szegedi Tudományegyetem ÁOK;<br>Department of Ophtalmology<br>Korányi fasor 10-11<br>Szeged,6720,<br>HUNGARY | 12 |
| 311926 | Yoreh, Barak<br>Rambam Medical Center; Ophthalmology<br>8 Haaliya Hashniya st<br>Haifa,3109601,<br>ISRAEL | 13 |
| 314730 | Morales Canton, Virgilio<br>Hospital de la Ceguera APEC<br>Vicente García Torres # 46,Col. Barrio San Lucas<br>Mexico, D.F.,04030,<br>MEXICO | 13 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 313002 | Herba, Ewa<br>Szpital Specjalistyczny nr 1; Oddzial Okulistyki<br>ul. Zeromskiego 7<br>Bytom,41-902,<br>POLAND | 12 |
| 313017 | Wylęgała, Edward<br>Gabinet Okulistyczny Prof Edward Wylegala<br>ul. Gallusa 4<br>Katowice,40-594,<br>POLAND | 13 |
| 313093 | Oleksy, Piotr<br>Centrum Medyczne UNO-MED<br>Ul. Dietla 19/3<br>Krakow,31-070,<br>POLAND | 24 |
| 322865 | Gawecki, Maciej<br>DOBRY WZROK SP Z O O<br>ul. Zabi Kruk 10<br>Gdańsk,80-822,<br>POLAND | 23 |
| 312261 | Lipkova, Blandina<br>Fakultna nemocnica s poliklinikou Zilina; Ocne oddelenie<br>ul. Vojtecha Spanyola 43<br>Zilina,012 07,<br>SLOVAKIA | 18 |
| 310902 | Charles, Steve<br>(Calzada,Jorge)<br>Charles Retina Institute<br>1432 Kimbrough Rd.<br>Germantown, TN, 38138,<br>UNITED STATES | 12 |
| 310914 | Danzig, Carl<br>Rand Eye<br>5 West Sample Road<br>Deerfield Beach,FL,33064,<br>UNITED STATES | 15 |
| 310918 | Wykoff, Charles C.<br>Retina Consultants of Houston<br>17350 St. Luke's Way, Ste. 120<br>The Woodlands,TX,77384,<br>UNITED STATES | 17 |
| 310923 | Patel, Sunil<br>Retina Res Institute of Texas<br>5441 Health Center Dr.<br>Abilene,TX,79606,<br>UNITED STATES | 40 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 310924 | Makkouk, Fuad<br>(Jhaveri, Chirag)<br>Retina Research Center<br>3705 Medical Pkwy #420<br>Austin,TX,78705,<br>UNITED STATES | 10 |
| 310937 | Khanani, Arshad<br>Sierra Eye Associates<br>950 Ryland Street<br>Reno,NV,89502,<br>UNITED STATES | 14 |
| 310939 | Newell, Charles<br>Southern Vitreoretinal Assoc<br>2439 Care Dr.<br>Tallahassee,FL,32308,<br>UNITED STATES | 11 |
| 310951 | Heier, Jeffrey<br>Ophthalmic Consultants of Boston<br>50 Staniford Street,Suite 600<br>Boston,MA,02114,<br>UNITED STATES | 12 |
| 311571 | Amini, Payam<br>California Eye Specialists<br>2619 East Colorado Blvd Suite 150<br>PASADENA,CA,91107,<br>UNITED STATES | 13 |
| 311588 | Lee, Seong<br>Strategic Clinical Research Group, LLC<br>101 Chuckwagon Trail<br>Willow Park,TX,76087,<br>UNITED STATES | 13 |
| 311619 | Chang, Emmanuel<br>Retina & Vitreous of Texas<br>2727 Gramercy St,Suite # 200<br>Houston,TX,77025,<br>UNITED STATES | 10 |
| 311733 | Javey, Golnaz<br>Piedmont Eye Center<br>116 Nationwide Dr.<br>Lynchburg,VA,24502,<br>UNITED STATES | 14 |
| 311740 | Wee, Raymond<br>(Kokame,Gregg)<br>Retina Consultants of Hawaii<br>98-1079 Moanalua Road,Suite 470<br>Aiea,HI,96701,<br>UNITED STATES | 10 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 311763 | Stern, Jeffrey<br>Capital Region Retina<br>1365 Washington Ave<br>ALBANY,NY,12206,<br>UNITED STATES | 10 |
| 311764 | Stoltz, Robert<br>Georgia Retina PC<br>833 Campbell Hill Street,Suite 300<br>Marietta,GA,30060,<br>UNITED STATES | 12 |
| 311827 | Hu, Allen<br>Cumberland Valley Retina PC<br>1150 Opal Court<br>Hagerstown, MD, 21740,<br>UNITED STATES | 35 |
| 312995 | Campochiaro, Peter<br>Johns Hopkins Med; Wilmer Eye Inst<br>600 North Wolfe Street<br>BALTIMORE,MD,21287,<br>UNITED STATES | 11 |

* Routine site inspection of this site was performed by the Office of Scientific Investigations.

**Overall Design:**
This was a Phase 3, prospective, randomized, double-masked, three parallel groups, multicenter study designed to compare the efficacy and safety of faricimab 6 mg with aflibercept 2 mg in subjects with diabetic macular edema (DME). Approximately 900 subjects were planned for randomization with a 1:1:1 ratio to receive:

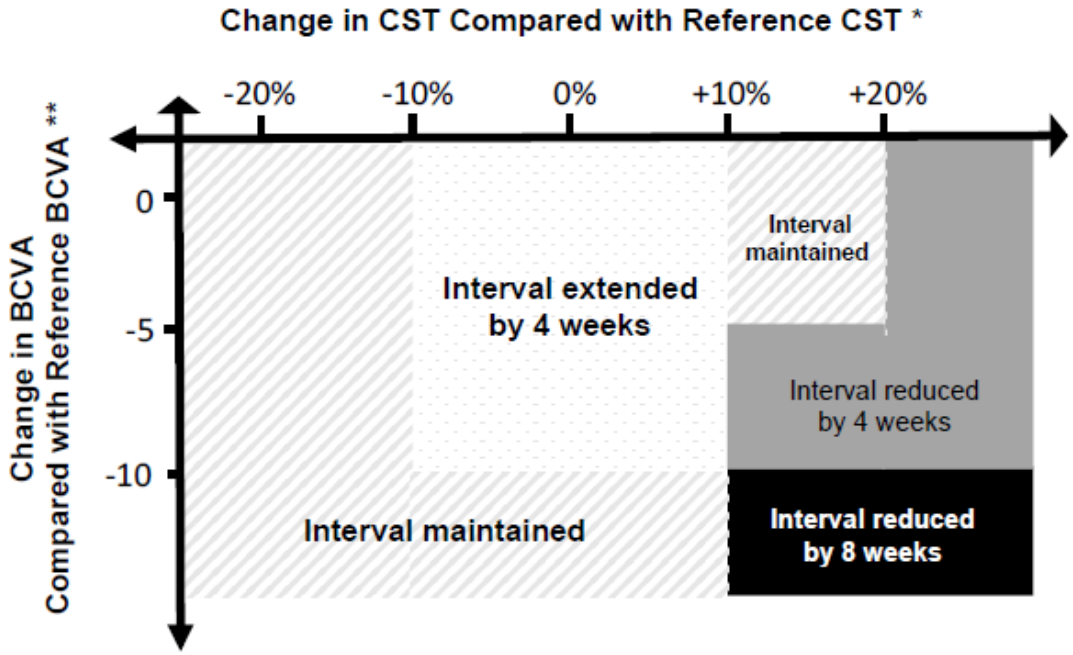
**Treatment Arm A**: 6 mg faricimab every 4 weeks (Q4W) to Week 20, followed by 6 mg faricimab every 8 weeks (Q8W) to Week 96, followed by final study visit at Week 100.
**Treatment Arm B**: 6 mg faricimab Q4W to at least Week 12, followed by Personalized Treatment Interval (PTI) dosing of 6 mg faricimab to Week 96, followed by final study visit at Week 100.
**Treatment Arm C**: 2 mg aflibercept Q8W to Week 16, followed by 2 mg aflibercept Q8W to Week 96, followed by the final study visit at Week 100.

**Treatment Schedule for Patients in the Personalized Treatment Interval Arm (Arm B)**
**Study Drug Dosing Interval Determination**
Patients randomized to the PTI arm (Arm B) were treated with faricimab on a Q4W dosing interval until at least the patient's Week 12 visit, or a later visit when CST met the predefined reference CST threshold (CST < 325 µm for Spectralis SD-OCT, or < 315 µm for Cirrus SD-OCT or Topcon SD-OCT), as determined by the central reading center (CRC). The reference CST (as defined in Figure 2) is used at study drug dosing visits by the interactive voice or web-based response system (IxRS) for the drug dosing interval decision-making.

After a patient's initial reference CST was established, their study drug dosing interval was increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point

forward, the study drug dosing interval was extended, reduced, or maintained based on assessments made at study drug dosing visits. The algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA compared with reference CST and reference BCVA, is outlined in Figure 2.

Figure 2:




BCVA = best-corrected visual acuity; CST = central subfield thickness; PTI = personalized treatment interval.

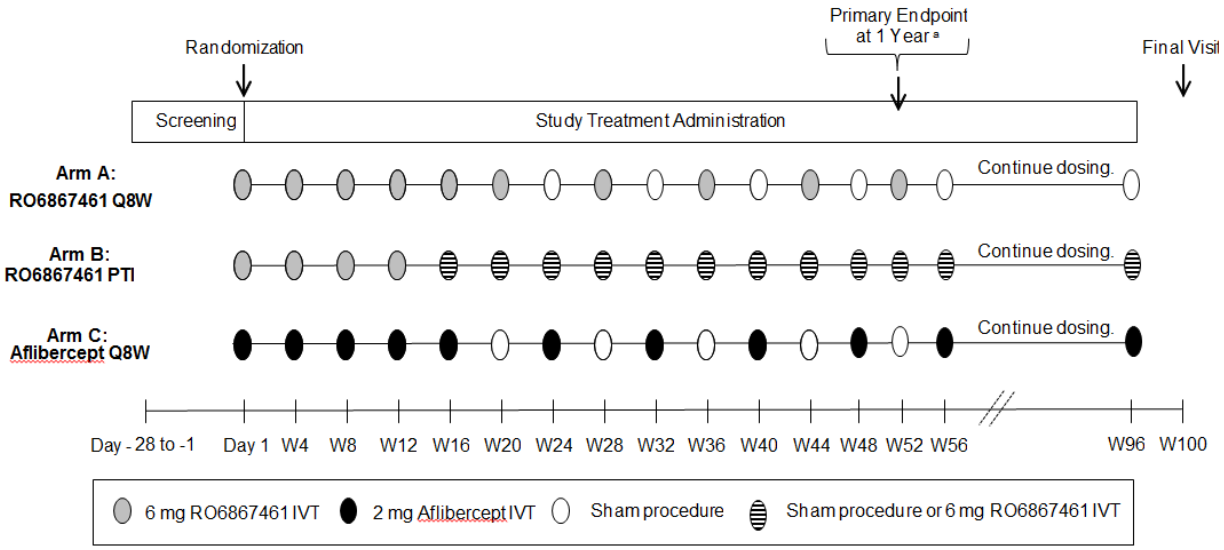
* Reference central subfield thickness (CST): the CST value when the initial CST threshold criteria are met. Reference CST was adjusted if CST decreased by > 10% from the previous reference CST for two consecutive study drug dosing visits and the values obtained were within 30 μm. The CST value obtained at the latter visit served as the new reference CST, starting immediately at that visit.

** Reference best-corrected visual acuity (BCVA): the mean of the three best BCVA scores obtained at any prior study drug dosing visit.

Patients in all three treatment arms were to complete scheduled study visits Q4W for the entire study duration (100 weeks).

The primary analysis was performed when all patients had either completed the study through Week 56 or had discontinued from the study prior to Week 56.

## Study Schema




[a] The definition of 1 year used for the primary efficacy endpoint—defined as the change from baseline in BCVA, as measured on the ETDRS chart at a starting distance of 4 meters at 1 year—is the average of the Week 48, 52, and 56 visits.

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal; Q8W=every 8 weeks; PTI = personalized treatment interval (see Section 3.1.1 for additional details); W = week.

## Inclusion Criteria

### General Inclusion Criteria

Patients had to meet the following general inclusion criteria for study entry:

- Willingness and the ability to provide signed informed consent
  - Additionally, at U.S. sites, patients had to provide Health Insurance Portability and Accountability Act (HIPAA) authorization, and in other countries, as applicable according to national laws.
- Age ≥ 18 years
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin or other injectable drugs (e.g., dulaglutide and liraglutide) for the treatment of diabetes and/or
  - Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
- HbA1c of ≤ 10% within 2 months prior to the Day 1 visit date
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the final dose of study treatment.

**Ocular Inclusion Criteria for Study Eye**
Patients had to meet the following ocular inclusion criteria for the study eye for entry in the study:

- Macular thickening secondary to DME involving the center of the fovea with CST
- ≥ 325 µm, as measured on Spectralis SD-OCT, or ≥ 315 µm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening
- BCVA of 73 to 25 letters, inclusive (20/40 to 20/320 approximate Snellen equivalent), using the ETDRS protocol at the initial testing distance of 4 meters (see the BCVA manual for additional details) on Day 1
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality color fundus photographs (CFPs, including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of DR and assessment of the retina) and other imaging modalities.

**Exclusion Criteria**

**General Exclusion Criteria**
Patients who met any of the following general exclusion criteria were excluded from study entry:

- Currently untreated diabetes mellitus or previously untreated patients who initiated oral or injectable anti-diabetic medication within 3 months prior to Day 1
- History of allergy or hypersensitivity to active drug aflibercept and any of its excipients, fluorescein, or any study treatment-related mandatory ingredients (e.g., disinfectants, anesthetics, etc.) that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or to aflibercept injections, study treatment procedure, dilating drops, or any of the anesthetic and antimicrobial preparations used by a patient during the study
- Active cancer within the previous 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of < 6 and a stable prostate-specific antigen for > 12 months
- Systemic treatment for suspected or active systemic infection
  – Ongoing use of prophylactic antibiotic therapy may be acceptable but had to be discussed with the Medical Monitor
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, historical or current clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the faricimab or aflibercept or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic
- > 100 mmHg while a patient is at rest). If a patient's initial reading exceeded these values, a second reading could be obtained later the same day or on another day during the screening period. If the patient's blood pressure was controlled by antihypertensive medication, the patient had to be taking the same medication continuously for at least 30 days prior to Day 1
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1

- Pregnancy or breastfeeding, or intention to become pregnant during the study. For further details see protocol.
- Participation in an investigational trial that involved treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 3 months or 5 half-lives prior to Day 1
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications and treatments indicated as prohibited therapy.

**Ocular Exclusion Criteria for Study Eye**

Patients who met any of the following exclusion criteria for the study eye were excluded from study entry:

- High-risk PDR in the study eye, using any of the following established criteria for high-risk PDR:
  - Any vitreous or pre-retinal hemorrhage
  - Neovascularization elsewhere ≥ 1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields on clinical examination or on CFPs
  - Neovascularization at disc ≥1/3 disc area on clinical examination
- Tractional retinal detachment, pre-retinal fibrosis, vitreomacular traction, or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye, as evaluated by the CRC
- Active rubeosis
- Uncontrolled glaucoma
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or implantation of anterior chamber intraocular lens
- Intravitreal anti-VEGF treatment within 3 months prior to Day 1 (applicable to patients whose study eyes were previously treated with intravitreal anti-VEGF agents) or any intravitreal anti-VEGF agents to study eye prior to Day 1 (applicable for patients who are treatment naive)
- Treatment with panretinal photocoagulation (PRP) within 3 months prior to Day 1
- Macular (focal, grid, or micropulse) laser within 3 months prior to Day 1
- Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to Day 1
- Any other intraocular surgery (e.g., corneal transplantation, glaucoma filtration, pars plana vitrectomy, corneal transplant, or radiotherapy)
- Any intravitreal or periocular (subtenon) corticosteroid treatment within 6 months prior to Day 1
- Any use of medicated intraocular implants, including Ozurdex, within 6 months of Day 1
- Any use of Iluvien implants at any time prior to Day 1
- Treatment for other retinal diseases that can lead to macular edema.

**Ocular Exclusion Criteria for Fellow Eye (Non-Study Eye)**
Patients who met the following exclusion criterion for the fellow eye (non-study eye) were excluded from study entry:

- Non-functioning non-study eye, defined as either:
  – BCVA of hand motion or worse
  – No physical presence of non-study eye (i.e., monocular).

**Exclusion Criteria for Both Eyes**
Patients who met the following exclusion criterion for either eye were excluded from study entry:

- Prior administration of intravitreal faricimab in either eye
- Any history of idiopathic or immune-mediated uveitis in either eye
- Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1

**Concurrent Ocular Conditions Exclusion Criteria**
Patients who met the following exclusion criteria related to concurrent ocular conditions were excluded from study entry:

- Any current or history of ocular disease other than DME that may have confounded assessment of the macula or affect central vision in the study eye (e.g., choroidal neovascularization, age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, retinal embolus, macular traction, macular hole, and other)
- Any current ocular condition which, in the opinion of the investigator, was currently causing or could be expected to contribute to irreversible vision loss due to a cause other than DME in the study eye (e.g., foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions)

**Test and Reference Therapies**
Faricimab and aflibercept were supplied by the Sponsor as a sterile liquid for IVT injection in single-use glass vials. The sham vial was empty and remained empty throughout the sham treatment.

**Treatment masking**
A sham procedure was administered to patients in all three treatment arms at applicable visits to maintain masking among treatment arms.

**Prohibited Medications/Treatments**
Patients could be discontinued from study treatment and/or the study to receive these therapies:

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
- Intravitreal anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye

- Intravitreal, periocular (subtenon), steroid implants (i.e., Ozurdex, Iluvien), or chronic topical ocular corticosteroids in study eye
- Treatment with Visudyne in study eye
- Administration of micropulse and focal or grid laser in study eye
- Other experimental therapies (except those comprising vitamins and minerals)

**Pharmacokinetics**
Plasma samples to determine concentrations of faricimab or aflibercept, free VEGF-A, free Ang-2, anti-drug (faricimab) antibodies (ADAs), and additional biomarkers (PD sample) were collected.

**Safety assessments** consisted of monitoring and recording AEs, including SAEs, and AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests, including IOP, slit-lamp examination, and indirect ophthalmoscopy.

**Statistical Methods**

**Primary Efficacy Endpoint -** Change from baseline in BCVA averaged over Weeks 48, 52, and 56

**Key Secondary Efficacy endpoint - P**roportion of patients with a ≥ 2-step improvement in DRS from baseline on the ETDRS DRSS at Week 52

**Analysis Populations**
- Intent-to treat (ITT) population – all randomized patients
- Treatment-naïve (TN) - all randomized patients who had not received any intravitreal anti-VEGF agents in the study eye prior to randomization
- Per protocol (PP) population – all patients randomized in the study who receive at least one dose of study treatment and who do not have a major protocol violation.
- Safety population – all patients who receive at least one injection of active study drug (faricimab or aflibercept).

