CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial #:	761235
Drug Name:	Faricimab 6 MG Intravitreal (IVT) Injection
Indication(s):	For the Treatment of: • Neovascular (wet) Age-Related Macular Degeneration (nAMD) • Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)
Applicant:	Genentech, Inc.
Date(s):	Stamp Date: May 28, 2021 PDUFA Date: January 28, 2022 Review Date: November 10, 2021
Review Priority:	Priority
Biometrics Division:	IV
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Keywords: Clinical Studies, MMRM, Diabetic Macular Edema, Neovascular Age-related Macular Degeneration, Diabetic Retinopathy, Best Corrected Visual Acuity

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

In this original Biologics License Application (BLA), the Applicant seeks approval of Faricimab 6 mg intravitreal (IVT) injection for the treatment of Neovascular Age-related Macular Degeneration (nAMD) and for the treatment of Diabetic Macular Edema - Diabetic Retinopathy (DME-DR).

nAMD Indication

Efficacy and safety support for the nAMD indication was based on data from two identically designed global, Phase 3, 112-week, multicenter, randomized, double-masked, active-controlled, noninferiority studies: Study GR40306 (TENAYA) and Study GR40844 (LUCERNE). The primary objective of the studies was to assess whether faricimab IVT injection administered up to every 16-week dosing interval reduce the treatment burden while maintaining comparable efficacy benefit compared to the active-control Eylea® (aflibercept 2 mg) IVT injection.

In TENAYA and LUCERNE studies, respectively, a total of 671 and 658 treatment-naïve subjects at least 50 years of age who met all the studies enrollment criteria were randomized in a 1:1 ratio and were to receive either faricimab administered up to every 16-week dosing interval after four initial monthly injections or aflibercept administered every 8-week interval after three initial monthly injections (see Figure 6). Subjects randomized to the faricimab arm were to receive injection at every 8-week (Q8W), 12-week (Q12W), or 16-week (Q16W) dosing interval depending on protocol-defined disease activity criteria as assessed at Week 20 and Week 24. Randomization in both studies was stratified by baseline best-corrected visual acuity (BCVA: ≥ 74 letters vs. 73−55 letters vs. ≤ 54 letters), low-luminance deficit (LLD: <33 letters vs. ≥ 33 letters), and region (US and Canada vs. Asia vs. Rest of the World [RoW]).

The main efficacy evaluation in both studies was based on BCVA assessed every 4-week through Week 112 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters). Although the total study duration of both studies is 112-week, this BLA was based on the first 48-week data with the remaining portions of the studies are still ongoing.

The primary efficacy endpoint in both studies was the change in BCVA from baseline averaged over Weeks 40, 44, and 48 (here after referred to as Week 40/44/48). The primary efficacy analysis was an evaluation of noninferiority of faricimab to aflibercept in the primary efficacy endpoint on the intent-to-treat (ITT) population including all randomized subjects regardless of the occurrence of intercurrent events (See more details in Section 3.2.1.2). The noninferiority margin was set at -4.0 letters.

The treatment groups in TENAYA/LUCERNE studies were well balanced with respect to the baseline demographic and disease characteristics in both studies (Table 4). And, during the first 48-week treatment period, about 4% of subjects discontinued the studies and the discontinuation rates were comparable between the treatment groups (Table 2).

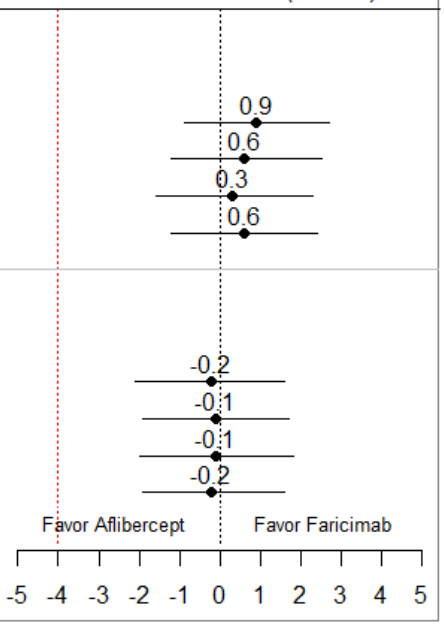
In both studies, faricimab treated subjects had a noninferior mean change in BCVA from baseline at Week 40/44/48 compared to aflibercept treated subjects (Figure 1). As shown, in TENAYA, the adjusted mean change in BCVA from baseline at Week 40/44/48 in the faricimab group was +5.7 letters and in the aflibercept group was +5.1 letters with a treatment difference of +**0.6 (95% CI: -1.2 to 2.4)**. Similarly, in LUCERNE, the adjusted mean change in the faricimab

group was +6.4 letters and in the aflibercept group was +6.6 letters with a treatment difference of **-0.1 (95% CI: -1.9 to 1.6)**. Additionally, a comparable number of subjects in each of the treatment groups in both studies gained and/or lost letters in BCVA from baseline at Week 40/44/48 (Figure 8).

Several sensitivity and supplementary analyses performed under various data handling strategies for missing and intercurrent data were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority finding (Table 7).

Figure 1: Adjusted Mean Change in BCVA from Baseline at Week 40/44/48 (ITT Population) (TENAYA/LUCERNE)

STUDY	Visit	Faricimab	Aflibercept	Difference (95% CI)
TENAYA (GR40306)	N	334	337	
	Baseline	61.3 (12.6)	61.5 (12.9)	
	Week 40	5.3 (0.8)	4.4 (0.7)	0.9 (-0.9, 2.7)
	Week 44	4.9 (0.7)	4.3 (0.7)	0.6 (-1.2, 2.5)
	Week 48	4.7 (0.7)	4.4 (0.7)	0.3 (-1.6, 2.3)
	Week 40/44/48	5.7 (0.6)	5.1 (0.6)	0.6 (-1.2, 2.4)
LUCERNE (GR40844)	N	331	327	
	Baseline	58.7 (14.0)	58.9 (13.3)	
	Week 40	5.9 (0.7)	6.1 (0.7)	-0.2 (-2.1, 1.6)
	Week 44	5.8 (0.7)	5.9 (0.7)	-0.1 (-1.9, 1.7)
	Week 48	5.7 (0.7)	5.8 (0.7)	-0.1 (-2.0, 1.8)
	Week 40/44/48	6.4 (0.6)	6.6 (0.6)	-0.2 (-1.9, 1.6)



Note: Adjusted mean changes in each treatment group and treatment differences (95% CI estimates) were based on MMRM model using the ITT population including all randomized subjects (See Section 3.2.1.2 for details). Red dashed line represents the noninferiority margin.

Additional analysis that compared the three faricimab dosing intervals (Q8W, Q12W, and Q16W) to aflibercept in the primary efficacy endpoint displayed that each dose of faricimab in both studies appeared comparable to aflibercept (Figure 11 and Table 13). It should be noted that, in both studies, most subjects randomized to the faricimab arm that completed the Week 20/24 and Week 48 visits were on a Q16W dosing interval (about 45%) followed by on a Q12W (about 33%) and on a Q8W (about 22%) dosing intervals.

In summary, based on the collective efficacy evidence from the two adequate and well controlled trials of TENAYA/LUCENRE studies, the reviewer concludes that the application for the nAMD indication provided substantial evidence for comparable efficacy benefit of faricimab administered up to every 16-week interval after four initial monthly injections compared to aflibercept administered every 8-week after three initial monthly injections.

Noting that faricimab in the TENAYA/LUCERNE studies was administered in three dosing intervals based on protocol-defined disease activity criteria, the reviewer defers to the medical review team regarding the appropriate dosing recommendation for use in clinical practice.

DME-DR Indications

Efficacy and safety support for the DME-DR indications was based on data from two identically designed global, Phase 3, 104-week, multicenter, randomized, double-masked, active-controlled, noninferiority studies: Study GR40349 (YOSEMITE) and Study GR40398 (RHINE). The primary objective of the studies was to assess whether faricimab administered in fixed dosing interval and in a protocol-defined personalized treatment interval (PTI) reduce the treatment burden while maintaining comparable efficacy benefit compared to the active-control Eylea® (aflibercept 2 mg).

In YOSEMITE and RHINE studies, respectively, a total of 940 and 951 treatment-naïve and non-naïve diabetic subjects at least 18 years of age who met all the studies enrollment criteria were randomized in a 1:1:1 ratio and were to receive: (i) faricimab administered every 8-week interval after six initial monthly injections (Faricimab Q8W), (ii) faricimab administered in a protocol-defined PTI dosing after four initial monthly injections (Faricimab PTI), or (iii) aflibercept administered every 8-week interval after five initial monthly injections (Aflibercept Q8W) (see Figure 14). Subjects randomized to the faricimab PTI arm were to receive injection at every 4-week (Q4W), Q8W, Q12W, or Q16W dosing interval based on objective assessment of pre-specified visual and anatomic disease activity criteria, after the first four monthly doses. Randomization in both studies was stratified by baseline BCVA (< 64 vs. ≥64 letters), prior anti-VEGF treatment use (yes vs. no), and region (US and Canada vs. Asia vs. RoW).

The main efficacy evaluation in both studies was based on BCVA assessed every 4-week through Week 104 as measured by the number of letters read at a starting distance of 4 meters (range: 0-100 letters) and based on diabetic retinopathy severity as measured by the Diabetic Retinopathy Severity Score (DRSS). Although the total study duration of both studies is 104-week, this BLA was based on the first 56-week data with the remaining portions of the studies are still ongoing.

The primary efficacy endpoint in both studies was the change in BCVA from baseline averaged over Weeks 48, 52, and 56 (here after referred to as Week 48/52/56). The primary efficacy analysis was an evaluation of noninferiority of each dose of faricimab to aflibercept in the primary efficacy endpoint on the ITT population including all randomized subjects regardless of the occurrence of intercurrent events (See more details in Section 3.2.2.2). The noninferiority margin was set at -4.0 letters. If noninferiority in the primary endpoint was established in the ITT population, superiority of each dose of faricimab to aflibercept in the primary efficacy endpoint was assessed in the treatment-naïve (TN) population followed by in the ITT population.


(b) (4)

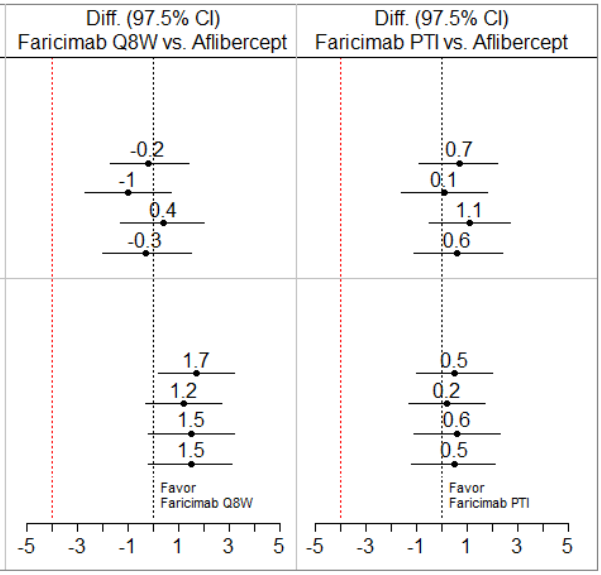
The treatment groups in YOSEMITE/RHINE studies were well balanced with respect to the baseline demographic and disease characteristics (Table 20). During the first 56-week treatment period, about 7% of subjects in YOSEMITE and 4% of subjects in RHINE discontinued and the discontinuation rates across the treatment groups were comparable (Table 18).

In both studies, subjects treated with either doses of faricimab (Q8W or PTI) had a noninferior mean change in BCVA from baseline at Week 48/52/56 compared to subjects treated with aflibercept (Figure 2). As shown, in YOSEMITE, the adjusted mean change in BCVA from baseline at Week 48/52/56 in the ITT population was +10.6 letters in faricimab Q8W, +11.5 letters in faricimab PTI, and +10.8 letters in aflibercept with a treatment difference of **-0.3 (97.5% CI: -2.0 to 1.5)** between faricimab Q8W and aflibercept and **+0.6 (97.5% CI: -1.1 to 2.4)** between faricimab PTI and aflibercept. Similarly, in RHINE, the adjusted mean change was +11.7 letters in faricimab Q8W, +10.7 letters in faricimab PTI, and +10.2 letters in aflibercept with a treatment difference of +**1.5 (97.5% CI: -0.2 to 3.1)** between faricimab Q8W and aflibercept and +**0.5 (97.5% CI: -1.2 to 2.1)** between faricimab PTI and aflibercept. Additionally, a comparable number of subjects in each of the treatment groups in both studies gained and/or lost letters in BCVA from baseline at Week 48/52/56 (Figure 17).

Several sensitivity and supplementary analyses performed under various data handling strategies for missing and intercurrent data were consistent with the primary efficacy results, leading to the same conclusion for a robust interpretation of the noninferiority finding (Table 24).

Figure 2: Adjusted Mean Change in BCVA from Baseline at Week 48/52/56 (ITT Population) (YOSEMITE/RHINE)

Study	Visit	Faricimab Q8W	Faricimab PTI	Aflibercept
YOSEMITE (GR40349)	N	315	313	312
	Baseline	62.0 (9.9)	61.9 (10.2)	62.2 (9.5)
	Week 48	10.7 (0.6)	11.5 (0.6)	10.8 (.06)
	Week 52	10.0 (0.6)	11.1 (0.6)	11.0 (0.6)
	Week 56	11.1 (0.6)	11.8 (0.6)	10.7 (0.6)
	Week 48/52/56	10.6 (0.6)	11.5 (0.6)	10.8 (0.6)
RHINE (GR40398)	N	316	317	315
	Baseline	61.9 (10.1)	62.5 (9.3)	62.1 (9.4)
	Week 48	11.8 (0.6)	10.6 (0.5)	10.1 (0.5)
	Week 52	11.7 (0.5)	10.7 (0.5)	10.5 (0.5)
	Week 56	11.7 (0.6)	10.8 (0.6)	10.1 (0.6)
	Week 48/52/56	11.7 (0.5)	10.7 (0.5)	10.2 (0.5)



Note: Adjusted mean changes in each treatment group and treatment differences (97.5% CI estimates) were based on MMRM model using the ITT population including all randomized subjects (See Section 3.2.2.2 for detail). Red dashed lines represent the noninferiority margin.

Although each dose of faricimab in both studies was noninferior to aflibercept in the primary efficacy endpoint on the ITT population, superiorities in the TN population (Table 23) and in the ITT population (Figure 2) were not established in both studies. (b) (4)

(b) (4)

In summary, based on the collective efficacy evidence from the two adequate and well controlled trials of YOSEMITE/RHINE studies, the reviewer concludes that the application for the DME indication provided substantial evidence for comparable (but not superior) efficacy benefit of each dose of faricimab (Q8W or PTI) compared to aflibercept.

(b) (4)

Finally, noting that faricimab in the YOSEMITE/RHINE studies was administered in a fixed and in a PTI dosing interval based on protocol-defined disease activity criteria, the reviewer defers to the medical review team regarding the appropriate dosing recommendation for use in clinical practice.

(b) (4)

2. INTRODUCTION

2.1. OVERVIEW

In this original BLA submission, the Applicant seeks approval of faricimab 6 mg administered up to every 16-week interval for the treatment of nAMD and DME-DR.

nAMD is a chronic eye disease generally caused by abnormal blood vessels that leak fluid or blood into the macula (the central part of the retina responsible for detailed vision); it is the leading cause of severe vision loss in adults over age 50. DR is the most common diabetic eye disease; it affects people diagnosed with diabetes mellitus and is a leading cause of blindness in adults. DME is the major cause of vision loss in people with DR; it occurs when blood vessels in the retina of patients with diabetes begin to leak into the macula. These leaks cause the macula to thicken and swell, gradually distorting acute vision.

There are currently two approved biologic products administered in a fixed dosing interval for the treatment of nAMD, DME, and DR in the class of anti-vascular endothelial growth factor (anti-VEGF) therapies: Lucentis® (ranibizumab 0.5 mg) IVT injection administered monthly and Eylea® (aflibercept 2.0 mg) IVT injection administered every 8-week after three initial monthly doses for the nAMD indication and after five initial monthly doses for the DME-DR indications.

Recently, Beovu® (Brolucizumab 6 mg) anti-VEGF therapy administered every 8-12 weeks interval after three initial monthly doses was approved for the treatment of nAMD. Avastin® (bevacizumab) is also used off-label for these indications.

In this BLA, the Applicant seeks approval of faricimab administered in a variable dosing interval (up to every 16-week) for the indications sought. Faricimab belongs to the class of anti-VEGF therapy.

Prior to the current BLA submission, the clinical development program for faricimab was discussed with the Agency on several occasions under investigational new drug (IND) 119225:

i) A Type C meeting was held on November 17, 2017 and the nAMD and DME protocol synopses were reviewed and discussed (SN 75).
ii) An End-of-Phase 2 (EOP2) meeting was held on April 24, 2018 and the further development plan of faricimab for the DME-DR indication including two Phase 3 protocols were reviewed and discussed (SN 86).
iii) An EOP2 meeting was held on August 22, 2018 and the further development of faricimab for the nAMD indication including two Phase 3 protocols (SN 94) were reviewed and discussed.
iv) A written response only Type C meeting was requested, and the Agency provided feedback on the draft SAPs for the Phase 3 studies for nAMD and DME-DR indications (SN 138).
v) A Type C meeting was held on July 1, 2020 and the proposed content and format of faricimab BLA for the treatment of nAMD and DME-DR was discussed prior to Phase 3 program data read out.
vi) A Type B meeting to discuss the planned BLA submission for faricimab and to obtain the Agency's agreement on the acceptability of the available clinical data of the Phase 3 studies

for the nAMD indication (TENAYA/LUCERNE) and for the DME-DR indications (YOSEMITE/RHINE) was requested, and the Applicant later cancelled after receiving the Agency's feedback.

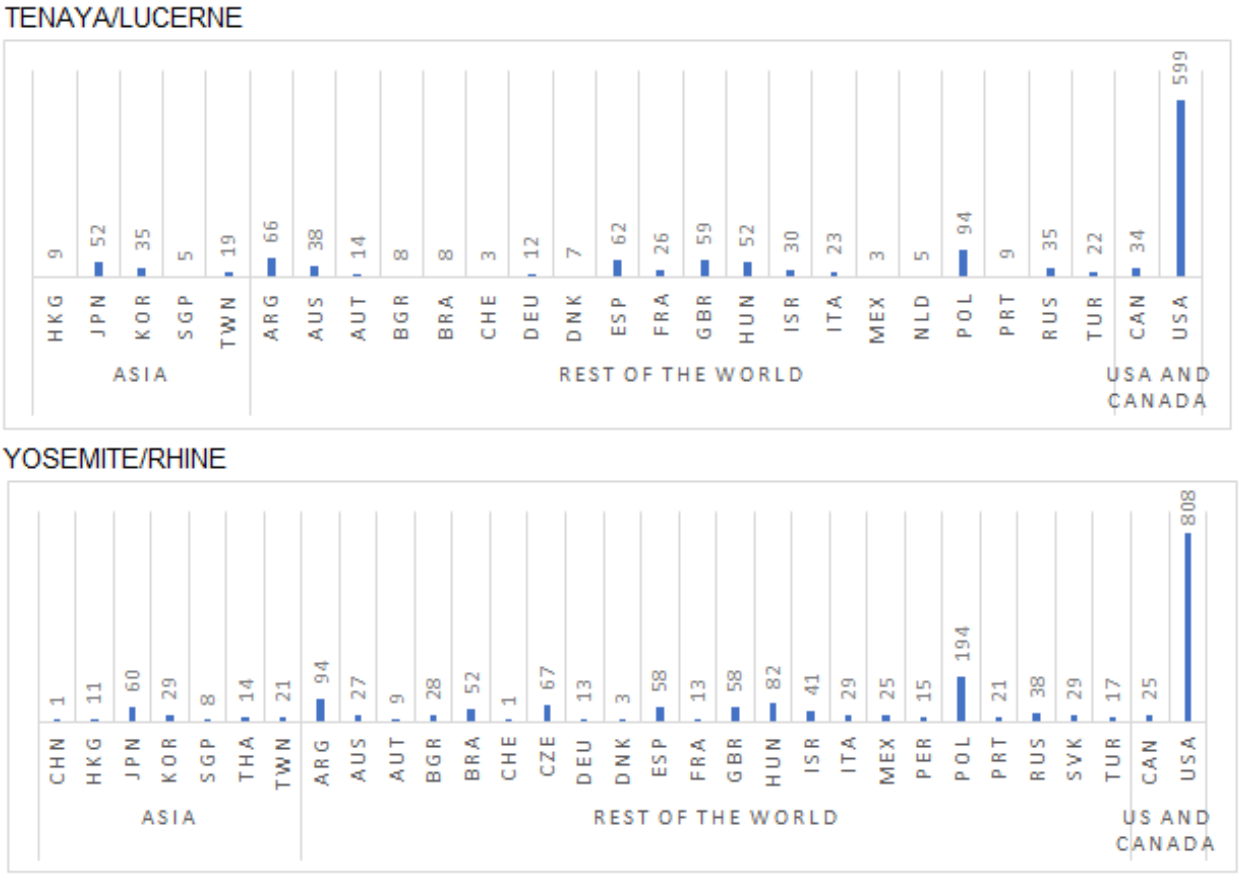
Specific Studies Reviewed

The BLA submission included data from four ongoing global pivotal Phase 3 studies – two similarly designed studies to support the nAMD indication (TENAYA [GR40306] and LUCERNE [GR40844]) and two similarly designed studies to support the DME-DR indications (YOSEMITE [GR40349] and RHINE [GR40398]).

In TENAYA and LUCERNE studies, respectively, a total of 671 and 658 subjects were enrolled globally. Similarly, in the YOSEMITE and RHINE studies, respectively, a total of 940 and 951 subjects were enrolled globally.

Figure 5 displays the number of subjects enrolled by region in the pooled TENAYA/LUERNE studies and in the pooled YOSEMITE/RHINE studies. As shown, most subjects enrolled in these studies were from USA. For more details on the design of the TENAYA/LUERNE studies for the nAMD indication and on the design of the YOSEMITE/RHINE studies for the DME-DR indications, see Section 3.2.1.1 and Section 3.2.2.1, respectively.

Figure 5: Number of Subjects Enrolled by Region
(Randomized Subjects)



Source: Based on Reviewer's Analysis

2.2. DATA SOURCES

The data source for this review included the clinical study reports, the analysis and tabulation datasets, study protocols and corresponding statistical analysis plans, and the integrated summary of safety and efficacy datasets. These are provided in an electronic submission located at \\CDSESUB1\evsprod\BLA761235\0001\. The primary analysis datasets are located at \\CDSESUB1\evsprod\BLA761235\0001\m5\datasets\.

The data analyzed in this review are based on the two Phase 3 studies (TENAYA [GR40306] and LUCERNE [GR40844]) for the nAMD indication and based on the two Phase 3 studies (YOSEMITE [GR40349] and RHINE [GR40398]) for the DME/DR indications.

3. STATISTICAL EVALUATION

3.1. DATA AND ANALYSIS QUALITY

The reviewer found the quality and integrity of the submitted data and analysis acceptable.

3.2. EVALUATION OF EFFICACY

In this section, the efficacy assessment for the TENAYA/LUCERNE studies to support the nAMD indication are discussed in Section 3.2.1 and for the YOSEMITE/RHINE studies to support the DME-DR indications are discussed in Section 3.2.2. Within these sections, descriptions of the study designs and the efficacy endpoints, the statistical methodologies used, the summary of patient disposition and demographic and baseline characteristics, and the efficacy results are presented and discussed.

3.2.1. TENAYA/LUCERNE Studies for nAMD Indication

3.2.1.1. Study Design and Endpoints

Study Design

Efficacy and safety support for faricimab for the treatment of nAMD was based on data from two identically designed 112-week, multicenter, randomized, double-masked, active-controlled noninferiority (NI) ongoing global Phase 3 studies: TENAYA and LUCERNE.

The primary objective of the two studies was to assess whether faricimab IVT injection administered up to every 16-week dosing interval after four initial monthly injections reduce the treatment burden while maintaining comparable efficacy benefit to the active-control Eylea® (aflibercept 2 mg) IVT injection administered every 8-week after three initial monthly injections. Of note, aflibercept administered every 8-week after three initial monthly injections was approved for the treatment of nAMD in the United States and many other countries since 2011.

In TENAYA and LUCERNE studies, respectively, a total of 671 and 658 treatment-naïve subjects at least 50 years of age with choroidal neovascularization (CNV) secondary to AMD who had a BCVA of 24 to 83 letters score at baseline (on Day 1) were enrolled. In these studies, eligible subjects who met all the study enrollment criteria were randomized in a 1:1 ratio and

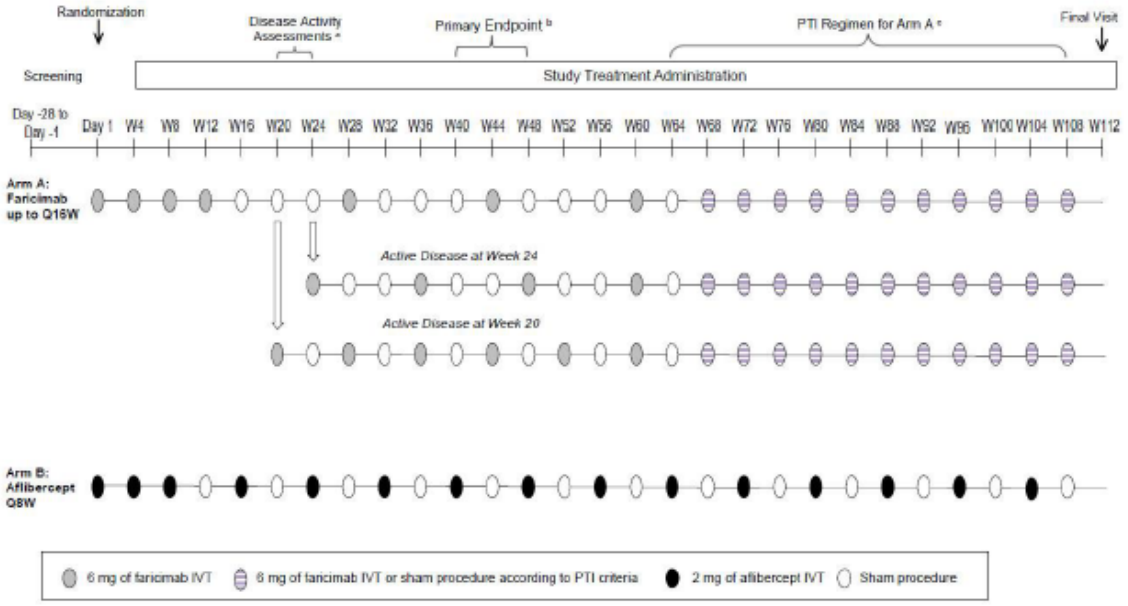
were to receive either faricimab 6 mg (334 subjects in TENAYA and 331 subjects in LUCERNE) or aflibercept 2 mg (337 subjects in TENAYA and 327 subjects in LUCERNE). Subjects in TENAYA study were enrolled in 149 sites in 15 countries and subjects in LUCERNE study were enrolled in 122 sites in 20 countries.

In both studies, randomization was stratified by baseline BCVA (≥ 74 letters vs. 73−55 letters vs. ≤ 54 letters), low-luminance deficit (LLD <33 letters vs. ≥ 33 letters), and region (US and Canada vs. Asia vs. the Rest of the World [ROW]). Twelve subjects in TENAYA study were mis-stratified (4 in faricimab and 8 in aflibercept): 4 subjects by incorrect BCVA category (0 in faricimab and 4 in aflibercept), and 9 subjects (including one subject mis-stratified by BCVA) were mis-stratified by incorrect LLD (4 in faricimab and 5 in aflibercept). Similarly, 12 subjects in the LUCERNE study were mis-stratified (4 in faricimab and 8 in aflibercept): 8 subjects by incorrect BCVA category (2 in faricimab and 6 in aflibercept), and 7 subjects were mis-stratified by incorrect LLD (3 in faricimab and 4 in aflibercept).

The total study duration of the TENAYA and LUCERNE studies is 112-week comprising 4-week screening period and 108-week treatment period. This BLA submission, however, was based on the first 52-week efficacy and safety data obtained between start of screening of each subject to the completion of efficacy assessment at Week 48 - the remaining portions of these studies are still ongoing. TENAYA study was initiated on February 19, 2019 and the data cut-off date for this submission was on October 26, 2020 and LUCERNE was initiated on March 11, 2019 and the data cutoff date for this submission was October 5, 2020.

Figure 6 displays the study schema for the TENAYA/LUCENRE studies.

Figure 6: Study Schema for TENAYA/LUCERNE Studies



Source: Figure 1 of TENAYA and LUCERNE Clinical Study Reports.

During the 48-week treatment period, subjects in the aflibercept group in both studies were dosed every 8-week (Q8W) after three initial monthly injections (at Day 0, Week 4, and Week 8) whereas subjects in faricimab group were dosed up to every 16-week (Q16W) dosing interval after four initial monthly injections (at Day 0, and Weeks 4, 8, and 12).

Staring Week 20, dosing for subjects randomized in the faricimab arm was based on protocol-defined disease activity criteria (DCA) as assessed at Week 20 and 24. That is, subjects with a confirmed DCA at Week 20 were to receive faricimab every 8-week (Q8W) starting Week 20 through Week 60, subjects with no confirmed DCA at Week 20 but with confirmed DCA at Week 24 were to receive faricimab every 12-week (Q12W) starting Week 24 through Week 60, and subjects with no confirmed DCA at both Week 20 and 24 were to receive faricimab every 16-week (Q16W) starting Week 28 through Week 60. Beyond Week 60, all subjects in the faricimab arm were to receive treatment using protocol-defined personalized treatment interval (PTI) criteria (See Appendix 2).