**Non-inferiority Margin**
The FDA Clinical Review team agreed to a non-inferiority margin of 4 letters.

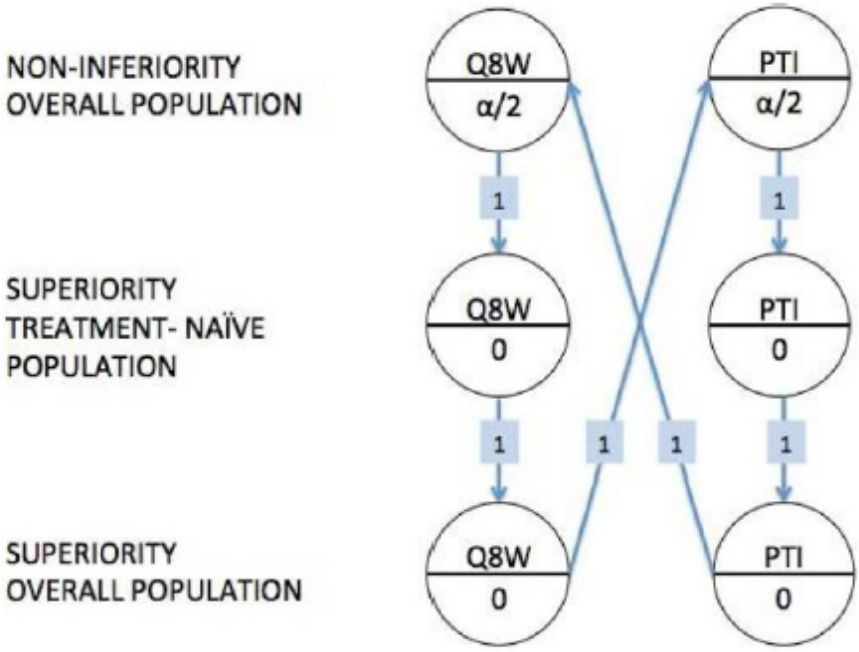
**Hypothesis Testing and Type I Error Control**

For each of the two faricimab arms (Q8W and PTI), the following three hypotheses were tested separately against the active comparator (aflibercept Q8W) at an overall significance level of $\alpha = 0.0496$ using a graph-based testing procedure to control for the overall type I error rate:
- Non-inferiority of faricimab compared with aflibercept Q8W in the ITT population with a non-inferiority margin of 4 letters
- Superiority of faricimab compared with aflibercept Q8W in the treatment-naive population

- Superiority of faricimab compared with aflibercept Q8W in the ITT population

The order in which hypothesis tests for the primary endpoint were performed is as follows:

**Graph-Based Testing Procedure for the Primary Endpoint**




PTI = personalized treatment interval; Q8W = every 8 weeks.
Note: $\alpha = 0.0496$.

The arrows denote the direction of α-propagation. If the tests for one treatment sequence were all positive, at the α/2 (= 0.0248) level then α/2 was propagated to the beginning of the other treatment sequence, which was tested at a significance level of α = 0.0496.

**Safety Analysis**
The safety analyses were conducted on the safety population. Safety evaluations through Week 52 included adverse events, clinical laboratory tests, and vital signs and the 4-month safety update.

**Compliance with Good Clinical Practices**
This study was conducted per the principles of Good Clinical Practices (GCP).

**Figure 6.3.1-2 Evaluation and Visit Schedule**

## Schedule of Activities

### *Screening* through Week 52 and Early Termination

| | | Visit Day | | Visit Week | | | | | | | | | | | | | ET |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | 1[a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | Visit[b] |
| Visit Window (days) | –28 to –1 | NA | (±3) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28) |
| Main informed consent[c] | x | | | | | | | | | | | | | | | | |
| Optional aqueous, vitreous and blood sample informed consent[c] | x | x | | | | | | | | | | | | | | | |
| Optional (RBR) residual samples and DNA whole blood sample informed consent[c] | x | x | | | | | | | | | | | | | | | |
| Review of inclusion and exclusion criteria | x | x | | | | | | | | | | | | | | | |
| Demographics (age, sex, and self-reported race/ethnicity) | x | | | | | | | | | | | | | | | | |
| Medical and surgical history including tobacco history[d] | x | | | | | | | | | | | | | | | | |
| Physical examination[e] | x | | | | | | | | | | | | | | | | x |
| Body weight and height | x | | | | | | | | | | | | | | | | |
| Vital signs[f] | x | x | | | | | | | | | | | | | | | x |
| NEI VFQ-25[g] | | x | | | | | | | x | | | | | | | x | x |
| *Refraction and* BCVA[h] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Pre-treatment IOP[i] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Urine pregnancy test[j, k] | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

*Screening* **through Week 52 and Early Termination**

| | Screening | Visit Day | | Visit Week | | | | | | | | | | | | | ET Visit[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1[a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | |
| Visit Window (days) | –28 to –1 | NA | (±3) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28) |
| Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis)[j, l] | x | *x* [l] | | | | | | | | | | | | | | | |
| $HbA_{1c}$[j] | x | | | | | | | | | | | | | | | x | x |
| Optional aqueous humor sample *for biomarkers*[m] | | x | x | | | | x | x | | | x | | | | | | x |
| *Optional PK plasma sample (if aqueous humor sample is collected)* [j, m] | | | *x* | | | | | | | | *x* | | | | | | |
| *Optional PD plasma sample (if aqueous humor sample is collected)* [j, m] | | | *x* | | | | | | | | *x* | | | | | | |
| Optional vitreous humor sample *for biomarkers*[n] | | Can be collected if vitrectomy is necessary | | | | | | | | | | | | | | | |
| *Optional PK plasma sample (if vitreous humor sample is collected)* [j, n] | | *Collect PK sample if vitreous humor sample is collected* | | | | | | | | | | | | | | | |
| Optional whole blood sample for DNA[j, o] | | x | | | | | | | | | | | | | | | |
| *Mandatory* plasma PK sample[j, p] | | x | | x | | | | | | x | | | | | | x | x |
| *Mandatory* plasma PD sample[j, p] | | x | | x | | | | | | x | | | | | | x | x |

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

*Screening* **through Week 52 and Early Termination**

| | | Visit Day | | Visit Week | | | | | | | | | | | | | ET |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | 1[a] | 7 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | Visit[b] |
| Visit Window (days) | –28 to –1 | NA | (±3) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28) |
| *Mandatory* plasma ADA sample [i, p] | | x | | x | | | | | | x | | | | | | x | x |
| Slitlamp examination | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Indirect ophthalmoscopy | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| SD-OCT [q] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Optional OCT-A [q, r] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| FFA [q] | *(x)* [q] | x | | | | | x | | | | | | | | | x | x |
| CFP [q] | x | | | | | | x | | | | | | | | | x | x |
| *Optional (Optos®) UWF CFP* [q] | *x* | *(x)* [q] | | | | | *x* | | | | | | | | | *x* | *x* |
| Administration of study treatment [s] | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Finger-counting test [t] | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| IOP (post-study treatment) [u] | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Adverse events [v] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications [w] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concurrent ocular procedures [x] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

ADA=anti-drug antibody; Ang-2=angiopoietin-2; BCVA=best-corrected visual acuity; CFP=color fundus photograph; *CRC = central reading center;* DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; $HbA_{1c}$=hemoglobin $A_{1c}$; ICF = Informed Consent Form; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; RBR=Research Biosample Repository; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; *UWF = ultra-wide field;* VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

*Screening* **through Week 52 and Early Termination**

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). *For the study visits windows, the sites should utilize patient's study visit calculator posted on DrugDev.*

There must be a minimum of 21 days between study treatment visits occurring from the Day 1 visit through the Week 96 visit. The final study visit at Week 100 should not occur earlier than 28 days after the last study treatment. *The fellow eye anti-VEGF* treatment *approved by the country regulatory agency for ocular use* may be *covered* by the Sponsor as long as the patient remains in the study (see Section 4.4.1). *The fellow eye anti-VEGF* treatments after the ET visit or the final study visit (Week 100) will not be *covered* by the Sponsor.

[a] The screening and Day 1 (randomization) visits may occur as a combined visit if all assessments are completed and evaluated within 2 business days. *The following two conditions must be met for the combined visit to occur: prior communication with the CRC so the screening images are evaluated in expedited manner; and availability of the historical $HbA_{1c}$ data (obtained within 2 months prior to Day 1 visit; it is permissible to use site's own $HbA_{1c}$ analyzer with print-out results). There is no need to wait for* (b) (4) *sample results.* When screening and randomization are combined and performed in 1 day, assessments listed for both visits should be conducted only once. If the combined visit is conducted within 2 business days, then the following safety assessments will be repeated on the day of patient's randomization and study treatment administration: *urine pregnancy test (if applicable),* slitlamp examination, indirect ophthalmoscopy, and pre-treatment IOP measurements (recorded on the Day 1 eCRF and dated accordingly). *Verify that patient did not start on any prohibited medication.*

[b] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following their last study treatment.

[c] Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment at the Day 1 visit. The optional Blood, Aqueous Humor, Vitreous Humor Samples Informed Consent Form as well as Optional (RBR) Informed Consent Form for residual samples and whole blood DNA sample collection can be signed either at the screening or Day 1 visit prior to sample collection.

[d] Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, cerebrovascular, and ophthalmic history), surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, *and height and weight* will be recorded at baseline.

[e] A targeted physical examination should include an evaluation of the head, ears, nose and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[f] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

[g] To be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

*Screening* **through Week 52 and Early Termination**

[h] Perform the assessments prior to dilating the eyes. *Both refraction and BCVA will be assessed at every study visit for both eyes. However, only study eye refraction from the Day 1, Week 56 and Week 96 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF from every study visit. The study eye visual acuity score from each study treatment visit must be entered to IxRS after each visit; IxRS needs the data to assign the correct study treatment at future visits.*

[i] Perform the assessments prior to dilating the eyes at screening and at each study visit, and if applicable, at the ET visit.

[j] Obtain prior to FFA (if applicable) and prior to study treatment.

[k] Starting *at screening*, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

[l] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, lymphocytes, bands, eosinophils, basophils, and monocytes (absolute). Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal). If the screening and Day 1 (randomization) visits occur as a combined visit, a historic $HbA_{1c}$ value must be available from within 2 months prior to Day 1. *If the screening and Day 1 visits are performed separately, then these samples collections can be done at either visit based on investigator judgment, but historical (obtained within 2 months of Day 1 visit) or current $HbA_{1c}$ results must be available at Day 1 prior to randomization to confirm eligibility.*

[m] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. *It is permissible to collect aqueous humor sample after FFA was performed at applicable visits. Associated optional PK and PD plasma samples have to be collected at the Day 7 and Week 32 visits. See the central lab manual for additional details. Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.*

[n] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. *Associated* PK blood sample (for plasma preparation) should also be collected and shipped to the *central lab*. Vitreous humor *and PK* samples will be analyzed primarily for faricimab concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for VEGF-A and Ang-2 concentrations and possibly other biomarkers.

[o] If the optional whole blood DNA sample is not obtained at the assigned visit (Day 1), the sample may be collected at any subsequent study visit when a blood draw is being performed for other purposes as specified (e.g., PK, ADA). This sample collection is not applicable for a site that has not been granted approval by the country regulators or site's Institutional Review Board or Ethics Committee. The DNA samples will be collected from patients who give specific consent to participate in this optional research.

[p] *At specified visits, the mandatory plasma PK, PD, and ADA samples will be collected prior to FFA assessment (if applicable) and prior to study treatment.*

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

*Screening* **through Week 52 and Early Termination**

[q] The CRC will review SD-OCT *(certain SS-OCT equipment may be acceptable; consult CRC) and 7-modified field or 4-wide field* CFP images obtained at screening for determination of patient eligibility. *The additional baseline UWF (Optos) CFP images can be taken at the screening or Day 1 visit.* At all subsequent visits, outputs from all types of imaging assessments will be sent to the relevant CRC. *The preferred method for FFA collection is UWF (Optos) at sites with capability, and 7 or 4-wide fields at all the other sites.* See the CRC manual for additional details. *The baseline FFA may be obtained either at screening or the Day 1 visit, but it is recommended to obtain it at the Day 1 visit if both eyes appear eligible to become the study eye. The FFA images should be obtained after lab samples have been collected.* **Note:** After randomization, if a patient misses a study visit when *CFP or FFA* ocular images are scheduled *or these images are not taken at the scheduled visit (e.g. equipment is broken)*, they *must* be obtained at the next scheduled visit the patient attends. *Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to the IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.*

[r] To be conducted at sites with OCT-A capability.

[s] At study treatment visits, randomized patients will receive *faricimab* at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which they are randomized, which will be masked.

[t] The finger-counting test should be conducted within *approximately* 15 minutes of study treatment administration for the study eye only by the unmasked investigator.

[u] Post-treatment IOP measurement in the study eye only *at* 30 (±15) minutes to be performed by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until the final study visit or if applicable until the ET visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[w] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by a patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or ET visit.

[x] Record all concurrent ocular procedures performed on the study or non–study eye between the Day 1 visit after study treatment and the final study visit or ET visit.

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

**Week 56 through Week 100 and Early Termination**

| | Week Visit | | | | | | | | | | | | ET Visit [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 56 | 60 | 64 | 68 | 72 | 76 | 80 | 84 | 88 | 92 | 96 | 100 | |
| Visit Window (days) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28 and <35) | (≥28) |
| Physical examination [b] | | | | | | | | | | | | x | x |
| Vital signs [c] | | | | | | | | | | | | x | x |
| NEI VFQ-25 [d] | | | | | | | | | | | | x | x |
| *Refraction and* BCVA [e] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Pre-treatment IOP [f] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Urine pregnancy test [g, h] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Whole blood sample (hematology, coagulation [aPTT and PT], serum chemistry, and urinalysis) [g, i] | x | | | | | | | | | | | | |
| $HbA_{1c}$ [g] | | | | | | | | | | | | x | x |
| Optional aqueous humor sample *for biomarkers* [j] | | | | | | x | x | x | x | | | | x |

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

**Week 56 through Week 100 and Early Termination**

| | Week Visit | | | | | | | | | | | | ET Visit [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 56 | 60 | 64 | 68 | 72 | 76 | 80 | 84 | 88 | 92 | 96 | 100 | |
| Visit Window (days) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28 and <35) | (≥28) |
| Optional vitreous humor sample *for biomarkers* [k] | Can be collected if vitrectomy is necessary. | | | | | | | | | | | | |
| *Optional PK plasma sample (if vitreous humor sample is collected)* [s,k] | *Collect PK sample if vitreous humor sample is collected* | | | | | | | | | | | | |
| *Mandatory plasma PK sample* [s] | | | | | | *x* | | | | | | *x* | *x* |
| *Mandatory* plasma PD sample [s] | | | | | | x | | | | | | x | x |
| *Mandatory* plasma ADA sample [s] | | | | | | x | | | | | | x | x |
| Slitlamp examination | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Indirect ophthalmoscopy | x | x | x | x | x | x | x | x | x | x | x | x | x |
| SD-OCT [l] *or SS-OCT (if applicable)* | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Optional OCT-A [l, m] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| FFA [l] | | | | | | | | | | | x | | x |
| CFP [l] | | | | | | | | | | | x | | x |
| *Optional (Optos) UWF CFP* [l] | | | | | | | | | | | *x* | | *x* |
| Administration of study treatment [n] | x | x | x | x | x | x | x | x | x | x | x | | |
| Finger-counting test [o] | x | x | x | x | x | x | x | x | x | x | x | | |
| IOP post-treatment [p] | x | x | x | x | x | x | x | x | x | x | x | | |

## Figure 6.3.1-2 Evaluation and Visit Schedule (continued)

**Week 56 through Week 100 and Early Termination**

| | Week Visit | | | | | | | | | | | | ET Visit [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 56 | 60 | 64 | 68 | 72 | 76 | 80 | 84 | 88 | 92 | 96 | 100 | |
| Visit Window (days) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (±7) | (≥28 and <35) | (≥28) |
| Adverse events [q] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications [r] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concurrent ocular procedures [s] | x | x | x | x | x | x | x | x | x | x | x | x | x |

ADA=anti-drug antibody; BCVA=best-corrected visual acuity; CFP=color fundus photograph; DME=diabetic macular edema; eCRF=electronic Case Report Form; ET=early termination; FFA=fundus fluorescein angiography; $HbA_{1c}$=hemoglobin $A_{1C}$; IOP=intraocular pressure; NEI VFQ-Q25=National Eye Institute 25-Item Visual Functioning Questionnaire; OCT-A=optical coherence tomography–angiography; PD=pharmacodynamic; PK=pharmacokinetic; SD-OCT=spectral-domain optical coherence tomography; SOC=standard of care; *UWF = ultra-wide field;* VA=visual acuity; VEGF-A=vascular endothelial growth factor–A.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment). There must be a minimum of 21 days between all study treatment visits occurring at the Day 1 visit through the Week 100 visit.

*The fellow eye anti-VEGF* treatment *approved by the country regulatory agency for ocular use* may be *covered* by the Sponsor as long as the patient remains in the study (see Section 4.4.1). *The fellow eye anti-VEGF* treatment after the ET visit or the final study visit (Week 100) will not be *covered* by the Sponsor.

[a] Patients who are discontinuing from the study early (prior to the final study visit at Week 100) but have not withdrawn consent should return for an ET visit after a minimum of 28 days have elapsed following the last study treatment.

[b] A targeted physical examination should include an evaluation of the head, ears, nose, and throat. If any abnormalities are noted during the study, the patient may be referred to another doctor. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[c] Vital signs include measurement of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; at the Day 1 visit, vital signs should be recorded before study treatment. Vital signs will be measured with the patient in a seated position after resting for 5 minutes.

[d] To be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

## Figure 6.3.1-2 Evaluation and Visit Schedule (continued)

## Week 56 through Week 100 and Early Termination

[e] Perform the assessments prior to dilating the eyes. *Both refraction and BCVA will be assessed at every study visit for both eyes. However, only study eye refraction from the Day 1, Week 56 and Week 96 visits will be entered on the refraction-specific eCRF. The BCVA assessment data for both eyes will be entered on the BCVA-specific eCRF from every study visit. The study eye visual acuity score from each study treatment visit must be entered to IxRS at the visit; IxRS needs the data to assign the correct study treatment at future visits.*

[f] Perform the assessments prior to dilating the eyes *and* prior to study treatment.

[g] Obtain prior to FFA (if applicable) and prior to study treatment.

[h] Starting *at screening*, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward it to the central laboratory for testing. If the serum pregnancy test is positive, do not administer study treatment.

[i] Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBC counts, WBC counts, and differentials, including neutrophils, lymphocytes, bands, eosinophils, basophils, and monocytes (absolute). Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, ALP, AST, ALT, and uric acid. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal).

[j] If a patient consents to collection of optional aqueous humor sample, collect the sample at indicated timepoints prior to study treatment administration. *It is acceptable to collect aqueous sample after FFA was performed at applicable visits.* Not applicable for a site that has not been granted approval by a site's Institutional Review Board or Ethics Committee.

[k] If vitrectomy is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. *Associated* PK blood sample (for plasma preparation) should also be collected and shipped to the *central lab*. Vitreous humor *and PK* samples will be analyzed primarily for faricimab concentrations and may also be analyzed for aflibercept concentrations. The remaining samples may be analyzed for *free* VEGF-A and *free* Ang-2 concentrations and possibly other biomarkers.

[l] The outputs from imaging assessments will be sent to the CRC. See the CRC manual for additional details. Note: After randomization, if a patient misses a study visit when ocular *CFP (and UWF CFP at applicable sites) and FFA* images are scheduled *or these images are not taken at the scheduled visit (e.g. equipment is broken)*, they *must* be obtained at the next scheduled visit the patient attends. *Please remember to forward OCT images to the CRC immediately after the visit as they need to be evaluated and data submitted to the IxRS by the CRC before the next study visit. If the OCT image was missed due to a missed visit or not taken, then notify the CRC immediately so they can inform IxRS that the expected data will not be available.*

[m] To be conducted at sites with OCT-A capability.

**Figure 6.3.1-2 Evaluation and Visit Schedule (continued)**

## Week 56 through Week 100 and Early Termination

[n] At study treatment visits, randomized patients will receive study drug at some visits and sham at other visits or aflibercept at some visits and sham at other visits. The timing of these treatments will depend on the treatment arm to which patients are randomized, which will be masked.

[o] The finger-counting test should be conducted within *approximately* 15 minutes of study treatment administration for the study eye only by the unmasked investigator.

[p] Post-treatment IOP measurement in the study eye only *at* 30 (±15) minutes to be performed by qualified personnel assigned to the unmasked role. If there are no safety concerns after 30 (±15) minutes following the study treatment, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. The adverse event will be recorded on the Adverse Event eCRF as applicable.

[q] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment (Day 1), all adverse events will be reported until *the patient's last or final study visit or, if applicable, until the ET visit*. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[r] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or the ET visit.

[s] Record all concurrent ocular procedures performed on the study or non–study eye between the Day 1 visit after study treatment and the final study visit or the ET visit.

### 6.3.2. Study Results

**Table 6.3.2-1 Subject Disposition - ITT Population**

| | Faricimab 6 mg Q8W n (%) | Faricimab 6 mg PTI n (%) | Aflibercept 2 mg Q8W n (%) |
|---|---|---|---|
| **Week 56 Analysis** | | | |
| **All randomized** | 315 (100) | 313 (100) | 312 (100) |
| **Randomized and treated** | 313 (99.4) | 313 (100) | 311 (99.7) |
| **Discontinued treatment prior to Week 56*** | | | |
| Total | 31 (9.9) | 30 (9.6) | 26 (8.4) |
| **Reason for Discontinuation** | | | |
| Adverse event | 6 (1.9) | 7 (2.2) | 3 (1.0) |
| Pregnancy | 0 | 1 (0.3) | 0 |
| Death | 7 (2.2) | 9 (2.9) | 4 (1.3) |
| Lack of efficacy | 1 (0.3) | 0 | 1 (0.3) |
| Lost to follow-up | 7 (2.2) | 7 (2.2) | 4 (1.3) |
| Protocol deviation | 0 | 0 | 1 (0.3) |
| Withdrawal by subject | 6 (1.9) | 5 (1.6) | 11 (3.5) |
| Physician decision | 3 (1.0) | 1 (0.3) | 1 (0.3) |
| Other reason | 1 (0.3) | 0 | 1 (0.3) |

Source: Study YOSEMITE CSR, Table 2
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Over 90% of subjects in both the faricimab and aflibercept treatment groups completed Week 56. The number of subjects who discontinued the study prior to Week 56 were 24 (8%) for faricimab Q8W, 24 (8%) for faricimab PTI, and 20 (6%) for aflibercept. Death was the most common reason for discontinuation for all three treatment groups, 3% for faricimab (Q8W plus PTI) and 1% for aflibercept.*

**Table 6.3.2-2 Summary of Major Protocol Deviations (ITT) – Week 56 Analysis**

| Type of Deviation | Faricimab 6 mg Q8W (N=315) n (%) | Faricimab 6 mg PTI (N=313) n (%) | Aflibercept 2 mg Q8W (N=312) n (%) |
|---|---|---|---|
| Total # patients with at least one major protocol deviation | 152 (48.3) | 145 (46.3) | 154 (49.4) |
| Total # Major Protocol Deviations | 290 | 227 | 249 |
| Total # patients with at least one procedural major protocol deviation | 141 (44.8) | 137 (43.8) | 143 (45.8) |
| Total Procedural Major Protocol Deviations | 263 | 209 | 233 |
| Selected missed visits | 73 (23.2) | 71 (22.7) | 79 (25.3) |
| SE: Major issues with images | 25 (7.9) | 18 (5.8) | 28 (9.0) |
| Optional samples collected from a Patient who did not provide consent | 25 (7.9) | 25 (8.0) | 19 (6.1) |
| Other significant procedural deviation issue | 24 (7.6) | 17 (5.4) | 19 (6.1) |
| ICF or ICF update not signed by patient in timely manner | 6 (1.9) | 9 (2.0) | 9 (2.9) |

| Type of Deviation | Faricimab 6 mg Q8W (N 315) n (%) | Faricimab 6 mg PTI (N 313) n (%) | Aflibercept 2 mg Q8W (N 312) n (%) |
|---|---|---|---|
| SAE/AESI not reported in timely manner | 9 (2.9) | 8 (2.6) | 6 (1.9) |
| Masked MD performed unmasked MD Task | 3 (1.0) | 6 (1.9) | 7 (2.2) |
| Incorrect BCVA entered in IxRS leading to incorrect stratification | 6 (1.9) | 5 (1.6) | 4 (1.3) |
| Study tx not administered b/c visit was beyond max visit window | 4 (1.3) | 9 (2.0) | 2 (0.6) |
| Incorrect IXRS data entry impacting treatment interval assuming subject is in Arm B | 5 (1.6) | 1 (0.3) | 2 (0.6) |
| Pt tx assignment is inadvertently unmasked | 1 (0.3) | 3 (1.0) | 4 (1.3) |
| Regular clinic staff performed study patient assessment/evaluation at scheduled study visit | 5 (1.6) | 3 (1.0) | 0 |
| SE: ETDRS, BCVA assessment not done or testing stopped too early | 0 | 1 (0.3) | 0 |
| VA examiner unmasked to the patient's study eye | 1 (0.3) | 0 | 0 |

Source: Study YOSEMITE CSR, Table 4
AESI = Adverse Event of Special Interest; BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IxRS = Interactive Voice Response System; MD = Doctor of Medicine; SAE = Serious Adverse Event; SE = Study Eye; tx = Treatment; VA = Visual acuity.
Table includes major protocol deviations related and not related to COVID-19 and occurred on or prior to Day 349 (last day of Week 48 analysis visit window). Selected missed visits are weeks 4, 8, 12, 20, 24, 36, 40, 44, and 48. Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Arm B = Faricimab 6 mg. PTI
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.

**Reviewer's Comment:** *A total of 451 subjects, 152 (48%) in the faricimab Q8W arm, 145 (46%), and 154 (49%) in the aflibercept arm had major protocol deviations during the study. There were no significant differences between treatment groups.*

**Table 6.3.2-3 Analysis Populations – Week 56 Analysis**

| Analysis Population | Faricimab 6 mg Q8W (N=315) n (%) | Faricimab 6 mg PTI (N=313) n (%) | Aflibercept 2 mg Q8W (N=312) n (%) |
|---|---|---|---|
| Intent-to-Treat (ITT) (as Randomized) | 315 | 313 | 312 |
| Safety (as Treated) | 313 | 313 | 311 |
| Per-Protocol (PP) (as Treated) | 251 | 275 | 274 |
| Treatment-Naïve (TN) (as Randomized) | 238 | 245 | 242 |

Source: Study YOSEMITE CSR, Table 3

**Table 6.3.2-4 Subject Demographics (ITT) – Week 56 Analysis**

| Analysis Population | Faricimab 6 mg Q8W (N=315) n (%) | Faricimab 6 mg PTI (N=313) n (%) | Aflibercept 2 mg Q8W (N=312) n (%) |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 61.6 (9.5) | 62.8 (10.0) | 62.2 (9.6) |
| Min, Median, Max | 26, 62, 85 | 24, 64, 85 | 28, 63, 84 |
| **Age group, n (%)** | | | |
| < 65years | 188 (59.7) | 169 (54.0) | 180 (57.7) |
| ≥ 65years | 127 (40.3) | 144 (46.0) | 132 (42.3) |
| **Sex, n (%)** | | | |
| Male | 187 (59.7) | 197 (62.9) | 178 (57.1) |
| Female | 128 (40.6) | 116 (37.1) | 134 (42.9) |
| **Race, n (%)** | | | |
| White | 241 (76.5) | 240 (76.7) | 253 (81.1) |
| Asian | 31 (9.8) | 26 (8.3) | 27 (8.7) |
| American Indian or Alaska Native | 6 (1.9) | 5 (1.6) | 7 (2.2) |
| Native Hawaiian or Other Pacific Islander | 2 (0.6) | 0 | 3 (1.0) |
| Black or African American | 22 (7.0) | 25 (8.0) | 12 (3.8) |
| Unknown | 13 (4.1) | 16 (5.1) | 10 (3.2) |
| Multiple | 0 | 1 (0.3) | 0 |

Source: Study YOSEMITE CSR Table 5

**Reviewer's Comment:** *Overall, the study population had a mean age of 62 years, was majority male (60%), and white (78%).*

**Table 6.3.2-5 Baseline Ocular Characteristics (ITT) – Week 56 Analysis**

| Baseline Characteristic | Faricimab 6 mg Q8W (N=315) n (%) | Faricimab 6 mg PTI (N=313) n (%) | Aflibercept 2 mg Q8W (N=312) n (%) |
|---|---|---|---|
| **Months since DME diagnosis, n (%)** | | | |
| n | 297 | 292 | 296 |
| Mean (SD) | 14 (21.7) | 17.6 (36.2) | 17.5 (27.6) |
| Min, Median, Max | 0, 3.4, 134 | 0, 2.3, 304 | 0, 3.4, 180 |
| Unknown | 18 | 21 | 16 |
| **BCVA (letters)** | | | |
| n | 315 | 313 | 312 |
| Mean (SD) | 62.0 (9.9) | 61.9 (10.2) | 62.2 (9.5) |
| Min, Median, Max | 28, 64, 81 | 25, 65, 73 | 27, 64, 73 |
| **CST (ILM-BM) (microns)** | | | |
| n | 312 | 312 | 308 |
| Mean (SD) | 492.3 (135.8) | 485.8 (130.8) | 484.5 (131.1) |
| Min, Median, Max | 291, 476.5, 1172 | 270, 461.5, 1043 | 208, 458.0, 982 |
| Missing/Ungradable | 3 | 1 | 4 |
| **Macular Ischemic Non-Perfusion** | | | |
| n | 315 | 313 | 312 |
| Yes | 127 (40.3) | 117 (37.4) | 122 (39.1) |
| **Macular Leakage** | | | |
| n | 315 | 313 | 312 |
| Yes | 305 (96.8) | 301 (96.2) | 293 (93.9) |
| **Previously treated with anti-VEGF** | | | |
| n | 315 | 313 | 312 |
| Yes | 77 (24.4) | 68 (21.7) | 70 (22.4) |
| No | 238 (75.6) | 245 (78.3) | 242 (77.6) |
| **Diabetic Retinopathy Status** | | | |
| n | 315 | 313 | 312 |
| 1-DRS Level 10, 12 (DR absent) | 2 (0.6) | 3 (1.0) | 4 (1.3) |
| 2–DRS Level 14A-14C, 14 Z, 15, 20 (DR questionable, microaneurysms only) | 4 (1.3) | 6 (1.9) | 10 (3.2) |
| 3-DRS Level 35A-35F (Mild NPDR) | 84 (26.7) | 92 (29.4) | 83 (26.6) |
| 4-DRS Level 4A-43B (Moderate NPDR) | 84 (26.7) | 86 (27.5) | 85 (27.2) |
| 5-DRS Level 47A-47D (Moderately Severe NPDR) | 67 (21.3) | 59 (18.8) | 54 (17.3) |
| 6-DRS Level 53A-53E (Severe NPDR) | 46 (14.6) | 40 (12.8) | 49 (15.7) |
| 7-DRS Level 61A-61B (Mild PDR) | 16 (5.1) | 11 (3.5) | 9 (2.9) |
| 8-DRS Level 65A-65C (Moderate PDR) | 6 (1.9) | 9 (2.9) | 7 (2.2) |
| 9-DRS Level 71A-71D (High Risk PDR) | 0 | 1 (0.3) | 2 (0.6) |
| 10-DRS Level 75 (High Risk PDR) | 0 | 0 | 0 |
| 11-DRS Level 81 (Advanced PDR) | 0 | 0 | 0 |
| 12-DRS Level 85A-85B (Advanced PDR) | 0 | 0 | 0 |
| 90-DRS Level 90 (Cannot Grade) | 4 (1.3) | 5 (1.6) | 7 (2.2) |
| Missing | 2 (0.6) | 1 (0.3) | 2 (0.6) |

Source: Study YOSEMITE CSR, Table 6

BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; ILM = Internal Limiting Membrane; NPDR = Non-Proliferative Diabetic Retinopathy; PTI = Personalized Treatment Interval (from Q4W up to Q16W); PDR = Proliferative Diabetic Retinopathy; VEGF = Vascular Endothelial Growth Factor.
Baseline is the last available value taken on or prior to randomization.
Invalid BCVA are excluded from analysis. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by the CRC.

**Reviewer's Comment:** *There were no significant differences in baseline ocular characteristics between treatment groups.*

**Primary Efficacy Results**

**Table 6.3.2-6 Change in Baseline in BCVA in the Study Eye Averaged over Week 48/52/56 – MMRM Method***

| | Faricimab 6 mg Q8W (N=315) | Faricimab 6 mg PTI (N=313) | Aflibercept 2 mg Q8W (N=312) | Difference (faricimab Q8W – Aflibercept) | Difference (faricimab PTI – Aflibercept) |
|---|---|---|---|---|---|
| **ITT Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 10.7 (9.4, 12.0) | 11.6 (10.3, 12.9) | 10.9 (9.6, 12.2) | | |
| Difference (97.5% CI) | | | | -0.2 (-2.0, 1.6) | 0.7 (-1.1, 2.5) |
| **PP Population[2]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 10.8 (9.4, 12.1) | 11.8 (10.5, 13.2) | 11.2 (9.9, 12.5) | | |
| Difference (97.5% CI) | | | | -0.4 (-2.3, 1.5) | 0.7 (-1.2, 2.5) |
| **TN Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 10.6 (9.1, 12.1) | 11.4 (9.9, 12.8) | 11.3 (9.8, 12.8) | | |
| Difference (97.5% CI) | | | | -0.7 (-2.8, 1.4) | 0.0 (-2.1, 2.2) |

Source: Study YOSEMITE CSR, Tables 8
* MMRM = mixed model repeated measurement
[1] Primary analysis – MMRM Method
[2] Supplementary analysis – MMRM Method

**Reviewer's Comment:** *For the **ITT, PP and TN populations**, the 97.5% confidence interval for the difference between the faricimab Q8W and aflibercept arms was more than or equal to -2.8.*

*The lower limit of the 97.5% confidence interval for the treatment differences between the **faricimab Q8W** arm and the aflibercept arm met the non-inferiority margin of 4 letters for the **TN population** but **did not demonstrate superiority** (-2.8).*

*The lower limit of the 97.5% confidence interval for the treatment differences between the **faricimab PTI** arm and the aflibercept arm met the non-inferiority margin of 4 letters for the **TN population** but **did not demonstrate superiority** (-2.1).*

**Key Primary Efficacy Sensitivity Analysis**

**Table 6.3.2-7 Change in Baseline in BCVA in the Study Eye Averaged over Week 48/52/56 – LOCF[1]: MMRM Method[2]**

| | Faricimab 6 mg Q8W (N=315) | Faricimab 6 mg PTI (N=313) | Aflibercept 2 mg Q8W (N=312) | Difference (faricimab Q8W – Aflibercept) | Difference (faricimab PTI – Aflibercept) |
|---|---|---|---|---|---|
| **ITT Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 10.6 (9.4, 11.8) | 11.3 (10.1, 12.6) | 10.7 (9.5, 12.0) | | |
| Difference (97.5% CI) | | | | -0.1 (-1.9, 1.6) | 0.6 (-1.1, 2.4) |

Source: Study YOSEMITE CSR, Tables 8
[1] LOCF – last observation carried forward
[2] MMRM - mixed-model repeated measurement

**Reviewer's Comment:** *The results of the primary and sensitivity analyses are similar.*

(b) (4)

(b) (4)

## 6.4. Study GR40398 (RHINE) – A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients with Diabetic Macular Edema

### 6.4.1. Study Design - Identical to Study GR40349 (YOSEMITE)

**List of Investigators**
There were 174 study center(s) in the following countries: United States (50), Canada (10), Argentina (6), Poland (8), Czech Republic (5), United Kingdom (18), Brazil (9), Spain (9), Hungary (4), Australia (7), Russian Federation (4), Portugal (4), Italy (5), Turkey (4), Germany (7), France (3), Denmark (3), Switzerland (1), Republic of Korea (5), Taiwan (3), Thailand (3), Hong Kong (2), Singapore (3). China (1).

**Table 6.4.1-1 Investigator(s) Who Randomized 10 or more Subjects**

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 315195 | Schlottmann, Patricio<br>ORGANIZACION MEDICA DE INVESTIGACION<br>Uruguay 725 PB<br>Capital Federal,C1015ABO,<br>ARGENTINA | 35 |
| 315196 | Zambrano, Alberto<br>Fundacion Zambrano<br>Callao 1046 1°A<br>CABA,1023,<br>ARGENTINA | 11 |
| 315201 | Furno Sola, Federico<br>Grupo Laser Vision<br>Mariano Moreno 1397<br>Rosario,S2000DLA,<br>ARGENTINA | 18 |
| 315203 | Alezzandrini, Arturo<br>Oftalmos<br>Av. Cordoba 1830<br>Capital Federal,C1120AAN,<br>ARGENTINA | 18 |
| 316515 | Salomão, Gustavo<br>CEMAPE - Centro Médico<br>Avenida Miruna, 648<br>São Paulo,SP,04084-002,<br>BRAZIL | 10 |
| 316521 | Belfort Jr., Rubens<br>Universidade Federal de Sao Paulo - UNIFESP*X; Oftalmologia<br>Rua Loefgreen, 1726<br>Sao Paulo,SP,04040-002,<br>BRAZIL | 10 |
| 312314 | Dusova, Jaroslava<br>FN Hradec Králové, Oční klinika; Ophthalmology clinic<br>Sokolská 581<br>Hradec Králové,500 05,<br>CZECH REPUBLIC | 11 |
| 312353 | Ernest, Jan<br>AXON Clinical<br>Ostrovskeho 3<br>Prague,150 00,<br>CZECH REPUBLIC | 28 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 313030 | Veith, Miroslav<br>Faculty Hospital Kralovske Vinohrady;<br>Ophthalmology clinic<br>Srobarova 50<br>Prague,100 34,<br>CZECH REPUBLIC | 12 |
| 312248 | Kerenyi, Agnes<br>Bajcsy-Zsilinszky Hospital<br>MAGLODI U. 89-91<br>BUDAPEST,1106,<br>HUNGARY | 14 |
| 315783 | Yoon, Young Hee<br>Asan Medical Center.<br>88, Olympic-ro 43-gil, Songpa-gu<br>Seoul,05505,<br>KOREA, REPUBLIC OF | 12 |
| 312400 | Raczynska, Dorota<br>OPTIMUM PROFESORSKIE CENTRUM OKULISTYKI<br>Ul. Cienista 30<br>Gdańsk,80-809,<br>POLAND | 12 |
| 312600 | Romanczak, Dominika<br>Centrum Zdrowia MDM<br>Warynskiego 10 A<br>Warszawa,00-631,<br>POLAND | 14 |
| 313000 | Romanowska-Dixon, Bożena<br>SP ZOZ Szpital Uniwersytecki w Krakowie<br>Oddział Kliniczny Okulistyki i Onkologii Okulistycznej<br>ul. Mikołaja Kopernika 36<br>Kraków,31-501,<br>POLAND | 12 |
| 313023 | Zatorska, Barbara<br>Caminomed<br>Wyszynskiego 3a<br>Tarnowskie Góry,42-600,<br>POLAND | 10 |
| 315579 | Sikorski, Bartosz<br>(Specjalistyczny Ośrodek Okulistyczny Oculomedica<br>Broniewskiego 9<br>Bydgoszcz,85-316,<br>POLAND | 22 |
| 318275 | Zaczek Zakrzewska, Karolina<br>Poradnia Okulistyczna i Salon Optyczny w Gliwicach- PRYZMAT<br>Tarnogórska 70/1<br>Gliwice,44-100,<br>POLAND | 10 |

| Site Number | Principal Investigator<br>Site Address | Number of Subjects Randomized |
|---|---|---|
| 316713 | Figueira, Joao<br>AIBILI - Association for Innovation and Biomedical Research on Light<br>Azinhaga de Santa Comba, Celas<br>Coimbra,3000-548,<br>PORTUGAL | 13 |
| 315703 | Lai, Chi-Chun<br>Chang Gung Medical Foundation - Linkou; Ophthalmology<br>No 5, Fu-Hsing Street, Kuei Shan Hsiang<br>Taoyuan,333,<br>TAIWAN | 10 |
| 313950 | Higgins, Patrick<br>Retina Center of New Jersey<br>1255 Broad Street, Suite 104<br>Bloomfield,NJ,07003,<br>UNITED STATES | 21 |
| 313951 | Brown, David M.<br>Retina Consultants of Houston<br>6560 Fannin St.,Suite 750<br>Houston,TX,77030,<br>UNITED STATES | 11 |
| 313952 | Taylor, Stanford<br>(Chittum, Mark<br>Retina Consultants of Southern<br>2770 N. Union Blvd,Suite 140<br>COLORADO SPRINGS,CO,80909,<br>UNITED STATES | 11 |
| 313954 | Marcus, Dennis<br>Southeast Retina Center<br>3685 Wheeler Road, Suite 201<br>Augusta, GA, 30909,<br>UNITED STATES | 12 |
| 313958 | Sheth, Veeral<br>University Retina and Macula Associates, PC<br>6320 W. 159th St., Suite A<br>Oak Forest,IL,60452,<br>UNITED STATES | 39 |
| 313995 | Wells, John A.<br>Palmetto Retina Center<br>124 Sunset Court<br>West Columbia,SC,29169,<br>UNITED STATES | 16 |
| 315417 | Burgess, Stuart<br>Fort Lauderdale Eye Institute<br>850 South Pine Island Road, Suite A-100<br>PLANTATION,FL,33324,<br>UNITED STATES | 11 |

* Routine site inspection of this site was performed by the Office of Scientific Investigations.