Efficacy Evaluation

Key efficacy evaluation in both studies was based on functional outcome measure, BCVA letter score, measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters and based on anatomical outcome measure, central subfield thickness (CST), measured using spectral-domain optical coherence tomography (SD-OCT) by masked readers. In both studies, BCVA and CST were measured every 4-week through Week 48 in the study eye. The study eye was defined as the eye that met the eligibility criteria. If both eyes met the eligibility criteria, the eye with the worse BCVA at the screening visit was selected as the study eye.

Other efficacy assessments included questionnaires to examine quality of life (QOL) as measured by the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

Study Endpoints

The primary efficacy endpoint in both studies was the change in BCVA letter score from baseline at Week 40/44/48. The following were some of the secondary efficacy endpoints assessed in both studies:

- Proportion of subjects who gained ≥15, ≥10, ≥5, and ≥0 letters from baseline at Week 40/44/48.
- Proportion of subjects who avoided a loss of ≥15, ≥10, and ≥5 letters from baseline at Week 40/44/48.
- Proportion of subjects in the faricimab arm on a Q8W, Q12W, and Q16W treatment interval at Week 48.
- Change in CST from baseline at Week 40/44/48

As additional analyses, the primary and secondary endpoints were assessed over time through Week 48.

3.2.1.2. Statistical Methodologies

In both studies, the primary efficacy analysis was performed at a family-wise significance level of 0.0497. Each of the studies underwent three unmasked independent Data Monitoring Committee (iDMC) reviews prior to the primary analysis where a nominal Type I error penalty of 0.0001 was allotted for each iDMC look.

Analysis Populations

Three analysis populations were defined for the analyses of the efficacy and safety variables in both studies. (i) intent-to-treat (ITT) population – included all randomized subjects, (ii) per-protocol (PP) population – included all randomized subjects who received at least one dose of study treatment and did not have a major protocol violation that impacted the efficacy evaluation or the treatment interval determination, and (iii) safety-evaluable population – included all randomized subjects who received at least one dose of study drug.

The primary efficacy assessment was based on the ITT population. Analyses based on the PP population was used as supporting.

Primary Estimand

The Applicant's primary estimand of interest was the difference in the mean change in BCVA from baseline at Week 40/44/48 between faricimab 6 mg and aflibercept 2mg, for all randomized subjects under the following data handling strategies for subjects with occurrence of intercurrent events (IEs):

- Data for subjects that discontinued the study drug due to an adverse event or lack of efficacy not due to COVID-19 or that used any prohibited systemic treatment or prohibited therapy in the Study eye not due to COVID-19 were used regardless of the occurrence of IEs under the treatment policy estimand strategy.

- Data for subjects that discontinued the study drug due to COVID-19, used any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19, or missed dose(s) with potentially major impact on efficacy due to COVID-19, or died due to COVID-19 were censored and assumed that subjects adhered to the treatment under a hypothetical estimand strategy.

Table 1 displays the summary of subjects with occurrence of IEs through Week 48 in the TENAYA/LUCERNE studies. As shown, a total of 66 (10%) subjects in TENAYA and 57 (9%) subjects in LUCERNE had at least one IEs through Week 48. In both studies, most of the IEs were due to missed dose(s) due to COVID-19 with potentially major impact on efficacy (58 of 66 subjects in TENAYA and 46 of 57 subjects in LUCERNE).

In both studies, the occurrence of IEs between the two treatment groups was well balanced.

Sample Size Determination

In each study, the sponsor planned to enroll a total of 640 subjects (320 per arm). A sample size of 320 subjects per arm provided at least 90% power to show noninferiority of faricimab to aflibercept in the mean change in BCVA at Week 40/44/48 using a noninferiority margin of -4.0 letters.

The sample size calculation was based on a two-sample t-test assuming a true treatment difference of zero and a common standard deviation of 14 letters for the mean change in BCVA, at a one-sided significance level of 2.5%, and a 10% dropout rate.

Table 1: Summary of Intercurrent Events Through Week 48 in TENAYA/LUCERNE Studies

	TENAYA (GR0306)			LUCERNE (GR40844)		
Intercurrent Events (IEs)	Faricimab (N = 334)	Aflibercept (N = 337)	Total (N = 671)	Faricimab (N = 331)	Aflibercept (N = 327)	Total (N = 658)
Patients with at least one type of IE	31 (9.3%)	35 (10.4%)	66 (9.8%)	33 (10.0%)	24 (7.3%)	57 (8.7%)
Patients who discontinued study due to treatment due to adverse events (AEs) or lack of efficacy not due to COVID-19	3 (0.9%)	3 (0.9%)	6 (0.9%)	8 (2.4%)	3 (0.9%)	11 (1.7%)
Patients who received any prohibited systemic treatment or prohibited therapy not due to COVID	0	0	0	0	0	0
Patients who discontinued study treatment due to COVID-19	3 (0.9%)	1 (0.3%)	4 (0.6%)	0	0	0
Patients who received any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19	3 (0.9%)	3 (0.9%)	6 (0.9%)	0	0	0
Patients with missed dose(s) with potentially major impact on efficacy due to COVID-19	27 (8.1%)	31 (9.2%)	58 (8.6%)	25 (7.6%)	21 (6.4%)	46 (7.0%)
COVID-19 death	0	0	0	0	0	0

Source: Table 9 of TENAYA and LUCERNE Clinical Study Reports.

Primary Efficacy Analysis for Primary Estimand

In both studies, the primary efficacy analysis for the primary estimand of interest was an evaluation of noninferiority of faricimab to aflibercept in the mean change in BCVA from baseline at Week 40/44/48 using a mixed model repeated measure analysis (MMRM). The model included the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous covariate of baseline BCVA, and randomization stratification factors as fixed effects. The model assumed an unstructured covariance structure to account for within-subject correlation.

The primary efficacy analysis was based on the ITT population including all randomized subjects. In the Applicant's primary efficacy analysis, subjects with intermittent missing data due to missed visit (due to COVID-19 or other reasons) and/or subjects whose data post-occurrence of IEs due to COVID-19 were censored were implicitly imputed using the MMRM model assuming a missing at random (MAR) missing data mechanism.

Based on the MMRM model, noninferiority of faricimab to aflibercept was confirmed if the lower limit of the two-sided 95.03% confidence interval (CI) estimate for the difference in the adjusted means of the change in BCVA from baseline at Week 40/44/48 between the treatment groups (*faricimab minus aflibercept*) was greater than -4.0 letters.

Sensitivity Analyses to the Primary Estimand

The Applicant performed the following sensitivity analyses for the primary estimand to assess the robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent data:

i) Analysis based on the PP population. In this analysis, subjects with a major protocol violation (that impacted the efficacy evaluation or the treatment interval determination) were excluded.

ii) Analysis based on the ITT population including all data regardless of occurrence of IEs under a treatment policy estimand strategy.

iii) Analysis based on the ITT population where all data after occurrence of IEs were censored and implicitly imputed by the MMRM model under a hypothetical estimand strategy.

In each of the cases, missing data due to intermittent missing visits and/or data censored due to occurrence of IEs were implicitly imputed by the MMRM model assuming MAR missing data mechanism.

As additional sensitivity analyses, the reviewer also performed the primary and the sensitivity analyses for the primary estimand by imputing intermittent missing data and data after occurrence of IEs using multiple imputation (MI) strategy and the last observation carried forward (LOCF) imputation approach.

Reviewer's Remark:

In the Applicant's primary estimand strategy, data for subjects with IEs not related to COVID-19 were used in the analysis but data for subjects with IEs due to COVID-19 were censored and imputed using the MMRM model assuming MAR missing data mechanism. Considering that the number of subjects with IEs not related to COVID-19 were minimal in the studies, and due to COVID-19 appeared not to be treatment-related (Table 1), the reviewer considered the treatment policy estimand strategy (i.e., including all data regardless of IEs), as the primary estimand. Analysis based on the Applicant's primary estimand of interest was used as supporting.

Secondary Efficacy Analysis

All secondary efficacy variables with continuous outcome were analyzed similarly to the primary efficacy variable. The same estimand used for the primary efficacy variable was adopted.

The secondary efficacy analysis for the binary efficacy outcomes of the proportion of subjects who gained ≥15, ≥10, ≥5, and ≥0 letters and those who avoided a loss of ≥15, ≥10, and ≥5 letters in BCVA from baseline at Week 40/44/48 compared the treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) test. Based on the CMH test, a weighted point and two-sided 95.03% CI estimates for the difference in proportions (*faricimab minus aflibercept*) adjusted for the study specific strata and using the CMH weights and normal approximation of the weighted estimates was provided.

The Applicant's secondary efficacy analysis was based on the ITT population, using observed data (without missing data imputation) under the primary estimand data handling strategy. That is, subjects with missing data at Week 40/44/48 (due to missing intermittent visit) and/or their data censored under the primary estimand strategy (i.e., due to occurrence of IE due to COVID-19) were excluded in the Applicant's secondary efficacy analyses.

Reviewer's Remark:

The reviewer disagrees with the Applicant's secondary efficacy analysis based on observed data because excluding subjects with missing BCVA data at Week 40/44/48 does not maintain the study randomization. Therefore, to maintain the study randomization, in this review, missing BCVA data under the reviewers primary estimand strategy (RE: Reviewer's Remark above) were first imputed (i) using multiple imputation strategy assuming MAR missing data mechanism as primary and (ii) using the LOCF approach as supporting. In the multiple imputation approach, the binary secondary endpoints at Week 40/44/48 were first derived for each multiply imputed BCVA dataset. Then, for each dataset, the secondary efficacy analysis was performed using CMH test and results from the multiple analyses were combined.

The Applicant's secondary efficacy analysis results based on observed data was used as further supporting analyses.

Type I Error Control (Plan for Multiplicity Adjustment)

The study-wise Type I Error was controlled at a 2-sdided significance level of 5%. A nominal Type I Error penalty of 0.0003 was assigned for three unmasked iDMC reviews prior to the primary analysis (0.0001 for each iDMC look). Thus, the primary efficacy analysis to determine noninferiority of faricimab to aflibercept was based on a family-wise significance level of 0.0497. Since there was no formal hypothesis testing planned for testing the secondary efficacy endpoints, p-values and CI reported in the analysis of these endpoints were intended for descriptive use only.

Subgroup Analysis

Subgroup analyses of the primary and secondary efficacy endpoints were performed for the following subgroups: sex, age (<75 years vs. ≥75 years), race (White vs. Other), baseline BCVA category (<54 vs. 55-73 vs. ≥74 letters), low-luminance deficit (LLD; < 32 vs. ≥33 letters), and region (US and Canada vs. Asia vs. RoW).

3.2.1.3. Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 2 shows the summary of subject disposition and the primary reasons for study discontinuation during the 48-week treatment period in TENAYA/LUCERNE studies. Overall, 671 and 658 subjects were randomized in the TENAYA and LUCERNE studies, respectively.

In TENAYA study, a total of 29 (4.3%) and 41 (6.1%) subjects discontinued from the study and from treatment before Week 48, respectively. Although the discontinuation rate from treatment was slightly higher in the faricimab group than in the aflibercept group in this study (8% vs. 5%), the discontinuation rate from the study was comparable between the treatment groups (about 4%).

In LUCERNE study, a total of 28 (4.3%) and 40 (6.1%) subjects discontinued from the study and from treatment before Week 48, respectively. In this study, both the discontinuation rates from the study and treatment were comparable in the treatment groups.

The most common reason for discontinuation from the study among all randomized subjects in both studies was withdrawal of consent by a subject (3% in TENAYA and 2% in LUERNE). In TENAYA study, a total of four subjects (3 in faricimab and 1 in aflibercept) discontinued treatment due to COVID-19. The discontinuation reason for the two subjects in faricimab was recorded in Table 2 as 'OTHER' and for the one subject recorded as 'PHYSICIAN DECISION, and for the one subject in aflibercept group recorded as 'WITHDRAWAL BY SUBJECT'. In the LUCERNE study, no subject discontinued due to COVID-19.

A total of five subjects in TENAYA (4 in faricimab and 1 in aflibercept) and seven subjects in LUCERNE (2 in faricimab and 5 in aflibercept) died during the 48-week treatment period. None of the deaths in both studies were due to COVID-19.

Table 2: Summary of Subject Disposition and Reasons for Study Discontinuation (All Randomized Subjects)

	TENAYA			LUCERNE		
	Faricimab	Aflibercept	Total	Faricimab	Aflibercept	Total
Number of Patients Randomized	334 (100%)	337 (100%)	671 (100%)	331 (100%)	327 (100%)	658 (100%)
Number of Patients Treated [1]	333 (99.7%)	336 (99.7%)	669 (99.7%)	331 (100%)	326 (99.7%)	657 (99.8%)
Discontinued from Study	15 (4.5%)	14 (4.2%)	29 (4.3%)	10 (3.0%)	18 (5.5%)	28 (4.3%)
Primary Reason for Discontinuation						
Adverse Event	0	3 (0.9%)	3 (0.4%)	2 (0.6%)	0	2 (0.3%)
Death	4 (1.2%)	1 (0.3%)	5 (0.7%)	2 (0.6%)	5 (1.5%)	7 (1.1%)
Lost to Follow-Up	2 (0.6%)	3 (0.9%)	5 (0.7%)	0	1 (0.3%)	1 (0.2%)
Protocol Deviation	0	0	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Withdrawal by Subject	7 (2.1%)	6 (1.8%)	13 (1.9%)	5 (1.5%)	8 (2.4%)	13 (2.0%)
Physician Decision	2 (0.6%)	1 (0.3%)	3 (0.4%)	0	2 (0.6%)	2 (0.3%)
Other	0	0	0	0	1 (0.3%)	1 (0.2%)
Discontinued from Treatment	26 (7.8%)	15 (4.5%)	41 (6.1%)	18 (5.4%)	22 (6.7%)	40 (6.1%)
Primary Reason for Discontinuation						
Adverse Event	2 (0.6%)	3 (0.9%)	5 (0.7%)	7 (2.1%)	1 (0.3%)	8 (1.2%)
Death	4 (1.2%)	1 (0.3%)	5 (0.7%)	2 (0.6%)	5 (1.5%)	7 (1.1%)
Lack of Efficacy	1 (0.3%)	0	1 (0.1%)	0	2 (0.6%)	2 (0.3%)
Lost to Follow-Up	4 (1.2%)	3 (0.9%)	7 (1.0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Protocol Deviation	1 (0.3%)	0	1 (0.1%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Withdrawal by Subject	10 (3.0%)	8 (2.4%)	18 (2.7%)	6 (1.8%)	8 (2.5%)	14 (2.1%)
• COVID-19	0	1 (0.3%)	1 (0.1%)	0	0	0
Physician Decision	2 (0.6%)	0	2 (0.3%)	0	4 (1.2%)	4 (0.6%)
• COVID-19	1 (0.3%)	0	1 (0.1%)	0	0	0
Other	2 (0.6%)	0	2 (0.3%)	1 (0.3%)	0	1 (0.2%)
• COVID-19	2 (0.6%)	0	2 (0.3%)	0	0	0

Source: Table 2 of TENAYA and LURCENRE Clinical Study Reports.
Note: The subject disposition summary was based on the period observed up until database lock.

Analysis Population

Table 3 shows summary of the analysis populations in the two studies. A total of 671 and 658 subjects were randomized in the TENAYA and LUCERNE studies, respectively. Of these randomized subjects, two subjects in TENAYA study (one in each treatment group) and one subject in the aflibercept group in LUCERNE study did not receive study medication and were excluded from the safety evaluable population. A total of 92 and 81 randomized subjects in the

TENAYA and LUCERNE studies, respectively, were excluded from the PP population due to major protocol deviations. Of these, 58 subjects in TENAYA (27 in faricimab and 31 in aflibercept) and 46 subjects in LUCERNE (25 in faricimab and 21 in aflibercept) had missed dose(s) due to COVID-19 with potentially major impact on efficacy.

Table 3: Summary of Analysis Populations in TENAYA/LUCERNE Studies

	TENAYA			LUCERNE		
	Faricimab	Aflibercept	Total	Faricimab	Aflibercept	Total
Intent-to-Treat Population	334	337	671	331	327	658
Safety-Evaluable Population (As treated)	333	336	669	331	326	657
Per-Protocol Population	284	295	579	286	291	577
Major protocol Deviation	50	42	92	45	36	81
Missed Doses due to COVID-19	27	31	58	25	21	46

Source: Table 3 of TENAYA and LUCERNE Clinical Study Reports.

Demographic and Baseline Characteristics

The summary of the baseline demographic and disease characteristics for subjects in the ITT population in the TENAYA/LUCERNE studies are presented in Table 4.

Most subjects in both studies were Caucasian (90% in TENAYA and 80% in LUCERNE), at least 75 years of age (62% in TENAYA and 56% in LUCERNE), and female (60% in TENAYA and 59% in LUCERNE). The average age of subjects in both studies was about 76 years (range 50 to 99 years). About 55% and 41% of subjects enrolled in TENAYA and LICERNE studies, respectively, were from the US and Canada. The average baseline BCVA in the study eye in TENAYA was 60 letters and in LUCERNE was 59 letters with most subjects had a baseline BCVA of ≥ 55 letters (74% in TENAYA and 68% in LUCERNE). Most subjects enrolled in both studies had AMD diagnosis in the last 30 days (74% in TENAYA and 65% in LUCERNE).

The baseline demographic and disease characteristics in both studies were well balanced between the treatment groups.

Table 4: Demographic and Baseline Characteristics in TENAYA/LUCERNE Studies (Intent-to-Treat Population)

	TENAYA			LUCERNE		
	Faricimab (N = 334)	Aflibercept (N = 337)	Total (N = 671)	Faricimab (N = 331)	Aflibercept (N = 327)	Total (N = 658)
Age (years)						
Mean (SD)	75.9 (8.6)	76.7 (8.8)	76.3 (8.6)	74.8 (8.5)	76.0 (8.6)	75.4 (8.5)
Median	77	77	77	75	76	76
Range	50 -99	51 - 94	50 - 99	50 - 95	50 - 95	50 – 95
Age Category						
< 75	130 (38.9%)	124 (36.8%)	254 (37.9%)	156 (47.1%)	131 (40.1%)	287 (43.6%)
≥ 75	204 (61.1%)	213 (63.2%)	417 (62.1%)	175 (52.9%)	196 (59.9%)	371 (56.4%)
< 65	34 (10.2%)	30 (8.9%)	64 (9.5%)	30 (9.1%)	33 (10.1%)	63 (9.6%)
65-<75	96 (28.7%)	94 (27.9%)	190 (28.3%)	126 (38.1%)	98 (30.0%)	224 (34.0%)
75-<85	157 (47.0%)	144 (42.7%)	301 (44.9%)	131 (39.6%)	137 (41.9%)	268 (40.7%)
≥85	47 (14.1%)	69 (20.5%)	116 (17.3%)	44 (13.3%)	59 (18.0%)	103 (15.7%)

	TENAYA			LUCERNE		
	Faricimab (N = 334)	Aflibercept (N = 337)	Total (N = 671)	Faricimab (N = 331)	Aflibercept (N = 327)	Total (N = 658)
Sex						
Female	191 (57.2%)	211 (62.6%)	402 (59.9%)	203 (61.3%)	188 (57.5%)	391 (59.4%)
Male	143 (42.8%)	126 (37.4%)	269 (40.1%)	128 (38.7%)	139 (42.5%)	267 (40.6%)
Race						
American Indian Or Alaska Native	1 (0.3%)	2 (0.6%)	3 (0.4%)	1 (0.3%)		1 (0.2%)
Asian	26 (7.8%)	28 (8.3%)	54 (8.0%)	38 (11.5%)	34 (10.4%)	72 (10.9%)
Black or African American	0	3 (0.9%)	3 (0.4%)	2 (0.6%)	5 (1.5%)	7 (1.1%)
White	303 (90.7%)	302 (89.6%)	605 (90.2%)	278 (84.0%)	270 (82.6%)	548 (83.3%)
Multiple	1 (0.3%)	0	1 (0.1%)	0	1 (0.3%)	1 (0.2%)
Unknown	3 (0.9%)	2 (0.6%)	5 (0.7%)	12 (3.6%)	17 (5.2%)	29 (4.4%)
Ethnicity						
Hispanic Or Latino	26 (7.8%)	26 (7.7%)	52 (7.7%)	35 (10.6%)	46 (14.1%)	81 (12.3%)
Not Hispanic Or Latino	303 (90.7%)	308 (91.4%)	611 (91.1%)	287 (86.7%)	274 (83.8%)	561 (85.3%)
Unknown	2 (0.6%)	2 (0.6%)	4 (0.6%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Not Reported	3 (0.9%)	1 (0.3%)	4 (0.6%)	4 (1.2%)	4 (1.2%)	8 (1.2%)
Region						
Asia	26 (7.8%)	26 (7.7%)	52 (7.7%)	35 (10.6%)	33 (10.1%)	68 (10.3%)
Rest of the World	126 (37.7%)	127 (37.7%)	253 (37.7%)	161 (48.6%)	162 (49.5%)	323 (49.1%)
US and Canada	182 (54.5%)	184 (54.6%)	366 (54.5%)	135 (40.8%)	132 (40.4%)	267 (40.6%)
Baseline BCVA (letters)						
Mean (SD)	61.3 (12.6)	61.5 (12.9)	61.4 (12.7)	58.7 (13.9)	58.9 (13.3)	58.8 (13.6)
Median	65	65	65	61	61	61
Range	26 - 78	24 - 78	24 – 78	24 - 78	24 - 78	24 - 78
Baseline BCVA Category						
< 54	87 (26.0%)	86 (25.5%)	173 (25.8%)	105 (31.7%)	107 (32.7%)	212 (32.2%)
55 - 73	200 (59.9%)	201 (59.6%)	401 (59.8%)	181 (54.7%)	180 (55.0%)	361 (54.9%)
≥74	47 (14.1%)	50 (14.8%)	97 (14.5%)	45 (13.6%)	40 (12.2%)	85 (12.9%)
Low-Luminance Deficit						
< 32	236 (70.7%)	242 (71.8%)	478 (71.2%)	238 (71.9%)	236 (72.2%)	474 (72.0%)
≥ 33	98 (29.3%)	95 (28.2%)	193 (28.8%)	93 (28.1%)	91 (27.8%)	184 (28.0%)
Time Since AMD Diagnosis						
0-10 days	62 (18.6%)	63 (18.7%)	125 (18.6%)	77 (23.3%)	63 (19.3%)	140 (21.3%)
10-31 days	186 (55.7%)	183 (54.3%)	369 (55.0%)	144 (43.5%)	145 (44.3%)	289 (43.9%)
1-3 months	45 (13.5%)	63 (18.7%)	108 (16.1%)	56 (16.9%)	75 (22.9%)	131 (19.9%)
4-6 months	13 (3.9%)	6 (1.8%)	19 (2.8%)	19 (5.7%)	17 (5.2%)	36 (5.5%)
>6 months	8 (2.4%)	8 (2.4%)	16 (2.4%)	21 (6.3%)	15 (4.6%)	36 (5.5%)
Unknown	20 (6.0%)	14 (4.2%)	34 (5.1%)	14 (4.2%)	12 (3.7%)	26 (4.0%)

Source: Source: Table 5 of TENAYA and LURCENRE Clinical Study Reports.

3.2.1.4. Results and Conclusions

Primary Efficacy Endpoint: Change in BCVA from Baseline at Week 40/44/48

The primary efficacy objective in both studies was an evaluation of noninferiority of faricimab to aflibercept in the primary efficacy variable of the change in BCVA from baseline at Week 40/44/48 using a noninferiority margin of -4.0 letters. The primary estimand of interest to address the primary efficacy objective of both studies was the difference in the mean change in BCVA from baseline at Week 40/44/48 (*faricimab minus aflibercept*) in all randomized subjects regardless of occurrence of IEs (see details in Section 3.2.1.2).

Table 5 shows the number of subjects with observed BCVA data at each study visit by the three estimand strategy: (i) numbers in black font are for the treatment policy estimand strategy (reviewer's preferred primary estimand strategy), (ii) numbers in black font excluding numbers in green font are for the Applicant's primary estimand of interest (i.e., data after occurrence IEs due to COVID-19 censored), and (iii) numbers in black font excluding numbers in blue font are for hypothetical estimand strategy (i.e., all data after occurrence of IEs censored). As shown, the Applicant's primary analysis for the primary estimand of interest excluded few subjects mainly at the primary endpoints of Weeks 40, 44, and 48. As outlined in Section 3.2.1.2, the primary efficacy analysis in this review was based on the treatment policy estimand strategy including all observed data regardless of occurrence of IEs.

Table 5: Number of Subjects with Observed BCVA Data by Visit by Three Estimand Strategy (TENAYA/LUCERNE)

		Visit (in weeks)												
Study	Treatment	0	4	8	12	16	20	24	28	32	36	40	44	48
TENAYA	Faricimab	334	327	325	322	322	308	278	284	293	286	299	289	289
												(-12)	(-11)	(-16)
										(-1)	(-1)	(-13)	(-12)	(-18)
	Missed Visit Due to COVID-19		0	0	0		6	6			30	18	24	24
	Aflibercept	337	331	325	326	320	308	285	276	285	297	291	285	296
													(-11)	(-17)
										(-1)			(-11)	(-17)
	Missed Visit Due to COVID-19		0	0	0		9	9			23	28	33	19
LUCERNE	Faricimab	331	328	327	326	321	320	295	292	287	293	294	298	298
													(-8)	(-12)	(-16)
					(-2)		(-1)	(-1)		(-2)	(-3)	(-11)	(-15)	(-20)
	Missed Visit Due to COVID-19		0	0	0		3	4			26	21	15	15
	Aflibercept	327	323	322	317	315	309	288	271	288	283	288	285	294
													(-12)	(-17)
							(-1)	(-2)	(-1)	(-2)	(-1)	(-2)	(-15)	(-20)
	Missed Visit Due to COVID-19		0	0	0		2	4			25	24	19	10

Source: Based on Reviewer's Analysis.

The number of subjects with missed selected visits due to COVID-19 are also displayed in Table 5. A total of 133 (20%) subjects in TENAYA (58 in Faricimab and 75 in Aflibercept) and 107 (16%) of subjects in LUCERNE (55 in Faricimab and 52 in Aflibercept) had at least one selected missed visit due to COVID- 19. Per the Applicant, the selected missed visits included Weeks 4, 8, 12, 20, 24, 36, 40, 44, and 48.

Based on the observed data in the treatment policy estimand strategy, Table 6 displays the summary of the mean change in BCVA from baseline at Weeks 40, 44, and 48 and from the average in BCVA at Week 40/44/48 visits including the adjusted mean estimates from the MMRM model and the treatment difference in the adjusted means.

Table 6: Summary of Mean Change in BCVA from Baseline at Week 40/44/48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)

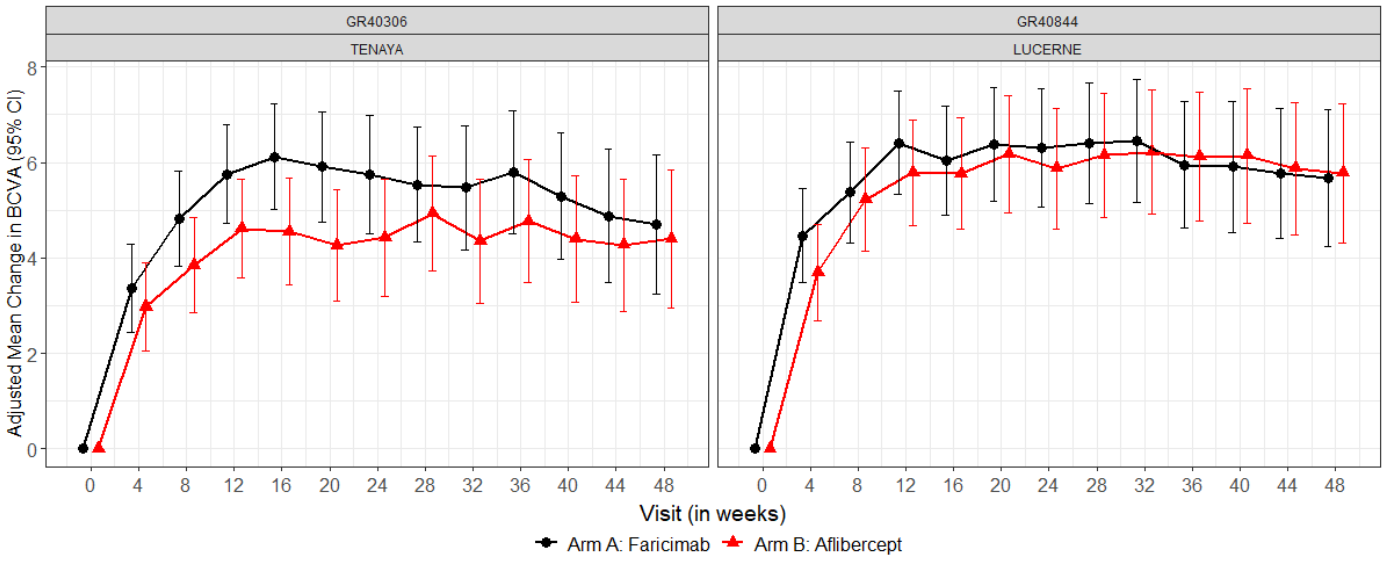
		TENAYA (GR40306)		LUCERNE (GR40844)	
AVISIT		Faricimab	Aflibercept	Faricimab	Aflibercept
Mean BCVA					
Baseline	Mean (SD)	61.3 (12.55)	61.5 (12.86)	58.7 (13.95)	58.9 (13.31)
	Median (Range)	65 (26 – 78)	65 (24 – 78)	61 (24 – 78)	61 (24 – 78)
Week 40	Mean (SD)	66.9 (15.62)	66.8 (15.91)	65.9 (16.16)	66.2 (15.52)
	Median (Range)	71 (7 – 92)	72 (13 – 91)	70.5 (7 – 91)	69 (13 – 89)
Week 44	Mean (SD)	67.6 (15.63)	66.8 (15.89)	66.1 (16.13)	66.4 (15.37)
	Median (Range)	72.0 (7 – 89)	71 (11 - 93)	71 (11 - 92)	70 (14 - 89)
Week 48	Mean (SD)	66.5 (16.35)	66.7 (16.35)	65.6 (16.38)	66.8 (16.11)
	Median (Range)	72 (7 - 91)	71 (11 - 94)	70.0 (14 - 91)	69.0 (0 - 90)
Mean Change in BCVA					
Week 40	Mean (SD)	5.8 (12.06)	5.5 (11.53)	6.8 (12.29)	7.0 (11.90)
	Median (Range)	6 (-53 - 34)	6 (-42 - 38)	7 (-63 - 45)	7 (-41 - 46)
Week 44	Mean (SD)	5.8 (12.57)	5.3 (12.14)	6.8 (11.78)	6.8 (11.61)
	Median (Range)	7 (-56 - 33)	7 (-53 - 41)	7 (-56 - 42)	7 (-38 - 46)
Week 48	Mean (SD)	5.3 (13.09)	5.3 (12.92)	6.6 (12.32)	6.7 (12.28)
	Median (Range)	7 (-56 - 37)	7 (-51 - 38)	7 (-53 - 41)	7 (-75 - 46)
Adjusted Mean Change in BCVA					
Week 40	LS Mean (95% CI)	5.3 (4.0, 6.6)	4.4 (3.1, 5.7)	5.9 (4.5, 7.3)	6.1 (4.7, 7.6)
	Diff (95% CI)	0.9 (-0.9, 2.7)	--	-0.2 (-2.1, 1.6)	--
Week 44	LS Mean (95% CI)	4.9 (3.5, 6.3)	4.3 (2.9, 5.7)	5.8 (4.4, 7.1)	5.9 (4.5, 7.3)
	Diff (95% CI)	0.6 (-1.2, 2.5)	--	-0.1 (-1.9, 1.7)	--
Week 48	LS Mean (95% CI)	4.7 (3.2, 6.2)	4.4 (3.0, 5.8)	5.7 (4.2, 7.1)	5.8 (4.3, 7.2)
	Diff (95% CI)	0.3 (-1.6, 2.3)	--	-0.1 (-2.0, 1.8)	--
Average Week 40/44/48	LS Mean (95% CI)	5.7 (4.4, 6.9)	5.1 (3.8, 6.3)	6.4 (5.2, 7.7)	6.6 (5.3, 7.8)
	Diff (95% CI)	0.6 (-1.2, 2.4)		-0.1 (-1.9, 1.6)	

Source: Reviewer's analysis based on ADOE.xpt dataset located at \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40306\analysis\adam\datasets\ for TENAYA and at \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40349\analysis\adam\datasets\ for LUCERNE.