### 6.4.2. Study Results

**Table 6.4.2-1 Subject Disposition - ITT Population**

| | Faricimab 6 mg Q8W n (%) | Faricimab 6 mg PTI n (%) | Aflibercept 2 mg Q8W n (%) | All Patients n (%) |
|---|---|---|---|---|
| **Week 56 Analysis** | | | | |
| **All randomized** | 317 (100) | 319 (100) | 315 (100) | 951 (100) |
| **Randomized and treated** | 317 (100) | 319 (100) | 314 (99.7) | 950 (99.7) |
| **Discontinued treatment prior to Week 56*** | | | | |
| Total | 24 (7.6) | 11 (3.4) | 19 (6.1) | 54 (5.7) |
| **Reason for Discontinuation** | | | | |
| Adverse event | 4 (1.3) | 3 (0.9) | 4 (1.3) | 11 (1.2) |
| Pregnancy | 0 | 0 | 0 | 0 |
| Death | 5 (1.6) | 0 | 5 (1.6) | 10 (1.1) |
| Lack of efficacy | 0 | 0 | 0 | 0 |
| Lost to follow-up | 6 (1.9) | 4 (1.3) | 3 (1.0) | 13 (1.4) |
| Protocol deviation | 0 | 0 | 0 | 0 |
| Withdrawal by subject | 7 (2.2) | 4 (1.3) | 5 (1.6) | 16 (1.7) |
| Physician decision | 1 (0.3) | 0 | 1 (0.3) | 2 (0.2) |
| Other reason | 1 (0.3) | 0 | 1 (0.3) | 2 (0.2) |
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Source: Study RHINE CSR, Table 2
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Over 90% of subjects in both the faricimab treatment groups and aflibercept treatment group completed Week 56. The number of subjects who discontinued the study prior to Week 56 were 19 (6%) for faricimab Q8W, 7 (2%) for faricimab PTI, and 16 (5%) for aflibercept. Withdrawal by subject was the most common reason for discontinuation for the faricimab treatment groups (Q8W and PTI) (23% for Q8W and 1% for PTI). Death (2%) was the most common reason for aflibercept.*

**Table 6.4.2-2 Summary of Major Protocol Deviations (ITT) – Week 56 Analysis**

| Type of Deviation | Faricimab 6 mg Q8W (N=317) n (%) | Faricimab 6 mg PTI (N=319) n (%) | Aflibercept 2 mg Q8W (N=315) n (%) |
|---|---|---|---|
| Total # patients with at least one major protocol deviation | 155 (48.9) | 161 (50.5) | 159 (50.5) |
| Total # Major Protocol Deviations | 292 | 258 | 269 |
| Total # patients with at least one procedural major protocol deviation | 145 (45.7) | 139 (43.6) | 146 (46.3) |
| Total Procedural Major Protocol Deviations | 276 | 225 | 248 |
| Selected missed visits | 72 (22.7) | 69 (21.6) | 69 (21.9) |
| Optional samples collected w/o signed optional ICF | 26 (8.2) | 31 (9.7) | 34 (10.8) |
| SE: Major issues with images | 31 (9.8) | 33 (10.3) | 25 (7.5) |
| Other significant procedural deviation | 22 (6.9) | 13 (4.1) | 15 (4.8) |
| ICF or ICF update not signed by patient in timely manner | 13 (4.1) | 7 (2.2) | 12 (3.8) |
| Study tx not administered b/c visit was beyond max visit window | 7 (2.2) | 10 (3.1) | 11 (3.5) |
| Incorrect BCVA entered in IxRS leading to incorrect stratification | 11 (3.5) | 5 (1.6) | 9 (2.9) |
| SAE/AESI not reported in timely manner | 7 (2.2) | 4 (1.3) | 5 (1.6) |
| Unmasked MD performed masked MD task | 5 (1.6) | 6 (1.9) | 0 |
| Regular clinic staff performed study patient assessment/evaluation at scheduled study visit | 2 (0.6) | 1 (0.3) | 4 (1.3) |
| SE: ETDRS, BCVA assessment not done or testing stopped too early | 2 (0.6) | 2 (0.6) | 2 (0.6) |
| Incorrect IXRS data entry impacting treatment interval assuming subject is in Arm B | 1 (0.3) | 2 (0.6) | 1 (0.3) |
| VA examiner unmasked to the patient's study eye | 1 (0.3) | 0 | 2 (0.6) |
| Pt tx assignment is inadvertently unmasked | 0 | 1 (0.3) | 1 (0.3) |

Source: Study RHINE CSR, Table 4
AESI = Adverse Event of Special Interest; BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IxRS = Interactive Voice Response System; MD = Doctor of Medicine; SAE = Serious Adverse Event; SE = Study Eye; tx = Treatment; VA = Visual acuity.
Table includes major protocol deviations related and not related to COVID-19 and occurred on or prior to Day 349 (last day of Week 48 analysis visit window). Selected missed visits are weeks 4, 8, 12, 20, 24, 36, 40, 44, and 48. Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Arm B = Faricimab 6 mg. PTI
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.

**Reviewer's Comment:** *A total of 475 subjects, 155 (49%) in the faricimab Q8W arm, 139 (44%), and 146 (46%) in the aflibercept arm had major protocol deviations during the study. There were no significant differences between treatment groups.*

**Table 6.4.2-3 Analysis Populations – Week 56 Analysis**

| Analysis Population | Faricimab 6 mg Q8W (N=315) n (%) | Faricimab 6 mg PTI (N=313) n (%) | Aflibercept 2 mg Q8W (N=312) n (%) |
|---|---|---|---|
| Intent-to-Treat (ITT) (as Randomized) | 317 | 319 | 315 |
| Safety (as Treated) | 317 | 319 | 314 |
| Per-Protocol (PP) (as Treated) | 258 | 271 | 273 |
| Treatment-Naïve (TN) (as Randomized) | 254 | 255 | 248 |

Source: Study RHINEE CSR, Table 3

**Table 6.4.2-4 Subject Demographics (ITT) – Week 56 Analysis**

| Analysis Population | Faricimab 6 mg Q8W (N=317) n (%) | Faricimab 6 mg PTI (N=319) n (%) | Aflibercept 2 mg Q8W (N=315) n (%) |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 62.5 (10.1) | 61.6 (10.1) | 62.3 (10.1) |
| Min, Median, Max | 27, 63.0, 91 | 26, 63.0, 87 | 28, 63.0, 86 |
| **Age group, n (%)** | | | |
| < 65years | 176 (55.5) | 183 (57.4) | 183 (58.1) |
| ≥ 65years | 141 (44.5) | 136 (42.6) | 132 (41.9) |
| **Sex, n (%)** | | | |
| Male | 194 (61.2) | 199 (62.4) | 186 (59.0) |
| Female | 123 (38.8) | 120 (37.6) | 129 (41.0) |
| **Race, n (%)** | | | |
| White | 250 (78.9) | 249 (78.1) | 253 (80.3) |
| Asian | 34 (10.7) | 36 (11.3) | 32 (10.2) |
| American Indian or Alaska Native | 0 | 0 | 1 (0.3) |
| Native Hawaiian or Other Pacific Islander | 2 (0.6) | 0 | 0 |
| Black or African American | 18 (5.7) | 23 (7.2) | 24 (7.6) |
| Unknown | 11 (3.5) | 10 (3.1) | 5 (1.6) |
| Multiple | 2 (0.6) | 1 (0.3) | 0 |

Source: Study RHINE CSR Table 5

**Reviewer's Comment:** *Overall, the study population had a mean age of 62 years, was majority male (61%), and white (79%).*

**Table 6.4.2-5 Baseline Ocular Characteristics (ITT) – Week 56 Analysis**

| Baseline Characteristic | Faricimab 6 mg Q8W (N=317) n (%) | Faricimab 6 mg PTI (N=319) n (%) | Aflibercept 2 mg Q8W (N=315) n (%) |
|---|---|---|---|
| **Months since DME diagnosis, n (%)** | | | |
| N | 275 | 277 | 273 |
| Mean (SD) | 18.9 (32.2) | 20.7 (33.0) | 20.3 (37.1) |
| Min, Median, Max | 0, 6.4, 380 | 0, 6.6, 242 | 0, 6.8, 365 |
| Unknown | 42 | 42 | 42 |
| **BCVA (letters)** | | | |
| N | 316 | 317 | 315 |
| Mean (SD) | 61.9 (10.1) | 62.5 (9.3) | 62.1 (9.4) |
| Min, Median, Max | 27, 65, 73 | 30, 65, 86 | 33, 65, 79 |
| Missing/Invalid | 1 | 2 | 0 |
| **CST (ILM-BM) (microns)** | | | |
| N | 314 | 316 | 312 |
| Mean (SD) | 466.2 (119.4) | 471.3 (127.0) | 477.3 (129.4) |
| Min, Median, Max | 273, 445.0, 936 | 285, 442.0, 980 | 266, 448.0, 1209 |
| Missing/Ungradable | 3 | 3 | 3 |
| **Macular Ischemic Non-Perfusion** | | | |
| N | 317 | 319 | 315 |
| Yes | 126 (39.7) | 138 (43.3) | 132 (41.9) |
| **Macular Leakage** | | | |
| N | 317 | 319 | 315 |
| Yes | 300 (94.6) | 309 (96.9) | 299 (94.9) |
| **Previously treated with anti-VEGF** | | | |
| N | 317 | 319 | 315 |
| Yes | 63 (19.9) | 64 (20.1) | 67 (21.3) |
| No | 254 (80.1) | 255 (79.9) | 248 (78.7) |
| **Diabetic Retinopathy Status** | | | |
| N | 317 | 319 | 315 |
| 1-DRS Level 10, 12 (DR absent) | 2 (0.6) | 4 (1.3) | 1 (0.3) |
| 2–DRS Level 14A-14C, 14 Z, 15, 20 (DR questionable, microaneurysms only) | 3 (0.9) | 10 (3.1) | 6 (1.9) |
| 3-DRS Level 35A-35F (Mild NPDR) | 90 (28.4) | 92 (28.8) | 94 (29.8) |
| 4-DRS Level 4A-43B (Moderate NPDR) | 88 (27.8) | 72 (22.6) | 79 (25.1) |
| 5-DRS Level 47A-47D (Moderately Severe NPDR) | 59 (18.6) | 63 (19.7) | 54 (17.1) |
| 6-DRS Level 53A-53E (Severe NPDR) | 50 (15.8) | 36 (11.3) | 51 (16.2) |
| 7-DRS Level 61A-61B (Mild PDR) | 12 (3.8) | 26 (8.2) | 11 (3.5) |
| 8-DRS Level 65A-65C (Moderate PDR) | 6 (1.9) | 10 (3.1) | 6 (1.9) |
| 9-DRS Level 71A-71D (High Risk PDR) | 2 (0.6) | 1 (0.3) | 3 (1.0) |
| 10-DRS Level 75 (High Risk PDR) | 0 | 0 | 0 |
| 11-DRS Level 81 (Advanced PDR) | 0 | 0 | 0 |

| Baseline Characteristic | Faricimab 6 mg Q8W (N 317) n (%) | Faricimab 6 mg PTI (N 319) n (%) | Aflibercept 2 mg Q8W (N 315) n (%) |
|---|---|---|---|
| 12-DRS Level 85A-85B (Advanced PDR) | 0 | 0 | 0 |
| 90-DRS Level 90 (Cannot Grade) | 2 (0.6) | 5 (1.6) | 5 (1.6) |
| Missing | 3 (0.9) | 0 | 5 (1.6) |

Source: Study RHINE CSR, Table 6
BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; ILM = Internal Limiting Membrane; NPDR = Non-Proliferative Diabetic Retinopathy; PTI = Personalized Treatment Interval (from Q4W up to Q16W); PDR = Proliferative Diabetic Retinopathy; VEGF = Vascular Endothelial Growth Factor.
Baseline is the last available value taken on or prior to randomization.
Invalid BCVA are excluded from analysis. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by the CRC.

**Reviewer's Comment:** *There were no significant differences in baseline ocular characteristics between treatment groups.*

## Primary Efficacy Results

### Table 6.4.2-6 Change in Baseline in BCVA in the Study Eye Averaged over Week 48/52/56 – MMRM Method*

| | Faricimab 6 mg Q8W (N=315) | Faricimab 6 mg PTI (N=313) | Aflibercept 2 mg Q8W (N=312) | Difference (faricimab Q8W – Aflibercept) | Difference (faricimab PTI – Aflibercept) |
|---|---|---|---|---|---|
| **ITT Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 11.8 (10.6, 13.0) | 10.8 (9.6, 11.9) | 10.3 (9.1, 11.4) | | |
| Difference (97.5% CI) | | | | 1.5 (-0.1, 3.2) | 0.5 (-1.1, 2.1) |
| **PP Population[2]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 11.9 (10.6, 13.2) | 10.7 (9.5, 12.0) | 10.4 (9.1, 11.6) | | |
| Difference (97.5% CI) | | | | 1.5 (-0.3, 3.3) | 0.3 (-1.4, 2.1) |
| **TN Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 11.7 (10.4, 13.0) | 11.2 (9.9, 12.4) | 10.5 (9.2, 11.9) | | |
| Difference (97.5% CI) | | | | 1.1 (-0.7, 3.0) | 0.6 (-1.2, 2.4) |

Source: Study RHINE CSR, Tables 8
* MMRM = mixed model repeated measurement
[1] Primary analysis – MMRM Method
[2] Supplementary analysis – MMRM Method

**Reviewer's Comment:** *For the **ITT, PP and TN populations**, the confidence interval for the difference between the faricimab Q8W and aflibercept arms was greater than 0.7.*

*The lower limit of the 97.5% confidence interval for the treatment differences between the faricimab Q8W arm and the aflibercept arm met the non-inferiority margin of 4 letters for the **TN population** but **did not demonstrate superiority** (-0.7).*

*The lower limit of the 97.5% confidence interval for the treatment differences between the faricimab PTI arm and the aflibercept arm met the non-inferiority margin of 4 letters for the **TN population** but **did not demonstrate superiority** (-1.2).*

**Key Primary Efficacy Sensitivity Analysis**

**Table 6.3.2-7 Change in Baseline in BCVA in the Study Eye Averaged over Week 48/52/56 – LOCF[1]: MMRM Method[2]**

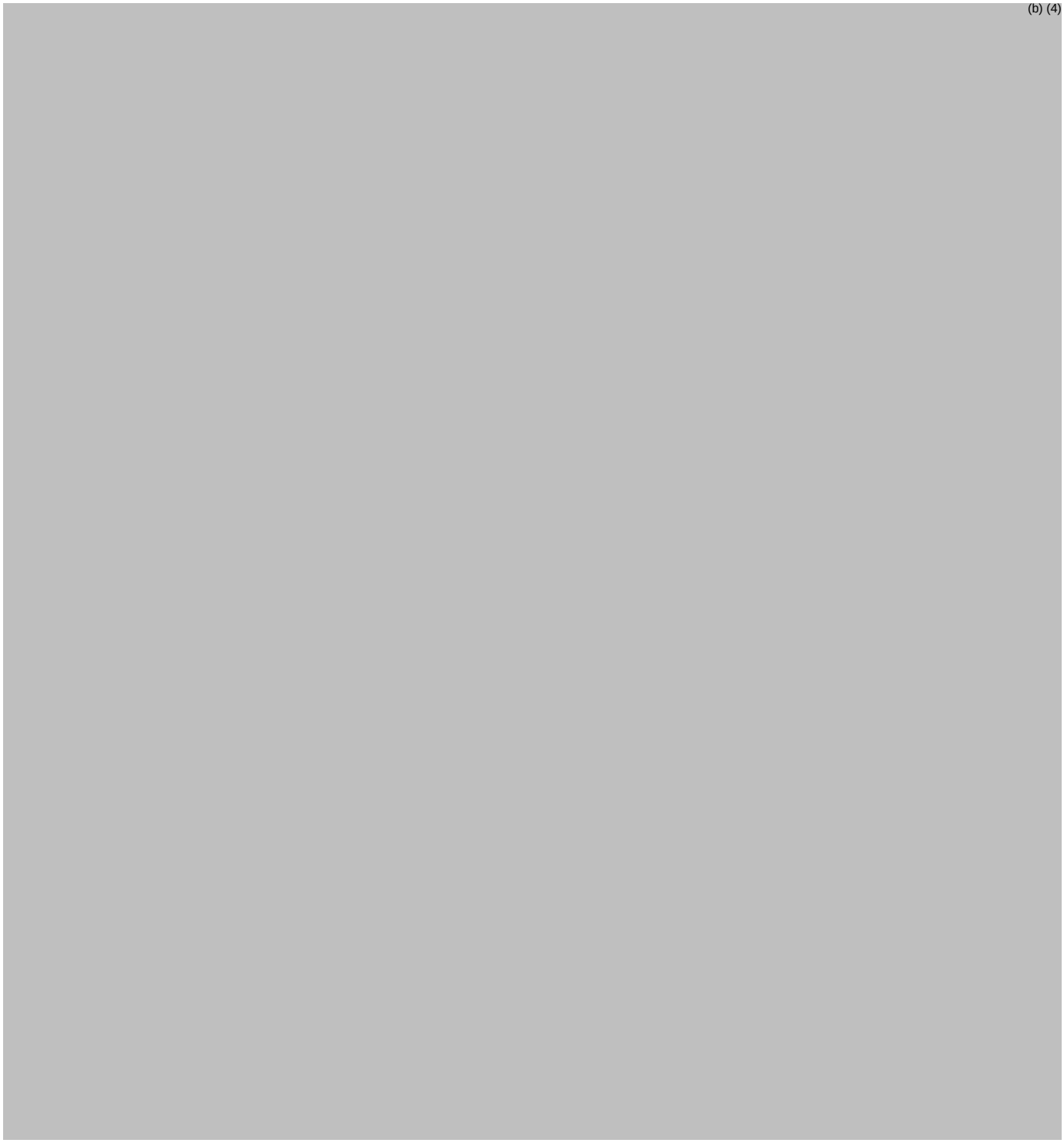
| | Faricimab 6 mg Q8W (N=315) | Faricimab 6 mg PTI (N=313) | Aflibercept 2 mg Q8W (N=312) | Difference (faricimab Q8W – Aflibercept) | Difference (faricimab PTI – Aflibercept) |
|---|---|---|---|---|---|
| **ITT Population[1]** | | | | | |
| Adjusted mean in change from baseline in BCVA averaged over Week 48/52/56 (97.5% CI) | 11.7 (10.6, 12.9) | 10.7 (9.6, 11.9) | 10.1 (9.0, 11.2) | | |
| Difference (97.5% CI) | | | | 1.6 (0.0, 3.2) | 0.6 (-1.0, 2.2) |

Source: Study YOSEMITE CSR, Tables 8
[1] LOCF – last observation carried forward
[2] MMRM - mixed-model repeated measurement

**Reviewer's Comment:** *The results of the primary and sensitivity analyses are similar.*

(b) (4)

(b) (4)



# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

The data from two studies, GR40306 (TENAYA) and GR40844 (LUCERNE), contained in this submission establishes the efficacy of faricimab ophthalmic solution, 6 mg (0.05 mL) administered by intravitreal injection every 28 days x 4 and then at fixed intervals of every 8 weeks for the treatment of neovascular age-related macular degeneration. While some patients were satisfactorily treated every 12 weeks or 16 weeks (depending on disease activity), these patients were only identified after multiple 8 week treatments. It was not possible to identify patients who could be treated every 12 or 16 prior to initiating treatment, nor has it been established whether these patients would have had better results if they were treated every 8 weeks. . At the time of the efficacy evaluation, the average number of injections in the q8, q12 and q16 week arms were ??, ?? and ?? respectively.

The data from two studies, GR40349 (YOSEMITE) and GR40398 (RHINE), contained in this submission establishes the efficacy of faricimab ophthalmic solution, 6 mg (0.05 mL) administered by intravitreal injection every 28 days x 4 and then at intervals of every 8 weeks for the **treatment of diabetic macular edema**. As a result of the slowly lengthening intervals, there was a very limited evaluation of 12 week or 16 week dosing.

(b) (4)

# 8. Review of Safety

## 8.1. Safety Review Approach

The review focuses on the safety database from two nAMD Studies GR40306 (TENAYA) and GR40844 (LUCERNE) and two DME/DR Studies GR40306 (TENAYA) and GR40844 (LUCERNE).

nAMD studies TENAYA and LUCERNE have:

- A study duration of 112 weeks
- A treatment group with faricimab 6 mg (0.05 mL), 4xq4w intravitreal injections followed by q8w.
- A treatment group with faricimab 6 mg (0.05 mL), 4xq4w intravitreal injections followed by fixed intervals of q8w, q12w, or q16w.

Supportive safety data are provided from two phase 2 nAMD studies, CR39521 (STAIRWAY) and BP29647 (AVENUE), one Phase 1 nAMD study, BP28936 and one safety study, JP39844 in Japanese patients.

DME/DR Studies GR40349 (YOSEMITE) and GR40398 (RHINE) have:

- A study duration of 96 weeks
- A treatment group with faricimab 6 mg (0.05 mL), 6xq4w intravitreal injections followed by q8w.
- A treatment group with faricimab 6 mg (0.05 mL), 4xq4w intravitreal injections followed

by intervals of q4w, q8w, q12w, or q16w.

Supportive safety data are provided from one phase 2 DME/DR study, BP30099 (BOULEVARD) and one Phase 1 safety study, JP39844 in Japanese patients.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

**Table 8.2.1-1 Exposure to Study Drug from Baseline to Week 48 and 90-Day Safety Update Report (SUR) Clinical Cutoff Date (CCOD) for TENAYA[1] and LUCERNE[2] – Cumulative Number of Injections (Pooled Safety Population)**

| | Week 48 Pooled TENAYA and LUCERNE (N=1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Treatment duration (weeks) | | | | |
| Mean (SD) | 46.2 (7.37) | 46.2 (7.78) | 78.0 (18.36) | 78.7 (17.98) |
| Min, Median, MAX | 0, 48.1, 50 | 0, 48.4, 50 | 0, 80.1, 109 | 0, 80.4, 109 |
| Number of study drug administrations | | | | |
| Mean (SD) | 6.4 (1.08) | 7.4 (1.14) | 8.9 (2.20) | 11.2 (2.37) |
| Min, Median, Max | 1, 6.0, 8 | 1, 8.0, 8 | 1, 9.0, 16 | 1, 12.0, 15 |

Source: SUR Table 3
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *The mean number of intravitreal injections of active study treatment were 9 and 11 for the faricimab and aflibercept treatment groups, respectively.*

**Table 8.2.1-2 Exposure to Study Drug from Baseline to Week 56 for YOSEMITE[1] and RHINE[2] – Cumulative Number of Injections (Pooled Safety Population)**

| | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Treatment duration (weeks) | | | | |
| Mean (SD) | 53.1 (9.87) | 53.7 (9.08) | 53.4 (9.48) | 53.4 (9.10) |
| Min, Median, MAX | 0, 56.1, 58 | 0, 56.1, 58 | 0, 56.1, 58 | 0, 56.1, 58 |
| Number of study drug administrations | | | | |
| Mean (SD) | 9.4 (1.46) | 8.5 (2.48) | 9.0 (2.08) | 9.3 (1.42) |
| Min, Median, Max | 1, 10.0, 11 | 1, 8.0, 15 | 1, 10.0, 15 | 1, 10.0, 10 |

Source: SUR Table 16
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 56, the mean number of intravitreal injections of active study treatment was 9 for all three treatment groups.*

**Table 8.2.1-3 Exposure to Study Drug from Baseline to 90-Day Safety Update Report (SUR) Clinical Cutoff Date (CCOD) for YOSEMITE[1] and RHINE[2] – Cumulative Number of Injections (Pooled Safety Population)**

| | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262 n (%)) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Treatment duration (weeks) | | | | |
| Mean (SD) | 84.7 (20.87) | 86.3 (18.91) | 85.5 (19.92) | 85.5 (19.34) |
| Min, Median, MAX | 0, 93.1, 98 | 0, 95.1, 98 | 0, 93.8, 98 | 0, 92.9, 98 |
| Number of study drug administrations | | | | |
| Mean (SD) | 13.2 (2.82) | 11.5 (3.95) | 12.4 (3.54) | 12.9 (2.64) |
| Min, Median, Max | 1, 14.0, 16 | 1, 10.0, 25 | 1, 13.0, 25 | 1, 14.0, 16 |

Source: SUR Table 16
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through the SUR clinical cutoff date (CCOD), the mean number of intravitreal injections of active study treatment were 13, 12, and 13 for the faricimab Q8W, faricimab PTI, and aflibercept Q8W treatment groups, respectively.*

**Table 8.2.1-4 Subject Disposition from 90-Day Safety Update Report (SUR) Clinical Cutoff Date (CCOD) for TENAYA[1] and LUCERNE[2] – (Pooled ITT Population)**

| | SUR CCOD Pooled TENAYA and LUCERNE (N=1329) | |
|---|---|---|
| | **Faricimab 6 mg (N=665) n (%)** | **Aflibercept 2 mg (N=664) n (%)** |
| **All randomized** | 665 (100) | 664 (100) |
| **Randomized and treated** | 664 (99.8) | 662 (99.7) |
| **Discontinued treatment in study eye*** | | |
| Total | 85 (12.8) | 71 (10.7) |
| **Reason for Discontinuation** | | |
| Adverse event | 20 (3.0) | 10 (1.5) |
| Pregnancy | 0 | 0 |
| Death | 19 (2.9) | 15 (2.3) |
| Lack of efficacy | 2 (0.3) | 2 (0.3) |
| Lost to follow-up | 5 (0.8) | 7 (1.1) |
| Protocol deviation | 2 (0.3) | 1 (0.2) |
| Withdrawal by subject | 29 (4.4) | 26 (3.9) |
| Physician decision | 6 (0.9) | 7 (1.1) |
| Other reason | 2 (0.3) | 3 (0.5) |

Source: SUR, t_ds_IT_nAMD_SUR
[1] TENAYA=Study GR40306
[2] LUCERNE=Study GR40844
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Through the SUR, the number of subjects who discontinued study treatment and study, respectively were 85 (13%) and 71 (11%) for faricimab Q8W and 71 (11%) and 64 (10%) for aflibercept. The most common reasons for discontinuation from the study for both treatment groups were Withdrawal by Subject (30 [5%] for faricimab Q8W and 25[4%] for aflibercept) and Death (19 [3%] for faricimab Q8W and 15[2%] for aflibercept).*

**Table 8.2.1-5 Subject Disposition from 90-Day Safety Update Report (SUR) Clinical Cutoff Date (CCOD) for YOSEMITE[1] and RHINE[2] – (Pooled ITT Population)**

| | SUR CCOD Pooled YOSEMITE and RHINE (N=1891) | | | |
|---|---|---|---|---|
| | Faricimab 6 m g Q8W (N=632) n (%) | Faricimab 6 mg PTI N=632 n (%) | Faricimab 6 mg All (N=1264) n (%) | Aflibercept 2 mg Q8W N=627) n (%) |
| **All randomized** | 632 (100) | 632 (100) | 1264 (100) | 627 (100) |
| **Randomized and treated** | 630 (99.7) | 632 (100) | 1262 (99.8) | 625 (99.7) |
| **Completed treatment in study eye*** | 327 (51.9) | 338 (53.5) | 665 (52.7) | 315 (50.4) |
| **Completed study assessments**** | 280 (44.3) | 293 (46.4) | 573 (45.3) | 275 (43.9) |
| **Discontinued treatment in study eye*** | | | | |
| Total | 88 (14.0) | 78 (12.3) | 166 (13.2) | 89 (14.2) |
| **Reason for Discontinuation** | | | | |
| Adverse event | 14 (2.2) | 16 (2.5) | 30 (2.4) | 10 (1.6) |
| Pregnancy | 0 | 1 (0.2) | 1 (0.1) | 1 (0.2) |
| Death | 26 (4.1) | 28 (4.4) | 54 (4.3) | 21 (3.4) |
| Lack of efficacy | 1 (0.2) | 0 | 1 (0.1) | 1 (0.2) |
| Lost to follow-up | 20 (3.2) | 13 (2.1) | 33 (2.6) | 15 (2.4) |
| Protocol deviation | 0 | 0 | 0 | 2 (0.3) |
| Withdrawal by subject | 20 (3.2) | 17 (2.7) | 37 (2.9) | 30 (4.8) |
| Study terminated by sponsor | 0 | 0 | 0 | 0 |
| Physician decision | 4 (0.6) | 1 (0.2) | 5 (0.4) | 4 (0.6) |
| Other reason | 3 (0.5) | 2 (0.3) | 5 (0.4) | 5 (0.8) |

Source: SUR, t_ds_IT_DME_SUR
PTI=Personalized Treatment Interval (Q4W up to Q16W)
[1] YOSEMITE= Study GR40349
[2] RHINE=Study GR40398
* Percentages are based on number of patients treated.
** Percentages are based on number of patients randomized.

**Reviewer's Comment:** *Through the SUR, the number of subjects who discontinued study treatment and study, respectively were 88 (14%) and 81 (13%) for faricimab Q8W, 78 (12%) and 68 (11%) for faricimab PTI, and 89 (14%) and 86 (14%) for aflibercept. The most common reasons for discontinuation from the study for all treatment groups were Death (25 [4%] for faricimab Q8W, 26 [4%] for faricimab PTI, and 22[4%] for aflibercept), Withdrawal by Subject (20 [3%] for faricimab Q8W, 15 [2%] for faricimab PTI, and 28[5%] for aflibercept, and Lost to Follow-up (19 [3%] for faricimab Q8W, 13 [2%] for faricimab PTI, and 15[2%] for aflibercept).*

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to

data quality or data integrity were identified in this review.

### 8.3.2. Categorization of Adverse Events

Adverse events were categorized as ophthalmic and systemic.

### 8.3.3. Routine Clinical Tests

Clinical laboratory parameters were as expected for the subject population under study. No clinically significant differences between treatment groups were observed for any of the analyzed laboratory parameters.

## 8.4. Safety Results

### 8.4.1. Deaths

**Table 8.4.1-1 Deaths Through Week 48 and SUR CCOD in nAMD Studies (TENAYA[1] and LUCERNE[2]) – Pooled Safety Population**

| Preferred Term | Week 48 Pooled TENAYA and LUCERNE (N=1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Total number of deaths | 9 (1.4) | 8 (1.2) | 19 (2.9) | 15 (2.3) |
| Primary cause of deaths | | | | |
| N | 9 | 8 | 19 | 15 |
| Cardiac failure | 0 | 2 (25.0) | 1 (5.3) | 2 (13.3) |
| Fall | 1 (11.1) | 1 (12.5) | 1 (5.3) | 1 (6.7) |
| Acute kidney injury | 0 | 1 (12.5) | 0 | 1 (6.7) |
| Brain edema | 1 (11.1) | 0 | 1 (5.3) | 0 |
| Cardiac failure congestive | 1 (11.1) | 0 | 2 (10.5) | 0 |
| Cardiopulmonary failure | 0 | 1 (12.5) | 0 | 1 (6.7) |
| Cerebrovascular accident | 1 (11.1) | 0 | 1 (5.3) | 0 |
| Unknown cause of death | 1 (11.1) | 1 (12.5) | 1 (5.3) | 2 (13.3) |
| Glioblastoma multiforme | 0 | 1 (12.5) | 0 | 1 (6.7) |
| Ill-defined disorder | 1 (11.1) | 0 | 1 (5.3) | 0 |
| Metastases to liver | 0 | 1 (12.5) | 0 | 1 (6.7) |
| Multiple organ dysfunction syndrome | 1 (11.1) | 0 | 1 (5.3) | 0 |
| Pancreatic carcinoma | 1 (11.1) | 0 | 1 (5.3) | 0 |
| Pneumonia | 1 (11.1) | 0 | 1 (5.3) | 1 (6.7) |
| Pneumonia bacterial | 1 (11.1) | 0 | 1 (5.3) | 0 |
| COVID-19 pneumonia | 0 | 0 | 1 (5.3) | 1 (6.7) |
| Bile duct cancer | 0 | 0 | 0 | 1 (6.7) |

| Preferred Term | Week 48 Pooled TENAYA and LUCERNE (N 1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N 1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Cardiac failure chronic | 0 | 0 | 1 (5.3) | 0 |
| Colon cancer stage IV | 0 | 0 | 0 | 1 (6.7) |
| Myocardial infarction | 0 | 0 | 1 (5.3) | 0 |
| Plasma cell myeloma | 0 | 0 | 1 (5.3) | 0 |
| Pulmonary embolism | 0 | 0 | 0 | 1 (6.7) |
| Pulmonary edema | 0 | 0 | 1 (5.3) | 0 |
| Respiratory failure | 0 | 0 | 1 (5.3) | 0 |
| Subdural hemorrhage | 0 | 0 | 1 (5.3) | 0 |
| Sudden death | 0 | 0 | 0 | 1 (6.7) |

Source: SUR Table 7
SUR=90-Day Safety Update
CCOD=Clinical Cutoff Date
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through Week 48, there were 9 and 8 deaths in the faricimab and aflibercept treatment groups, respectively. Through SUR CCOD, there were19 and 15 deaths in the faricimab and aflibercept treatment groups. The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.*

**Table 8.4.1-2 Death Through Week 56 in DME Studies (YOSEMITE[1] and RHINE[2]) – (Pooled Safety Population)**

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Total number of deaths | 13 (2.1) | 9 (1.4) | 22 (1.7) | 9 (1.4) |
| Primary cause of deaths | | | | |
| N | 13 | 9 | 22 | 9 |
| Acute myocardial infarction | 1 (7.7) | 3 (33.3) | 4 (18.2) | 0 |
| Myocardial infarction | 1 (7.7) | 0 | 1 (4.5) | 2 (22.2) |
| Bladder cancer | 1 (7.7) | 1 (11.1) | 2 (9.1) | 1 (11.1) |
| Cardiac arrest | 2 (15.4) | 0 | 2 (9.1) | 0 |
| Cardiac failure | 2 (15.4) | 0 | 2 (9.1) | 0 |
| Adenocarcinoma of colon | 0 | 2 (22.2) | 2 (9.1) | 0 |
| COVID-19 | 0 | 0 | 0 | 1 (11.1) |
| Cerebral hemorrhage | 0 | 1 (11.1) | 1 (4.5) | 0 |
| Completed suicide | 1 (7.7) | 0 | 1 (4.5) | 0 |
| Coronary artery disease | 0 | 0 | 0 | 1 (11.1) |
| Diabetic complication | 0 | 0 | 0 | 1 (11.1) |
| Diabetic gangrene | 1 (7.7) | 0 | 1 (4.5) | 0 |
| Embolism | 0 | 0 | 0 | 1 (11.1) |
| General physical health deterioration | 1 (7.7) | 0 | 1 (4.5) | 0 |
| Hypotension | 1 (7.7) | 0 | 1 (4.5) | 0 |
| Left atrial dilatation | 0 | 0 | 0 | 1 (11.1) |
| Leukemia | 1 (7.7) | 0 | 1 (4.5) | 0 |
| Pneumonia aspiration | 0 | 1 (11.1) | 1 (4.5) | 0 |
| Sepsis | 0 | 1 (11.1) | 1 (4.5) | 0 |
| Type 1 diabetes mellitus | 1 (7.7) | 0 | 1 (4.5) | 0 |
| COVD-19 pneumonia | 0 | 0 | 0 | 1 (11.1) |
| Pneumonia | 0 | 0 | 0 | 0 |
| Chronic kidney disease | 0 | 0 | 0 | 0 |
| Pancreatic carcinoma metastatic | 0 | 0 | 0 | 0 |
| Acute pulmonary edema | 0 | 0 | 0 | 0 |
| Acute respiratory failure | 0 | 0 | 0 | 0 |
| Anemia | 0 | 0 | 0 | 0 |
| Cardiac failure congestive | 0 | 0 | 0 | 0 |
| Coronavirus infection | 0 | 0 | 0 | 0 |
| Dyspnea | 0 | 0 | 0 | 0 |
| Hemorrhage intracranial | 0 | 0 | 0 | 0 |

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Hemorrhagic stroke | 0 | 0 | 0 | 0 |
| Hernia obstructive | 0 | 0 | 0 | 0 |
| Ischemic stroke | 0 | 0 | 0 | 0 |
| Pulmonary fibrosis | 0 | 0 | 0 | 0 |

Source: SUR, Table 22
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 48, there were 13 (2%), 9 (1%), and 9 (1%) deaths in the faricimab Q8W, faricimab PTI and aflibercept Q8W treatment groups, respectively. The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.*