As shown, in both studies, subjects treated with faricimab at intervals of up to every 16-week had a noninferior mean change in BCVA from baseline at Week 40/44/48 compared to subjects treated with aflibercept because the 95.03% lower confidence limit for the difference in the adjusted means between the treatment groups (faricimab minus aflibercept) was greater than the NI margin of -4.0 letters. For example, in TENAYA study, the adjusted means for the change in BCVA from baseline at Week 40/44/48 was +5.7 letters in the faricimab group and +5.1 letters in the aflibercept group with a treatment difference of +**0.6 (95% CI: -1.2 to 2.4)**. Similarly, in LUCERNE study, the adjusted means for the change in BCVA from baseline at Week 40/44/48 was +6.4 letters in the faricimab group and +6.6 letters in the aflibercept group with a treatment difference of -**0.1 (95% CI: -1.9 to 1.6)**.

Figure 7 below displays the adjusted mean change in BCVA from baseline through Week 48 including the 95.03% confidence interval estimates (vertical bars at each visit) in the two studies. As shown, in TENAYA study, the adjusted estimates through Week 48 were numerically lower in the aflibercept group compared to in the faricimab group but, in the LUCERNE study, the results through Week 48 appeared comparable between the treatment groups.

Figure 7: Plot of Adjusted Mean Change in BCVA from Baseline Through Week 48 (Treatment Policy Estimand) (ITT Population) (LUCERNE/TENAYA)



Source: Based on Reviewer's Analysis

Sensitivity/Supporting Analyses to the Primary Efficacy Endpoint

To assess the robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent data, sensitivity and supporting analyses were performed.

As sensitivity analyses, missing data in the treatment policy estimand strategy were imputed using LOCF and multiple imputation approaches and analyzed using MMRM model. As supporting analysis, the primary efficacy variable was analyzed using MMRM model on the PP population, and for the Applicant's primary estimand of interest and for the hypothetical estimand strategy.

Table 7 below shows the sensitivity and supplementary efficacy analyses results. As shown, the various sensitivity and supplementary analyses results were consistent with the primary efficacy analysis results, leading to the same conclusion for a robust interpretation of the noninferiority finding.

Table 7: Adjusted Mean Change in BCVA from Baseline at Week 40/44/48 (Sensitivity Analysis) (ITT Population) (TENAYA/LUCERNE)

		TENAYA (GR40306)		LUCERNE (GR40844)	
AVISIT		Faricimab	Aflibercept	Faricimab	Aflibercept
Sensitivity Analysis: using MMRM Method					
LOCF	LS Mean (95% CI)	5.7 (4.5, 6.9)	5.1 (3.8, 6.3)	6.6 (5.4, 7.9)	6.6 (5.3, 7.8)
	Diff (95% CI)	0.7 (-1.1, 2.4)	--	0.0 (-1.7, 1.7)	--
Multiple Imputation	LS Mean (95% CI)	5.7 (4.4, 6.9)	5.1 (3.8, 6.3)	6.4 (5.2, 7.7)	6.6 (5.4, 7.9)
	Diff (95% CI)	0.6 (-1.2, 2.4)	--	-0.2 (-2.0, 1.6)	
Supplementary Analyses: using MMRM Method					
PP Population	LS Mean (95% CI)	5.9 (4.5, 7.2)	5.6 (4.2, 6.9)	6.6 (5.2, 7.9)	6.7 (5.4, 8.0)
	Diff (95% CI)	0.3 (-1.6, 2.2)	--	-0.1 (-2.0, 1.8)	--
Applicant's Primary Estimand	LS Mean (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
	Diff (95% CI)	0.7 (-1.1, 2.5)	--	0.0 (-1.7, 1.8)	--
Hypothetical Estimand	LS Mean (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.7 (5.5, 7.9)	6.5 (5.3, 7.8)
	Diff (95% CI)	0.7 (-1.1, 2.5)	--	0.2 (-1.6, 1.9)	--

Source: Based on Reviewer's Analysis

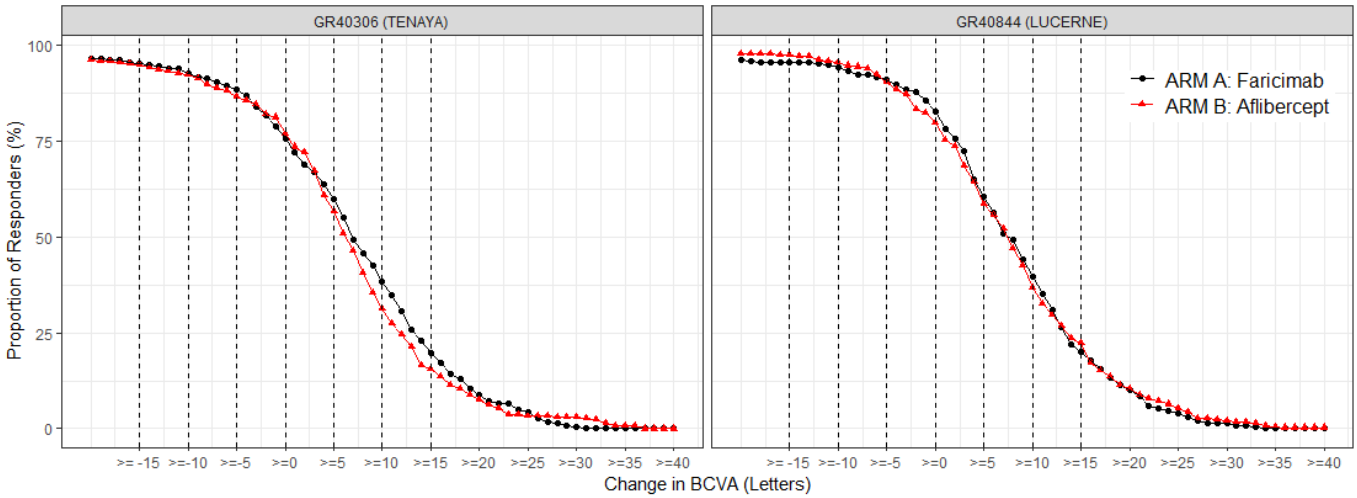
Secondary Efficacy Endpoint: Proportion of Subjects Who Gained/Lost Letters in BCVA from Baseline at Week 40/44/48

The proportion of subjects who gained ≥15, ≥10, ≥5, and ≥0 letters and those who avoided a loss of ≥15, ≥10, and ≥5 letters from baseline at Week 40/44/48 were defined as the secondary efficacy endpoints in both TENAYA and LUERNE studies. Figure 8 displays the cumulative distribution of the change in BCVA at Week 40/44/48 based on missing data imputed using multiple imputation. As shown, in both studies, the treatment groups across the seven BCVA-related binary secondary endpoints (highlighted by the dashed lines) appeared comparable.

Table 8 displays the summary of the proportion of subjects who gained ≥15 and ≥10 letters from baseline at Week 40/44/48 in the two studies based on observed data, and missing data imputed using multiple imputation (MI) and LOCF approaches.

As shown, in both studies, the treatment groups appeared comparable in these endpoints. For example, using the MI approach, 20% of faricimab treated subjects and 16% of aflibercept treated subjects in TENAYA study gained ≥15 letters from baseline at Week 40/44/48 with a treatment difference of 3.9% (95% CI: -1.8% to 9.6%). Similarly, in LUCERNE study, 22% of faricimab treated subjects and 20% of aflibercept treated subjects gained ≥15 letters from baseline at Week 40/44/48 with a treatment difference of -1.9% (95% CI: -8.0% to 4.2%). The results based on the observed data and missing data imputed using the LOCF approach provided similar conclusion except for minor numerical differences.

Figure 8: Cumulative Distribution of the Change in BCVA from Baseline at Week 40/48/52 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)



Source: Based on Reviewer's Analysis. Missing BCVA data were imputed using multiple imputation.

Table 8: Proportion of Subjects Who Gained ≥15 and ≥10 Letters in BCVA from Baseline at Week 40/44/48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)

Study	Summary	Faricimab	Aflibercept	Difference (95.03% CI)
Gained >=15 letters				
TENAYA	Observed, n/N (%)	59/306 (19.3)	49/316 (15.5)	
	CMH Estimate (95.03% CI)	19.1 (14.9, 23.3)	15.6 (11.8, 19.4)	3.4 (-2.2, 9.1)
	LOCF, n/N (%)	66/334 (19.8)	49/337 (14.5)	
	CMH Estimate (95.03% CI)	19.7 (15.5, 23.8)	14.6 (11.0, 18.2)	5.0 (-0.4, 10.5)
	MI: CMH Estimate (95.03% CI)	19.5 (15.2, 23.7)	15.6 (11.8, 19.4)	3.9 (-1.8, 9.6)
LUCERNE	Observed, n/N (%)	62/315 (19.7)	67/306 (21.9)	
	CMH Estimate (95.03% CI)	20.0 (15.7, 24.3)	21.6 (17.2, 26.1)	-1.6 (-7.8, 4.5)
	LOCF, n/N (%)	64/331 (19.3)	69/327 (21.1)	
	CMH Estimate (95.03% CI)	19.5 (15.4, 23.6)	21.0 (16.7, 25.2)	-1.5 (-7.4, 4.5)
	MI: CMH Estimate (95.03% CI)	19.6 (15.4, 23.9)	21.5 (17.1, 26.0)	-1.9 (-8.0, 4.2)
Gained >=10 letters				
TENAYA	Observed, n/N (%)	114/306 (37.3)	99/316 (31.3)	
	CMH Estimate (95.03% CI)	37.0 (31.8, 42.3)	31.5 (26.5, 36.5)	5.5 (-1.7, 12.8)
	LOCF, n/N (%)	124/334 (37.1)	104/337 (30.9)	
	CMH Estimate (95.03% CI)	19.7 (15.5, 23.8)	14.6 (11.0, 18.2)	6.0 (-0.9, 13.0)
	MI: CMH Estimate (95.03% CI)	37.4 (32.2, 42.6)	30.3 (25.5, 35.1)	7.1 (-0.0, 14.2)
LUCERNE	Observed, n/N (%)	121/315 (38.4)	109/306 (35.6)	
	CMH Estimate (95.03% CI)	38.8 (33.7, 44.0)	35.3 (30.2, 40.5)	3.5 (-3.8, 10.8)
	LOCF, n/N (%)	128/331 (38.7)	112/327 (34.3)	
	CMH Estimate (95.03% CI)	19.5 (15.4, 23.6)	21.0 (16.7, 25.2)	4.9 (-2.2, 11.9)
	MI: CMH Estimate (95.03% CI)	37.3 (32.2, 42.4)	34.7 (29.6, 39.8)	2.6 (-0.1, 9.8)

Source: Based on Reviewer's Analysis. Abbreviation: MI – Multiple Imputation; LOCF – Last Observation Carried Forward.
Note: Treatment differences and two-sided 95.03% CI were based on stratified CMH test using the CMH weights and normal approximation of the weighted estimates. CMH estimates and corresponding CIs presented in the table are in percentage.

As supporting analyses, the proportion of subjects who gained ≥15 and ≥10 letters from baseline at Week 40/44/48 were analyzed based on the observed data using the Applicant's primary estimand strategy and using the hypothetical estimand strategy (Table 9). As shown, except for minor numerical differences, the results are consistent with the results based on the treatment policy estimand strategy (Table 8)

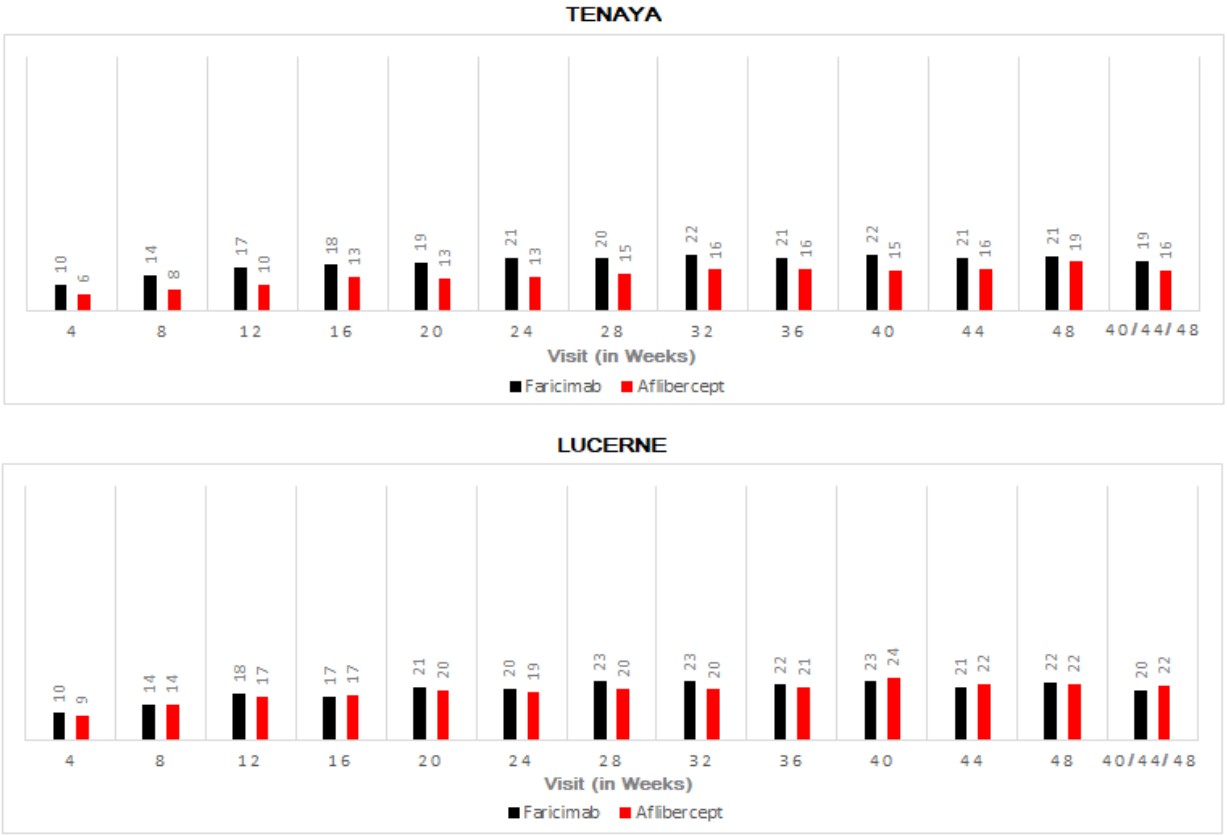
Table 9: Proportion of Subjects Who Gained ≥10 and ≥5 Letters from Baseline at Week 40/44/48 (ITT Population) (Supporting Analysis) (TENAYA/LUCERNE)

	Letters Gained	Study	Faricimab	Aflibercept	Difference (95.03% CI)
Applicant's Primary Estimand	≥15 Letters	TENAYA	58/292 (19.9)	48/300 (16.0)	4.1 (-1.8, 10.0)
		LUCERNE	60/302 (19.9)	65/291 (22.3)	-1.8 (-8.2, 4.5)
	≥10 Letters	TENAYA	108/292 (37.0)	96/300 (32.0)	5.1 (-2.3, 12.5)
		LUCERNE	117/302 (38.7)	104/291 (35.7)	3.8 (-3.6, 11.2)
Hypothetical Estimand	≥15 Letters	TENAYA	57/291 (19.6)	48/300 (16.0)	3.8 (-2.1, 9.7)
		LUCERNE	59/299 (19.7)	63/289 (21.8)	-1.4 (-7.8, 4.9)
	≥10 Letters	TENAYA	107/291 (36.8)	96/300 (32.0)	4.9 (-2.5, 12.3)
		LUCERNE	116/299 (38.8)	102/289 (35.3)	4.2 (-3.2, 11.7)

[1] Based on Reviewer's Analysis. Differences and corresponding 95.03% confidence intervals are in percentage

Figure 9 displays the proportion of subjects who gained ≥15 letters from baseline at each visit through Week 48 in the TENAYA/LUCERNE studies. As shown, the gain in BCVA through Week 48 appeared comparable between the treatment groups.

Figure 9: Proportion of Subjects Who Gained ≥15 Letters from Baseline Through Week 48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)



Source: Based on Reviewer's Analysis.

The proportion of subjects who avoided losing ≥15 and ≥10 letters from baseline at Week 40/44/48 in the two studies is also summarized in Table 10. As shown, in both studies, a comparable proportion of subjects avoided losing ≥15 and ≥10 letters from baseline at Week 40/44/48 in the two treatment groups.

For example, in TENAYA study, 95% of faricimab treated subjects and 94% of aflibercept treated subjects avoided losing ≥15 letters from baseline at Week 40/44/48 with a treatment difference of 0.7% (95% CI: -3.1% to 4.5%). Similarly, in LUCERNE study, 95% of faricimab treated subjects and 96% of aflibercept treated subjects avoided losing ≥15 letters from baseline at Week 40/44/48 with a treatment difference of -1.8% (95% CI: -5.6% to 1.9%).

The results for the proportion of subjects who avoided losing ≥5 letters from baseline at Week 40/44/48 are also comparable between the treatment groups in both studies (Figure 8).

Table 10: Proportion of Subjects Who Avoided Loss of ≥15 and ≥10 Letters in BCVA from Baseline at Week 40/44/48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)

Study	Summary	Faricimab	Aflibercept	Difference (95.03% CI)
Avoided Losing **≥15** letters				
TENAYA	Observed, n/N (%)	290/306 (95.2)	297/316 (94.0)	
	CMH Estimate (95.03% CI)	94.8 (92.3, 97.3)	94.0 (91.3, 96.6)	0.8 (-2.8, 4.4)
	LOCF, n/N (%)	318/334 (95.2)	318/337 (94.4)	
	CMH Estimate (95.03% CI)	95.2 (92.9, 97.5)	94.4 (91.9, 96.8)	0.9 (-2.5, 4.2)
	MI: CMH Estimate (95.03% CI)	94.6 (92.0, 97.2)	94.1 (91.4, 96.8)	0.5 (-3.2, 4.2)
LUCERNE	Observed, n/N (%)	301/315 (95.6)	298/306 (97.4)	
	CMH Estimate (95.03% CI)	95.6 (93.3, 97.8)	97.4 (95.7, 99.2)	-1.8 (-4.7, 1.0)
	LOCF, n/N (%)	316/331 (95.5)	319/327 (97.6)	
	CMH Estimate (95.03% CI)	95.5 (93.3, 97.7)	97.6 (95.9, 99.2)	-2.1 (-4.8, 0.7)
	MI: CMH Estimate (95.03% CI)	94.6 (91.7, 97.4)	96.1 (93.6, 98.6)	-1.6 (-5.4, 2.2)
Avoided Losing **≥10** letters				
TENAYA	Observed, n/N (%)	280/306 (91.5)	287/316 (90.8)	
	CMH Estimate (95.03% CI)	91.6 (88.5, 94.7)	90.8 (87.7, 94.0)	0.7 (-3.7, 5.2)
	LOCF, n/N (%)	309/334 (92.5)	308/337 (91.4)	
	CMH Estimate (95.03% CI)	92.5 (89.7, 95.3)	91.4 (88.4, 94.4)	1.1 (-3.0, 5.2)
	MI: CMH Estimate (95.03% CI)	91.5 (88.4, 94.8)	91.3 (88.1, 94.5)	0.3 (-4.2, 4.8)
LUCERNE	Observed, n/N (%)	295/315 (93.7)	289/306 (94.4)	
	CMH Estimate (95.03% CI)	93.6 (91.0, 96.3)	94.5 (92.0, 97.0)	-0.8 (-4.5, 2.8)
	LOCF, n/N (%)	310/331 (93.7)	310/327 (94.8)	
	CMH Estimate (95.03% CI)	93.6 (91.0, 96.3)	94.8 (92.4, 97.2)	-1.2 (-4.7, 2.4)
	MI: CMH Estimate (95.03% CI)	92.9 (90.0, 95.8)	94.0 (91.2, 96.8)	-1.1. (-5.1, 3.0)

Source: Based on Reviewer's Analysis. Abbreviation: MI – Multiple Imputation; LOCF – Last Observation Carried Forward.
Note: Treatment differences and two-sided 97.5% CI were based on stratified CMH test using the CMH weights and normal approximation of the weighted estimates. CMH estimates and corresponding 95.03% confidence intervals are in percentage.

As supporting analyses, the proportion of subjects who avoided losing ≥15 and ≥10 letters from baseline at Week 40/44/48 were compared between the treatment groups based on the observed data using the Applicant's primary estimand strategy and using the hypothetical estimand strategy (Table 11). As shown, except for minor numerical differences, the results are consistent with the treatment policy estimand strategy (Table 10).

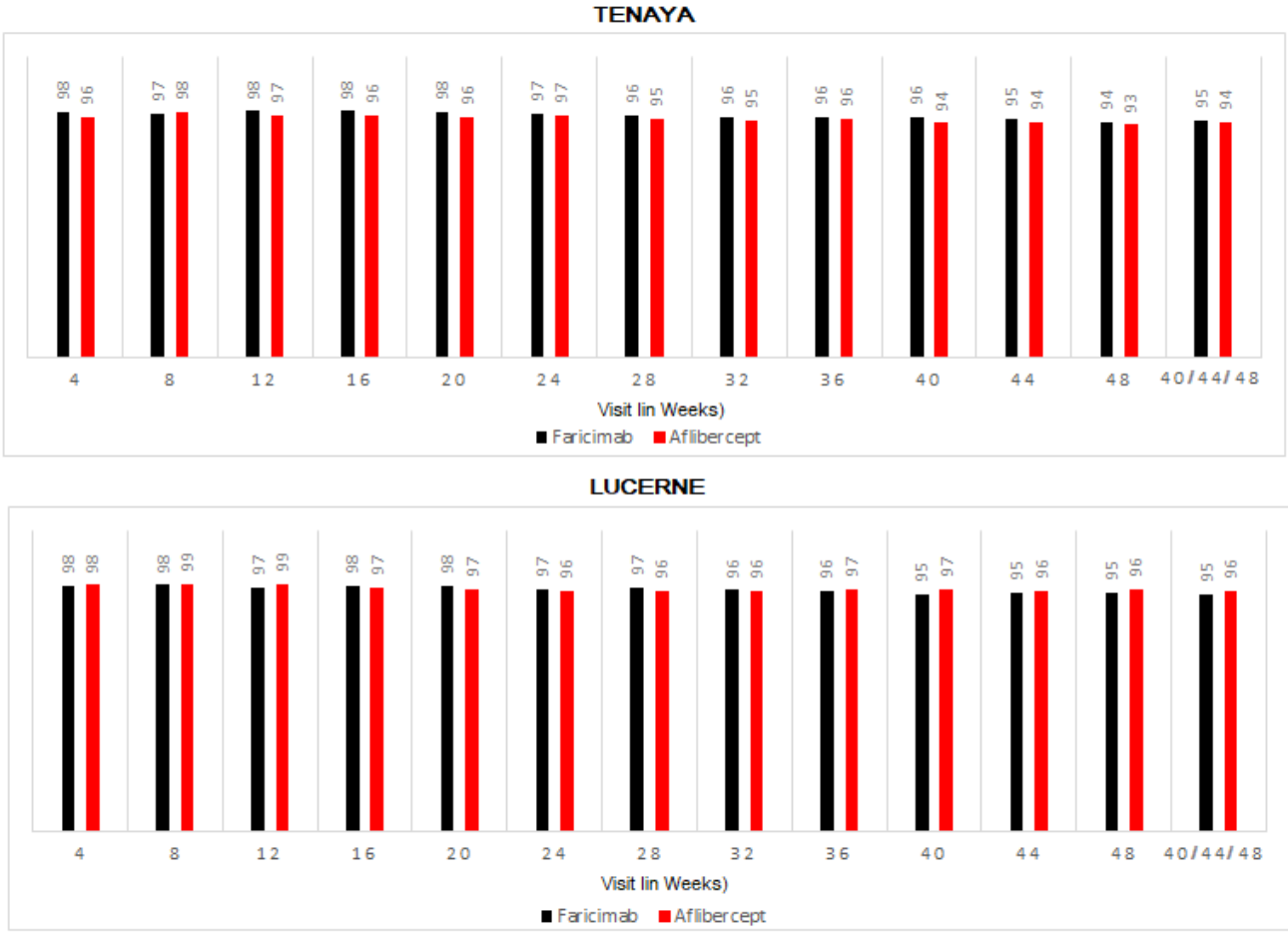
Table 11: Proportion of Subjects Who Avoided Losing ≥15 and ≥10 Letters in BCVA from Baseline at Week 40/44/48 (Supporting Analyses) (ITT Population) (TENAYA/LUCERNE)

	Letters Gained	Study	Faricimab	Aflibercept	Difference (95.03% CI) [1]
Applicant's Primary Estimand	≥15 Letters	TENAYA	278/292 (95.2)	283/300 (94.3)	0.9 (-2.7, 4.5)
		LUCERNE	289/302 (95.7)	283/291 (97.3)	-1.6 (-4.5, 1.3)
	≥10 Letters	TENAYA	267/292 (91.4)	277/300 (92.3)	-0.8 (-5.2, 3.5)
		LUCERNE	283/302 (93.7)	275/291 (94.5)	-0.8 (-4.6, 2.9)
Hypothetical Estimand	≥15 Letters	TENAYA	277/291 (95.2)	283/300 (94.3)	0.9 (-2.7, 4.5)
		LUCERNE	287/299 (96.0)	281/289 (97.2)	-1.3 (-4.1, 1.6)
	≥10 Letters	TENAYA	266/291 (91.4)	277/300 (92.3)	-0.9 (-5.2, 3.5)
		LUCERNE	281/299 (94.0)	273/289 (94.5)	-0.5 (-4.2, 3.2)

Note: Based on Reviewer's Analysis Using Observed Data.

Figure 10 displays the proportion of subjects who avoided losing ≥15 letters from baseline at each visit through Week 48. As shown, the proportion of subjects who avoided losing ≥15 letters in BCVA through Week 48 appeared comparable across the treatment groups.

Figure 10: Proportion of Subjects Who Avoided Losing ≥15 Letters from Baseline Through Week 48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)



Source: Based on Reviewer's Analysis.

Secondary Efficacy Endpoint: Proportion of Subjects on Faricimab Q8W, Q12W, and Q16W Treatment Intervals at Week 48

In TENAYA/LUCERNE studies, subjects in the faricimab arm were to receive treatment up to 16-week dosing interval (Q16W) after four initial monthly injections. Starting Week 20, subjects in this arm were to receive treatment every 8-week (Q8W) if protocol-defined disease activity criteria (DAC) were confirmed at Week 20 or every 12-week (Q12W) if DAC were confirmed at only Week 24 but not at Week 20 or every 16-week (Q16W) if DAC were not confirmed at both Week 20 and Week 24 visits.

Prior to the Week 20/24 visits, 9 and 5 subjects in the faricimab arm in TENAYA and LUCERNE studies, respectively, discontinued treatment resulting in a total of 325 and 326 subjects in the faricimab arm in TENAYA and LUCERNE studies, respectively, that completed the Week 20/24 visits. Thus, depending on the protocol-defined DAC outcome evaluated at the Week 20 and Week 24 visits, subjects that completed the Week 20/24 visits in the faricimab arm received treatment on a Q8W, Q12W, or Q16W dosing intervals.