**Table 8.2.1-3 Death Through SUR Clinical Cut Off Date (CCOD) in DME Studies (YOSEMITE[1] and RHINE[2]) – Pooled Safety Population**

| Preferred Term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Total number of deaths | 25 (4.0) | 26 (4.1) | 51 (4.0) | 22 (3.5) |
| Primary cause of deaths | | | | |
| N | 25 | 26 | 51 | 22 |
| Death | 2 (8.0) | 4 (15.4) | 6 (11.8) | 1 (4.5) |
| Acute myocardial infarction | 1 (4.0) | 1 (3.8) | 2 (3.9) | 2 (9.1) |
| Myocardial infarction | 2 (8.0) | 2 (7.7) | 4 (7.8) | 4 (18.2) |
| Bladder cancer | 2 (8.0) | 0 | 2 (3.9) | 0 |
| Cardiac arrest | 2 (8.0) | 0 | 2 (3.9) | 1 (4.5) |
| Cardiac failure | 0 | 3 (11.5) | 3 (5.9) | 0 |
| Adenocarcinoma of colon | 0 | 0 | 0 | 1 (4.5) |
| COVID-19 | 2 (8.0) | 2 (7.7) | 4 (7.8) | 1 (4.5) |
| Cerebral hemorrhage | 1 (4.0) | 1 (3.8) | 2 (3.9) | 0 |
| Completed suicide | 0 | 0 | 0 | 1 (4.5) |
| Coronary artery disease | 0 | 0 | 0 | 1 (4.5) |
| Diabetic complication | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Diabetic gangrene | 0 | 0 | 0 | 0 |
| Embolism | 1 (4.0) | 0 | 1 (2.0) | 0 |

| Preferred Term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| General physical health deterioration | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Hypotension | 0 | 0 | 0 | 1 (4.5) |
| Left atrial dilatation | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Leukemia | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Pneumonia aspiration | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Sepsis | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Type 1 diabetes mellitus | 0 | 0 | 0 | 1 (4.5) |
| COVD-19 pneumonia | 1 (4.0) | 2 (7.7) | 3 (5.9) | 1 (4.5) |
| Pneumonia | 1 (4.0) | 1 (3.8) | 2 (3.9) | 0 |
| Chronic kidney disease | 1 (4.0) | 0 | 1 (2.0) | 1 (4.5) |
| Pancreatic carcinoma metastatic | 0 | 1 (3.8) | 1 (2.0) | 1 (4.5) |
| Acute pulmonary edema | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Acute respiratory failure | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Anemia | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Cardiac failure congestive | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Coronavirus infection | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Dyspnea | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Hemorrhage intracranial | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Hemorrhagic stroke | 1 (4.0) | 0 | 1 (2.0) | 0 |
| Hernia obstructive | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Ischemic stroke | 0 | 1 (3.8) | 1 (2.0) | 0 |
| Pulmonary fibrosis | 0 | 1 (3.8) | 1 (2.0) | 0 |

Source: SUR, Table 22
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD, there were 25 (4%), 26 (4%), and 22 (4%) deaths in the faricimab Q8W, faricimab PTI and aflibercept Q8W treatment groups, respectively. The deaths that occurred during the studies are consistent with the age and past medical history of the subjects enrolled.*

### 8.4.2. Serious Adverse Events

**Table 8.4.2-1 Ocular Serious Adverse Events in nAMD Studies (TENAYA[1] and LUCERNE[2]) Through Week 48 and SUR* CCOD** - Pooled Safety Population**

| Preferred Term | Week 48 Pooled TENAYA and LUCERNE (N=1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 11 (1.7) | 13 (2.0) | 17 (2.6) | 23 (3.5) |
| Total number of events | 15 | 13 | 22 | 26 |
| Neovascular Age-related macular degeneration | 2 (0.3) | 3 (0.5) | 3 (0.5) | 6 (0.9) |
| Retinal epithelial tear | 4 (0.6) | 0 | 4 (0.6) | 0 |
| Uveitis | 2 (0.3) | 1 (0.2) | 2 (0.3) | 1 (0.2) |
| Viral uveitis | 2 (0.3) | 0 | 2 (0.3) | 0 |
| Vitritis | 2 (0.3) | 0 | 2 (0.3) | 0 |
| Age-related macular degeneration | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Cataract | 1 (0.2) | 0 | 2 (0.3) | 1 (0.2) |
| Cataract cortical | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Chorioretinitis | 1 (0.2) | 0 | 1 (0.2) | 0 |
| Corneal abrasion | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Corneal edema | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Endophthalmitis | 0 | 1 (0.2) | 2 (0.3) | 1 (0.2) |
| Eye allergy | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Facial bone fracture | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Intraocular pressure increased | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) |
| Subretinal fibrosis | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Vitreous hemorrhage | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Visual acuity decreased | 0 | 0 | 1 (0.2) | 1 (0.2) |
| Cataract operation complication | 0 | 0 | 0 | 1 (0.2) |
| Cataract traumatic | 0 | 0 | 0 | 1 (0.2) |
| Hyphema | 0 | 0 | 0 | 1 (0.2) |
| Non-infectious endophthalmitis | 0 | 0 | 0 | 1 (0.2) |
| Retinal degeneration | 0 | 0 | 0 | 1 (0.2) |
| Retinal rear | 0 | 0 | 0 | 1 (0.2) |
| Retinopathy hemorrhagic | 0 | 0 | 0 | 1 (0.2) |
| Rhegmatogenous retinal detachment | 0 | 0 | 1 (0.2) | 0 |
| Tractional retinal detachment | 0 | 0 | 1 (0.2) | 0 |
| Vitreous hemorrhage | 0 | 0 | 0 | 1 (0.2) |

Source: SUR Table 8
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through Week 48, the incidence of ocular serious adverse event was 2% for the faricimab and aflibercept treatment groups.*

*Through SUR CCOD, the incidence of ocular serious adverse event was 3% for the faricimab and 4% for the aflibercept treatment groups.*

**Table 8.4.2-2 Non-Ocular Serious Adverse Events Occurring in≥ 0.5% Subjects in nAMD Studies (TENAYA[1] and LUCERNE[2]) Through Week 48 and SUR* CCOD** - Pooled Safety Population**

| Preferred Term | Week 48 Pooled TENAYA and LUCERNE (N=1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **NON-OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 68 (10.3) | 82 (12.4) | 105 (15.8) | 121 (18.3) |
| Total number of events | 93 | 169 | 169 | 250 |
| Atrial fibrillation | 4 (0.6) | 5 (0.8) | 6 (0.9) | 6 (0.9) |
| Cardiac failure congestive | 3 (0.5) | 5 (0.8) | 5 (0.8) | 6 (0.9) |
| Cerebrovascular accident | 3 (0.5) | 4 (0.6) | 4 (0.6) | 6 (0.9) |
| Pneumonia | 2 (0.3) | 5 (0.8) | 4 (0.6) | 7 (1.1) |
| COVID-19 | 4 (0.6) | 2 (0.3) | 5 (0.8) | 4 (0.6) |
| Cardiac failure | 2 (0.3) | 3 (0.5) | 3 (0.5) | 3 (0.5) |
| Syncope | 2 (0.3) | 3 (0.5) | 3 (0.5) | 5 (0.8) |
| Constipation | 1 (0.2) | 3 (0.5) | 1 (0.2) | 3 (0.5) |
| Osteoarthritis | 3 (0.5) | 1 (0.2) | 5 (0.8) | 2 (0.3) |
| Dyspnea | 0 | 3 (0.5) | 3 (0.5) | 3 (0.5) |
| Gastrointestinal hemorrhage | 0 | 3 (0.5) | 0 | 4 (0.6) |
| Sepsis | 0 | 3 (0.5) | 1 (0.2) | 5 (0.8) |
| COVID-19 pneumonia | 0 | 0 | 4 (0.6) | 6 (0.9) |
| Coronary artery disease | 0 | 0 | 2 (0.3) | 4 (0.6) |
| Angina pectoris | 0 | 0 | 3 (0.5) | 2 (0.3) |
| Chronic obstructive pulmonary disease | 0 | 0 | 3 (0.5) | 2 (0.3) |
| Fall | 0 | 0 | 2 (0.3) | 3 (0.5) |
| Lung neoplasm malignant | 0 | 0 | 4 (0.6) | 1 (0.2) |
| Transient ischemic attack | 0 | 0 | 2 (0.3) | 3 (0.5) |
| Acute kidney injury | 0 | 0 | 1 (0.2) | 3 (0.5) |
| Anemia | 0 | 0 | 1 (0.2) | 3 (0.5) |

| Preferred Term | Week 48 Pooled TENAYA and LUCERNE (N 1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N 1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Bile duct cancer | 0 | 0 | 1 (0.2) | 3 (0.5) |
| cholecystitis | 0 | 0 | 3 (0.5) | 1 (0.2) |
| Hypertension | 0 | 0 | 1 (0.2) | 3 (0.5) |
| Pulmonary embolism | 0 | 0 | 0 | 4 (0.6) |
| Urinary tract infection | 0 | 0 | 3 (0.5) | 1 (0.2) |
| Femur fracture | 0 | 0 | 0 | 3 (0.5) |

Source: SUR Table 14
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through Week 48, the incidence of non-ocular serious adverse event was 10% for the faricimab and 12% for the aflibercept treatment groups.*

*Through SUR CCOD, the incidence of non-ocular serious adverse event was 16% for the faricimab and 18% for the aflibercept treatment groups.*

**Table 8.4.2-3 Ocular Serious Adverse Events in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 56 - Pooled Safety Population**

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 15 (2.4) | 19 (3.0) | 34 (2.7) | 8 (1.3) |
| Total number of events | 20 | 21 | 41 | 8 |
| Diabetic retinal edema | 3 (0.5) | 2 (0.3) | 5 (0.4) | 0 |
| Endophthalmitis | 2 (0.3) | 2 (0.3) | 4 (0.3) | 1 (0.2) |
| Cataract | 2 (0.3) | 0 | 2 (0.2) | 2 (0.3) |
| Vitreous hemorrhage | 2 (0.3) | 1 (0.2) | 3 (0.2) | 1 (0.2) |
| Uveitis | 0 | 3 (0.5) | 3 (0.3) | 0 |
| Visual acuity reduced transiently | 1 (0.2) | 1 (0.2) | 2 (0.2) | 1 (.2) |
| Ocular hypertension | 0 | 2 (0.3) | 2 (0.2) | 0 |
| Retinal tear | 0 | 2 (0.3) | 2 (0.2) | 0 |

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Cataract subcapsular | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Chemical burns of eye | 0 | 0 | 0 | 1 (0.2) |
| Chorioretinitis | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Device dislocation | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Diabetic retinopathy | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Dry eye | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Glaucoma | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Influenza | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Intraocular pressure increased | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Keratouveitis | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Macular fibrosis | 0 | 0 | 0 | 1 (0.2) |
| Narrow anterior chamber angle | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Retinal artery occlusion | 0 | 0 | 0 | 1 (0.2) |
| Retinal neovascularization | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Retinal vein occlusion | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Rhegmatogenous retinal detachment | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Uveitic glaucoma | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Viral keratouveitis | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Visual impairment | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Posterior capsule opacification | 0 | 0 | 0 | 0 |
| Cataract nuclear | 0 | 0 | 0 | 0 |
| Diabetic eye disease | 0 | 0 | 0 | 0 |
| Diabetic vascular disorder | 0 | 0 | 0 | 0 |
| Macular edema | 0 | 0 | 0 | 0 |
| Ocular ischemic syndrome | 0 | 0 | 0 | 0 |
| Open angle glaucoma | 0 | 0 | 0 | 0 |
| Posterior capsule rupture | 0 | 0 | 0 | 0 |
| Swelling of eyelid | 0 | 0 | 0 | 0 |

Source: DSUR, Table 24
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 56, the incidence of ocular serious adverse event was 2% for the faricimab Q8W, 3% for the faricimab PTI and 1% for the aflibercept Q8W treatment groups.*

**Table 8.4.2-4 Ocular Serious Adverse Events in DME Studies (YOSEMITE[1] and RHINE[2]) Through SUR CCOD - Pooled Safety Population**

| Preferred Term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 25 (4.0) | 31 (4.9) | 56 (4.4) | 18 (2.9) |
| Total number of events | 33 | 38 | 71 | 18 |
| Diabetic retinal edema | 4 (0.6) | 3 (0.5) | 7 (0.6) | 1 (0.2) |
| Endophthalmitis | 2 (0.3) | 4 (0.6) | 6 (0.5) | 1 (0.2) |
| Cataract | 7 (1.1) | 6 (0.9) | 13 (1.0) | 5 (0.8) |
| Vitreous hemorrhage | 2 (0.3) | 0 | 2 (0.2) | 0 |
| Uveitis | 0 | 3 (0.5) | 3 (0.2) | 0 |
| Visual acuity reduced transiently | 0 | 0 | 0 | 0 |
| Ocular hypertension | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Retinal tear | 0 | 3 (0.5) | 3 (0.2) | 0 |
| Cataract subcapsular | 1 (0.2) | 1 (0.2) | 2 (0.2) | 2 (0.3) |
| Chemical burns of eye | 0 | 0 | 0 | 1 (0.2) |
| Chorioretinitis | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Device dislocation | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Diabetic retinopathy | 1 (0.2) | 1 (0.2) | 2 (0.2) | 3 (0.5) |
| Dry eye | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Glaucoma | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Influenza | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Intraocular pressure increased | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Keratouveitis | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Macular fibrosis | 0 | 0 | 0 | 1 (0.2) |
| Narrow anterior chamber angle | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Retinal artery occlusion | 0 | 1 (0.2) | 1 (<0.1) | 2 (0.3) |
| Retinal neovascularization | 0 | 0 | 0 | 0 |
| Retinal vein occlusion | 0 | 3 (0.5) | 3 (0.2) | 0 |
| Rhegmatogenous retinal detachment | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Uveitic glaucoma | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Viral keratouveitis | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Visual impairment | 0 | 2 (0.3) | 2 (0.2) | 0 |
| Posterior capsule opacification | 1 (0.2) | 1 (0.2) | 2 (0.2) | 0 |
| Cataract nuclear | 1 (0.2) | 0 | 1 (<0.1) | 1 (0.2) |
| Diabetic eye disease | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Diabetic vascular disorder | 0 | 1 (0.2) | 1 (<0.1) | 0 |

| Preferred Term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Macular edema | 1 (0.2) | 0 | 1 (<0.1) | 0 |
| Ocular ischemic syndrome | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Open angle glaucoma | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Posterior capsule rupture | 0 | 1 (0.2) | 1 (<0.1) | 0 |
| Swelling of eyelid | 0 | 0 | 0 | 1 (0.2) |

Source: SUR, Table 24
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD, the incidence of ocular serious adverse event was 4% for the faricimab Q8W, 5% for the faricimab PTI and 3% for the aflibercept Q8W treatment groups.*

**Table 8.2.2-5 Non-Ocular Serious Adverse Events Occurring in ≥ 0.5% Subjects in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 56 - Pooled Safety Population**

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) | Faricimab 6 mg PTI (N=632) | Faricimab 6 mg All (N=1262) | Aflibercept 2 mg Q8W (N=625) |
| **NON-OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 393 ((62.4) | 385 (60.9) | 778 (61.6) | 390 (62.4) |
| Overall total number of events | 1352 | 1150 | 2502 | 1168 |
| **Infections and infestations** | | | | |
| Total number of patients with ≥ 1 adverse event | 183 (29.0) | 159 (25.2) | 342 (27.1) | 204 (32.6) |
| Overall total number of events | 290 | 229 | 519 | 312 |
| Nasopharyngitis | 44 (7.0%) | 37 (5.9) | 81 (6.4) | 53 (8.5) |
| Urinary tract infection | 20 (3.2) | 19 (3.0) | 39 (3.1) | 34 (5.4) |
| COVID-19 | 0 | 0 | 0 | 0 |
| **Vascular Disorders** | | | | |
| Total number of patients with ≥ 1 adverse event | 49 (7.8) | 63 (10.0) | 112 (8.9) | 56 (9.0) |
| Overall total number of events | 64 | 74 | 138 | 66 |
| Hypertension | 32 (5.1) | 37 (5.9) | 69 (5.5) | 37 (5.9) |

| Preferred Term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) | Faricimab 6 mg PTI (N=632) | Faricimab 6 mg All (N=1262) | Aflibercept 2 mg Q8W (N=625) |
| **Injury, Poisoning and procedural complications** | | | | |
| Total number of patients with ≥ 1 adverse event | 63 (10.0) | 55 (8.7) | 118 (9.4) | 55 (8.8) |
| Overall total number of events | 91 | 82 | 173 | 68 |
| Fall | 24 (3.8) | 18 (2.8) | 42 (3.3) | 17 (2.7) |

Source: SUR, Table 31
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 56, the incidence of non-ocular serious adverse event was 62% for the faricimab Q8W, 61% for the faricimab PTI and 62% for the aflibercept Q8W treatment groups.*

**Table 8.4.2-6 Non-Ocular Serious Adverse Events Occurring in ≥ 0.5% Subjects in DME Studies (YOSEMITE[1] and RHINE[2]) Through SUR CCOD - Pooled Safety Population**

| | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **NON-OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 456 (72.4) | 462 (73.1) | 918 (72.7) | 462 (73.9) |
| Overall total number of events | 1996 | 1846 | 3842 | 1795 |
| **Infections and infestations** | | | | |
| Total number of patients with ≥ 1 adverse event | 256 (40.6) | 234 (37.0) | 490 (38.8) | 258 (41.3) |
| Overall total number of events | 443 | 381 | 824 | 464 |
| Nasopharyngitis | 58 (9.2) | 44 (7.0) | 102 (8.1) | 66 (10.6) |
| Urinary tract infection | 31 (4.9) | 30 (4.7) | 61 (4.8) | 51 (8.2) |
| COVID-19 | 31 (4.9) | 43 (6.8) | 74 (5.9) | 25 (4.0) |
| **Vascular Disorders** | | | | |
| Total number of patients with ≥ 1 adverse event | 69 (11.0) | 93 (14.7) | 162 (12.8) | 78 (12.5) |
| Overall total number of events | 91 | 109 | 200 | 96 |
| Hypertension | 43 (6.8) | 53 (8.4) | 96 (7.6) | 51 (8.2) |

| | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | | |
|---|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Faricimab 6 mg All (N=1262) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **Injury, Poisoning and procedural complications** | | | | |
| Total number of patients with ≥ 1 adverse event | 97 (15.4) | 83 (13.1) | 180 (14.3) | 84 (13.4) |
| Overall total number of events | 136 | 121 | 257 | 110 |
| Fall | 35 (5.6) | 27 (4.3) | 62 (4.9) | 22 (3.5) |

Source: SUR, Table 31
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through the SUR CCOD, the incidence of non-ocular serious adverse event was 72% for the faricimab Q8W, 73% for the faricimab PTI and 74% for the aflibercept Q8W treatment groups.*

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

**Table 8.4.3-1 Ocular Adverse Events Leading to Study Discontinuation in nAMD Studies (TENAYA[1] and LUCERNE[2]) Through Week 48 and SUR* CCOD** - Pooled Safety Population**

| Preferred term | Week 48 Pooled TENAYA and LUCERNE (N=1326) | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **OCULAR** | | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 2 (0.3) | 3 (0.5) |
| Total number of events | 0 | 0 | 2 | 3 |
| Worsening neovascular Age-related Macular degeneration | 0 | 0 | 2 (0.3) | 2 (0.3) |
| Visual acuity reduced | 0 | 0 | 0 | 1 (0.2) |

Source: SUR Table t_ae_pt_cod_OCUL_DSC_SE_nAMD_SUR
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *No subjects from either treatment groups discontinued from the study due to an ocular adverse event through Week 56. Through SUR CCOD, two (0.3%) subjects from the faricimab group and 3 (0.5%) subjects from the aflibercept group discontinued from the study due to an ocular adverse event.*

**Table 8.4.3-2 Non-Ocular Adverse Events Leading to Study Discontinuation in nAMD Studies (TENAYA[1] and LUCERNE[2]) Through Week 48 and SUR[*] CCOD** - Pooled Safety Population**

| Preferred term | Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **NON-OCULAR** | | |
| **Week 48** | | |
| Total number of patients with ≥ 1 adverse event | 8 (1.2) | 10 (1.5) |
| Overall total number of events | 9 | 11 |
| **Cardiac Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 3 (0.5) |
| Total number of events | 1 | 3 |
| Cardiac failure | 1 (0.2) | 2 (0.3) |
| Cardiopulmonary failure | 0 | 1 (0.2) |
| **Neoplasm Benign, Malignant and Unspecified (include cysts and polyps)** | | |
| Total number of patients with ≥ 1 adverse event | 0 | 4 (0.6) |
| Total number of events | 0 | 4 |
| Bile duct cancer | 0 | 1 (0.2) |
| Lung neoplasm malignant | 0 | 1 (0.2) |
| Neuroendocrine carcinoma metastatic | 0 | 1 (0.2) |
| Tongue neoplasm malignant stage unspecified | 0 | 1 (0.2) |
| **Nervous System Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 0 |
| Total number of events | 5 | 0 |
| Cognitive disorder | 2 (0.3) | 0 |
| Brain edema | 1 (0.2) | 0 |
| Subarachnoid hemorrhage | 1 (0.2) | 0 |
| Thrombotic cerebral infarction | 1 (0.2) | 0 |
| **General Disorders and General Administration Site Conditions** | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 1 (0.2) |
| Total number of events | 2 | 1 |
| Death | 0 | 1 (0.2) |
| Ill-defined disorder | 1 (0.2) | 0 |
| Multiple organ dysfunction disorder | 1 (0.2) | 0 |
| **Infections and infestations** | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 |

| Preferred term | Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Total number of events | 1 | 0 |
| Pneumonia | 1 (0.2) | 0 |
| **Injury, Poisoning and procedural complications** | | |
| Total number of patients with ≥ 1 adverse event | 0 | 1 (0.2) |
| Total number of events | 0 | 1 |
| Fall | 0 | 1 (0.2) |
| **Renal and Urinary Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 0 | 1 (0.2) |
| Total number of events | 0 | 1 |
| Acute kidney injury | 0 | 1 (0.2) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 0 | 1 (0.2) |
| Total number of events | 0 | 1 |
| Lung perforation | 0 | 1 (0.2) |
| | | |
| **SUR CCOD** | | |
| Total number of patients with ≥ 1 adverse event | 29 (4.4) | 21 (3.2) |
| Overall total number of events | 31 | 24 |
| **Neoplasm Benign, Malignant and Unspecified (include cysts and polyps)** | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 8 (1.2) |
| Total number of events | 4 | 8 |
| Bile duct cancer | 1 (0.2) | 1 (0.2) |
| Lung neoplasm malignant | 1 (0.2) | 1 (0.2) |
| Colon cancer stage IV | 0 | 1 (0.2) |
| Glioblastoma multiforme | 0 | 1 (0.2) |
| Metastases to liver | 0 | 1 (0.2) |
| Neuroendocrine carcinoma metastatic | 0 | 1 (0.2) |
| Pancreatic carcinoma | 1 (0.2) | 0 |
| Plasma cell myeloma | 1 (0.2) | 0 |
| Prostate cancer | 0 | 1 (0.2) |
| Tongue neoplasm malignant stage unspecified | 0 | 1 (0.2) |
| **Cardiac Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 6 (0.9) | 3 (0.5) |
| Total number of events | 6 | 3 |
| Cardiac failure | 2 (0.3) | 2 (0.3) |
| Cardiac failure congestive | 2 (0.3) | 0 |
| Cardiac failure chronic | 1 (0.2) | 0 |
| Cardiopulmonary failure | 0 | 1 (0.2) |
| Myocardial infarction | 1 (0.2) | 0 |
| **Nervous System Disorders** | | |

| Preferred term | Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Total number of patients with ≥ 1 adverse event | 8 (1.2) | 1 (0.2) |
| Total number of events | 9 | 3 |
| Cognitive disorder | 2 (0.3) | 0 |
| Dementia Alzheimer's type | 1 (0.2) | 1 (0.2) |
| Brain edema | 1 (0.2) | 0 |
| Cerebrovascular accident | 1 (0.2) | 0 |
| Dementia | 1 (0.2) | 0 |
| Metabolic encephalopathy | 1 (0.2) | 0 |
| Subarachnoid hemorrhage | 1 (0.2) | 0 |
| Thrombotic cerebral infarction | 1 (0.2) | 0 |
| Transient ischemic attack | 0 | 1 (0.2) |
| Vascular dementia | 0 | 1 (0.2) |
| **Infections and infestations** | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 3 (0.5) |
| Total number of events | 4 | 3 |
| COVID-19 pneumonia | 1 (0.2) | 1 (0.2) |
| Pneumonia | 1 (0.2) | 1 (0.2) |
| Kidney infection | 1 (0.2) | 0 |
| Pneumonia bacterial | 1 (0.2) | 0 |
| Sepsis | 0 | 1 (0.2) |
| **General Disorders and General Administration Site Conditions** | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 3 (0.5) |
| Total number of events | 3 | 3 |
| Death | 1 (0.2) | 2 (0.3) |
| Ill-defined disorder | 1 (0.2) | 0 |
| Multiple organ dysfunction syndrome | 1 (0.2) | 0 |
| Sudden death | 0 | 1 (0.2) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 2 (0.3) |
| Total number of events | 2 | 2 |
| Lung perforation | 0 | 1 (0.2) |
| Pulmonary embolism | 0 | |
| Pulmonary edema | 1 (0.2) | 0 |
| Respiratory failure | 1 (0.2) | 0 |
| **Injury, Poisoning and procedural complications** | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 1 (0.2) |
| Total number of events | 2 | 1 |
| Fall | 1 (0.2) | 1 (0.2) |
| Subdural hemorrhage | 1 (0.2) | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | |

| Preferred term | Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 |
| Total number of events | 1 | 0 |
| Spinal osteoarthritis | 1 (0.2) | 0 |
| **Renal and Urinary Disorders** | 0 | 1 (0.2) |
| Total number of patients with ≥ 1 adverse event | 0 | 1 |
| Total number of events | 0 | 1 (0.2) |
| Acute kidney injury | 0 | 1 (0.2) |

Source: CSR Table t_ae_NOCUL_DSC_W48_SE-nAMD_HLS and SUR Table t_ae_cod_NOCUL_DSC_SE_nAMD_SUR
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through Week 48, 1% of subjects treated with faricimab and 2% of aflibercept subjects discontinued from the study due to a non-ocular adverse event. Through SUR CCOD, 4% of faricimab subjects and 3% of aflibercept subjects discontinued from the study due to a non-ocular adverse event.*

**Table 8.4.3-3 Ocular Serious Adverse Events Leading to Study Discontinuation in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 56 - Pooled Safety Population**

| Preferred term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 2 (0.3) | 1 (0.2) |
| Total number of events | 3 | 2 | 1 |
| Allergy to chemicals | 0 | 1 (0.2) | 0 |
| Endophthalmitis | 0 | 1 (0.2) | 0 |
| Intraocular pressure increased | 1 (0.2) | 0 | 0 |
| Retinal artery occlusion | 0 | 0 | 1 (0.2) |
| Rhegmatogenous detachment | 1 (0.2) | 0 | 0 |
| Vitritis | 1 (0.2) | 0 | 0 |

Source: CSR Table 46
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 56, less than 1% of faricimab Q8W (0.3%), faricimab PTI (0.3%), and aflibercept (0.2%) subjects discontinued the study due to an ocular adverse event.*

**Table 8.4.3-4 Ocular Serious Adverse Events Leading to Study Discontinuation in DME Studies (YOSEMITE[1] and RHINE[2]) Through SUR CCOD - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 5 (0.8) | 2 (0.3) |
| Total number of events | 5 | 5 | 2 |
| Dry eye | 1 (0.2) | 1 (0.2) | 0 |
| Endophthalmitis | 0 | 2 (0.3) | 0 |
| Cataract | 1 (0.2) | 0 | 1 (0.2) |
| Retinal artery occlusion | 0 | 1 (0.2) | 1 (0.2) |
| Allergy to chemicals | 0 | 1 (0.2) | 0 |
| Intraocular pressure increased | 1 (0.2) | 0 | 0 |
| Rhegmatogenous detachment | 1 (0.2) | 0 | 0 |
| Vitritis | 1 (0.2) | 0 | 0 |

Source: SUR, Table t_ae_pt_OCUL_DSC_SE_DME_SUR
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD, 0.6% faricimab Q8W, 0.8% of faricimab PTI, and 0.3% of aflibercept subjects discontinued the study due to an ocular adverse event.*

**Table 8.4.3-7 Non-Ocular Serious Adverse Events Leading to Study Treatment Discontinuation in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 56 - Pooled Safety Population**

| Preferred term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **NON-OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 14 (2.2) | 10 (1.6) | 8 (1.3) |
| Overall total number of events | 16 | 10 | 8 |

| Preferred term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **Cardiac Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 6 (1.0) | 3 (0.5) | 3 (0.5) |
| Total number of events | 7 | 3 | 3 |
| Myocardial infarction | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Acute myocardial infarction | 1 (0.2) | 0 | 1 (0.2) |
| Cardiac failure | 0 | 2 (0.3) | 0 |
| Cardiac arrest | 1 (0.2) | 0 | 0 |
| Cardiac failure congestive | 1 (0.2) | 0 | 0 |
| Coronary artery disease | 0 | 0 | 1 (0.2) |
| Left atrial dilatation | 1 (0.2) | 0 | 0 |
| Left ventricular dilatation | 1 (0.2) | 0 | 0 |
| Pericarditis | 1 (0.2) | 0 | 0 |
| **Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)** | | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 3 (0.5) | 1 (0.2) |
| Total number of events | 2 | 3 | 1 |
| Adenocarcinoma | 0 | 0 | 1 (0.2) |
| Bladder cancer | 1 (0.2) | 0 | 0 |
| Colon cancer | 0 | 1 (0.2) | 0 |
| Lung neoplasm malignant | 1 (0.2) | 0 | 0 |
| Neoplasm | 0 | 1 (0.2) | 0 |
| Plasma cell myeloma | 0 | 1 (0.2) | 0 |
| **General Disorders and General Administration Site Conditions** | | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 3 (0.5) | 0 |
| Total number of events | 2 | 3 | 0 |
| Death | 1 (0.2) | 3 (0.5) | 0 |
| General physical health deterioration | 1 (0.2) | 0 | 0 |
| **Nervous System Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 0 | 2 (0.3) |
| Total number of events | 2 | 0 | 2 |
| Cerebral hemorrhage | 1 (0.2) | 0 | 0 |
| Dementia Alzheimer's type | 0 | 0 | 1 (0.2) |
| Ischemic stroke | 1 (0.2) | 0 | 0 |
| Spinal cord compression | 0 | 0 | 1 (0.2) |
| **Immune System Disorders** | | | |

| Preferred term | Week 56 Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Contrast media allergy | 0 | 0 | 1 (0.2) |
| **Infections and Infestations** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Sepsis | 1 (0.2) | 0 | 0 |
| **Metabolism and Nutrition Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Diabetic complication | 1 (0.2) | 0 | 0 |
| **Psychiatric Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Completed suicide | 0 | 0 | 1 (0.2) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 1 (0.2) | 0 |
| Total number of events | 0 | 1 | 0 |
| Pneumonia aspiration | 0 | 1 (0.2) | 0 |
| **Vascular Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Embolism | 1 (0.2) | 0 | 0 |

Source: SUR, Table t_ae_par_NOCUL_DSC_W56_SE_DME_HLS
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 56, 2.2% faricimab Q8W, 1.6% of faricimab PTI, and 1.3% of aflibercept subjects discontinued from study treatment due to a non-ocular adverse event.*

**Table 8.4.3-6 Non-Ocular Serious Adverse Events Leading to Study Discontinuation in DME Studies (YOSEMITE[1] and RHINE[2]) Through SUR CCOD - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **NON-OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 23 (3.7) | 23 (3.6) | 21 (3.4) |
| Overall total number of events | 26 | 25 | 21 |
| **Cardiac Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 8 (1.3) | 8 (1.3) | 8 (1.3) |
| Total number of events | 9 | 9 | 8 |
| Myocardial infarction | 2 (0.3) | 3 (0.5) | 4 (0.6) |
| Cardiac failure | 0 | 4 (0.6) | 0 |
| Acute myocardial infarction | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Cardiac failure congestive | 2 (0.3) | 0 | 0 |
| Cardiac arrest | 1 (0.2) | 0 | 0 |
| Cardiopulmonary failure | 0 | 1 (0.2) | 0 |
| Left atrial dilatation | 1 (0.2) | 0 | 0 |
| Left ventricular dilatation | 1 (0.2) | 0 | 0 |
| Pericarditis | 1 (0.2) | 0 | 0 |
| Cardio-respiratory arrest | 0 | 0 | 1 (0.2) |
| Coronary artery disease | 0 | 0 | 1 (0.2) |
| Hypertensive heart disease | 0 | 0 | 1 (0.2) |
| **General Disorders and General Administration Site Conditions** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 5 (0.8) | 1 (0.2) |
| Total number of events | 3 | 5 | 1 |
| Death | 2 (0.3) | 4 (0.6) | 1 (0.2) |
| General physical health deterioration | 1 (0.2) | 0 | 0 |
| Hernia obstructive | 0 | 1 (0.2) | 0 |
| **Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 4 (0.6) | 2 (0.3) |
| Total number of events | 3 | 4 | 2 |
| Pancreatic carcinoma metastatic | 0 | 1 (0.2) | 1 (0.2) |
| Bladder cancer | 1 (0.2) | 0 | 0 |
| Colon cancer | 0 | 1 (0.2) | 0 |
| Colorectal cancer metastatic | 1 (0.2) | 0 | 0 |
| Lung neoplasm malignant | 1 (0.2) | 0 | 0 |
| Neoplasm | 0 | 1 (0.2) | 0 |

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Plasma cell myeloma | 0 | 1 (0.2) | 0 |
| Adenocarcinoma | 0 | 0 | 1 (0.2) |
| **Infections and Infestations** | | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 2 (0.3) | 3 (0.5) |
| Total number of events | 4 | 2 | 3 |
| COVID-19 pneumonia | 2 (0.3) | 2 (0.3) | 0 |
| Coronavirus infection | 1 (0.2) | 0 | 0 |
| Sepsis | 1 (0.2) | 0 | 0 |
| COVID-19 | 0 | 0 | 1 (0.2) |
| Lower respiratory tract infection | 0 | 0 | 1 (0.2) |
| Pneumonia | 0 | 0 | 1 (0.2) |
| **Nervous System Disorder** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 2 (0.3) | 2 (0.3) |
| Total number of events | 3 | 2 | 2 |
| Cerebral hemorrhage | 1 (0.2) | 1 (0.2) | 0 |
| Ischemic stroke | 1 (0.2) | 1 (0.2) | 0 |
| Hemorrhagic stroke | 1 (0.2) | 0 | 0 |
| Dementia Alzheimer's type | 0 | 0 | 1 (0.2) |
| Spinal cord compression | 0 | 0 | 1 (0.2) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 3 (.05) | 0 |
| Total number of events | 1 | 3 | 0 |
| Acute pulmonary edema | 0 | 1 (0.2) | 0 |
| Acute respiratory failure | 1 (0.2) | 0 | 0 |
| Pneumonia aspiration | 0 | 1 (0.2) | 0 |
| Pulmonary fibrosis | 0 | 1 (0.2) | 0 |
| **Renal and Urinary Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 1 (0.2) |
| Total number of events | 1 | 0 | 1 |
| Renal failure | 1 (0.2) | 0 | 0 |
| Chronic kidney disease | 0 | 0 | 1 (0.2) |
| **Metabolism and Nutrition Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Diabetic complications | 1 (0.2) | 0 | 0 |
| **Vascular Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Embolism | 1 (0.2) | 0 | 0 |

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **Gastrointestinal Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Intestinal Ischemia | 0 | 0 | 1 (0.2) |
| **Immune System Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Contrast Media Allergy | 0 | 0 | 1 (0.2) |
| **Injury, Poisoning and procedural complications** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Overall total number of events | 0 | 0 | 1 |
| Skin laceration | 0 | 0 | 1 (0.2) |
| **Psychiatric Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Overall total number of events | 0 | 0 | 1 |
| Completed suicide | 0 | 0 | 1 (0.2) |

Source: SUR, Table t_ae_par_NOCUL_DSC_SE_DME_SUR
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD, 3.7% faricimab Q8W, 3.6% of faricimab PTI, and 3.4% of aflibercept subjects discontinued the study due to a non-ocular adverse event.*

**Table 8.4.3-6 Non-Ocular Serious Adverse Events Leading to Study Discontinuation in DME Studies (YOSEMITE[1] and RHINE[2]) Through SUR CCOD - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **NON-OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 23 (3.7) | 23 (3.6) | 21 (3.4) |
| Overall total number of events | 26 | 25 | 21 |
| **Cardiac Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 8 (1.3) | 8 (1.3) | 8 (1.3) |
| Total number of events | 9 | 9 | 8 |

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Myocardial infarction | 2 (0.3) | 3 (0.5) | 4 (0.6) |
| Cardiac failure | 0 | 4 (0.6) | 0 |
| Acute myocardial infarction | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Cardiac failure congestive | 2 (0.3) | 0 | 0 |
| Cardiac arrest | 1 (0.2) | 0 | 0 |
| Cardiopulmonary failure | 0 | 1 (0.2) | 0 |
| Left atrial dilatation | 1 (0.2) | 0 | 0 |
| Left ventricular dilatation | 1 (0.2) | 0 | 0 |
| Pericarditis | 1 (0.2) | 0 | 0 |
| Cardio-respiratory arrest | 0 | 0 | 1 (0.2) |
| Coronary artery disease | 0 | 0 | 1 (0.2) |
| Hypertensive heart disease | 0 | 0 | 1 (0.2) |
| **General Disorders and General Administration Site Conditions** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 5 (0.8) | 1 (0.2) |
| Total number of events | 3 | 5 | 1 |
| Death | 2 (0.3) | 4 (0.6) | 1 (0.2) |
| General physical health deterioration | 1 (0.2) | 0 | 0 |
| Hernia obstructive | 0 | 1 (0.2) | 0 |
| **Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 4 (0.6) | 2 (0.3) |
| Total number of events | 3 | 4 | 2 |
| Pancreatic carcinoma metastatic | 0 | 1 (0.2) | 1 (0.2) |
| Bladder cancer | 1 (0.2) | 0 | 0 |
| Colon cancer | 0 | 1 (0.2) | 0 |
| Colorectal cancer metastatic | 1 (0.2) | 0 | 0 |
| Lung neoplasm malignant | 1 (0.2) | 0 | 0 |
| Neoplasm | 0 | 1 (0.2) | 0 |
| Plasma cell myeloma | 0 | 1 (0.2) | 0 |
| Adenocarcinoma | 0 | 0 | 1 (0.2) |
| **Infections and Infestations** | | | |
| Total number of patients with ≥ 1 adverse event | 4 (0.6) | 2 (0.3) | 3 (0.5) |
| Total number of events | 4 | 2 | 3 |
| COVID-19 pneumonia | 2 (0.3) | 2 (0.3) | 0 |
| Coronavirus infection | 1 (0.2) | 0 | 0 |
| Sepsis | 1 (0.2) | 0 | 0 |
| COVID-19 | 0 | 0 | 1 (0.2) |
| Lower respiratory tract infection | 0 | 0 | 1 (0.2) |
| Pneumonia | 0 | 0 | 1 (0.2) |

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **Nervous System Disorder** | | | |
| Total number of patients with ≥ 1 adverse event | 3 (0.5) | 2 (0.3) | 2 (0.3) |
| Total number of events | 3 | 2 | 2 |
| Cerebral hemorrhage | 1 (0.2) | 1 (0.2) | 0 |
| Ischemic stroke | 1 (0.2) | 1 (0.2) | 0 |
| Hemorrhagic stroke | 1 (0.2) | 0 | 0 |
| Dementia Alzheimer's type | 0 | 0 | 1 (0.2) |
| Spinal cord compression | 0 | 0 | 1 (0.2) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 3 (.05) | 0 |
| Total number of events | 1 | 3 | 0 |
| Acute pulmonary edema | 0 | 1 (0.2) | 0 |
| Acute respiratory failure | 1 (0.2) | 0 | 0 |
| Pneumonia aspiration | 0 | 1 (0.2) | 0 |
| Pulmonary fibrosis | 0 | 1 (0.2) | 0 |
| **Renal and Urinary Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 1 (0.2) |
| Total number of events | 1 | 0 | 1 |
| Renal failure | 1 (0.2) | 0 | 0 |
| Chronic kidney disease | 0 | 0 | 1 (0.2) |
| **Metabolism and Nutrition Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Diabetic complications | 1 (0.2) | 0 | 0 |
| **Vascular Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 | 0 |
| Total number of events | 1 | 0 | 0 |
| Embolism | 1 (0.2) | 0 | 0 |
| **Gastrointestinal Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Intestinal Ischemia | 0 | 0 | 1 (0.2) |
| **Immune System Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Total number of events | 0 | 0 | 1 |
| Contrast Media Allergy | 0 | 0 | 1 (0.2) |
| **Injury, Poisoning and procedural complications** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Overall total number of events | 0 | 0 | 1 |
| Skin laceration | 0 | 0 | 1 (0.2) |