Table 12 displays the summary of the number of subjects that received faricimab on a Q8W, Q12W, or Q16W dosing intervals among those who completed the Week 20/24 and Week 48 visits in the ITT population. As shown, in both studies, most subjects randomized to the faricimab arm that completed the Week 20/24 and the Week 48 visits were on a Q16W dosing interval (about 45%) followed by on a Q12W dosing interval (about 33%) and on a Q8W interval (about 22%).

Table 12: Proportion of Subjects in the Faricimab Arm on a Q8W, Q12W, and Q16W Dosing Interval Among Subjects Completing Week 20/24 and Week 48 Visits (ITT Population)

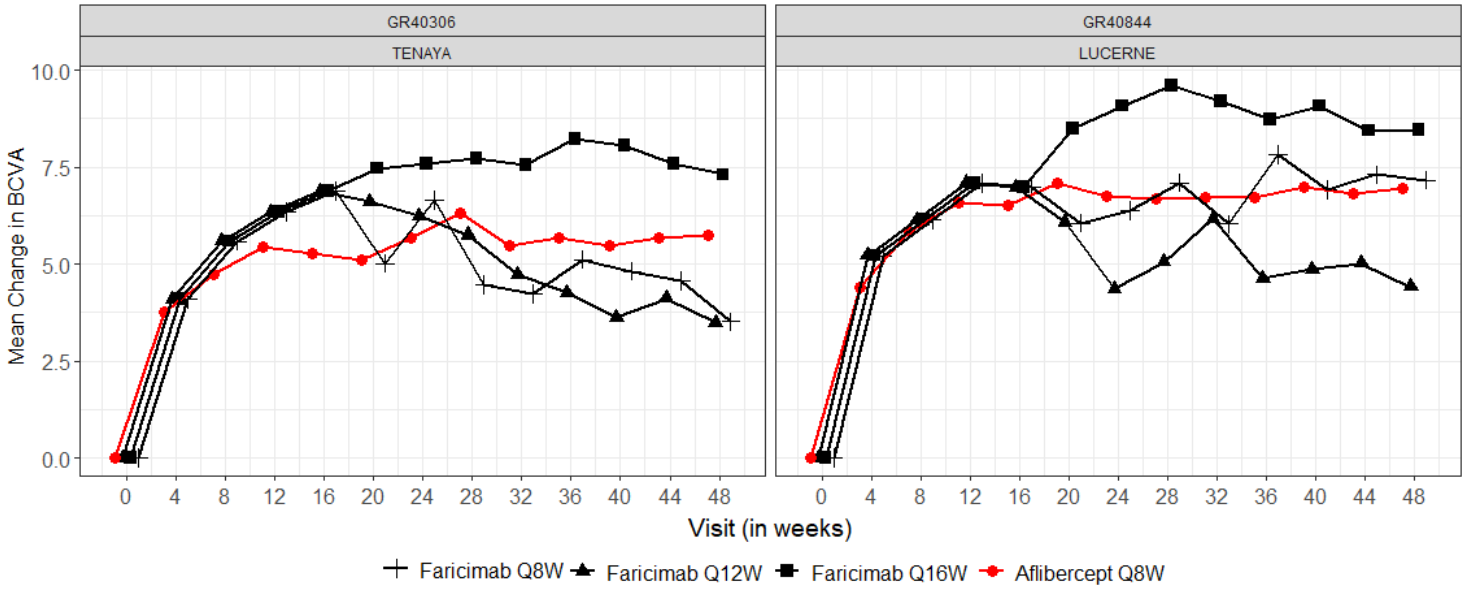
		TENAYA Faricimab (N = 334)	LUCERNE Faricimab (N = 331)	Pooled Faricimab (N = 665)
Subjects who completed Week 20/24 visits	N	325	326	651
	Q8W	68 (20.9%)	75 (23.0%)	142 (21.8%)
	Q12W	109 (33.5%)	110 (33.7%)	219 (33.6%)
	Q16W	148 (45.5%)	141 (43.3%)	289 (44.4%)
Subjects who completed Week 48 visit	N	315	316	631
	Q8W	64 (20.3%)	70 (22.2%)	134 (21.2%)
	Q12W	107 (34.0%)	104 (32.9%)	211 (33.4%)
	Q16W	144 (45.7%)	142 (44.9%)	286 (45.3%)

Source: Based on Reviewer's Analysis.

Figure 11 displays the mean change in BCVA through Week 48 in the three faricimab dosing frequency groups and in the aflibercept group. It should be noted that since the dosing interval across the three faricimab dosing groups was the same prior to Week 20, the mean change in BCVA prior to the Week 20 visits were averaged across the three dosing groups.

Starting Week 20, where dosing in the faricimab group was based on disease activity criteria, the mean change in BCVA after Week 20 in the three faricimab dosing groups differ. Subjects in the faricimab Q16W dosing group displayed a greater mean change in BCVA through Week 48 compared to subjects in the aflibercept group and compared to subjects in the faricimab Q8W and Q12W dosing groups. At the primary efficacy time points of Week 40, 44, and 48, subjects in the faricimab Q12W dosing interval displayed lower BCVA gain compared to aflibercept.

Figure 11: Adjusted Mean Change in BCVA from Baseline Through Week 48 by Faricimab Dosing Frequency (ITT Population) (TENAYA/LUCERNE)



Source: Reviewer's analysis based on ADOE.xpt dataset located at \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40306\analysis\adam\datasets\ for TENAYA and \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40349\analysis\adam\datasets\ for LUCERNE.

A treatment comparison of the three doses of faricimab versus aflibercept was made using the MMRM model similarly to the primary analysis. As shown in Table 13, subjects treated with the three dosing intervals of faricimab had a comparable mean change in BCVA from baseline at Week 40/44/48 compared to subjects treated with aflibercept.

Table 13: Adjusted Mean Change in BCVA from Baseline at Week 40/44/48 by Faricimab Dosing Frequency (ITT Population) (TENAYA/LUCERNE)

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	TENAYA		LUCERNE	
	LS Means	Difference (95% CI) vs	LS Means	Difference (95% CI) vs
Faricimab				
Q8W	4.2 (1.3, 7.0)	-0.9 (-4.0, 2.2)	6.9 (4.2, 9.5)	0.3 (-2.7, 3.2)
Q12W	3.9 (1.7, 6.2)	-1.1 (-3.7, 1.5)	4.4 (2.3, 6.5)	-2.1 (-4.6, 0.3)
Q16W	7.6 (5.8, 9.4)	2.6 (0.4, 4.7)	8.4 (6.5, 10.2)	1.7 (-0.5, 3.9)
Aflibercept	5.1 (3.9, 6.3)	--	6.6 (5.4, 7.8)	--

Source: Based on Reviewer's Analysis.

Table 14 displays the proportion of subjects who gained and avoid losing ≥ 15 letters from baseline at Week 40/44/48 by faricimab dosing frequency. As shown, more subjects in the faricimab Q16W relative to the Q8W and Q12W dosing interval gained ≥ 15 letters from baseline at Week 40/44/48 compared to aflibercept. A lower proportion of subjects in the faricimab Q12W dosing interval gained ≥ 15 letters from baseline at Week 40/44/48 compared to aflibercept and compared to the faricimab Q8W and Q16W dosing intervals.

Table 14: Proportion of Subjects Who Gained and Avoid Losing ≥ 15 Letters from Baseline at Week 40/44/48 by Faricimab Dosing Frequency (ITT Population)

	TENAYA		LUCERNE	
Gained ≥ 15 Letters	Proportion (%)	Difference (95% CI) vs Aflibercept	Proportion (%)	Difference (95% CI) vs Aflibercept
Faricimab				
Q8W	17.4	1.8 (-8.4, 12.0)	26.5	4.5 (-7.1, 16.0)
Q12W	13.9	-1.3 (-9.1, 6.6)	12.2	-9.7 (-17.4, -2.0)
Q16W	24.1	8.5 (0.4, 16.6)	22.5	0.7 (-7.6, 9.0)
Aflibercept	15.6	--	21.8	--
Avoided Losing ≥ 15 Letters				
Faricimab				
Q8W	90.5	-3.5 (-11.2, 4.2)	94.2	-3.0 (-8.8, 2.8)
Q12W	94.1	0.0 (-5.2, 5.3)	96.2	-1.2 (-5.2, 2.8)
Q16W	97.2	3.2 (-0.6, 7.0)	96.4	-1.1 (-4.7, 2.5)
Aflibercept	94.0	--	97.2	--

Source: Based on Reviewer's Analysis.

Secondary Efficacy Endpoint: Change in CST from Baseline at Week 40/44/48

The central subfield thickness (CST) was assessed by optical coherence tomography (OCT) to measure the extent and progression of macular swelling. The effectiveness of faricimab compared to aflibercept in the reduction of CST from baseline at Week 40/44/48 was evaluated.

Treatment comparison between faricimab versus aflibercept in the mean change in CST from baseline at Week 40/44/48 was made using MMRM model on the treatment policy estimand strategy. The model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST as a continuous covariate, and the study specific stratification factors. An unstructured covariance structure was used to account for the within subject correlation. The estimate of the difference between the treatment groups was based on a composite contrast over Weeks 40, 44 and 48. As shown in Table 15, faricimab treated subjects in both studies demonstrated comparable reductions in CST from baseline at Week 40/44/48 compared to subjects treated with aflibercept.

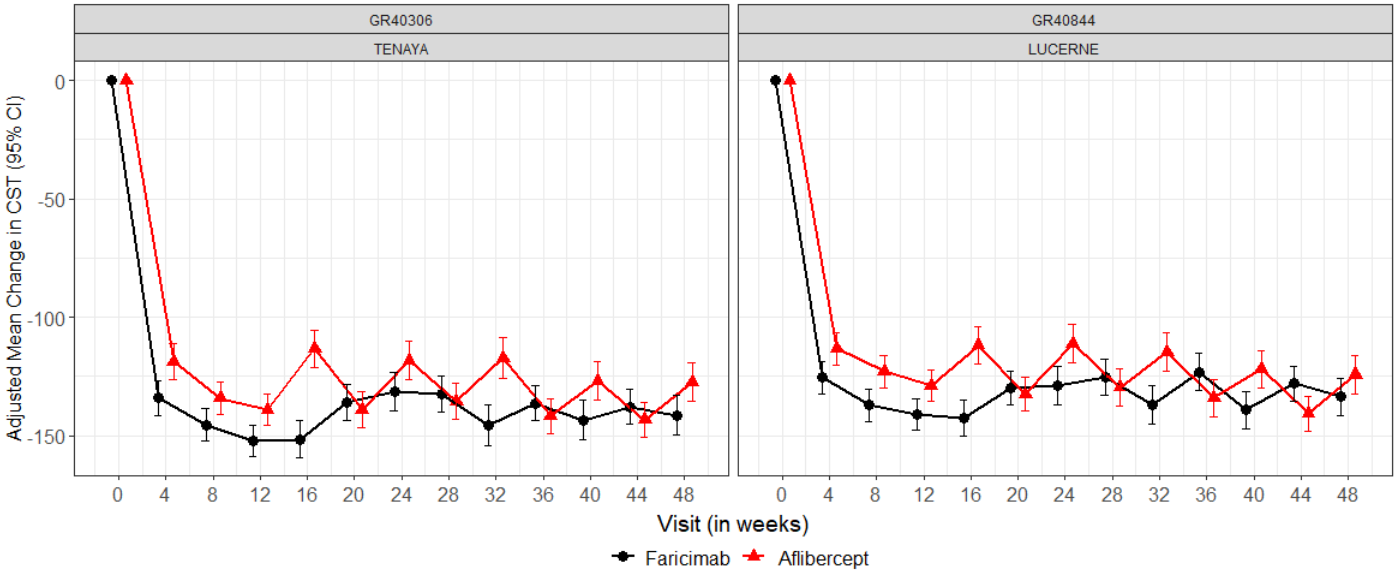
Table 15: Change from Baseline in CST in the Study Eye at Week 40/44/48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)

		TENAYA (GR40306)		LUCERNE (GR40844)	
AVISIT		Faricimab	Aflibercept	Faricimab	Aflibercept
Week 40	LS Mean (SE)	-144.4 (4.2)	-126.7 (4.2)	-139.2 (4.0)	-121.9 (4.1)
	Diff (95% CI)	-16.7 (-26.7, -6.6)	--	-17.3 (-27.2, -7.5)	
Week 44	LS Mean (SE)	-137.8 (3.8)	-143.3 (3.8)	-127.9 (3.7)	-140.6 (3.8)
	Diff (95% CI)	5.6 (-3.0, 14.2)	--	12.6 (3.8, 21.6)	
Week 48	LS Mean (SE)	-141.3 (4.2)	-127.4 (4.2)	-133.4 (4.0)	-124.2 (4.1)
	Diff (95% CI)	-13.9 (-23.8, -4.0)	--	-9.3 (-19.1, 0.6)	
Week 40/44/48	LS Mean (SE)	-136.8 (3.0)	-128.5 (3.0)	-136.1 (3.0)	-131.5 (3.1)
	Diff (95% CI)	-8.3 (-16.5, -0.1)	--	-4.6 (-13.1, 3.8)	--

Source: Reviewer's analysis based on ADOE.xpt dataset located at \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40306\analysis\adam\datasets\ for TENAYA and \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40349\analysis\adam\datasets\ for LUCERNE.

Figure 12 below displays the adjusted mean change in CST from baseline through Week 48 including the 95% confidence interval estimates (vertical bars at each visit) in the two studies. As shown, faricimab treated subjects had comparable reductions in CST from baseline through Week 48 compared to aflibercept treated subjects.

Figure 12: Adjusted Mean change in CST from Baseline through Week 48 (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)



Source: Based on Reviewer's Analysis.

The summary of the adjusted mean change in CST from baseline at Week 40/44/48 and plot of the change in CST from baseline through Week 48 are presented by farcicmab dosing frequencies in Table 16 and Figure 13, respectively.

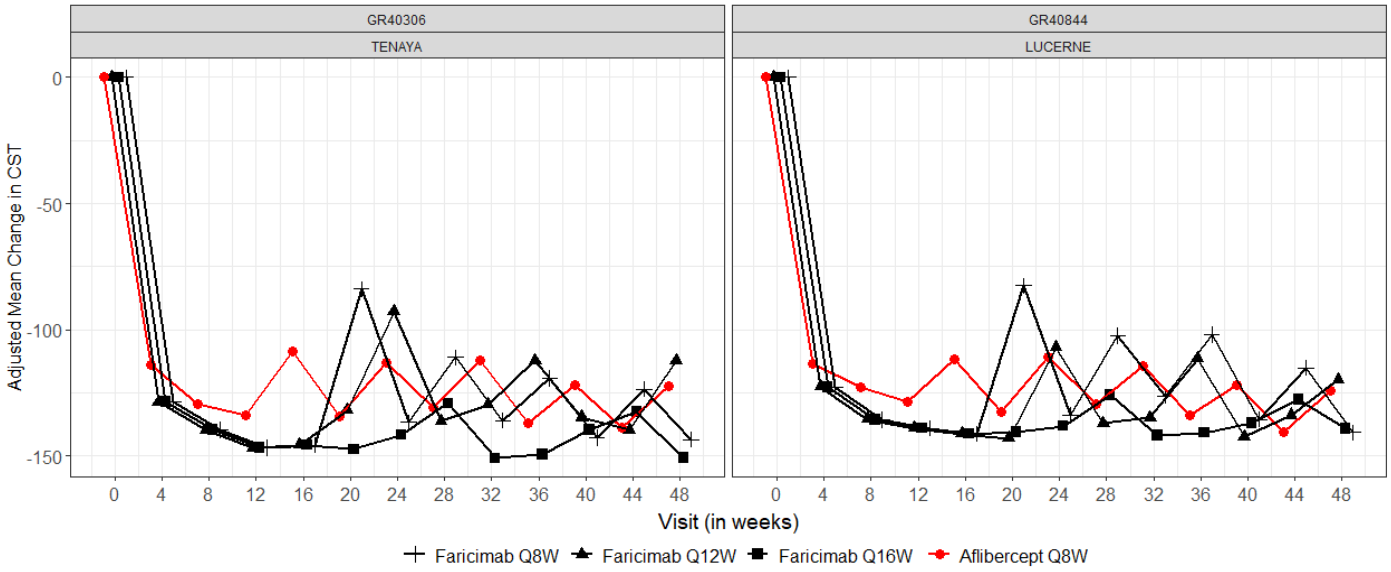
As shown, the three faricimab dosing frequencies showed numerically comparable reduction in CST compared to aflibercept.

Table 16: Mean Change in CST from Baseline at Week 40/44/48 by Faricimab Dosing Frequency (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)

	TENAYA		LUCERNE	
	LS Means (95% CI)	Difference (95% CI) vs Aflibercept	LS Means (95% CI)	Difference (95% CI) vs Aflibercept
Faricimab				
Q8W	-137.2 (6.70)	-9.0 (-23.5, 5.5)	-133.4 (6.58)	-1.6 (-15.9, 12.7)
Q12W	-129.4 (5.29)	-1.3 (-13.3, 10.7)	-134.9 (5.25)	-3.1 (-15.1, 8.9)
Q16W	-141.6 (4.48)	-13.4 (-24.1, -2.8)	-137.6 (4.63)	-5.8 (-16.8, 5.1)
Aflibercept	-128.1 (3.03)	--	-131.8 (3.09)	--

Source: Based on Reviewer's Analysis.

Figure 13: Adjusted Mean change in CST from Baseline Through Week 48 By Faricimab Dosing Frequency (Treatment Policy Estimand) (ITT Population) (TENAYA/LUCERNE)



Source: Based on Reviewer's Analysis.

3.2.1.5. Efficacy Conclusion

Based on the collective efficacy evidence from the two adequate and well controlled trials of TENAYA/LUCERNE studies, the reviewer concludes that subjects treated with faricimab at intervals of up to every 16-week had a noninferior mean change in BCVA from baseline at Week 40/44/48 compared to subjects treated with aflibercept. Additionally, in both studies, a comparable number of subjects in both treatment groups gained and/or lost letters in BCVA from baseline at Week 40/44/48.

In both studies, most subjects randomized to the faricimab arm that completed the Week 20/24 and the Week 48 visits were on a Q16W dosing interval (about 45%) followed by on a Q12W dosing interval (about 33%) and on a Q8W interval (about 22%). Analysis that compared the three faricimab dosing intervals (Q8W, Q12W, and Q16W) to aflibercept in the primary efficacy endpoint showed that each dose of faricimab in both studies appeared comparable to aflibercept (Table 13).

3.2.2. YOSEMITE/RHINE Studies for DME-DR Indications

3.2.2.1. Study Design and Endpoints

Study Design

Efficacy and safety support for faricimab for the treatment of DME-DR was based on data from two identically designed 104-week, multicenter, randomized, double-masked, active-controlled noninferiority (NI) ongoing global Phase 3 studies: YOSEMITE and RHINE studies.

The primary objective of the two studies was to assess whether faricimab IVT injection administered in a protocol-defined personalized treatment interval (PTI) and in a fixed dosing interval provided comparable efficacy benefit to the active-control Eylea® (aflibercept 2 mg). Of note, aflibercept administered every 8-week interval after five initial monthly injections was approved in the United States on July 2014 for the treatment of DME and on May 2019 for the treatment of DR.

In YOSEMITE and RHINE studies, respectively, a total of 940 and 951 both treatment-naïve and non-naïve diabetic subjects at least 18 years of age with macular thickening secondary to DME involving the center of the fovea who had baseline BCVA of 73 to 25 letters and hemoglobin A1c level of < 10% within 2 months prior to Day 1 visit were enrolled. In these studies, eligible subjects that met all the enrollment criteria were randomized in a 1:1:1 ratio and were to receive faricimab 6 mg at a fixed dosing interval (315 in YOSEMITE and 317 in RHINE), faricimab 6 mg at PTI dosing interval (313 in YOSEMITE and 319 in RHINE), or aflibercept 2 mg at a fixed dosing interval (312 in YOSEMITE and 315 in RHINE). Subjects in YOSEMITE study were enrolled in 179 sites in 16 countries and subjects in RHINE study were enrolled in 174 sites in 24 countries.

In both studies, randomization was stratified by baseline BCVA category (< 64 vs. ≥ 64 letters), prior anti-VEGF treatment use (yes vs. no), and region (US and Canada vs. Asia vs. RoW). In YOSEMITE and RHINE study, respectively, a total of 39 and 35 subjects were mis-stratified by incorrect BCVA category and 24 and 33 subjects were mis-stratified by incorrect prior anti-VEGF therapy use.

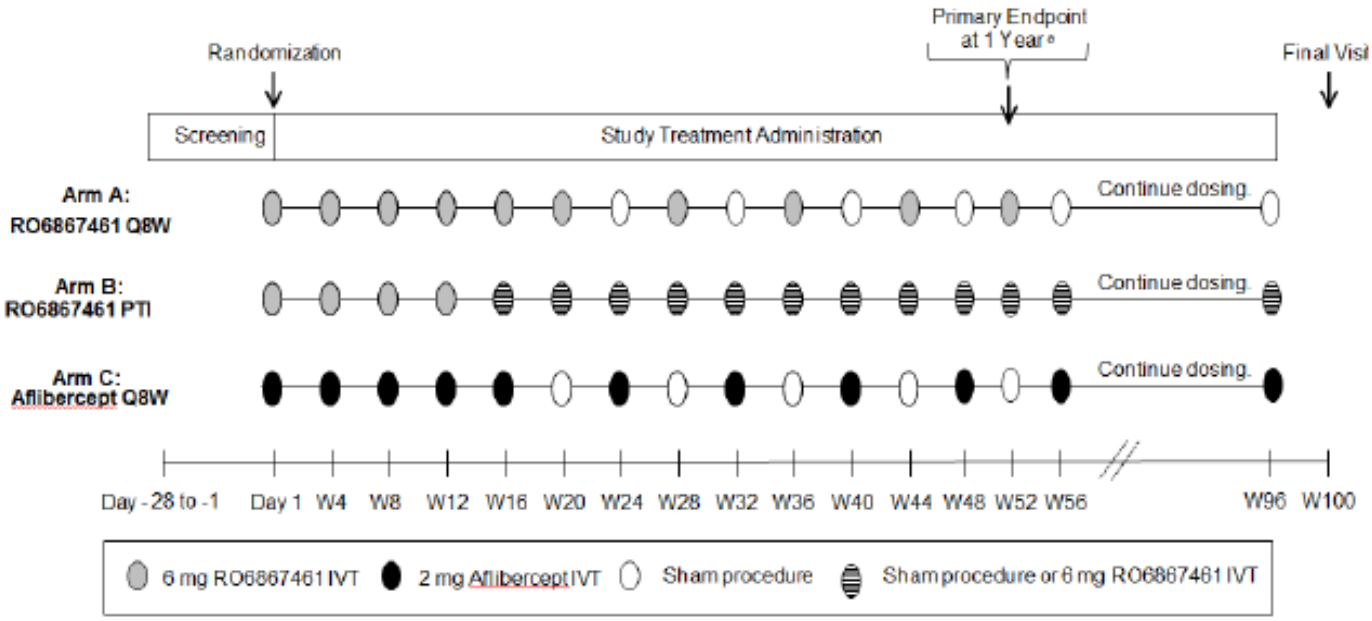
The total study duration of the YOSEMITE/RHINE studies is 104-week comprising 4-week screening period and 100-week treatment period. This BLA submission, however, was based on the first 60-week efficacy and safety data obtained between start of screening of each subject to the completion of efficacy assessment at Week 56 - the remaining portions of these studies are still ongoing. YOSEMITE was initiated on September 05, 2018 and the data cut-off date for this submission was on October 20, 2020 and RHINE was initiated on October 09, 2018 and the data cutoff date for this submission was October 19, 2020.

During the 56-week treatment period, in both studies, subjects randomized in aflibercept group were dosed every month for the first five injections (at Day 1, and Weeks 4, 8, 12, and 16) and every 8-week interval afterwards (here after referred to as ‘Aflibercept Q8W’), subjects randomized in the faricimab 6 mg fixed dosing interval group were dosed monthly for the first six injections (at Day 1, and Weeks 4, 8, 12, 16, and 20) and every 8-week interval afterwards (here after referred to as ‘Faricimab Q8W’), and subjects randomized to faricimab PTI dosing

interval group were dosed monthly for the first four injections (at Day 1, and Weeks 4, 8, and 12) and in a protocol-defined PTI dosing interval afterwards (here after referred to as 'Faricimab PTI'). Subjects randomized to the faricimab PTI arm were to receive injection at every 4-week (Q4W), 8-week (Q8W), 12-week (Q12W), or 16-week (Q16W) dosing interval based on objective assessment of pre-specified visual and anatomic disease activity criteria, after the first four monthly doses (See Appendix 2 for protocol-defined PTI criteria).

Figure 14 displays the study schema for the YOSEMITE/RHINE studies.

Figure 14: Study Schema for YOSEMITE/RHINE Studies



Source: Figure 1 of YOSEMITE and RHINE Clinical Study Reports.

Efficacy Evaluation

Key efficacy evaluation in both studies was based on (i) functional outcome measure: BCVA letter score as measured using the ETDRS chart at a starting distance of 4 meters, (ii) anatomical outcome measure: central subfield thickness (CST) as measured using spectral-domain optical coherence tomography (SD-OCT) by masked readers, and (iii) based on diabetic retinopathy severity as measured by the diabetic retinopathy severity score (DRSS).

The DRSS, a validated method measuring changes in DR, characterizes retinopathy based on assessment of abnormalities in seven defined fields of fundus photographs (FP). It is graded according to a 10-step severity score dividing DR severity into levels ranging from DR absent to high-risk proliferative diabetic retinopathy (PDR) (See Table 20 for detail).

In both studies, BCVA and CST were measured every 4-week through Week 56 in the study eye and DRSS was measured at Day 1, Week 16, and Week 52 in the study eye. The study eye was defined as the eye that met all the eligibility criteria. If both eyes met the eligibility criteria, the eye with the worse BCVA at the screening visit was selected as the study eye.

Study Endpoints

The primary and key secondary efficacy endpoints in both studies were ***the change in BCVA letter score from baseline averaged over Weeks 48, 52, and 56 (here after referred to as Week 48/52/56)*** and ***the proportion of subjects who achieved a ≥ 2-step improvement in DRSS from baseline at Week 52***, respectively.

The following were some of the secondary efficacy endpoints assessed in both studies:

- Proportion of subjects who gained ≥15, ≥10, ≥5, and ≥0 letters from baseline at Week 48/52/56.
- Proportion of subjects who avoided losing ≥15, ≥10, and ≥5 letters from baseline at Week 48/52/56.
- Proportion of subjects who achieved a ≥ 3-step and ≥ 4-step improvement in DRSS from baseline at Week 52.
- Proportion of subjects who develop new PDR at Week 52 and over time
- Proportion of subjects who progressed to high-risk PDR at Week 52 and over time
- Proportion of subjects in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52
- Change in CST from baseline at Week 48/52/56 and over time

As additional analyses, the primary and key secondary endpoints were assessed over time through Week 56.

3.2.2.2. Statistical Methodologies

In both studies, the primary efficacy analysis was performed at a family-wise significance level of 0.0496. Each of the studies underwent four unmasked independent Data Monitoring Committee (iDMC) reviews prior to the primary analysis where a nominal Type I error penalty of 0.0001 was allotted for each iDMC look.

Analysis Populations

Four analysis populations were defined for the analyses of the efficacy and safety variables in both studies. (i) intent-to-treat (ITT) population – included all randomized subjects, (ii) treatment-naïve (TN) population – included all randomized subjects in the study who had not received any anti-VEGF agents in the study eye prior to randomization, (iii) per-protocol (PP) population – included all randomized subjects who received at least one dose of study treatment and did not have a major protocol violation that impacted the efficacy evaluation or the treatment interval determination, and (iv) safety-evaluable population – included all randomized subjects who received at least one dose of study drug in the study eye.

The primary efficacy assessment was based on the ITT population. Analyses based on the PP population was used as supporting.

Primary Estimand

The Applicant's primary estimand of interest was the difference in the mean change in BCVA from baseline at Week 48/52/56 between each dose of faricimab (Q8W and PTI) versus

aflibercept Q8W, for all randomized subjects under the following data handling strategies for subjects with occurrence of intercurrent events (IEs):

- Data for subjects that discontinued the study drug due to an adverse event or lack of efficacy not due to COVID-19 or that used any prohibited systemic treatment or prohibited therapy in the Study eye not due to COVID-19 were used regardless of the occurrence of IEs under the treatment policy estimand strategy.

- Data for subjects that discontinued the study drug due to COVID-19, used any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19, or missed dose(s) with potentially major impact on efficacy due to COVID-19, or died due to COVID-19 were censored and assumed that these subjects adhered to the treatment under a hypothetical estimand strategy.

Table 17 displays the summary of subjects with occurrence of IEs through Week 56 in both studies. As shown, a total of 84 (9%) subjects in YOSEMITE study and 91 (10%) subjects in RHINE study had at least one IEs through Week 56. In both studies, most of the IEs were due to missed dose(s) due to COVID-19 with potentially major impact on efficacy (63 of 84 subjects in YOSEMITE and 76 of 91 subjects in RHINE). In both studies, the occurrence of IEs not related to COVID-19 were very few and comparable between the treatment groups. However, more subjects in the faricimab Q8W group in both studies missed doses due to COVID-19 compared to in the two other treatment groups.

Table 17: Summary of Intercurrent Events Through Week 56 in YOSEMITE/RHINE Studies

	YOSEMITE			RHINE		
Intercurrent Events (IEs)	Faricimab Q8W (N = 315)	Faricimab PTI (N = 313)	Aflibercept (N = 312)	Faricimab Q8W (N = 317)	Faricimab PTI (N = 319)	Aflibercept (N = 315)
Patients with at least one type of Intercurrent Event	39 (12.4%)	25 (8.0%)	20 (6.4%)	37 (11.7%)	25 (7.8%)	29 (9.2%)
Patients who discontinued study due to treatment due to adverse events (AEs) or lack of efficacy not due to COVID-19	7 (2.2%)	7 (2.2%)	4 (1.3%)	4 (1.3%)	4 (1.3%)	5 (1.6%)
Patients who received any prohibited systemic treatment or prohibited therapy not due to COVID	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	0
Patients who discontinued study treatment due to COVID-19	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	3 (1.0%)
Patients who received any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)
Patients with missed dose(s) with potentially major impact on efficacy due to COVID-19	31 (9.8%)	17 (5.4%)	15 (4.8%)	33 (10.4%)	21 (6.6%)	22 (7.0%)
COVID-19 death	0	1 (0.3%)	0	0	0	0

Source: Table 9 of YOSEMITE and RHINE Clinical Study Reports.

Sample Size Determination

In each study, the sponsor planned to enroll a total of 900 subjects (300 per arm). A sample size of 300 subjects per arm provided at least 90% power to show noninferiority of each dose faricimab (Q8W and PTI) to aflibercept Q8W in the mean change in BCVA at Week 48/52/56 using a noninferiority margin of -4.0 letters.

The sample size calculation was based on two-sample t-test assuming a true treatment difference of zero and a common standard deviation of 11 letters for the mean change in BCVA from baseline at Week 48/52/56, at a one-sided significance level of 1.25%, and a 10% dropout rate.

Primary Efficacy Analysis for Primary Estimand

In both studies, the primary efficacy analysis for the primary estimand of interest was an evaluation of noninferiority of each dose of faricimab to aflibercept in the mean change in BCVA from baseline at Week 48/52/56 using a mixed model repeated measure analysis (MMRM). The model included the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous covariate of baseline BCVA, and randomization stratification factors as fixed effects. The model assumed an unstructured covariance structure to account for within-subject correlation. The noninferiority margin was set at -4.0 letters.

The primary efficacy analysis was based on the ITT population including all randomized subjects. In the Applicant's primary efficacy analysis, subjects with intermittent missing data due to missed visit (due to COVID-19 or other reasons) and/or subjects whose data post-occurrence of IEs due to COVID-19 were censored were implicitly imputed using the MMRM model assuming a missing at random (MAR) missing data mechanism.

Based on the MMRM model, a given dose of faricimab was considered noninferior to aflibercept if the lower limit of the two-sided 97.52% confidence interval (CI) estimate for the treatment difference in the adjusted means of the change in BCVA from baseline at Week 48/52/56 (*faricimab minus aflibercept*) was greater than -4.0 letters.

If noninferiority of a given dose of faricimab to aflibercept in the primary efficacy variable in the ITT population was established, superiority in the TN and ITT population was assessed in that order using the same analysis strategy. Superiority was declared if the lower limit of the two-sided 97.52% confidence interval (CI) estimates for the treatment differences in the primary efficacy variable was greater than zero. See below for the testing strategy (*RE: Type I Error Control*).

Sensitivity Analyses to the Primary Estimand

The Applicant performed the following sensitivity analyses for the primary estimand to assess the robustness of the primary efficacy analysis results with respect to the handling of missing and/or intercurrent data:

i) Analysis based on the PP population. In this analysis, subjects with a major protocol violation (that impacted the efficacy evaluation or the treatment interval determination) were excluded.

ii) Analysis based on the ITT population including all data regardless of occurrence of IE (a treatment policy estimand strategy).

iii) Analysis based on the ITT population where all data after occurrence of IEs were censored and implicitly imputed by the MMRM model under the hypothetical estimand strategy.

In each of the cases, missing data due to intermittent missing visits and/or data censored due to occurrence of IEs were implicitly imputed by the MMRM model assuming MAR missing data mechanism.

As additional sensitivity analyses, the reviewer also performed the primary and the sensitivity analyses for the primary estimand by imputing intermittent missing data and data after occurrence of IEs using multiple imputation (MI) strategy and the last observation carried forward (LOCF) imputation approach.

Reviewer's Remark: *In the Applicant's primary estimand strategy, data for subjects with IEs not related to COVID-19 were used in the analysis but data for subjects with IEs due to COVID-19 were censored and imputed using the MMRM model assuming MAR missing data mechanism. Considering that the number of subjects with IEs due to none-COVID-19 were minimal in both studies and due to COVID-19 appeared not to be treatment-related (Table 17), the reviewer considered the treatment policy estimand strategy outlined in item (ii) above as the primary estimand. In this strategy, all data regardless of occurrence of IEs were used in the analysis. The Applicant's primary estimand of interest where all data after occurrence of IEs due to COVID-19 were censored was used as supporting.*

Secondary Efficacy Analysis: Key Secondary Endpoint

The Applicant's secondary estimand of interest for the key secondary endpoint was the difference in the proportion of subjects with a ≥2-step improvement in DRSS from baseline at Week 52 between each dose of faricimab (Q8W and PTI) versus aflibercept Q8W, for all randomized subjects under the same data handling strategies for subjects with occurrence of IEs as in the primary efficacy endpoint (*RE: Primary Estimand*).

The secondary efficacy analysis for the secondary estimand of interest was an evaluation of noninferiority of each dose of faricimab to aflibercept in the proportion of subjects with a ≥2-step improvement in DRSS from baseline at Week 52 based on a stratified Cochran-Mantel-Haenszel (CMH) test using observed data on the ITT population. The noninferiority margin was set at -10%.

Based on the CMH test, a weighted point and two-sided 97.52% CI estimates for the difference in proportions (*each dose of faricimab minus aflibercept*) adjusted for the study specific strata and using the CMH weights and normal approximation of the weighted estimates was provided. Based on the two-sided 97.52% CI estimates, a given dose of faricimab was considered noninferior to aflibercept if the lower limit of the CI was greater than -10%. If noninferiority was established for a given dose of faricimab in the ITT population, superiority in the TN and ITT population was assessed in that order using the same analysis strategy.

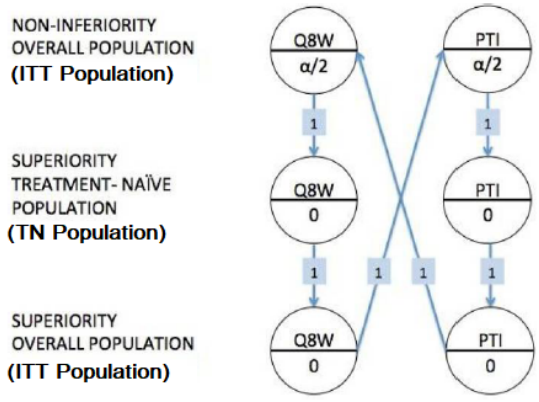
All secondary efficacy variables with continuous outcome were analyzed similarly to the primary efficacy variable. The same estimand used for the primary efficacy variable was adopted. And all other binary secondary efficacy outcomes were analyzed similarly to the key secondary efficacy variable.

(b) (4)

Type I Error Control (Plan for Multiplicity Adjustment)

The study-wise Type I Error rate was controlled at a 2-sided significance level of 5%. A nominal Type I Error penalty of 0.0004 was assigned for four unmasked iDMC reviews conducted prior to the primary analysis (0.0001 for each iDMC look). Thus, the primary efficacy analysis to determine noninferiority of each dose of faricimab to aflibercept in the primary efficacy endpoint in the ITT population followed by superiority in the primary endpoint in the TN and ITT population was based on a significance level of 0.0496.

For the noninferiority and superiority tests in the primary endpoint, pairwise comparisons of each dose of faricimab to aflibercept was to be conducted based on the following graph-based testing procedure:



Source: Figure 3 of the Applicant's Clinical Study Reports for YOSEMITE and RHINE Studies.

PTI: Personalized Treatment Interval;
Q8W: Every 8-week.

Note: α = 0.0496.

(b) (4)

(b) (4)

Subgroup Analysis

Subgroup analyses of the primary and key secondary efficacy endpoints were performed for the following subgroups: age (<65 vs. ≥65 years), gender (female vs. male), race (white vs. others), baseline BCVA category (≤ 63 vs. ≥64 letters), use of prior anti-VEGF therapy (yes vs. no), region (US and Canada vs. Asia vs. RoW), baseline DRSS (<47 vs. 47-53 vs. >53), and baseline HbA1c (≤ 8% vs. > 8%).

3.2.2.3. Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 18 shows the summary of subject disposition and the primary reasons for study discontinuation during the 56-week treatment period in the YOSMITE/RHINE studies. Overall, 940 and 951 subjects were randomized in YOSMITE and RHINE studies, respectively. Most subjects in both studies completed the 56-week treatment period.

In YOSMITE study, a total of 68 (7%) subjects discontinued from the study (*8% in faricimab Q8W, 8% in faricimab PTI, and 6% in aflibercept*) and 87 (9%) subjects discontinued from treatment (*10% in faricimab Q8W, 10% in faricimab PTI, and 8% in aflibercept*) prior to Week 56. In this study, the discontinuation rates from the study and from treatment were comparable across the treatment groups. The most common reason for discontinuation from the study in YOSMITE was death (2.0%) followed by withdrawal of consent by a subject (1.8%) and lost to follow-up (1.4%). A total of 20 subjects (*7 in faricimab Q8W, 9 in faricimab PTI, and 4 in aflibercept*) died during the 56-week treatment period. Two subjects discontinued from study and from treatment due to COVID-19 (1 subject in faricimab PTI categorized as ‘death’ and 1 subject in faricimab Q8W categorized as ‘Withdrawal by subject’).

In the RHINE study, a total of 42 (4%) subjects discontinued from the study (*6% in faricimab Q8W, 2% in faricimab PTI, and 5% in aflibercept*) and 54 (6%) subjects discontinued from treatment (*8% in faricimab Q8W, 3% in faricimab PTI, and 6% in aflibercept*) prior to Week 56. In this study, the discontinuation rates from the study and from treatment were comparable between the faricimab Q8W and aflibercept arms but the rates in the faricimab PTI arm was slightly smaller than in the two arms. The most common reason for discontinuation from the study was withdrawal of consent by a subject (1.3%) followed by lost to follow-up (1.1%) and death (1.1%). A total of 10 subjects (*5 each in faricimab Q8W and in aflibercept*) died during the 56-week treatment period. Three subjects discontinued from treatment due to COVID-19 (1 subject each in faricimab Q8W and aflibercept categorized as ‘Withdrawal by subject’ and 1 subject in aflibercept categorized as ‘Other’).

Table 18: Summary of Subject Disposition and Reasons for Study Discontinuation (YOSEMITE/RHINE)
(All Randomized Subjects)

	YOSEMITE				RHINE			
	Faricimab Q8W	Faricimab PTI	Aflibercept	Total	Faricimab Q8W	Faricimab PTI	Aflibercept	Total
Number of Patients Randomized	315 (100%)	313 (100%)	312 (100%)	940 (100%)	317 (100%)	319 (100%)	315 (100%)	951 (100%)
Number of Patients Treated	313 (99.4%)	313 (100%)	311 (99.7%)	937 (99.7%)	317 (100%)	319 (100%)	314 (99.7%)	950 (99.9%)
Discontinued from Study	24 (7.6%)	24 (7.7%)	20 (6.4%)	68 (7.2%)	19 (6.0%)	7 (2.2%)	16 (5.1%)	42 (4.4%)
Primary Reason for Discontinuation								
Adverse Event	5 (1.6%)	6 (1.9%)	2 (0.6%)	13 (1.4%)	2 (0.6%)	1 (0.3%)	3 (1.0%)	6 (0.6%)
Death	7 (2.2%)	9 (2.9%)	4 (1.3%)	20 (2.1%)	5 (1.6%)	0	5 (1.6%)	10 (1.1%)
COVID-19	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0
Lack of Efficacy	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0
Lost to Follow-Up	5 (1.6%)	6 (1.9%)	2 (0.6%)	13 (1.4%)	5 (1.6%)	2 (0.6%)	3 (1.0%)	10 (1.1%)
Protocol Deviation	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	0	0	0	0
Withdrawal by Subject	5 (1.6%)	3 (1.0%)	9 (2.9%)	17 (1.8%)	5 (1.6%)	4 (1.3%)	3 (1.0%)	12 (1.3%)
COVID-19	1 (0.3%)	0	0	1 (0.1%)	0	0	0	0
Physician Decision	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
Other	0	0	0	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
Discontinued from Treatment	31 (9.9%)	30 (9.6%)	26 (8.4%)	87 (9.3%)	24 (7.6%)	11 (3.4%)	19 (6.1%)	54 (5.7%)
Primary Reason for Discontinuation								
Adverse Event	6 (1.9%)	7 (2.2%)	3 (1.0%)	16 (1.7%)	4 (1.3%)	3 (0.9%)	4 (1.3%)	11 (1.2%)
Pregnancy	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0
Death	7 (2.2%)	9 (2.9%)	4 (1.3%)	20 (2.1%)	5 (1.6%)	0	5 (1.6%)	10 (1.1%)
COVID-19	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0
Lack of Efficacy	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	0	0	0	0
Lost to Follow-Up	7 (2.2%)	7 (2.2%)	4 (1.3%)	18 (1.9%)	6 (1.9%)	4 (1.3%)	3 (1.0%)	13 (1.4%)
Protocol Deviation	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0
Withdrawal by Subject	6 (1.9%)	5 (1.6%)	11 (3.5%)	22 (2.3%)	7 (2.2%)	4 (1.3%)	5 (1.6%)	16 (1.7%)
COVID-19	1 (0.3%)	0	0	1 (0.1%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
Physician Decision	3 (1.0%)	1 (0.3%)	1 (0.3%)	5 (0.5%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
Other	1 (0.3%)	0	1 (0.3%)	2 (0.2%)	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
COVID-19	0	0	0	0	0	0	1 (0.3%)	1 (0.1%)

Source: Table 2 of YOSEMITE and RHINE Clinical Study Reports.

Analysis Population

The number of subjects in the two studies are displayed in Table 19 by analysis populations. A total of 940 and 951 subjects were randomized in the YOSMITE and RHINE studies, respectively. Of these randomized subjects, three subjects in YOSMITE (2 in faricimab Q8W and 1 in aflibercept) and one subject in the aflibercept group in RHINE did not receive study medication and were excluded from the safety evaluable population.

A total of 140 and 149 randomized subjects in the YOSMITE and RHINE studies, respectively, were excluded from the PP population due to major protocol deviations. Of these, 63 (7%) subjects in YOSMITE (31 in faricimab Q8W, 17 in faricimab PTI, and 15 in aflibercept) and 76 (8%) subjects in RHINE (33 in faricimab Q8W, 21 in faricimab PTI, and 22 in aflibercept) had missed dose(s) due to COVID-19 with potentially major impact on efficacy.

Table 19: Summary of Analysis Populations (YOSEMITE/RHINE)

	YOSEMITE			RHINE		
	Faricimab Q8W	Faricimab PTI	Aflibercept	Faricimab Q8W	Faricimab PTI	Aflibercept
Intent-to-Treat Population (As randomized)	315	313	312	317	319	315
Safety-Evaluable Population (As treated)	313	313	311	317	319	314
Per-Protocol Population (As Treated)	251	275	274	258	271	273
Major Protocol Deviation	64	38	38	59	48	42
Missed Doses due to COVID-19	31	17	15	33	21	22

Source: Table 3 of YOSEMITE and RHINE Clinical Study Reports.

Demographic and Baseline Characteristics

The summary of the baseline demographic and disease characteristics for subjects in the ITT population in the YOSEMITE/RHINE studies are presented in Table 20. Most subjects in both studies were Caucasian (78% in YOSMITE and 79% in RHINE) and male (60% in YOSMITE and 61% in RHINE). The average age of subjects in both studies was about 62 years (range: 24 to 85 years in YOSMITE and 26 to 91 in RHINE) with a slight majority of subjects (about 57%) in both studies were < 65 years of age. About 54% and 35% of subjects enrolled in YOSMITE and RHINE studies, respectively, were from the United States and Canada.

Subjects in both studies had an average baseline BCVA in the study eye of 62 letters with a slight majority (about 54%) of subjects in both studies had a baseline BCVA of ≥64 letters. Forty seven percent (47%) of subjects in YOSMITE and 34% of subjects in RHINE had DME diagnosis in the last 3 months. Most subjects in both studies (about 87%) had mild-to-severe nonproliferative diabetic retinopathy (NPDR) and about 7% had mild-to-high risk proliferative diabetic retinopathy (PDR) at baseline. In YOSEMITE study, 23% of enrolled subjects were previously treated with anti-VEGF therapy and 77% were treatment naïve. Similarly, in the RHINE study, 20% of enrolled subjects were previously treated with anti-VEGF therapy and 80% were treatment naïve. In both studies, the baseline demographic and disease characteristics were well balanced across the three treatment groups.

Table 20: Summary of Demographic and Baseline Characteristics (ITT Population)

	YOSMITE				RHINE			
	Faricimab Q8W (N = 315)	Faricimab PTI (N = 313)	Aflibercept (N = 312)	Total (N = 940)	Faricimab Q8W (N = 317)	Faricimab PTI (N = 319)	Aflibercept (N = 315)	Total (N = 951)
Age (years)								
Mean (SD)	61.5 (9.5)	62.7 (10.0)	62.2 (9.6)	62.2 (9.7)	62.5 (10.1)	61.6 (10.1)	62.2 (10.1)	62.1 (10.1)
Median	62	64	63	63	63	63	63	63
Range	26 -85	24 -85	28 - 84	24 – 85	27 – 91	26 – 87	28 – 86	26 – 91
Age Group								
< 65 years	188 (59.7%)	169 (54.0%)	180 (57.7%)	537 (57.1%)	176 (55.5%)	183 (57.4%)	183 (58.1%)	542 (57.0%)
>= 65 years	127 (40.3%)	144 (46.0%)	132 (42.3%)	403 (42.9%)	141 (44.5%)	136 (42.6%)	132 (41.9%)	409 (43.0%)
>=65-<75 years	105 (33.3%)	115 (36.7%)	105 (33.7%)	325 (34.6%)	111 (35.0%)	110 (34.5%)	104 (33.0%)	325 (34.2%)
>=75-<85 years	21 (6.7%)	28 (8.9%)	27 (8.7%)	76 (8.1%)	29 (9.1%)	25 (7.8%)	27 (8.6%)	81 (8.5%)
>=85 years	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
Sex								
Female	128 (40.6%)	116 (37.1%)	134 (42.9%)	378 (40.2%)	123 (38.8%)	120 (37.6%)	129 (41.0%)	372 (39.1%)
Male	187 (59.4%)	197 (62.9%)	178 (57.1%)	562 (59.8%)	194 (61.2%)	199 (62.4%)	186 (59.0%)	579 (60.9%)
Race								
American Indian or Alaska Native	6 (1.9%)	5 (1.6%)	7 (2.2%)	18 (1.9%)	0	0	1 (0.3%)	1 (0.1%)
Asian	31 (9.8%)	26 (8.3%)	27 (8.7%)	84 (8.9%)	34 (10.7%)	36 (11.3%)	32 (10.2%)	102 (10.7%)
Black or African American	22 (7.0%)	25 (8.0%)	12 (3.8%)	59 (6.3%)	18 (5.7%)	23 (7.2%)	24 (7.6%)	65 (6.8%)
Native Hawaiian Or Other Pacific Islander	2 (0.6%)	0	3 (1.0%)	5 (0.5%)	2 (0.6%)	0	0	2 (0.2%)
White	241 (76.5%)	240 (76.7%)	253 (81.1%)	734 (78.1%)	250 (78.9%)	249 (78.1%)	253 (80.3%)	752 (79.1%)
Multiple	0	1 (0.3%)	0	1 (0.1%)	2 (0.6%)	1 (0.3%)	0	3 (0.3%)
Unknown	13 (4.1%)	16 (5.1%)	10 (3.2%)	39 (4.1%)	11 (3.5%)	10 (3.1%)	5 (1.6%)	26 (2.7%)
Ethnicity								
Hispanic or Latino	37 (11.7%)	40 (12.8%)	37 (11.9%)	114 (12.1%)	56 (17.7%)	78 (24.5%)	67 (21.3%)	201 (21.1%)
Not Hispanic or Latino	273 (86.7%)	268 (85.6%)	272 (87.2%)	813 (86.5%)	252 (79.5%)	232 (72.7%)	240 (76.2%)	724 (76.1%)
Not Reported	2 (0.6%)	4 (1.3%)	2 (0.6%)	8 (0.9%)	6 (1.9%)	4 (1.3%)	5 (1.6%)	15 (1.6%)
Unknown	3 (1.0%)	1 (0.3%)	1 (0.3%)	5 (0.5%)	3 (0.9%)	5 (1.6%)	3 (1.0%)	11 (1.2%)
Region								
Asia	21 (6.7%)	19 (6.1%)	20 (6.4%)	60 (6.4%)	29 (9.1%)	29 (9.1%)	26 (8.3%)	84 (8.8%)
Rest of the World	127 (40.3%)	126 (40.3%)	124 (39.7%)	377 (40.1%)	178 (56.2%)	179 (56.1%)	180 (57.1%)	537 (56.5%)
US and Canada	167 (53.0%)	168 (53.7%)	168 (53.8%)	503 (53.5%)	110 (34.7%)	111 (34.8%)	109 (34.6%)	330 (34.7%)

	YOSMITE				RHINE			
	Faricimab Q8W (N = 315)	Faricimab PTI (N = 313)	Aflibercept (N = 312)	Total (N = 940)	Faricimab Q8W (N = 317)	Faricimab PTI (N = 319)	Aflibercept (N = 315)	Total (N = 951)
Baseline BCVA (letters)								
Mean (SD)	62.0 (9.9)	61.9 (10.2)	62.2 (9.5)	62.0 (9.9)	61.9 (10.1)	62.5 (9.3)	62.1 (9.4)	62.1 (9.6)
Median	64	65	64	64	65	65	65	65
Range	28 – 81	25 – 73	27 – 73	25 – 81	27 – 73	30 – 86	33 – 79	27 - 86
Baseline BCVA Category								
< 63	143 (45.4%)	142 (45.4%)	143 (45.8%)	428 (45.5%)	143 (45.1%)	146 (45.8%)	145 (46.0%)	434 (45.6%)
>= 64	172 (54.6%)	171 (54.6%)	169 (54.2%)	512 (54.5%)	174 (54.9%)	173 (54.2%)	170 (54.0%)	517 (54.4%)
Prior Anti-VEGF								
Yes	77 (24.4%)	68 (21.7%)	70	215	63 (19.9%)	64 (20.1%)	67	194 (20.4%)
No (Treatment Naïve)	238 (75.6%)	245 (78.3%)	242 (77.6%)	725 (77.1%)	254 (80.1%)	255 (79.9%)	248 (78.7%)	757 (79.6%)
Months since DME diagnosis								
<=3 months	143 (45.4%)	153 (48.9%)	145 (46.5%)	441 (46.9%)	104 (32.8%)	104 (32.6%)	111 (35.2%)	319 (33.5%)
> 3 months	154 (48.9%)	139 (44.4%)	151 (48.4%)	444 (47.2%)	171 (53.9%)	173 (54.2%)	162 (51.4%)	506 (53.2%)
Unknown	18 (5.7%)	21 (6.7%)	16 (5.1%)	55 (5.9%)	42 (13.2%)	42 (13.2%)	42 (13.3%)	126 (13.2%)
DR Status (Code)								
1. DR Absent (10, 12)	2 (0.6%)	3 (1.0%)	4 (1.3%)	9 (1.0%)	2 (0.6%)	4 (1.3%)	1 (0.3%)	7 (0.7%)
2. DR Questionable (14,15,20)	4 (1.3%)	6 (1.9%)	10 (3.2%)	20 (2.1%)	3 (0.9%)	10 (3.1%)	6 (1.9%)	19 (2.0%)
3. Mild NPDR (35)	84 (26.7%)	92 (29.4%)	83 (26.6%)	259 (27.6%)	90 (28.4%)	92 (28.8%)	94 (29.8%)	276 (29.0%)
4. Moderate NPDR (43)	84 (26.7%)	86 (27.5%)	85 (27.2%)	255 (27.1%)	88 (27.8%)	72 (22.6%)	79 (25.1%)	239 (25.1%)
5. Moderately Sever NPDR (47)	67 (21.3%)	59 (18.8%)	54 (17.3%)	180 (19.1%)	59 (18.6%)	63 (19.7%)	54 (17.1%)	176 (18.5%)
6. Sever NPDR (53)	46 (14.6%)	40 (12.8%)	49 (15.7%)	135 (14.4%)	50 (15.8%)	36 (11.3%)	51 (16.2%)	137 (14.4%)
7. Mild PDR (61)	16 (5.1%)	11 (3.5%)	9 (2.9%)	36 (3.8%)	12 (3.8%)	26 (8.2%)	11 (3.5%)	49 (5.2%)
8. Moderate PDR (65)	6 (1.9%)	9 (2.9%)	7 (2.2%)	22 (2.3%)	6 (1.9%)	10 (3.1%)	6 (1.9%)	22 (2.3%)
9. High Risk PDR (71)	0	1 (0.3%)	2 (0.6%)	3 (0.3%)	2 (0.6%)	1 (0.3%)	3 (1.0%)	6 (0.6%)
10. High Risk PDR (75)	0	0	0	0	0	0	0	0
Cannot Grade (90)	4 (1.3%)	5 (1.6%)	7 (2.2%)	16 (1.7%)	2 (0.6%)	5 (1.6%)	5 (1.6%)	12 (1.3%)
Missing	2 (0.6%)	1 (0.3%)	2 (0.6%)	5 (0.5%)	3 (0.9%)	0	5 (1.6%)	8 (0.8%)

Source: Tables 5 and 6 of YOSEMITE and RHINE Clinical Study Reports.
DR Status (Code): 1- DR Absent; 2-DR Questionable; 3-Mild NPDR; 4-Moderate NPDR; 5-Moderately Severe NPDR; 6-Severe NPDR; 7-Mild PDR; 8-Moderate PDR; 9-High-risk PDR; 10-High-risk PDR; 90: Cannot be Graded.

3.2.2.4. Results and Conclusions

Primary Efficacy Endpoint: Change in BCVA from Baseline at Week 48/52/56 in the ITT Population – Noninferiority Evaluation

The primary efficacy objective of both studies was an evaluation of noninferiority of each dose of faricimab (Q8W and PTI) to aflibercept in the primary efficacy endpoint in the ITT population followed by superiority in the TN and ITT populations. The primary estimand of interest to address the studies efficacy objective was the difference in the mean change in BCVA from baseline at Week 48/52/56 (*each dose of faricimab minus aflibercept*) in all randomized subjects regardless of occurrence of IEs (see details in Section 3.2.2.2).

Table 21 shows the number of subjects with observed BCVA data at each study visit by the three estimand strategy: (i) numbers in black font are for the treatment policy estimand strategy (reviewer's preferred primary estimand strategy), (ii) numbers in black font excluding the numbers in green font are for the Applicant's primary estimand of interest (i.e., data after occurrence IEs due to COVID-19 censored), and (iii) numbers in black font excluding the numbers in blue font are for the hypothetical estimand strategy (i.e., all data after occurrence of IEs censored). As shown, the Applicant's primary analysis for the primary estimand of interest excluded few subjects mainly at the primary endpoints of Weeks 48, 52, and 56. As outlined in Section 3.2.2.2, the primary efficacy analysis in this review is based on the treatment policy estimand strategy including all observed data regardless of occurrence of IEs.

The number of subjects with missed selected visits due to COVID-19 are also displayed in Table 21. A total of 139 (15%) subjects in YOSEMITE (47 in faricimab Q8W, 44 in faricimab PTI, and 48 in aflibercept) and 160 (17%) subjects in RHINE (56 in faricimab Q8W, 53 in faricimab PTI, and 51 in aflibercept) had at least one selected missed visit due to COVID- 19. Per the Applicant, the selected missed visits included Weeks 44, 48, 52, and 56.

Table 21: Number of Subjects with Observed BCVA Data by Visit by Three Estimand Strategy

Study/ Treatment	Visit (in Weeks)														
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56
YOSEMITE															
Faricimab Q8W	315	310	309	305	296	294	292	283	267	267	274	268	264 (-9)	264 (-10)	260 (-19)
		(-1)	(-2)	(-2)	(-2)	(-2)	(-2)	(-4)	(-3)	(-2)	(-2)	(-2)	(-11)	(-12)	(-22)
Missed Visit Due to COVID-19												18	21	21	14
Faricimab PTI	313	308	308	303	296	292	293	287	268	268	269	269	266 (-2)	267 (-9)	263 (-13)
				(-2)	(-1)		(-1)	(-1)	(-1)	(-1)	(-1)	(-1)	(-3)	(-11)	(-14)
Missed Visit Due to COVID-19												12	17	14	20
Aflibercept	312	306	304	302	299	296	294	284	275	268	263	266	266	253 (-3)	256 (-9)
							(-1)	(-1)	(-2)	(-1)	(-1)	(-2)	(-2)	(-3)	(-11)

Study/ Treatment	Visit (in Weeks)														
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Missed Visit Due to COVID-19												15	17	31	20
RHINE															
Faricimab Q8W	316	307	306	306	301	294	293	285	278	275	276	270	255	268	268
													(-6)	(-15)	(-21)
					(-1)								(-6)	(-16)	(-22)
Missed Visit Due to COVID-19												21	33	22	24
Faricimab PTI	317	308	313	305	306	304	307	295	284	282	288	288	288	283	285
											(-1)	(-1)	(-4)	(-9)	(-16)
							(-1)	(-1)	(-1)	(-1)	(-3)	(-3)	(-6)	(-11)	(-18)
Missed Visit Due to COVID-19												17	18	26	16
Aflibercept	315	309	309	302	296	295	297	287	280	275	274	272	278	271	261
													(-3)	(-7)	(-9)
												(-1)	(-3)	(-7)	(-9)
Missed Visit Due to COVID-19												21	20	23	25

Source: Based on Reviewer's Analysis.

Based on the observed data in the treatment policy estimand strategy, Table 22 displays the summary of the mean change in BCVA from baseline at Weeks 48, 52, and 56 and the adjusted mean estimates for each treatment group at these visits including at Week 48/52/56 and the treatment differences in the adjusted means from the MMRM model.