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **Psychiatric Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 0 | 0 | 1 (0.2) |
| Overall total number of events | 0 | 0 | 1 |
| Completed suicide | 0 | 0 | 1 (0.2) |

Source: SUR, Table t_ae_par_NOCUL_DSC_SE_DME_SUR
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD, 3.7% faricimab Q8W, 3.6% of faricimab PTI, and 3.4% of aflibercept subjects discontinued from the study due to a non-ocular adverse event.*

### 8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

**Table 8.4.4-1 Ocular Adverse Events Occurring in ≥ 1% of Subjects in nAMD Studies (TENAYA[1] and LUCERNE[2]) SUR* CCOD** - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **OCULAR** | | |
| Total number of patients with ≥ 1 adverse event | 319 (48.0) | 308 (46.5) |
| Total number of events | 768 | 708 |
| Conjunctival hemorrhage | 56 (8.4) | 56 (8.5) |
| Neovascular age-related Macular degeneration | 53 (8.0) | 50 (7.6) |
| Vitreous detachment | 27 (4.1) | 26 (3.9) |
| Eye pain | 23 (3.5) | 25 (3.8) |
| Dry eye | 23 (3.5) | 35 (5.3) |
| Cataract | 38 (5.7) | 27 (4.1) |
| Intraocular pressure increased | 25 (3.8) | 24 (3.6) |
| Vitreous floaters | 25 (3.8) | 14 (2.1) |
| Retinal pigment epithelial tear | 19 (2.9) | 10 (1.5) |
| Foreign body sensation in eyes | 10 (1.5) | 14 (2.1) |
| Punctate keratitis | 12 (1.8) | 16 (2.4) |
| Blepharitis | 15 (2.3) | 16 (2.4) |
| Posterior capsule opacification | 15 (2.3) | 14 (2.1) |
| Dry age-related macular degeneration | 12 (1.8) | 12 (1.8) |
| Lacrimation increased | 6 (0.90 | 9 (1.4) |

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Photopsia | 6 (0.9) | 10 (1.5) |
| Eye irritation | 11 (1.7) | 4 (0.6) |
| Corneal abrasion | 10 (1.5) | 9 (1.4) |
| Ocular discomfort | 8 (1.2) | 4 (0.6) |
| Medication error | 8 (1.2) | 7 (1.1) |
| Ocular hypertension | 9 (1.4) | 5 (0.8) |
| Eye pruritus | 8 (1.2) | 5 (0.8) |
| Hordeolum | 7 (1.1) | 6 (0.9) |
| Iritis | 7 (1.1) | 2 (0.3) |

Source: SUR Table 5
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *In the nAMD studies, the overall ocular adverse event rates were similar between pooled faricimab and aflibercept treatment groups. The most common ocular adverse events were conjunctival hemorrhage (8%) and worsening nAMD (8%) for both treatment groups.*

**Table 8.4.4-2 Non-Ocular Adverse Events Occurring in ≥ 2% of Subjects in nAMD Studies (TENAYA[1] and LUCERNE[2]) SUR* CCOD** - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **Non-OCULAR** | | |
| Total number of patients with ≥ 1 adverse event | 439 (66.1) | 448 (67.7) |
| Total number of events | 1466 | 1526 |
| Nasopharyngitis | 48 (7.2) | 52 (7.9) |
| Urinary tract infection | 42 (6.3) | 42 (6.3) |
| Hypertension | 31 (4.7) | 31 (4.7) |
| Upper respiratory tract infection | 20 (3.0) | 20 (3.0) |
| Arthralgia | 31 (4.7) | 25 (3.8) |
| Fall | 31 (4.7) | 33 (5.0) |
| Bronchitis | 19 (2.9) | 10 (1.5) |
| Headache | 22 (3.3) | 16 (2.4) |
| Sinusitis | 19 (2.9) | 15 (2.3) |

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Back pain | 21 (3.2) | 22 (3.0) |
| COVID-19 | 24 (3.6) | 18 (2.7) |
| Cough | 19 (2.9) | 10 (1.5) |
| Dizziness | 17 (2.6) | 12 (1.8) |
| Basal cell carcinoma | 16 (2.4) | 8 (1.2) |
| Contusion | 11 (1.7) | 13 (2.0) |
| Atrial fibrillation | 10 (1.5) | 13 (2.0) |
| Diarrhea | 9 (1.4) | 14 (2.1) |
| Influenza | 13 (2.0) | 9 (1.4) |
| Pain in extremity | 7 (1.1) | 15 (2.3) |
| Pneumonia | 8 (1.2) | 13 (2.0) |

Source: SUR Table 13
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Overall, there were no significant differences between groups in non-ocular adverse events in the nAMD studies.*

**Table 8.4.4-3 Ocular Adverse Events Occurring in ≥ 1% of Subjects in DME Studies (YOSEMITE[1] and RHINE[2]) SUR CCOD – Pooled Safety Population**

| Preferred term | Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Total number of patients with ≥ 1 adverse event | 299 (47.5) | 299 (47.3) | 273 (43.7) |
| Total number of events | 646 | 615 | 482 |
| Conjunctival hemorrhage | 50 (7.9) | 42 (6.6) | 40 (6.4) |
| Cataract | 76 (12.1) | 60 (9.5) | 58 (9.3) |
| Vitreous detachment | 31 (4.9) | 26 (4.1) | 25 (4.0) |
| Vitreous floaters | 32 (5.1) | 16 (2.5) | 17 (2.7) |
| Intraocular pressure increased | 31 (4.9) | 21 (3.3) | 16 (2.6) |
| Dry eye | 29 (4.6) | 26 (4.1) | 16 (2.6) |
| Eye pain | 13 (2.1) | 20 (3.2) | 21 (3.4) |
| Conjunctivitis | 9 (1.4) | 13 (2.1) | 11 (1.8) |
| Cataract Cortical | 8 (1.3) | 11 (1.7) | 9 (1.4) |

| Preferred term | Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Diabetic retinal edema | 10 (1.6) | 16 (2.5) | 14 (2.2) |
| Medication error | 9 (1.4) | 9 (1.4) | 6 (1.0) |
| Punctate keratitis | 9 (1.4) | 10 (1.6) | 9 (1.4) |
| Posterior capsule opacification | 12 (1.9) | 7 (1.1) | 11 (1.8) |
| Blepharitis | 15 (2.4) | 9 (1.4) | 5 (0.8) |
| Vision blurred | 7 (1.1) | 3 (0.5) | 7 (1.1) |
| Vitreous hemorrhage | 5 (0.8) | 1 (0.2) | 3 (0.5) |
| Cataract nuclear | 10 (1.6) | 13 (2.1) | 8 (1.3) |
| Diabetic retinopathy | 4 (0.6) | 13 (2.1) | 7 (1.1) |
| Cataract subcapsular | 19 (3.0) | 14 (2.2) | 9 (1.4) |
| Macular fibrosis | 4 (0.6) | 2 (0.3) | 9 (1.4) |
| Sensation of foreign body | 6 (1.0) | 1 (0.2) | 3 (0.5) |
| Ocular hypertension | 2 (0.3) | 8 (1.3) | 2 (0.3) |
| Lacrimation increased | 4 (0.6) | 11 (1.7) | 4 (0.6) |
| Eye pruritus | 6 (1.0) | 4 (0.6) | 5 (0.8) |
| Eye irritation | 6 (1.0) | 3 (0.5) | 6 (1.0) |
| Visual impairment | 3 (0.5) | 7 (1.1) | 4 (0.6) |
| Corneal erosion | 7 (1.1) | 1 (0.2) | 2 (0.3) |
| Hordeolum | 2 (0.3) | 3 (0.5) | 8 (1.3) |

Source: SUR, Table 20
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *In the DME studies, the overall ocular adverse event rates were similar between pooled faricimab Q8W, faricimab PTI, and aflibercept treatment groups. The most common ocular adverse events were cataract (7%) and conjunctival hemorrhage 95%) for all treatment groups.*

**Table 8.4.4-4 Non-Ocular Adverse Events Occurring in ≥ 5% of Subjects in DME Studies (YOSEMITE[1] and RHINE[2]) SUR CCOD – Pooled Safety Population**

| Preferred term | Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **NON-OCULAR** | | | |
| Total number of patients with ≥ 1 adverse event | 456 (72.4) | 462 (73.1) | 462 (73.9) |
| Overall total number of events | 1996 | 1846 | 1795 |
| **Infections and Infestations** | | | |
| Total number of patients with ≥ 1 adverse event | 256 (40.6) | 234 (37.0) | 258 (41.3) |
| Total number of events | 443 | 381 | 464 |
| Nasopharyngitis | 58 (9.2) | 44 (7.0) | 66 (10.6) |
| Urinary tract infection | 31 (4.9) | 30 (4.7) | 51 (8.2) |
| COVID-19 | 31 (4.9) | 43 (6.8) | 25 (4.0) |
| **Vascular Disorders** | | | |
| Total number of patients with ≥ 1 adverse event | 69 (11.0) | 93 (14.7) | 78 (12.5) |
| Total number of events | 91 | 109 | 96 |
| Hypertension | 43 (6.8) | 53 (8.4) | 51 (8.2) |
| **Injury, Poisoning and procedural complications** | | | |
| Total number of patients with ≥ 1 adverse event | 97 (15.4) | 83 (13.1) | 84 (13.4) |
| Total number of events | 136 | 121 | 110 |
| Fall | 35 (5.6) | 27 (4.3) | 22 (3.5) |

Source: SUR, Table 31
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Overall, there were no significant differences between groups in non-ocular adverse events in the DME studies.*

### 8.4.5. Laboratory Findings

No notable trends or clinically relevant imbalances between treatment groups were observed for any of the analyzed laboratory parameters.

### 8.4.6. Vital Signs

There were no clinically relevant imbalances between treatment groups for vital signs

### 8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were not collected.

### 8.4.8. **Immunogenicity**

Through Week 48 in the nAMD studies, 75 patients were ADA-positive at any point. The incidence of treatment-emergent ADA-positive patients was 10% (68/657 patients) in the faricimab arm with a median time to onset of ADA of 20.1 weeks

Through Week 56 in the DME studies, 113 patients were ADA-positive at any point. The incidence of treatment-emergent ADA-positive patients was comparable across the faricimab treatment arms (8.2% in the faricimab Q8W arm and 8.7% in the faricimab PTI arm with a similar median time to onset of ADA (approximately 28 weeks).

Refer to the Clinical Pharmacology review for further details.

**Reviewer's Comment:** *Overall, the clinical significance of anti-faricimab antibodies on safety is unclear.*

## 8.5. Analysis of Submission-Specific Safety Issues

**Table 8.5-1 Adverse Events of Intraocular Inflammation in the Study Eye in nAMD Studies (TENAYA[1] and LUCERNE[2]) SUR* CCOD** - Pooled Safety Population**

| Preferred term | | | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|---|---|
| | | | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **OCULAR** | | | | |
| **Intraocular Inflammation** | | | | |
| Total number of patients with ≥ 1 adverse event | | | 18 (2.7) | 12 (1.8) |
| Total number of events | | | 23 | 13 |
| Iridocyclitis | | | 3 (0.5) | 1 (0.2) |
| Iritis | | | 7 (1.1) | 2 (0.3) |
| Uveitis | | | 3 (0.5) | 2 (0.3) |
| Vitritis | | | 4 (0.6) | 1 (0.2) |
| Chorioretinitis | | | 1 (0.2) | 0 |
| Keratic precipitates | | | 1 (0.2) | 1 (0.2) |
| Post procedural inflammation | | | 0 | 3 (0.5) |
| Anterior chamber flare | | | 0 | 1 (0.2) |
| Non-infectious endophthalmitis | | | 0 | 1 (0.2) |

Source: SUR Table 12
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through Week 48 and SUR CCOD in the nAMD studies, the intraocular inflammation adverse event rates were not significantly different between pooled faricimab (2% and 3%, respectively) and aflibercept (1% and 2%, respectively) treatment groups.*

**Table 8.5-2 Adverse Events of Intraocular Inflammation in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 48 and SUR CCOD – Pooled Safety Population**

| Preferred term | Pooled YOSEMITE and RHINE (N=1887) | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| Total number of patients with ≥ 1 adverse event | 9 (1.4) | 11 (1.7) | 7 (1.1) |
| Total number of events | 10 | 16 | 10 |
| Iritis | 2 (0.3) | 4 (0.6) | 2 (0.3) |
| Uveitis | 3 (0.5) | 5 (0.8) | 0 |
| Vitritis | 2 (0.3) | 0 | 2 (0.3) |
| Iridocyclitis | 2 (0.3) | 2 (0.3) | 1 (0.2) |
| Anterior chamber inflammation | 0 | 0 | 0 |
| Chorioretinitis | 0 | 1 (0.2) | 0 |
| Keratic precipitates | 0 | 1 (0.2) | 0 |
| Keratouveitis | 0 | 1 (0.2) | 0 |
| Post procedural inflammation | 0 | 1 (0.2) | 0 |

Source: SUR, Table 30
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through Week 48 and SUR CCOD in the DME studies, the intraocular inflammation adverse event rates were not significantly different between pooled faricimab Q8W (1.3% and 1.4%, respectively), faricimab PTI (1.4% and 1.7%) and aflibercept (0.6% and 1.1%, respectively) treatment groups.*

**Table 8.5-3 Adverse Events of Retinal Vascular Occlusive Disease in the Study Eye in nAMD Studies (TENAYA[1] and LUCERNE[2]) Through SUR* CCOD** - Pooled Safety Population**

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| **OCULAR** | | |
| **Retinal Vascular Occlusive Disease** | | |
| Total number of patients with ≥ 1 adverse event | 1 (0.2) | 0 |
| Total number of events | 1 | 0 |

| Preferred term | SUR CCOD Pooled TENAYA and LUCERNE (N=1326) | |
|---|---|---|
| | Faricimab 6 mg (N=664) n (%) | Aflibercept 2 mg (N=662) n (%) |
| Retinal artery embolism | 1 (0.2) | 0 |

Source: SUR, Table t_ae_pt_cod_SOCUL_OCC_SE_nAMD_SUR
* SUR = 90-Day Safety Update Report
** CCOD = Clinical Cutoff Date (9 Aprilm2021)
[1] TENAYA= Study GR40306
[2] LUCERNE= Study GR40844

**Reviewer's Comment:** *Through SUR CCOD in the nAMD studies, aflibercept subject and one subject in the faricimab treatment group experienced a retinal vascular occlusive disease adverse event.*

**Table 8.5-4 Adverse Events of Retinal Vascular Occlusive Disease in the Study Eye in DME Studies (YOSEMITE[1] and RHINE[2]) Through Week 48 and SUR CCOD – Pooled Safety Population**

| Preferred term | SUR CCOD Pooled YOSEMITE and RHINE | | |
|---|---|---|---|
| | Faricimab 6 mg Q8W (N=630) n (%) | Faricimab 6 mg PTI (N=632) n (%) | Aflibercept 2 mg Q8W (N=625) n (%) |
| **OCULAR** | | | |
| **Retinal Vascular Occlusive Disease** | | | |
| Total number of patients with ≥ 1 adverse event | 2 (0.3) | 6 (0.9) | 4 (0.6) |
| Total number of events | 2 | 6 | 4 |
| Retinal vein occlusion | 1 (0.2) | 4 (0.6) | 0 |
| Retinal artery occlusion | 1 (0.2) | 2 (0.3) | 2 (0.3) |
| Arterial occlusive disease | 0 | 0 | 1 (0.2) |
| Retinal artery embolism | 0 | 0 | 1 (0.2) |

Source: SUR, Table t_ae_pt_par_SOCUL_OCC_SE_DME_SUR
SUR = 90-Day Safety Update
CCOD = Clinical Cutoff Date 9April2021
[1] YOSEMITE = Study GR40349
[2] RHINE = Study GR40398

**Reviewer's Comment:** *Through SUR CCOD in the DME studies, the retinal vascular occlusive disease adverse event rates were 0.3% for the faricimab Q8W treatment group, 0.9%) 0.9%for the faricimab PTI group, 0.6% for the aflibercept treatment group.*

## 8.6. Safety Analyses by Demographic Subgroups

No clinically significant differences in adverse events were identified related to age (< 65, ≥ 65, < 75 and ≥ 75 years of age) or gender. Because of the low numbers of patients of different races, it

is difficult to discern differences or commonalities in adverse events.

## 8.7. Specific Safety Studies/Clinical Trials

None.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies have been conducted.

### 8.8.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

This drug has not been tested in pediatric patients. There are no proposed pediatric indications.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Faricimab is not a narcotic and does not have abuse potential.

## 8.9. Safety in the Postmarket Setting

Faricimab is not a marketed drug product. There are no Post-marketing data to report.

## 8.10. Integrated Assessment of Safety

On August 26, 2021, the Applicant submitted the 90-day Safety Update report. No new safety signals were identified for faricimab.

The safety database contained in this submission supports the relative safety of faricimab ophthalmic solution, 6 mg/0.05 mL administered by intravitreal injection every 28 days x 3 and then every 8 weeks for the treatment of age-related macular degeneration.

# 9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

See labeling recommendations in Appendix 13.3.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

# 12. Post-marketing Requirements and Commitments

The following Phase 4 clinical study commitment is recommended:

Conduct a post-marketing study to evaluate corneal endothelial health of eyes treated with faricimab. The study should assess corneal endothelial health using specular microscopy of a minimum of 100 eyes at baseline and at the end of a study of at least 6 months duration.

# 13. Appendices

## 13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

## 13.2. **Financial Disclosure**

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 761235
Submission Date(s): May 28, 2021
Applicant: Genentech, Inc.
Product: Vabysmo (faricimab-xxxx injection) 6 mg (0.05mL)

Reviewer: Lucious Lim, MD
Date of Review: October 25, 2021
Covered Clinical Studies (Name and/or Number):
GR40306 (TENAYA)
GR40844 (LUCERNE)
GR40349 (YOSEMITE)
GR40398 (RHINE)
BP29647 (AVENUE)
BP30099 (BOULEVARD)
CR39521 (STAIRWAY)

| | | |
|---|---|---|
| Was a list of clinical investigators provided? | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified:<br>GR40306 1016 investigators (principal and sub-investigators)<br>GR40844 749 investigators (principal and sub-investigators)<br>GR40349 1133 investigators (principal and sub-investigators)<br>GR40398 1121 investigators (principal and sub-investigators)<br>BP29647 605 investigators (principal and sub-investigators)<br>BP30099 556 investigators (principal and sub-investigators)<br>CR39521 241 investigators (principal and sub-investigators) | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): None | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):<br>GR40306 7 investigators<br>GR40844 8 investigators<br>GR40349 7 investigators<br>GR40398 6 investigators<br>BP29647 4 investigators<br>BP30099 12 investigators<br>CR39521 2 investigators | | |

| | | |
|---|---|---|
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 19<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements? | Yes ☒ | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided? | Yes ☒ | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 401 | | |
| Is an attachment provided with the reason? | Yes ☐ | No ☐ (Request explanation from applicant) |

## 13.3. Labeling Recommendations

BLA 761235 is recommended for approval with the draft labeling revisions found in this review. This is a draft label. The Division of Ophthalmology continues to work with the applicant on final labeling. See the CDTL memo for final labeling.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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