As shown, in both studies, subjects treated with either doses of faricimab (Q8W or PTI) had a noninferior mean change in BCVA from baseline at Week 48/52/56 compared to subjects treated with aflibercept because the 97.5% lower confidence limits for the differences in the adjusted means between each dose of faricimab to aflibercept was greater than the noninferiority margin of -4.0 letters.

For example, in the YOSEMITE study, the adjusted means for the change in BCVA from baseline at Week 48/52/56 was +10.6 letters in faricimab Q8W, +11.5 letters in faricimab PTI, and +10.8 letters in aflibercept with a treatment difference of **-0.3 (97.5% CI: -2.0 to 1.5)** between faricimab Q8W and aflibercept and **+0.6 (97.5% CI: -1.1 to 2.4)** between faricimab PTI and aflibercept.

Similarly, in the RHINE study, the adjusted means for the change in BCVA from baseline at Week 48/52/56 was +11.7 letters in faricimab Q8W, +10.7 letters in faricimab PTI, and +10.2 letters in aflibercept with a treatment difference of +**1.5 (97.5% CI: -0.2 to 3.1)** between faricimab Q8W and aflibercept and +**0.5 (97.5% CI: -1.2 to 2.1)** between faricimab PTI and aflibercept.

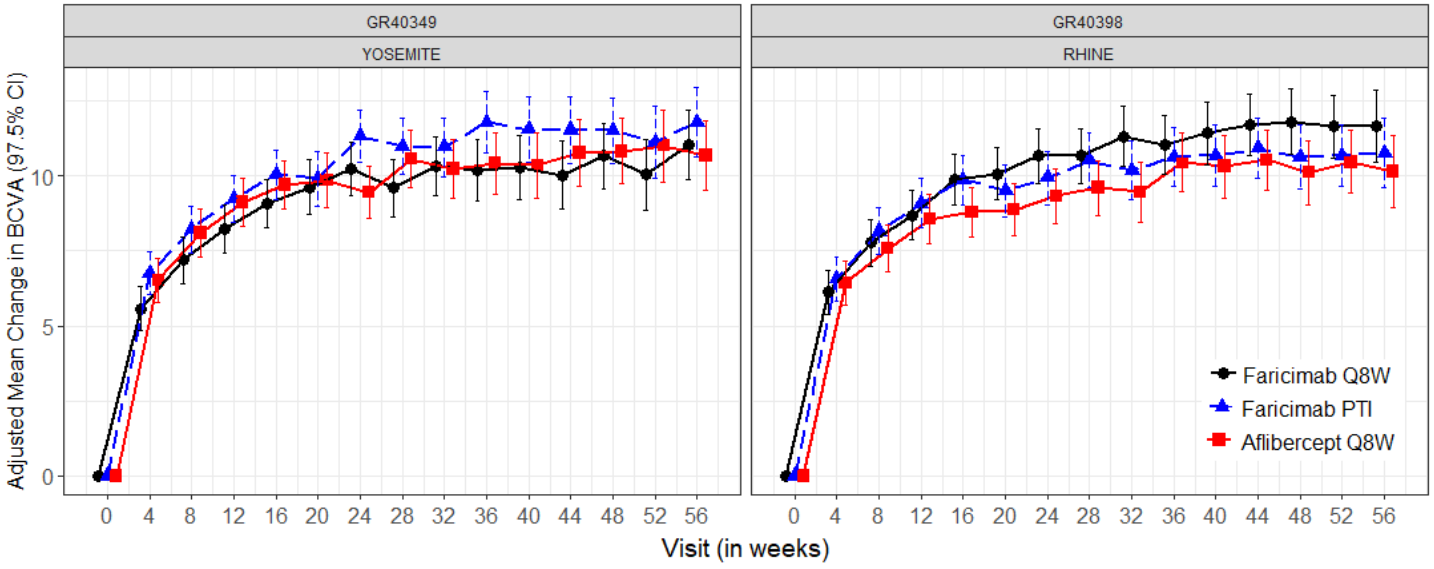
Table 22: Adjusted Mean Change in BCVA from Baseline at 48/52/56 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)

		YOSEMITE			RHINE		
AVISIT	Summary	Faricimab Q8W	Faricimab PTI	Aflibercept	Faricimab Q8W	Faricimab PTI	Aflibercept
Mean BCVA							
Baseline	Mean (SD)	62.0 (9.92)	61.9 (10.23)	62.2 (9.50)	61.9 (10.11)	62.5 (9.29)	62.1 (9.43)
	Median, Range	64, 28 - 81	65, 25 - 73	64, 27 - 73	65, 27 - 73	65, 30 - 86	65, 33 - 79
Week 48	Mean (SD)	73.2 (11.57)	74.1 (11.68)	73.4 (11.72)	73.6 (10.44)	73.1 (11.17)	72.3 (11.67)
	Median, Range	76, 13 - 97	76, 23 - 95	75, 0 - 91	75, 23 - 93	75, 0 - 94	74, 2 – 94
Week 52	Mean (SD)	72.3 (13.45)	73.9 (11.67)	73.4 (12.12)	73.5 (10.81)	72.9 (10.99)	73.0 (10.93)
	Median, Range	75, 0 - 95	76, 24 - 95	75, 11 - 94	75, 35 - 95	75, 30 - 94	75, 29 - 95
Week 56	Mean (SD)	74.1 (11.89)	74.5 (11.17)	73.1 (12.53)	73.8 (10.99)	73.2 (10.99)	73.1 (12.30)
	Median, Range	77, 5 - 96	76, 20 - 95	76, 0 - 92	75, 22 - 96	75, 26 - 95	75, 0 - 94
Mean Change in BCVA							
Week 48	Mean (SD)	10.9 (9.33)	11.8 (10.05)	11.1 (10.19)	11.8 (10.10)	10.5 (10.26)	10.6 (9.79)
	Median, Range	10.5, -40 - 50	12, -40 - 44	12, -71 - 44	11, -47 – 46	11, -66 - 44	11, -39 - 43
Week 52	Mean (SD)	10.2 (10.80)	11.4 (10.35)	11.4 (9.86)	11.7 (10.06)	10.7 (9.55)	11.2 (9.41)
	Median, Range	11, -44 - 52	11, -44 - 46	12, -29 - 44	12, -29 – 44	11, -40 - 46	12, -31 – 48
Week 56	Mean (SD)	11.8 (10.40)	12.1 (10.15)	10.6 (10.58)	11.6 (10.78)	10.7 (9.60)	11.0 (11.83)
	Median, Range	12, -48 - 54	12, -42 - 42	11, -71 - 44	12, -47 - 46	11, -44 - 47	11, -70 - 47
Adjusted Mean Change in BCVA (LS Means)							
Week 48	LS Mean (95% CI)	10.7 (9.6, 11.8)	11.5 (10.4, 12.6)	10.8 (9.7, 11.9)	11.8 (10.7, 12.9)	10.6 (9.6, 11.7)	10.1 (9.0, 11.2)
	Diff (97.5% CI)	-0.2 (-1.7, 1.4)	0.7 (-0.9, 2.2)	--	1.7 (0.2, 3.2)	0.5 (-1.0, 2.0)	--
Week 52	LS Mean (95% CI)	10.0 (8.8, 11.2)	11.1 (9.9, 12.3)	11.0 (9.8, 12.2)	11.6 (10.6, 12.7)	10.7 (9.6, 11.7)	10.5 (9.4, 11.5)
	Diff (97.5% CI)	-1.0 (-2.7, 0.7)	0.1 (-1.6, 1.8)	--	1.2 (-0.3, 2.7)	0.2 (-1.3, 1.7)	--
Week 56	LS Mean (95% CI)	11.0 (9.9, 12.2)	11.8 (10.6, 12.9)	10.7 (9.5, 11.8)	11.6 (10.5, 12.8)	10.8 (9.6, 11.9)	10.1 (8.9, 11.3)
	Diff (97.5% CI)	0.4 (-1.3, 2.0)	1.1 (-0.5, 2.7)	--	1.5 (-0.2, 3.2)	0.6 (-1.1, 2.3)	--
Average Week 48/52/56	LS Mean (95% CI)	10.6 (9.3, 11.8)	11.5 (10.2, 12.7)	10.8 (9.6, 12.1)	11.7 (10.5, 12.9)	10.7 (9.5, 11.8)	10.2 (9.1, 11.4)
	Diff (97.5% CI)	-0.3 (-2.0, 1.5)	0.6 (-1.1, 2.4)	--	1.5 (-0.2, 3.1)	0.5 (-1.2, 2.1)	--

Source: Reviewer's analysis based on ADOE.xpt dataset located at \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40349\analysis\adam\datasets\ for YOSEMITE and \\CDSESUB1\evsprod\BLA761235\m5\datasets\gr40398\analysis\adam\datasets\ for RHINE.

Figure 15 displays plots of the adjusted mean change in BCVA from baseline at each visit through Week 56 including the 97.5% confidence interval estimates (vertical bars at each visit) in the two studies. As shown, the adjusted mean changes at each visit through Week 56 appeared comparable across the treatment groups (confidence intervals overlap).

Figure 15: Plot of Adjusted Mean change in BCVA from Baseline through Week 56 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)



Source: Based on Reviewer's Analysis

Primary Efficacy Endpoint: Change in BCVA from Baseline at Week 48/52/56 in the TN and ITT Population – Superiority Evaluation

Since each dose of faricimab was noninferior to aflibercept in the primary efficacy endpoint in the ITT population, based on the pre-specified order of hypotheses testing (see Section 3.2.2.2 – Type I Error Control), superiority of each dose of faricimab to aflibercept in the primary efficacy endpoint was assessed next in the TN population followed by superiority in the ITT population, if superiority in the TN population was achieved.

Table 23 presents the adjusted mean change in BCVA from baseline at Week 48/52/56 and the treatment differences in the adjusted means in the TN population. As shown, although the results in the TN population were very similar to in the ITT population**, superiority of each dose of faricimab to aflibercept in the primary efficacy endpoint was not achieved in the TN population in both studies** (the 97.5% confidence intervals included zero). Consequently, since superiority in the TN population was not achieved, based on the pre-specified order of hypotheses testing, no alpha remained for superiority testing of each dose of faricimab to aflibercept in the ITT population. Despite the lack of alpha, superiority in the primary efficacy endpoint in the ITT population was also not achieved in both studies because the 97.5% confidence interval estimates included zero (see Table 22).

Table 23: Adjusted Mean change in BCVA from Baseline at Week 48/52/56 (Treatment Policy Estimand) (TN Population) (YOSEMITE/RHINE)

			Faricimab Q8W	Faricimab PTI	Aflibercept
YOSEMITE	Average Week 48/52/56	N	238	245	242
		LS Mean (95% CI)	10.5 (9.0, 12.0)	11.2 (9.7, 12.7)	11.2 (9.8, 12.7)
		Diff (97.5% CI)	-0.8 (-2.9, 1.4)	-0.0 (-2.1, 2.1)	--
RHINE	Average Week 48/52/56	N	253	253	248
		LS Mean (95% CI)	11.6 (10.3, 12.9)	11.1 (9.8, 12.3)	10.5 (9.2, 11.8)
		Diff (97.5% CI)	1.1 (-0.8, 2.9)	0.5 (-1.3, 2.4)	--

Source: Based on Reviewer's Analysis.

Sensitivity/Supporting Analyses to the Primary Efficacy Endpoint

To assess the robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent data, several sensitivity/supporting analyses were performed. As sensitivity analyses, missing data in the treatment policy estimand strategy were imputed using LOCF and multiple imputation approaches and analyzed using MMRM model. As supporting analyses, the primary efficacy outcome was analyzed using MMRM model on the PP population, using the Applicant's primary estimand of interest on the ITT population, and using the hypothetical estimand strategy on the ITT population.

Table 24 below displays the sensitivity/supplementary efficacy analyses results. As shown, the various sensitivity/supplementary analyses results were consistent with the primary efficacy analysis results, leading to the same conclusion for a robust interpretation of the noninferiority finding.

Table 24: Mean Change in BCVA from Baseline at Week 48/52/56 (Sensitivity Analysis) (YOSEMITE/RHINE)

	YOSEMITE			RHINE		
AVISIT	Faricimab Q8W	Faricimab PTI	Aflibercept	Faricimab 2Q8	Faricimab PTI	Aflibercept
Sensitivity Analysis: using MMRM Method						
LOCF – ITT Population [1]						
LS Mean (95% CI)	10.4 (9.2, 11.7)	11.3 (10.1, 12.5)	10.7 (9.4, 11.9)	11.6 (10.5, 12.8)	10.7 (9.6, 11.8)	10.1 (8.9, 11.2)
Diff (95% CI)	-0.2 (-2.0, 1.5)	0.7 (-1.1, 2.4)	--	1.6 (-0.0, 3.2)	0.6 (-1.0, 2.2)	--
Multiple Imputation – ITT Population [1]						
LS Mean (95% CI)	10.6 (9.4, 11.9)	11.5 (10.3, 12.8)	10.9 (9.6, 12.1)	11.7 (10.5, 12.8)	10.6 (9.5, 11.8)	10.4 (9.2, 11.5)
Diff (95% CI)	-0.3 (-2.1, 1.5)	0.7 (-1.1, 2.4)	--	1.3 (-0.3, 3.0)	0.3 (-1.4, 1.9)	--
Supplementary Analyses: using MMRM Method						
PP Population [1]						
LS Mean (95% CI)	10.6 (9.3, 12.0)	11.6 (10.3, 12.9)	11.0 (9.7, 12.3)	11.8 (10.6, 13.1)	10.7 (9.5, 12.0)	10.3 (9.1, 11.5)
Diff (95% CI)	-0.4 (-2.3, 1.5)	0.6 (-1.2, 2.4)	--	1.6 (-0.2, 3.3)	0.4 (-1.3, 2.2)	--
Applicant's Primary Estimand – ITT Population						
LS Mean (95% CI)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
Diff (95% CI)	-0.2 (-2.0, 1.6)	0.7 (-1.1, 2.5)	--	1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)	--
Hypothetical Estimand - ITT Population						
LS Mean (95% CI)	10.8 (9.5, 12.0)	11.6 (10.4, 12.9)	10.9 (9.7, 12.2)	11.9 (10.7, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
Diff (95% CI)	-0.1 (-1.9, 1.6)	0.7 (-1.1, 2.5)	--	1.6 (0.0, 3.3)	0.5 (-1.2, 2.1)	--

Source: Based on Reviewer's Analysis.
[1] Based on treatment policy estimand strategy.

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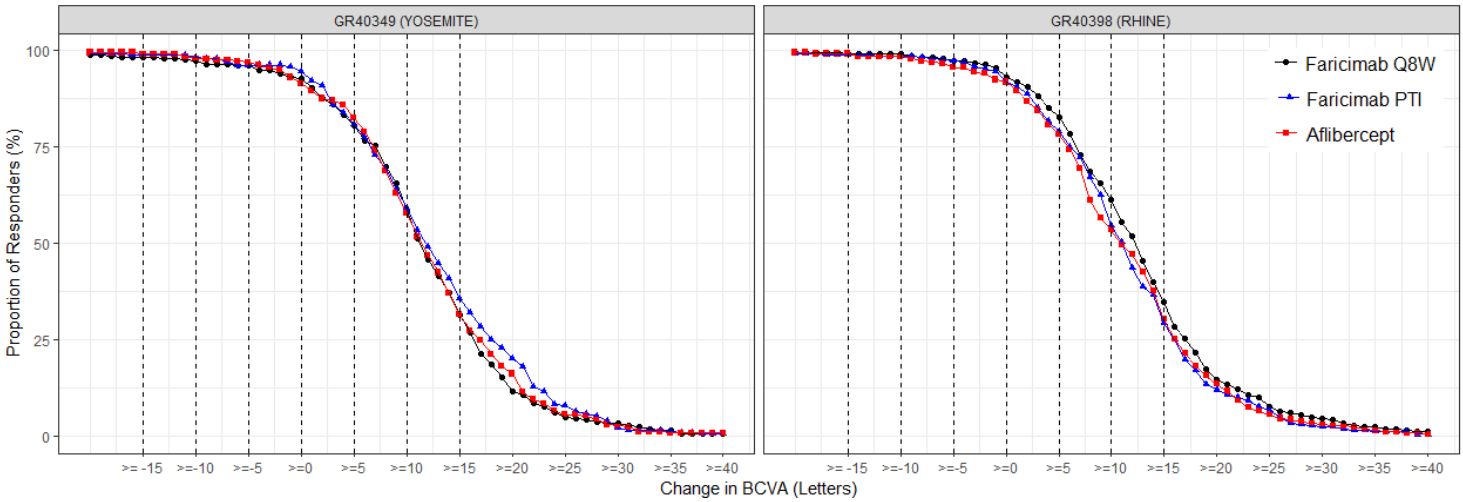
Secondary Efficacy Endpoints: Proportion of Subjects Who Gained/Lost Letters in BCVA from Baseline at Week 48/52/56

In both YOSEMITE and RHINE studies, the proportion of subjects who gained ≥15, ≥10, ≥5, and ≥0 letters and those who avoided losing ≥15, ≥10, and ≥5 letters from baseline at Week 48/52/56 were defined as secondary efficacy endpoints.

For these binary secondary endpoints, the same analyses and data handling strategies were adopted as in the analysis of the key secondary efficacy endpoint. That is, these endpoints were analyzed on the ITT population under the treatment policy estimand strategy using observed data (without missing data imputation) and based on missing BCVA data imputed using multiple imputation and LOCF approaches.

Figure 17 displays the cumulative distribution of the change in BCVA at Week 48/52/56 based on missing data imputed using multiple imputation. As shown, in both studies, the treatment groups across the seven BCVA-related binary secondary endpoints (highlighted by the dashed lines) were comparable.

Figure 17: Cumulative Distribution of the Change in BCVA from Baseline at Week 48/52/56 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)



Source: Based on Reviewer's Analysis. Missing BCVA data were imputed using multiple imputation.

Treatment comparisons in the proportion of subjects who gained ≥15 and ≥10 letters from baseline at Week 48/52/56 were performed using the CMH test. As shown in Table 31, the proportion of subjects who gained ≥15 and ≥10 letters from baseline at Week 48/52/56 appeared comparable across the treatment groups in both studies.

In the YOSEMIT study, 30%, 34%, and 31% of subjects in the faricimab Q8W, PTI, and aflibercept groups, respectively, gained ≥ 15 letters in BCVA from baseline at Week 48/52/56 and 56%, 58%, and 55%, respectively, gained ≥ 10 letters in BCVA from baseline at Week 48/52/56. Similarly, in the RHINE study, 34%, 27%, and 30% of subjects in the faricimab Q8W, PTI, and aflibercept groups, respectively, gained ≥ 15 letters in BCVA from baseline at Week 48/52/56 and 58%, 53%, and 52%, respectively, gained ≥ 10 letters in BCVA from baseline at Week 48/52/56.

Table 31: Proportion of Subjects Who Gained ≥15 and ≥10 Letters in BCVA from Baseline at Week 48/52/56 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)

Study	Analysis Method	Faricimab Q8W	Faricimab PTI	Aflibercept	Difference (97.5% CI) Faricimab Q8W vs. Aflibercept	Difference (97.5% CI) Faricimab PTI vs. Aflibercept
Gained >=15 letters (%)						
YOSEMITE	Observed	29.7 (23.8, 35.7)	34.5 (28.5, 40.5)	31.0 (25.2, 36.9)	-1.3 (-9.7, 7.0)	3.2 (-5.2, 11.6)
	LOCF	28.3 (22.7, 33.9)	33.6 (27.9, 39.3)	30.6 (25.0, 36.2)	-2.3 (-10.2, 5.6)	2.8 (-5.1, 10.8)
	MI	30.1 (24.2, 36.0)	34.4 (28.5, 40.4)	31.1 (25.3, 36.9)	-1.0 (-9.2, 7.2)	3.2 (-5.1, 11.5)
RHINE	Observed	34.1 (28.0, 40.2)	27.9 (22.5, 33.4)	29.4 (23.6, 35.2)	4.7 (-3.7, 13.1)	-1.7 (-9.7, 6.2)
	LOCF	32.6 (26.9, 38.3)	26.9 (21.7, 32.2)	27.8 (22.3, 33.3)	4.8 (-3.1, 12.7)	-1.0 (-8.6, 6.6)
	MI	33.5 (27.5, 39.5)	27.0 (21.7, 32.4)	29.5 (23.3, 34.8)	4.5 (-3.8, 12.7)	-2.2 (-10.0, 5.7)
Gained >=10 letters (%)						
YOSEMITE	Observed	56.5 (49.9, 63.1)	57.5 (51.2, 63.8)	56.8 (50.3, 63.3)	-0.3 (-9.6, 8.9)	0.6 (-8.4, 9.7)
	LOCF	55.0 (48.7, 61.3)	55.6 (49.6, 61.7)	54.8 (48.5, 61.0)	0.2 (-8.7, 9.1)	0.8 (-7.9, 9.5)
	MI	55.6 (49.2, 62.1)	57.5 (51.2, 63.8)	55.2 (48.7, 61.6)	0.1 (-8.7, 9.6)	2.3 (-6.7, 11.2)
RHINE	Observed	58.6 (52.3, 64.9)	53.2 (47.0, 59.4)	53.4 (47.1, 59.7)	5.2 (-3.7, 14.1)	-0.5 (-9.3, 8.3)
	LOCF	57.6 (51.6, 63.7)	53.6 (47.5, 59.7)	51.0 (44.9, 57.1)	6.6 (-1.9, 15.2)	2.5 (-6.1, 11.1)
	MI	58.1 (51.8, 64.3)	53.3 (47.1, 59.4)	52.0 (45.6, 58.4)	6.0 (-2.9, 15.0)	1.1 (-7.8, 10.0)

Source: Based on Reviewer's Analysis.

Supporting analyses performed for the proportion of subjects who gained ≥15 and ≥10 letters from baseline at Week 48/52/56 using the Applicant's primary estimand strategy provided consistent efficacy results with the treatment policy estimand strategy except for small numerical differences (Table 32).

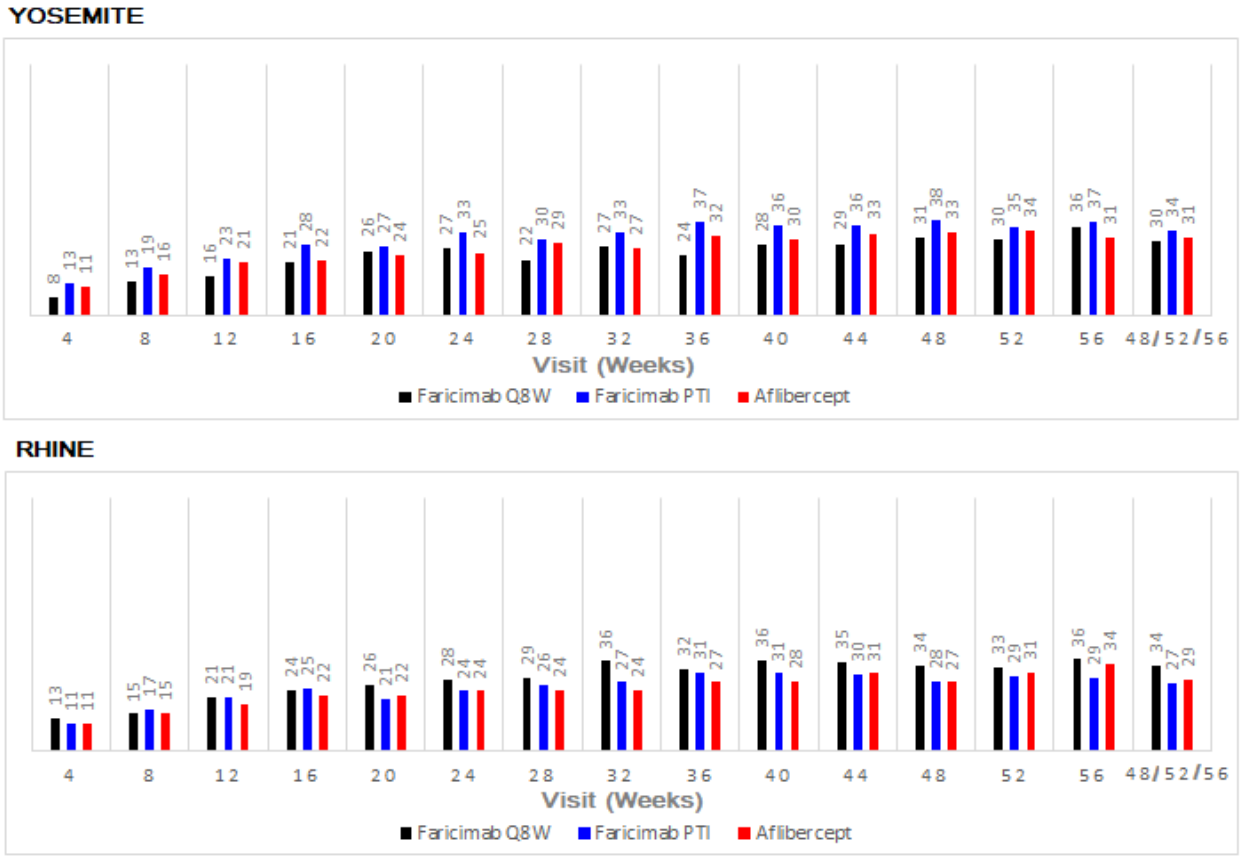
Table 32: Proportion of Subjects Who Gained ≥15 and ≥10 Letters in BCVA from Baseline at Week 48/52/56 (Applicant's Primary Estimand) (ITT Population)

Study	Analysis Method	Faricimab Q8W	Faricimab PTI	Aflibercept	Difference (97.5% CI) Faricimab 2Q8 vs. Aflibercept	Difference (97.5% CI) Faricimab PTI vs. Aflibercept
Gained >=15 letters (%)						
YOSEMITE	Observed	29.2 (23.1, 35.3)	35.5 (29.3, 41.7)	31.8 (25.8, 37.7)	-2.6 (-11.1, 5.9)	3.5 (-5.1, 12.1)
	LOCF	29.3 (23.6, 34.9)	33.6 (27.9, 39.3)	30.9 (25.3, 36.5)	-1.7 (-9.6, 6.3)	2.5 (-5.5, 10.5)
	MI	30.6 (24.6, 36.7)	34.8 (28.9, 40.8)	31.8 (25.9, 37.6)	-1.1 (-9.5, 7.3)	2.9 (-5.5, 11.3))
RHINE	Observed	33.8 (27.6, 40.0)	28.5 (22.9, 34.0)	30.3 (24.3, 36.3)	3.5 (-5.1, 12.2)	-2.0 (-10.1, 6.2)
	LOCF	32.3 (26.6, 38.0)	27.3 (22.0, 32.5)	27.8 (22.3, 33.3)	4.5 (-3.4, 12.4)	-0.7 (-8.3, 6.9
	MI	34.0 (27.9, 40.0)	28.2 (22.6, 33.7)	29.6 (23.8, 35.4)	4.4 (-4.1, 12.9)	-1.6 (-9.6, 6.4)
Gained >=10 letters (%)						
YOSEMITE	Observed	57.2 (50.5, 64.0)	58.3 (51.8, 64.8)	57.6 (51.0, 64.2)	-0.4 (-9.6, 9.1)	0.7 (-8.5, 9.9)
	LOCF	55.9 (49.6, 62.2)	55.9 (49.8, 62.0)	55.1 (48.8, 61.4)	0.8 (-8.0, 9.7)	0.8 (-7.9, 9.5)
	MI	56.6 (50.0, 63.2)	57.7 (51.3, 64.1)	55.8 (49.4, 62.3)	0.1 (-8.5, 10.0)	1.8 (-7.3, 10.9)
RHINE	Observed	59.3 (52.8, 65.7)	53.0 (46.7, 59.3)	53.9 (47.5, 60.3)	5.4 (-3.7, 14.5)	-1.1 (-10.0, 7.9)
	LOCF	58.6 (52.6, 64.6)	53.9 (47.8, 60.0)	51.0 (44.9, 57.1)	7.6 (-1.0, 16.2)	2.8 (-5.8, 11.4)
	MI	59.1 (52.8, 65.4)	53.2 (46.9, 59.5)	51.5 (45.1, 57.8)	7.7 (-1.4, 16.7)	1.6 (-7.4, 10.6)

Source: Based on Reviewer's Analysis.

Figure 18 displays the proportion of subjects who gained ≥15 letters from baseline at each visit through week 56 in the YOSEMITE/RHINE studies. As shown, the gain in BCVA through Week 56 was comparable across the treatment groups.

Figure 18: Proportion of Subjects Who Gained ≥15 Letters from Baseline at Each Study Visit (Treatment Policy Estimand) (ITT Population)



Source: Based on Reviewer's Analysis. Missing BCVA data imputed using multiple imputation

A summary of the proportion of subjects who avoided a loss of ≥15 and ≥10 letters in BCVA from baseline at Week 48/52/56 is presented in Table 40 in Appendix 1. As shown, a comparable proportion of subjects in each treatment group avoided a loss of ≥15 and ≥10 letters in both studies.

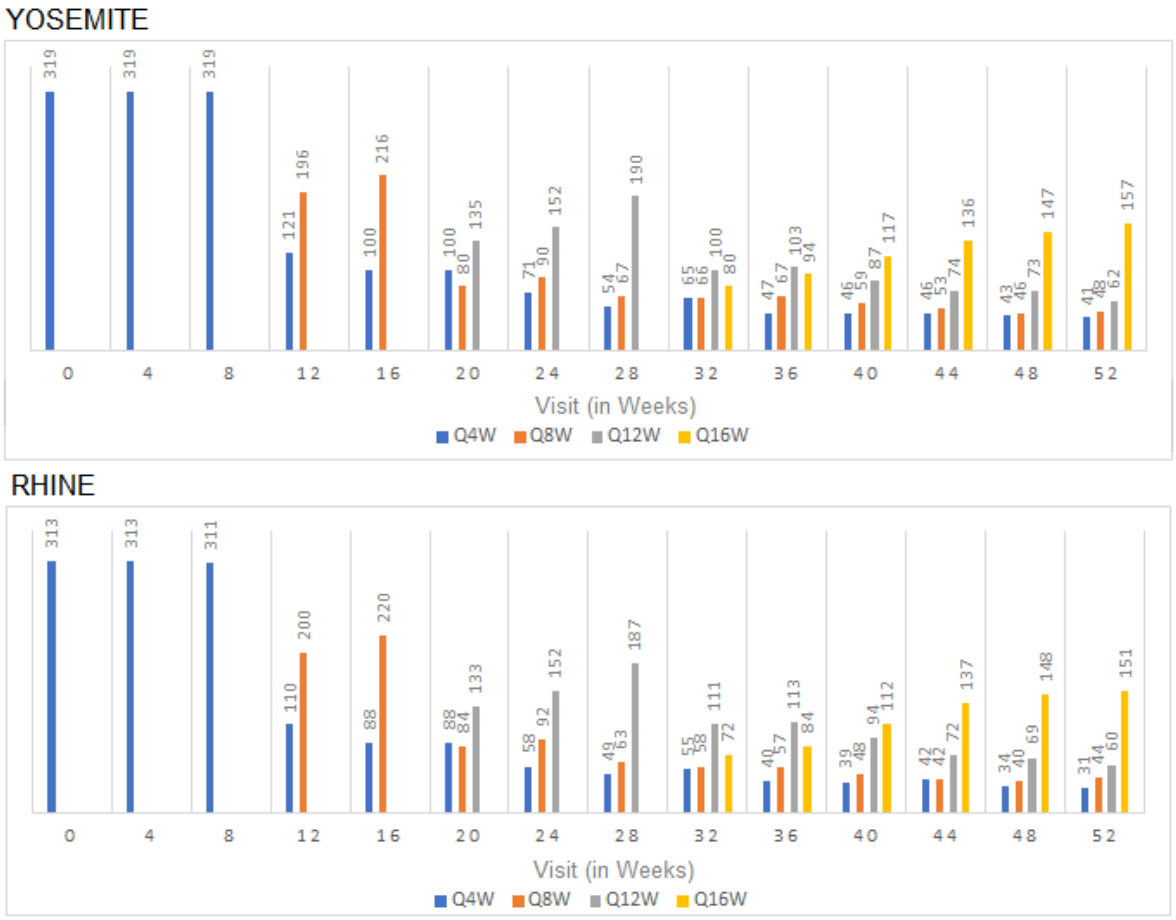
Secondary Efficacy Endpoint: Proportion of Subjects in the Faricimab PTI Arm on Q4W, Q8W, Q12W, and Q16W Dosing Intervals Through Week 52

In YOSEMITE/RHINE studies, subjects in the faricimab PTI arm were to receive treatment in a Q4W, Q8W, Q12W, or Q16W dosing interval based on objective assessment of pre-specified visual and anatomic disease activity criteria, after the first four monthly doses.

Figure 19 shows the number of subjects that qualified for each faricimab dosing at each visit through Week 52. In both studies, all subjects randomized to faricimab initially received treatment every 4-week (Q4W) for the first four injections. Then, subjects qualified to receive injection every 8-week (Q8W) starting Week 20, every 12-week (Q12W) starting Week 24, and

every 16-week (Q16W) starting Week 32. For example, from the total of 317 subjects in YOSEMITE study that received injection at Week 12, 196 subjects will receive the next injection at Week 20 based on Q8W dosing interval.

Figure 19: Number of Subjects in the Faricimab PTI group on Q4W, Q8W, Q12W, and Q16W Dosing at Each Visit Through Week 52 (ITT Population)



Source: Based on Reviewer's Analysis.

At Week 52, 74% of subjects in YOSEMITE and 71% of subjects in RHINE were on either the Q12W or Q16W combined dosing intervals (Table 33). Among the subjects with the Q12W and Q16W dosing interval at Week 52, 68% of subjects in YOSEMITE and 64% of subjects in RHINE maintained the dosing interval without an injection interval decrease below Q12W through Week 52.

Table 33: Proportion of Subjects in the Faricimab PTI Group on Q4W, Q8W, Q12W, and Q16W Dosing Interval at Week 52 (ITT Population)

Study	N	Q4W	Q8W	Q12W	Q16W	Q12W/Q16W	Maintained
YOSEMITE	286	31 (10.8%)	44 (15.4%)	60 (21.0%)	151 (52.8%)	211 (73.8%)	194 (67.8%)
RHINE	308	41 (13.3%)	48 (15.1%)	62 (20.1%)	157 (51.0%)	219 (71.1%)	198 (64.3%)
Pooled	594	72 (12.1%)	92 (15.5%)	122 (20.5%)	308 (51.9%)	430 (72.3%)	392 (66.0%)

Source: Based on Reviewer's Analysis.

The mean change in BCVA from baseline at Week 52 and the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 52 for subjects randomized in the faricimab PTI arm that received treatment in a Q4W, Q8W, Q12W, and Q16W dosing intervals at Week 52 are summarized in Table 34. As shown, subjects in each dosing frequencies of faricimab PTI dosing interval displayed comparable efficacy benefit compared to aflibercept as well as compared to faricimab Q8W fixed dosing interval.

Table 34: Summary of Change in BCVA at Week 48/52/56 and Proportion of Subjects Who Achieved ≥2-Step improvement in DRSS at Week 52 by Faricimab Dosing Interval (Treatment Policy Estimand) (ITT Population)

		Mean Change in BCVA from Baseline at Week 48/52/56				Proportion of subjects who Achieved ≥2-step improvement in DRSS at Week 52
		YOSEMITE		RHINE		(b) (4)
Treatment Group	Dosing Interval	N	Mean (SD)	N	Mean (SD)	
Faricimab PTI Dosing Interval	Q4W	31	7.5 (9.5)	41	8.2 (11.9)	
	Q8W	44	11.6 (9.8)	48	8.8 (9.9)	
	Q12W	60	10.8 (10.8)	62	12.3 (10.6)	
	Q16W	151	12.6 (9.5)	157	11.2 (10.6)	
Faricimab	2Q8	315	10.0 (10.82	316	11.9 (10.09)	
Aflibercept	2Q8	312	11.6 (9.69)	315	11.2 (9.40)	

Source: Based on Reviewer's Analysis.

Secondary Efficacy Endpoint: Change in CST from Baseline at Week 40/44/48

The central subfield thickness (CST) was assessed by optical coherence tomography (OCT) to measure the extent and progression of macular swelling. The effectiveness of each dose of faricimab (Q8W or PTI) compared to aflibercept in the reduction of CST from baseline averaged over Week 48/52/56 was evaluated in this section.

Treatment comparison between each dose of faricimab versus aflibercept in the mean change in CST from baseline at Week 48/52/56 was made using MMRM model on the treatment policy estimand strategy. The model adjusted for treatment group, visit, visit-by-treatment group interaction, the continuous covariate of baseline CST, and the study specific stratification factors. An unstructured covariance structure was used. The estimate of the difference between each dose of faricimab to aflibercept was based on a composite contrast over Weeks 48, 52 and 56. As shown in Table 35, faricimab treated subjects in both studies demonstrated comparable reductions in CST from baseline at Week 48/52/56 compared to aflibercept treated subjects.

Table 35: Adjusted Mean Change in CST from Baseline at Week 48/52/56 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)

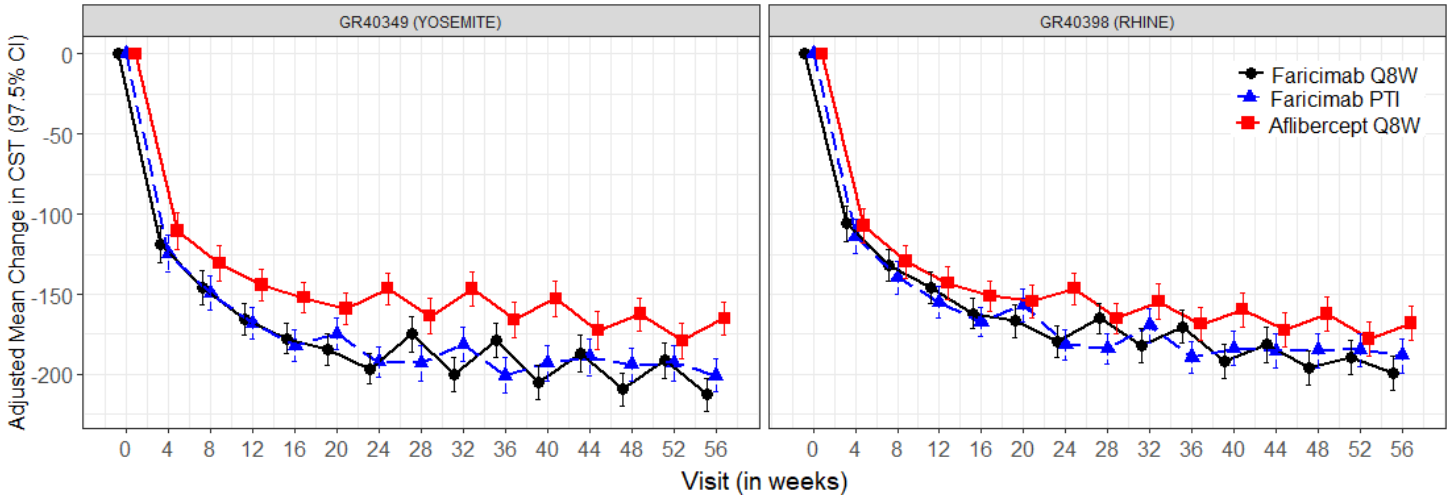
	Mean (SE)			Difference (97.5% CI)	
	Faricimab Q8W	Faricimab PTI	Aflibercept	Q8W vs. Aflibercept	PTI vs. Aflibercept
YOSEMITE					
Week 48	-209.5 (4.6)	-194.0 (4.6)	-162.4 (4.6)	-47.1 (-61.6, -32.5)	-31.5 (-46.1, -17.0)
Week 52	-191.1 (4.9)	-192.9 (4.9)	-179.1 (5.0)	-12.0 (-27.8, 3.8)	-13.8 (-29.6,2.0)
Week 56	-212.6 (4.6)	-200.8 (4.6)	-165.2 (4.7)	-47.4 (-62.2, -32.7)	-35.6 (-50.3, -20.8)
Week 48/52/56	-204.4 (4.2)	-195.9 (4.2)	-168.9 (4.2)	-35.5 (-48.8, -22.2)	-27.0 (-40.2, -13.7)

	Mean (SE)			Difference (97.5% CI)	
	Faricimab Q8W	Faricimab PTI	Aflibercept	Q8W vs. Aflibercept	PTI vs. Aflibercept
RHINE					
Week 48	-196.1 (4.8)	-185.1 (4.7)	-162.3 (4.8)	-33.7 (-49.0, -18.5)	-22.8 (-37.8, -7.8)
Week 52	-189.8 (4.8)	-184.7 (4.7)	-177.7 (4.7)	-12.0 (-27.1, 3.0)	-7.0 (-21.9, 7.9)
Week 56	-199.0 (4.8)	-188.4 (4.7)	-167.9 (4.8)	-31.2 (-46.4, -15.9)	-20.5 (-35.6, -5.4)
Week 48/52/56	-195.0 (4.2)	-186.1 (4.1)	-169.3 (4.2)	-25.6 (-38.9, -12.4)	-16.8 (-29.9, -3.7)

Source: Based on Reviewer's Analysis

Figure 20 below displays the adjusted mean change in CST from baseline through Week 56 including the 97.5% confidence interval estimates (vertical bars at each visit) in the two studies. As shown, patients treated with faricimab 2Q8 or PTI dosing interval displayed numerically better reductions in CST from baseline through Week 56 compared to aflibercept treated patients.

Figure 20: Adjusted Mean Change in CST from Baseline Over Time (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)



Source: Based on Reviewer's Analysis

3.2.2.5. Efficacy Conclusion

Based on the collective efficacy evidence from the two adequate and well controlled trials of YOSEMITE/RHINE studies, the reviewer concludes that subjects treated with either faricimab Q8W or PTI had a noninferior mean change in BCVA from baseline at Week 48/52/56 compared to subjects treated with aflibercept in the ITT population. However, superiority of each of dose of faricimab in the primary endpoint was not established in the TN as well as in the ITT population.

(b) (4)

In the YOSEMITE/RHINE studies, subjects in the faricimab PTI arm received treatment in a Q4W, Q8W, Q12W, or Q16W dosing interval based on protocol-defined disease activity criteria, after the first four monthly doses. At Week 52, 12%, 16%, 21%, and 52% of subjects were on a Q4W, Q8W, Q12W, and Q16W dosing interval, respectively. And among the 73% of subjects who were on Q12W/Q16W dosing interval at Week 52, 66% of subjects maintained the dosing interval without an injection interval decrease below Q12W through Week 52. As shown in Table 34, efficacy analysis by the PTI dosing interval displayed that subjects that received faricimab in Q12W or Q16W dosing interval had comparable letter gains in BCVA compared to faricimab Q8W and aflibercept Q8W dosing intervals.

3.3. SAFETY EVALUATION

In TENAYA/LUCERNE studies for nAMD indication and in YOSEMITE/RHINE studies for the DME-DR indication, safety was evaluated based on the safety evaluable population including all randomized subjects who received at least a single dose of double-blind treatment. The safety parameters included extent of exposure to study drug, adverse events (AEs), clinical laboratory evaluation, and additional safety variables which included intraocular pressure, vital signs, electrocardiogram, and ophthalmic examinations.

In this review, a high-level safety summary is provided from the individual studies and from the pooled data by indication. For a comprehensive safety evaluation, the reviewer defers to the FDA clinical review document.

3.3.1. TENAYA and LUCERNE Studies

Study Exposure

Table 36 shows a summary of study treatment exposure through Week 48 in the TANAYA and LUCERNE studies. In these studies, most of the randomized subjects received at least one dose of study treatment. Two randomized subjects (1 from each treatment group) who did not receive any treatment were excluded from the safety-evaluable population.

The median duration of exposure through Week 48 in both studies was comparable between the treatment groups (48 Weeks). The mean number of study drug administration through Week 48 was lower in the faricimab arm by about one injection compared to in the aflibercept arm (6.4 versus 7.4).

Table 36: Summary of Study Treatment Exposure in the Study Eye through Week 48 from Individual and Pooled nAMD Studies (Pooled Safety-Evaluable Population)

	TENAYA		LUCERNE		Pooled	
	Faricimab (N = 333)	Aflibercept (N = 336)	Faricimab (N = 331)	Aflibercept (N = 326)	Faricimab (N = 664)	Aflibercept (N = 662)
Treatment Duration						
N	333	336	331	326	664	662
Mean (SD)	46.0 (7.92)	46.3 (7.51)	46.4 (6.78)	46.0 (8.06)	46.2 (7.37)	46.2 (7.78)
Median	48.1	48.1	48.1	48.1	48.1	48.1
Range	0 - 50	0 - 50	0 - 50	0 - 50	0 - 50	0 - 50
Number of Study Drug Administration						
N	333	336	331	326	664	662
Mean (SD)	6.3 (1.11)	7.4 (1.12)	6.5 (1.05)	7.5 (1.16)	6.4 (1.08)	7.4 (1.14)
Median	6.0	8.0	6.0	8.0	6.0	8.0
Range	1 - 8	1 - 8	1 - 8	1 - 8	1 - 8	1 - 8

Source: Table 10 of Applicant's Summary of Clinical Safety Summary Document.

Adverse Events

In the pooled TENAYA and LUCERNE studies, a total of 1326 subjects were exposed to the study drug (664 in faricimab and 662 in aflibercept).

A high-level safety summary of the individual and pooled TENAYA and LUERNE studies are presented in Table 37. As shown, the incidence of overall AEs (71% vs. 73%), ocular AEs (38% vs. 37%), series AEs (SAEs; 13% vs. 15%), ocular SAEs (2% vs. 2%), AEs of special interest (AESI; 2 vs. 3%), and AE of intraocular inflammation (IOI; 2% vs. 1%) were comparable between the treatment groups. The non-ocular AEs and SAEs were also comparable between the treatment groups.

In the pooled data, a comparable number of subjects in the faricimab (8 subjects) and in the aflibercept arm (10 subjects) discontinued the study due to AE. However, slightly more subjects in the faricimab arm (11 subjects) than in the aflibercept arm (4 subjects) discontinued from the study treatment due to AE.

Table 37: Overview of Safety Through Week 48 from Individual and Pooled nAMD Studies (Pooled Safety-Evaluable Patients)

	TENAYA		LUCERNE		Pooled	
	Faricimab (N = 333)	Aflibercept (N = 336)	Faricimab (N = 331)	Aflibercept (N = 326)	Faricimab (N = 664)	Aflibercept (N = 662)
Total number of patients with at least one AE	238 (71.5%)	235 (69.9%)	233 (70.4%)	248 (76.1%)	471 (70.9%)	483 (73.0%)
Ocular: Study Eye	121 (36.3%)	128 (38.1%)	133 (40.2%)	118 (36.2%)	254 (38.3%)	246 (37.2%)
Non-ocular: Study Eye	174 (52.3%)	174 (51.8%)	172 (52.0%)	189 (58.0%)	346 (52.1%)	363 (54.8%)
Total number of patients with at least one SAEs	34 (10.2%)	44 (13.1%)	49 (14.8%)	57 (17.5%)	83 (12.5%)	101 (15.3%)
Ocular: Study Eye	4 (1.2%)	6 (1.8%)	7 (2.1%)	7 (2.1%)	11 (1.7%)	13 (2.0%)
Non-ocular: Study Eye	30 (9.0%)	34 (10.1%)	38 (11.5%)	48 (14.7%)	68 (10.2%)	82 (12.4%)
Total number of patients with at least one AESI	3 (0.9%)	12 (3.6%)	11 (3.3%)	8 (2.5%)	14 (2.1%)	20 (3.0%)
Ocular: Study Eye	3 (0.9%)	6 (1.8%)	5 (1.5%)	6 (1.8%)	8 (1.2%)	12 (1.8%)
Non-ocular: Study Eye	0	1 (0.3%)	0	0	0	1 (0.2%)
Total number of patients with at least one AE of IOI in the study eye	5 (1.5%)	2 (0.6%)	8 (2.4%)	6 (1.8%)	13 (2.0%)	8 (1.2%)
Number of Patients with IOI, Retinal Vasculitis, or Retinal Vascular Occlusive Events	5 (1.5%)	2 (0.6%)	9 (2.7%)	6 (1.8%)	14 (2.1%)	8 (1.2%)
Total number of patients withdrawn from study due to an AE	3 (0.9%)	4 (1.2%)	5 (1.5%)	6 (1.8%)	8 (1.2%)	10 (1.5%)
Total number of patients withdrawn from study treatment due to an AE	3 (0.9%)	3 (0.9%)	8 (2.4%)	1 (0.3%)	11 (1.7%)	4 (0.6%)
Total number of deaths	5 (1.5%)	1 (0.3%)	4 (1.2%)	7 (2.1%)	9 (1.4%)	8 (1.2%)
Adjudicated APTC Events	3 (0.9%)	3 (0.9%)	4 (1.2%)	3 (0.9%)	7 (1.1%)	6 (0.9%)
Non-fatal MI	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.3%)
Non-fatal Stroke	0	1 (0.3%)	2 (0.6%)	0	2 (0.3%)	1 (0.2%)
Death	2 (0.6%)	1 (0.3%)	0	2 (0.6%)	2 (0.3%)	3 (0.5%)

Source: Table 14 of Applicant's Summary of Clinical Safety Summary Document.
Abbreviations: AE: Adverse Event; SAEs: Serious Adverse Events; IOI: Intraocular Inflammation; AESI: Adverse Event of Special Interest; ATPTC: Antiplatelet Trialists' Collaboration. APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).

A total of 17 deaths were reported in the combined TENAYA/LUCERNE studies through Week 48: 9 deaths in faricimab (5 in TENAYA and 4 in LUCERNE) and 8 in aflibercept (1 in TENAYA and 7 in LUCERNE).

In both studies, adjudicated arterial thromboembolic events based on Anti-Platelet Trialists' Collaboration (APTC) Endpoint were assessed. The APTC events included a non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). The summary of these events for the individual studies and for the pooled analysis are presented in Table 37. During the 48-week treatment period, the rate of APTC events were comparable between the treatment groups.

3.3.2. YOSEMITE and RHINE Studies

Study Exposure

Table 38 shows a summary of study treatment exposure through Week 56 in the YOSEMITE and RHINE studies. In these studies, most of the randomized subjects received at least one dose of study treatment. Two subjects each randomized to faricimab Q8W and to aflibercept who did not receive a dose of study drug were excluded from the safety-evaluable population.

The median duration of exposure through Week 56 in both studies was comparable across the three treatment groups (56 Weeks). Through Week 56, a median of 10 doses were administered in the faricimab 2Q8 and aflibercept arms and a median of 8 doses were administered in the faricimab PTI group. In the pooled study, a total of 98 dose interruptions (DIs) in 69 subjects, 91 DIs in 64 subjects, and 80 DIs in 63 subjects had occurred in the faricimab Q8W, PTI, and aflibercept groups, respectively. Most subjects (80% = 156/196) had a single interruption and 20% of subjects had at least one interruption through Week 56.

Adverse Events

In the pooled YOSEMITE and RHINE studies, a total of 1887 subjects were exposed to the study drug (630 in faricimab Q8W, 632 in faricimab PTI, and 625 in aflibercept).

A high-level safety summary of the individual and pooled YSEMITE/RHINE studies are presented in Table 39. As shown, the incidence of overall AEs (81% vs. 77% vs. 78%), ocular AEs (37% vs. 36% vs. 34%), series AEs (SAEs; 24% vs. 20% vs. 18%), ocular SAEs (2% vs. 3% vs 1%), and AE of special interest (AESI; 4% vs. 4% vs. 2%) were comparable between the treatment groups. The non-ocular AEs and SAEs were also comparable across the treatment groups. In the pooled data, a comparable number of subjects discontinued the study due to AE (3% vs. 2% vs. 1%) and from study treatment due to AE (2% vs. 2% vs. 1%).

A total of 31 deaths were reported in the combined YOSEMITE and RHINE studies through Week 56:13 deaths in faricimab Q8W (8 in YOSEMITE and 5 in RHINE), 9 deaths in faricimab PTI (9 in YOSEMITE and 0 in RHINE), and 9 in aflibercept (5 in YOSEMITE and 4 in RHINE).

In both studies, adjudicated arterial thromboembolic events based on Anti-Platelet Trialists' Collaboration (APTC) Endpoint were assessed. The APTC events included a non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). The summary of these events for the individual studies and for the pooled analysis are included in Table 39. During the 56-week treatment period, the rate of APTC events were comparable across the treatment groups (2% in faricimab 2Q8, 1% in faricimab PTI, and 1% in aflibercept).

Table 38: Summary of Study Treatment Exposure in the Study Eye Through Week 56 from Individual and Pooled DME/DR Studies (Pooled Safety-Evaluable Population)

	YOSEMITE			RHINE			Pooled		
	Faricimab 2Q8 (N = 313)	Faricimab PTI (N = 313)	Aflibercept (N = 311)	Faricimab 2Q8 (N = 317)	Faricimab PTI (N = 319)	Aflibercept (314)	Faricimab 2Q8 (N = 630)	Faricimab PTI (632)	Aflibercept (N = 625)
Treatment Duration									
N	313	313	311	317	319	314	630	632	625
Mean (SD)	53.1 (9.75)	52.9 (10.43)	53.2 (9.54)	53.1 (10.00)	54.5 (7.45)	53.7 (8.65)	53.1 (9.87)	53.7 (9.08)	53.4 (9.10)
Median	56.1	56.1	56.1	56.1	56.1	56.1	56.1	56.1	56.1
Range	0 - 58	3 - 58	0 - 58	0 - 58	0 - 58	0 - 58	0 - 58	0 - 58	0 - 58
Number of Study Drug Administration									
N	313	313	311	317	319	314	630	632	625
Mean (SD)	9.5 (1.41))	8.4 (2.45)	9.2 (1.47)	9.3 (1.52)	8.7 (2.50)	9.3 (1.36)	9.4 (1.46)	8.5 (2.48)	9.3 (1.42)
Median	10.0	8.0	10.0	10.0	8.0	10.0	10.0	8.0	10.0
Range	1 - 11	2 - 15	1 - 10	1 - 10	1 - 15	1 - 10	1 - 11	1 - 15	1 - 10
Dose Interruptions									
Number of doses interrupted	38	54	38	60	37	42	98	91	80
Interruption per patient	29	33	29	40	31	34	69	64	63
1	24	26	23	28	26	29	52	52	52
2	2	3	3	7	4	4	9	7	7
3	2	1	3	3	1	0	5	2	3
4	1	1	0	1	0	0	2	1	0
5	0	1	0	1	0	1	1	1	1
10	0	1	0	0	0	0	0	1	0

Source: Table 36 of Applicant's Summary of Clinical Safety Summary Document.

Table 39: Overview of Safety Through Week 56 from Individual and Pooled DME/DR Studies (Pooled Safety-Evaluable Patients)

	YOSEMITE			RHINE			Pooled		
	Faricimab 2Q8 (N = 313)	Faricimab PTI (N = 313)	Aflibercept (N = 311)	Faricimab 2Q8 (N = 317)	Faricimab PTI (N = 319)	Aflibercept (314)	Faricimab 2Q8 (N = 630)	Faricimab PTI (632)	Aflibercept (N = 625)
Total number of patients with at least one AE	257 (82.1%)	253 (80.8%)	244 (78.5%)	256 (80.8%)	233 (73.0%)	244 (77.7%)	513 (81.4%)	486 (76.9%)	488 (78.1%)
Ocular: Study Eye	98 (31.3%)	106 (33.9%)	102 (32.8%)	137 (43.2%)	119 (37.3%)	113 (36.0%)	235 (37.3%)	225 (35.6%)	215 (34.4%)
Non-ocular: Study Eye	204 (65.2%)	210 (67.1%)	203 (65.3%)	189 (59.6%)	175 (54.9%)	187 (59.6%)	393 (62.4%)	385 (60.9%)	390 (62.4%)
Total number of patients with at least one SAEs	82 (26.2%)	77 (24.6%)	56 (18.0%)	67 (21.1%)	49 (15.4%)	58 (18.5%)	149 (23.7%)	126 (19.9%)	114 (18.2%)
Ocular: Study Eye	6 (1.9%)	9 (2.9%)	2 (0.6%)	9 (2.8%)	10 (3.1%)	6 (1.9%)	15 (2.4%)	19 (3.0%)	8 (1.3%)
Non-ocular: Study Eye	75 (24.0%)	64 (20.4%)	50 (16.1%)	52 (16.4%)	39 (12.2%)	52 (16.6%)	127 (20.2%)	103 (16.3%)	102 (16.3%)
Total number of patients with at least one AESI	12 (3.8%)	15 (4.8%)	6 (1.9%)	15 (4.7%)	11 (3.4%)	7 (2.2%)	27 (4.3%)	26 (4.1%)	13 (2.1%)
Ocular: Study Eye	6 (1.9%)	8 (2.6%)	1 (0.3%)	9 (2.8%)	9 (2.8%)	5 (1.6%)	15 (2.4%)	17 (2.7%)	6 (1.0%)
Non-ocular: Study Eye	0	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)
Total number of patients withdrawn from study due to an AE	10 (3.2%)	11 (3.5%)	6 (1.9%)	6 (1.9%)	1 (0.3%)	3 (1.0%)	16 (2.5%)	12 (1.9%)	9 (1.4%)
Total number of patients withdrawn from study treatment due to an AE	6 (1.9%)	8 (2.6%)	3 (1.0%)	4 (1.3%)	4 (1.3%)	4 (1.3%)	10 (1.6%)	12 (1.9%)	7 (1.1%)
Total number of deaths	8 (2.6%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	0	5 (1.6%)	13 (2.1%)	9 (1.4%)	9 (1.4%)
Adjudicated APTC Events	9 (2.9%)	10 (3.2%)	9 (2.9%)	4 (1.3%)	2 (0.6%)	5 (1.6%)	13 (2.1%)	12 (1.9%)	14 (2.2%)
Non-fatal MI	4 (1.3%)	2 (0.6%)	4 (1.3%)	0	0	2 (0.6%)	4 (0.6%)	2 (0.3%)	6 (1.0%)
Non-fatal Stroke	3 (1.0%)	2 (0.6%)	3 (1.0%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	4 (0.6%)	4 (0.6%)	4 (0.6%)
Death	2 (0.6%)	6 (1.9%)	2 (0.6%)	3 (0.9%)	0	2 (0.6%)	5 (0.8%)	6 (0.9%)	4 (0.6%)

Source: Table 32 and Table 33 of the Applicant's Clinical Safety Summary Document.
Abbreviations: AE: Adverse Event; SAEs: Serious Adverse Events; IOI: Intraocular Inflammation; AESI: Adverse Event of Special Interest; ATPTC: Antiplatelet Trialists' Collaboration. APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Source: Table 40 of Applicant's Summary of Clinical Safety Document

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

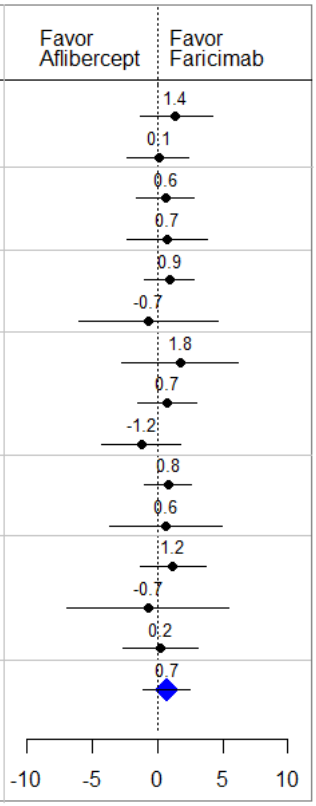
In this section, the primary efficacy variables of the change in BCVA from baseline at Week 40/44/48 in TENAYA/LUCERNE studies for the nAMD indication and the change in BCVA from baseline at Week 48/52/56 in the YOSEMITE/RHINE studies for the DME/DR indications were summarized by subgroup variables.

4.1. TENAYA AND LUCERNE STUDIES FOR NAMD INDICATION

In the TENAYA/LUCENE studies, the primary efficacy variable of the change in BCVA from baseline at Week 40/44/48 was summarized by the subgroups of age, gender, and race, and by the stratification factors of baseline BCVA category, low-luminance deficit (LLD) category, and region. It should be noted that, due to small sample sizes, some categories of race, *such as, American Indian or Alaska Native, Asian, Black or African American, and Multiple and unknown races,* were pooled together as 'Others' in the subgroup summary. See Table 4 for the sample sizes used within each subgroup.

Figure 21: Adjusted Mean Change in BCVA from Baseline at Week 40/44/48 by Subgroup (Treatment Policy Estimand) (ITT Population) (TENAYA)

Subgroup	Labels	Faricimab (N = 334)	Aflibercept (N = 337)	Difference (95% CI)
Age	< 75 years	8.1 (1.0)	6.7 (1.0)	1.4 (-1.3, 4.2)
	>= 75 years	4.3 (0.9)	4.3 (0.8)	0.1 (-2.3, 2.4)
Gender	Female	5.7 (0.8)	5.1 (0.8)	0.6 (-1.6, 2.8)
	Male	6.1 (1.1)	5.3 (1.1)	0.7 (-2.3, 3.8)
Race	White	5.7 (0.7)	4.8 (0.7)	0.9 (-1.0, 2.8)
	Others	7.6 (2.0)	8.3 (1.8)	-0.7 (-6.0, 4.6)
Baseline BCVA	< 54 Letters	9.5 (1.6)	7.7 (1.6)	1.8 (-2.7, 6.2)
	55 - 73 Letters	5.3 (0.8)	4.6 (0.8)	0.7 (-1.5, 3.0)
	>= 74 Letters	1.9 (1.1)	3.1 (1.1)	-1.2 (-4.3, 1.8)
LLD	< 32 Letters	7.3 (0.7)	6.4 (0.6)	0.8 (-1.0, 2.6)
	>= 33 Letters	2.5 (1.5)	1.9 (1.6)	0.6 (-3.7, 4.9)
Region	US and Canada	6.6 (0.9)	5.4 (0.9)	1.2 (-1.3, 3.7)
	Asia	6.5 (2.2)	7.2 (2.2)	-0.7 (-6.9, 5.5)
	ROW	4.7 (1.0)	4.4 (1.0)	0.2 (-2.6, 3.1)
Overall		5.8 (0.6)	5.1 (0.6)	0.7 (-1.1, 2.5)



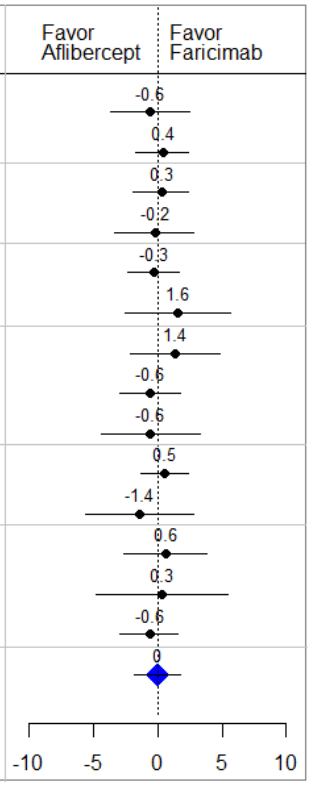
Source: Based on Reviewer's Analysis.

Figure 21 above and Figure 22 below show the summary of the mean change in BCVA from baseline at Week 40/44/48 by the subgroup variables in the TENAYA and LUCERNE studies, respectively. As shown, within the levels of each of the subgroup variables, the average letters

gained from baseline at Week 40/44/48 was comparable between the treatment groups in both studies. Additionally, the adjusted mean differences in the change in BCVA at Week 40/44/48 between the two treatment groups across the subgroup levels were consistent with the overall population.

Figure 22:Adjusted Mean Change in BCVA from Baseline at Week 40/44/48 by Subgroup (Treatment Policy Estimand) (ITT Population) (LUCERNE)

Subgroup	Labels	Faricimab (N = 334)	Aflibercept (N = 337)	Difference (95% CI)
Age	< 75 years	6.7 (1.1)	7.2 (1.2)	-0.6 (-3.7, 2.5)
	>= 75 years	6.5 (0.8)	6.2 (0.7)	0.4 (-1.7, 2.4)
Gender	Female	6.5 (0.8)	6.3 (0.8)	0.3 (-1.9, 2.4)
	Male	6.7 (1.1)	6.9 (1.1)	-0.2 (-3.3, 2.8)
Race	White	6.4 (0.7)	6.7 (0.7)	-0.3 (-2.3, 1.7)
	Others	7.6 (1.5)	6.0 (1.5)	1.6 (-2.5, 5.7)
Baseline BCVA	< 54 Letters	9.7 (1.2)	8.4 (1.2)	1.4 (-2.1, 4.8)
	55 - 73 Letters	5.9 (0.8)	6.4 (0.9)	-0.6 (-2.9, 1.8)
	>= 74 Letters	2.0 (1.3)	2.6 (1.4)	-0.6 (-4.4, 3.3)
LLD	< 32 Letters	7.5 (0.7)	7.0 (0.7)	0.5 (-1.3, 2.4)
	>= 33 Letters	4.2 (1.5)	5.5 (1.5)	-1.4 (-5.6, 2.8)
Region	US and Canada	6.3 (1.1)	5.7 (1.2)	0.6 (-2.6, 3.8)
	Asia	7.5 (1.8)	7.2 (1.8)	0.3 (-4.8, 5.5)
	ROW	6.6 (0.8)	7.2 (0.8)	-0.6 (-2.9, 1.6)
Overall		6.6 (0.6)	6.6 (0.6)	0.0 (-1.8, 1.8)



Source: Based on Reviewer's Analysis.

4.2. YOSEMITE/RHINE STUDIES FOR DME-DR INDICATIONS

In the YOSEMITE/RHINE studies, the primary efficacy variable of the change in BCVA from baseline at Week 48/52/56 was summarized by the subgroups of age, gender, and race, and by the stratification factors of baseline BCVA category, prior anti-VEGF use, and region. It should be noted that, due to small sample sizes, some categories of race, *such as, American Indian or Alaska Native, Asian, Black or African American, and Multiple and unknown races*, were pooled together as 'Others' in the subgroup summary. See Table 20 for the sample sizes used within each subgroup.

Figure 23 and Figure 24 below display summary of the mean change in BCVA from baseline at Week 48/52/56 by the subgroup variables in the YOSEMITE and RHINE studies, respectively. As shown, in both studies, the average letters gained from baseline at Week 48/52/56 within the levels of each of the subgroup variables was comparable between each dose of faricimab compared to aflibercept. Additionally, across the subgroup levels, the differences in the mean change in BCVA at Week 48/52/56 between each dose of faricimab and aflibercept were consistent with that of in the overall population.

Figure 23: Adjusted Mean Change in BCVA from Baseline at Week 48/52/56 by Subgroup (Treatment Policy Estimand) (ITT Population) (YOSEMITE)

Subgroup	Labels	Faricimab 2Q8 (N = 315)	Faricimab PTI (N = 313)	Aflibercept (N = 312)
Age	< 65 Years	12.2 (0.7)	13.2 (0.8)	12.4 (0.7)
	>= 65 Years	8.3 (0.8)	9.7 (0.8)	8.8 (0.8)
Gender	Female	10.2 (0.9)	10.8 (0.9)	11.3 (0.9)
	Male	11.0 (0.7)	12.0 (0.7)	10.7 (0.7)
Race	White	11.0 (0.6)	12.3 (0.6)	11.6 (0.6)
	Others	9.6 (1.4)	9.2 (1.4)	7.8 (1.6)
Baseline BCVA	< 63 Letters	11.8 (0.9)	14.0 (0.9)	13.0 (0.9)
	>= 64 Letters	9.8 (0.7)	9.6 (0.7)	9.1 (0.7)
Prior Anti-VEGF Use	Yes	11.3 (0.9)	12.5 (0.9)	9.3 (0.9)
	No	10.5 (0.7)	11.3 (0.7)	11.4 (0.7)
Region	US and Canada	10.6 (0.7)	13.3 (0.7)	12.4 (0.7)
	Asia	11.1 (1.8)	8.1 (1.8)	6.9 (1.8)
	ROW	10.9 (0.9)	9.8 (0.9)	9.6 (0.9)
Overall		10.6 (0.6)	11.5 (0.6)	10.8 (0.6)

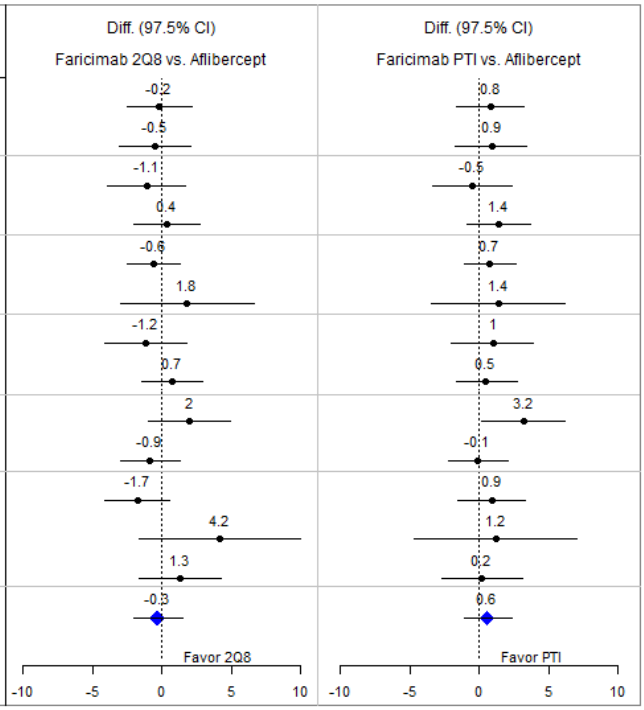
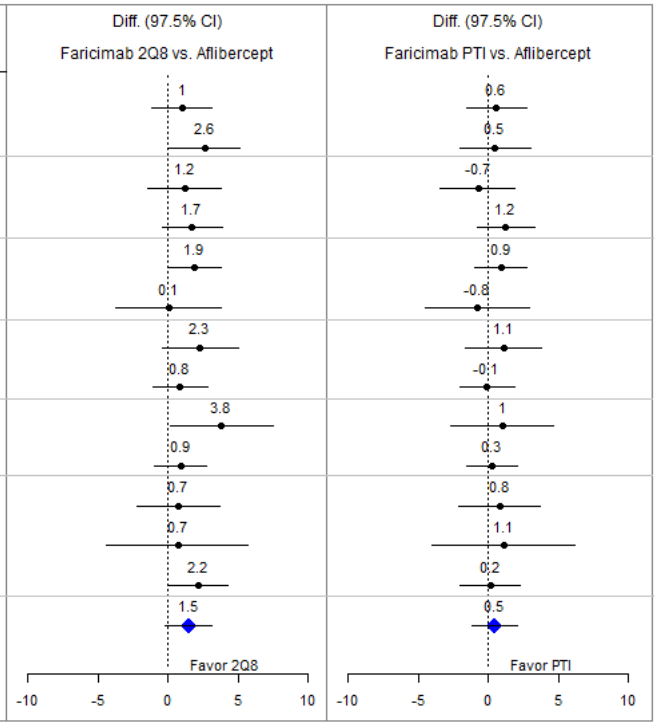


Figure 24: Adjusted Mean Change in BCVA from Baseline at Week 48/52/56 by Subgroup (Treatment Policy Estimand) (ITT Population) (RHINE)

Subgroup	Labels	Faricimab 2Q8 (N = 315)	Faricimab PTI (N = 313)	Aflibercept (N = 312)
Age	< 65 Years	12.0 (0.7)	11.6 (0.7)	11.0 (0.7)
	>= 65 Years	11.6 (0.8)	9.6 (0.8)	9.0 (0.8)
Gender	Female	11.6 (0.8)	9.7 (0.8)	10.4 (0.8)
	Male	11.9 (0.7)	11.4 (0.6)	10.1 (0.7)
Race	White	11.8 (0.6)	10.8 (0.6)	9.9 (0.6)
	Others	11.6 (1.2)	10.6 (1.1)	11.5 (1.2)
Baseline BCVA	< 63 Letters	14.9 (0.9)	13.7 (0.8)	12.6 (0.8)
	>= 64 Letters	9.2 (0.6)	8.2 (0.6)	8.3 (0.6)
Prior-Ant-VEGF Use	Yes	11.9 (1.1)	9.1 (1.2)	8.1 (1.1)
	No	11.8 (0.6)	11.2 (0.6)	10.9 (0.6)
Region	US and Canada	11.9 (0.9)	11.9 (0.9)	11.1 (0.9)
	Asia	10.9 (1.5)	11.4 (1.5)	10.3 (1.6)
	ROW	11.9 (0.7)	9.9 (0.7)	9.7 (0.7)
Overall		11.7 (0.5)	10.7 (0.5)	10.2 (0.5)



Source: Based on Reviewer's Analysis.

5. SUMMARY AND CONCLUSIONS

5.1. STATISTICAL ISSUES

There are no major statistical issues in the submission. However, the following data handling and analyses issues were identified and addressed during the review.

First, in the Applicant's primary analyses in the TENAYA/LUCERNE studies for the nAMD indication and in the YOSEMITE/RHINE studies for DME-DR indications, data for subjects with intercurrent events (IEs) not related to COVID-19 were used in the analyses whereas data for subjects with IEs due to COVID-19 were censored and imputed using the MMRM model assuming MAR missing data mechanism. Considering that the number of subjects with IEs not related to COVID-19 were minimal in the studies, and due to COVID-19 appeared not to be treatment-related (Table 1 and Table 17), the primary analyses in this review was performed based on all data regardless of the occurrence IEs under the treatment policy estimand strategy. It should be noted that the conclusion of noninferiority in the primary efficacy endpoint under the different intercurrent data handling strategies was maintained except for minor numerical differences.

Secondly, the Applicant analyses for all binary secondary efficacy endpoints including the key secondary endpoint for the DR indication in YOSEMITE/RHINE studies were based on observed data (without missing data imputation). Under the Applicant's strategy, subjects with IEs due to COVID-19 and/or with missed visits at the endpoint time were excluded from the analyses. The reviewer disagreed with the Applicant's analysis strategy based on observed data because excluding subjects with occurrence of IEs due to COVID-19 and/or missed visits did not maintain the study randomization. Therefore, to maintain the study randomization, in this review, all data regardless of occurrence of IEs were used in the analysis under the treatment policy estimand strategy. Under this strategy, missing data due to intermittent missed visits were first imputed (i) using multiple imputation strategy assuming MAR missing data mechanism as primary and (ii) using the LOCF approach as supporting. It should be noted that the same conclusion was reached regardless of the different estimand and data handling strategies used except for minor numerical differences.

Finally, in the TENAYA/LUCERNE studies, faricimab dosing for the nAMD indication was administered based on protocol-defined disease activity criteria. In these studies, 45% of subjects

were on every 16-week dosing interval (Q16W), 33% were on every 12-week dosing interval (Q12W), and 22% were on every 8-week (Q8W) dosing interval. Similarly, in YOSEMITE/RHINE studies, faricimab dosing for the DME-DR indications was based on a fixed dosing interval (Q8W), and in a personalized treatment interval (PTI) based on objective assessment of pre-specified visual and anatomic disease activity criteria. In these studies, among the subjects that completed the Week 52 visit in the PTI dosing arm, about 12% were on Q4W, 16% were on Q8W, 21% were on Q12W, and 52% were on Q16W.

Noting the variable dosing administrations used in the studies, in the DOSAGE AND ADMINSTRATION section of the draft label (see table below), the Applicant proposed the following dosing instruction for the nAMD and DME-DR indications without specifying the disease activity criteria used in the clinical trials. Thus, the reviewer defers to the medical review team regarding the appropriate dosing recommendation for use in clinical practice for the indications sought.

5.2. COLLECTIVE EVIDENCE

Support for the efficacy and safety of faricimab for the treatment of nAMD and DME-DR was based on four pivotal studies designed to assess whether faricimab reduce the treatment burden while maintaining comparable efficacy benefit to the active-control, aflibercept.

For the nAMD indication, the primary efficacy evidence to support noninferiority of faricimab administered up to every 16-week dosing interval after four initial monthly doses to aflibercept administered every 8-week after three initial monthly doses was based on two pivotal Phase 3 trials (TENAYA and LUCERNE studies). In both studies, subjects treated with faricimab had a noninferior mean change in BCVA from baseline at Week 40/44/48 compared to subjects treated with aflibercept because the 95% lower confidence limit for the treatment differences in the adjusted means was greater than the noninferiority margin of -4.0 letters (Figure 1). Additionally, in both treatment groups, a comparable proportion of subjects had gained ≥15, ≥10, ≥5, and ≥0 letters or avoided a loss of ≥15, ≥10, and ≥5 letters from baseline at Week 40/44/48 in the two studies (Figure 8).

For the DME-DR indication, the primary efficacy evidence to support the noninferiority of faricimab administered every 8-week after six initial monthly doses (Faricimab Q8W) and faricimab administered in a PTI dosing after four initial monthly doses (Faricimab PTI) to aflibercept administered every 8-week after five initial monthly doses was based on two pivotal Phase 3 trials (YOSEMITE and RHINE studies). In both studies, subjects treated with faricimab Q8W and PTI doses had a noninferior mean change in BCVA from baseline at Week 48/52/56 compared to subjects

treated with aflibercept because the 97.5% lower confidence limits for the treatment differences in the adjusted means were greater than the noninferiority margin of -4.0 letters (Figure 2). Additionally, across the three treatment groups, a comparable proportion of subjects had gained ≥15, ≥10, ≥5, and ≥0 letters or avoided a loss of ≥15, ≥10, and ≥5 letters from baseline at Week 48/52/56 in the two studies (Figure 17).

5.3. Conclusion and Recommendation

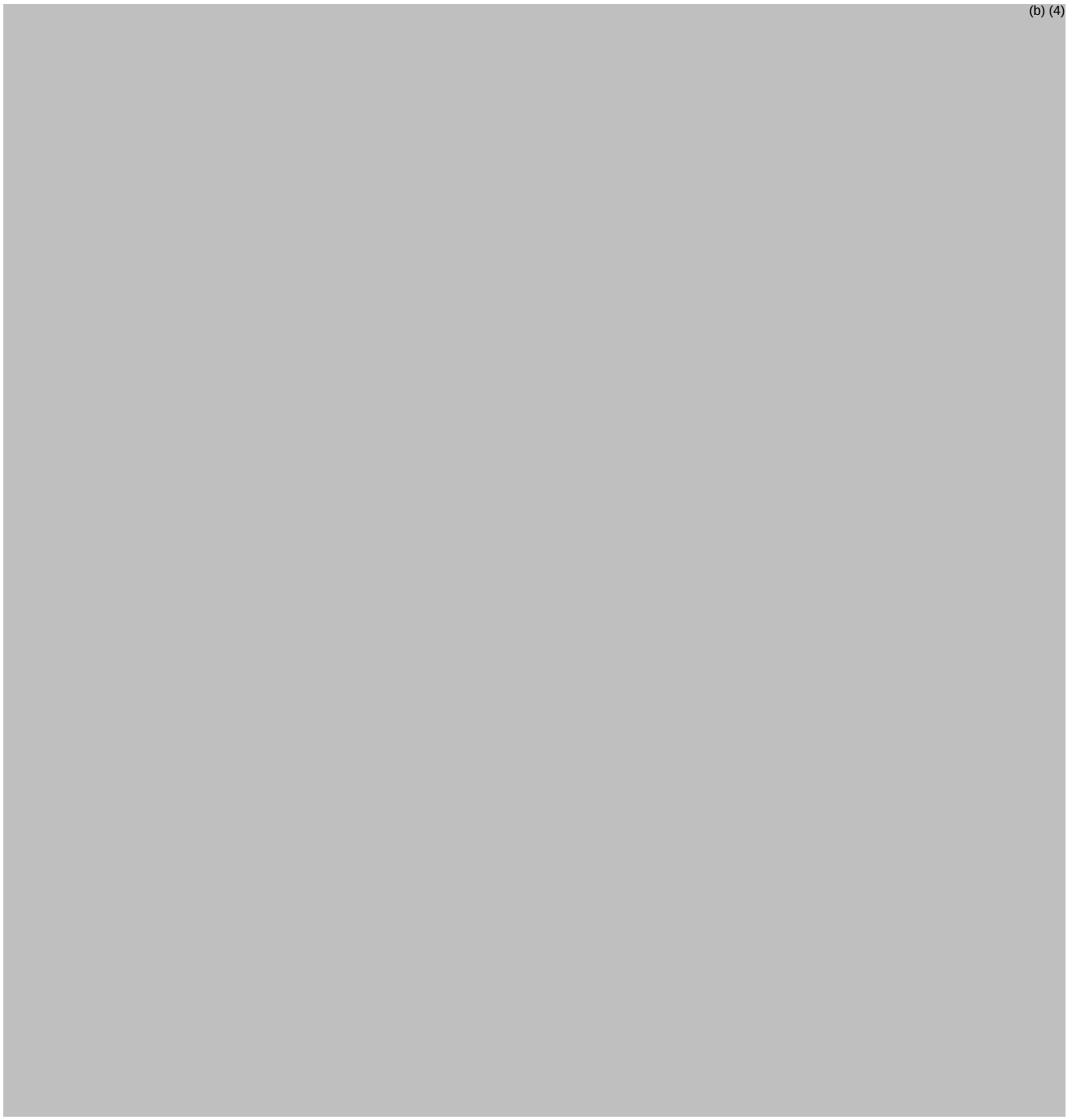
Based on the collective efficacy evidence from the two adequate and well controlled trials of TENAYA/LUCENRE studies, the reviewer concludes that the application for the nAMD indication provided substantial evidence for comparable efficacy benefit of faricimab administered up to every 16-week interval after four initial monthly injections compared to aflibercept administered every 8-week after three initial monthly injections.

Similarly, based on the collective efficacy evidence from the two adequate and well controlled trials of YOSEMITE/RHINE studies, the reviewer concludes that the application for the DME indication provided substantial evidence for comparable (but not superior) efficacy benefit of both doses of faricimab Q8W and PTI compared to aflibercept Q8W.

Finally, noting that faricimab in the TENAYA/LUCERNE studies and faricimab PTI dosing in YOSEMITE/RHINE studies were administered based on protocol defined disease activity criteria, the reviewer defers to the medical review team regarding the appropriate dosing recommendation for use in clinical practice for the indications sought.

5.4. LABELING RECOMMENDATION

The Applicant's proposed texts, tables, and figures presented in Section 14.1 (for the nAMD indication) and in Section 14.2 (for the DME indication) of the draft label appear acceptable. Regarding the tables and figures reported in these sections, the reviewer has the following recommendations:



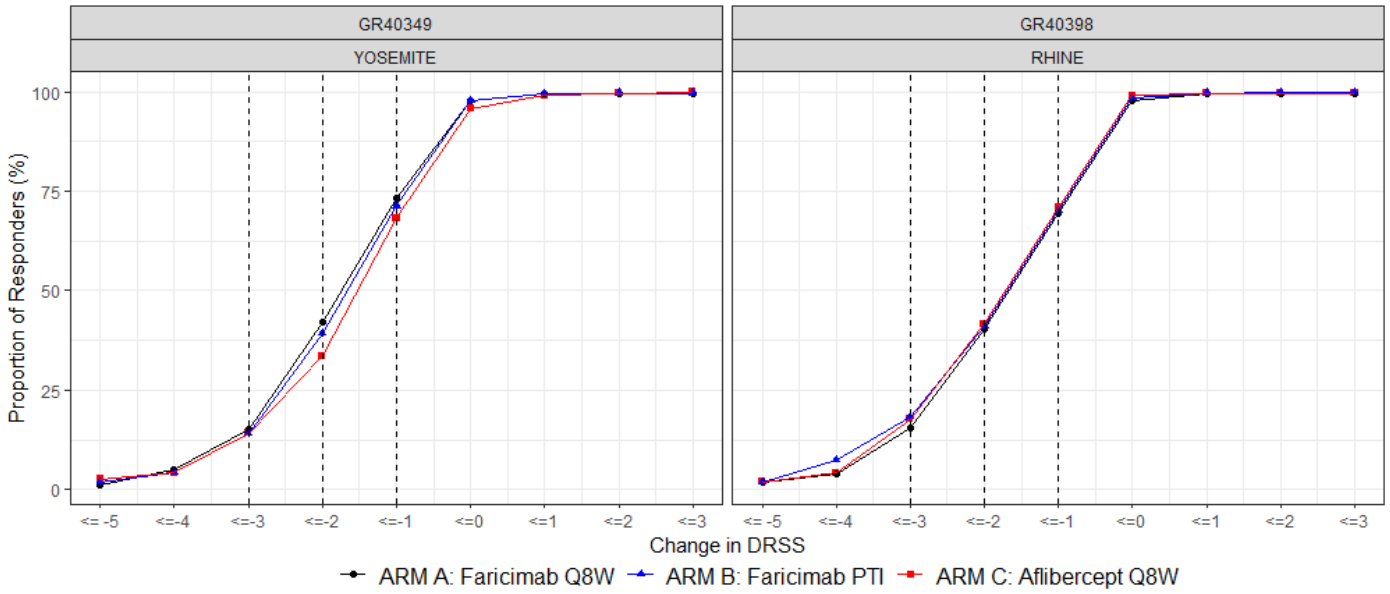
Appendix 1:

Table 40: Proportion of Subjects Who Avoided a Loss of ≥15 and ≥10 Letters in BCVA from Baseline at Week 48/52/56 (Treatment Policy Estimand) (ITT Population)

Study	Analysis Method	Faricimab Q8W	Faricimab PTI	Aflibercept	Difference (97.5% CI) Faricimab Q8W vs. Aflibercept	Difference (97.5% CI) Faricimab PTI vs. Aflibercept
Avoided a Loss of >=15 letters (%)						
YOSEMITE	Observed	98.2 (96.5, 100.0)	98.2 (96.5, 100.0)	98.9 (97.6, 100)	-0.7 (-2.9, 1.5)	-0.7 (-2.9, 1.5)
	LOCF	98.7 (97.3, 100.0)	98.1 (96.3, 99.8)	97.5 (95.5, 99.4)	1.3 (-1.2, 3.7)	0.6 (-2.0, 3.3)
RHINE	Observed	98.6 (97.0, 100.0)	98.4 (96.8, 100.0)	98.3 (96.7, 100.0)	0.2 (-2.1, 2.5)	0.0 (-2.3, 2.3)
	LOCF	98.1 (96.4, 99.8)	98.7 (97.3, 100.0)	98.4 (96.9, 100.0)	-0.3 (-2.6, 2.0)	0.3 (-1.8, 2.4)
Avoided a Loss of >=10 letters (%)						
YOSEMITE	Observed	96.5 (94.1, 98.9)	97.9 (96.0, 99.8)	97.8 (95.9, 99.8)	-1.4 (-4.5, 1.7)	0.0 (-2.6, 2.7)
	LOCF	97.1 (95.0, 99.2)	96.8 (94.6, 99.0)	95.5 (92.9, 98.1)	1.6 (-1.8, 4.9)	1.3 (-2.2, 4.7)
RHINE	Observed	97.8 (95.9, 99.8)	97.7 (95.9, 99.6)	98.0 (96.2, 99.8)	-0.2 (--2.8, 2.5)	-0.3 (-2.9, 2.3)
	LOCF	97.8 (96.0, 99.6)	98.1 (96.4, 99.8)	98.1 (96.4, 99.8)	-0.3 (-2.8, 2.2)	-0.0 (-2.4, 2.4)

Source: Based on Reviewer's Analysis.

Figure 27: Cumulative Distribution of the Change in DRSS from Baseline at Week 52 (Treatment Policy Estimand) (ITT Population) (YOSEMITE/RHINE)



Source: Based on Reviewer's Analysis where missing DRSS data were imputed using the last observation carried forward approach.

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Appendix 2: Personalized Treatment Interval

3.1.1.1 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 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.

Interval extended by 4 weeks:

- If the CST value increased or decreased by ≤10% **without** an associated ≥10-letter BCVA decrease

Interval maintained:

- If the CST decreased by >10% **or**
- CST value increased or decreased by ≤10% **with** an associated ≥10-letter BCVA decrease **or**
- CST value increased between >10% and ≤20% **without** an associated ≥5-letter BCVA decrease

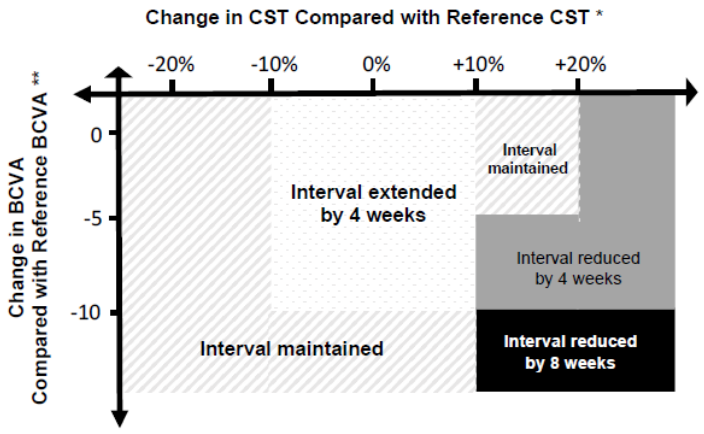
Interval reduced by 4 weeks:

- If the CST value increased between >10% and ≤20% **with** an associated ≥5- to <10-letter BCVA decrease **or**
- CST value increased by >20% **without** an associated ≥10-letter BCVA decrease

Interval reduced by 8 weeks:

- If the CST value increased by >10% **with** an associated ≥10-letter BCVA decrease.

Figure 2 Algorithm for IxRS-Determined Study Drug Dosing Intervals



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.

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