CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761235Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader, Division Director, and Office Director Review of BLA 761235

Review Completion Date	See DARRTS Stamp Date
From	William M. Boyd, M.D., Wiley Chambers, M.D., Charles Ganley, M.D.
Subject	Cross-Discipline Team Leader, Division Director, and Office Director Review
BLA #	761235
Applicant	Genentech, Inc.
Date of Submission	May 28, 2021
PDUFA Goal Date	January 28, 2022 (Rare Pediatric Disease Priority Review Voucher)
Proprietary Name	Vabysmo
Established or Proper Name	faricimab-svoa
Dosage Form(s)	Intravitreal injection
Applicant Proposed Indications	Treatment of patients with: • Neovascular (wet) age-related macular degeneration (nAMD) • Diabetic macular edema (DME) • Diabetic retinopathy (DR)
Dosing Regimen(s)	Neovascular (wet) age-related macular degeneration: The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. Diabetic macular edema: VABYSMO is recommended to be dosed by following one of these two dose regimens: 1) 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography is achieved, then the interval of dosing may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on CST and visual acuity evaluations through week 52; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months) over the next 28 weeks. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (b) (4)
Regulatory Action	Approval for treatment of patients with: • Neovascular (wet) age-related macular degeneration (nAMD) • Diabetic macular edema (DME)
Indication(s)/Population(s)	Neovascular (wet) age-related macular degeneration (nAMD) Diabetic macular edema (DME)

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DEPI=Division of Epidemiology
DMPP= Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management
DPV=Division of Pharmacovigilance
OBP=Office of Biotechnology Products
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPMA=Office of Pharmaceutical Manufacturing Assessment
OPRO=Office of Program and Regulatory Operations
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSM=Office of Special Medicine

1. Summary

Faricimab is a humanized antibody of the CrossMAb format that binds vascular endothelial growth factor A (VEGF) and angiopoietin-2 (Ang-2). BLA 761235 Vabysmo (faricimab-svoa) injection, for intravitreal injection will be approved for the treatment of Neovascular (wet) age-related macular degeneration (nAMD) and Diabetic macular edema (DME).

Discussion of Dosing Schedule

As noted in the Medical Officer's Clinical Review, the primary clinical support for the proposed indications was derived from four Phase 3 trials, two trials (Lucerne and Tenaya) in patients with neovascular age-related macular edema (AMD) and two trials (Rhine and Yosemite) in patients with diabetic macular edema (DME). While each of these four trials is a two-year study, only the first year data has been submitted to the application. While the Division of Ophthalmology does not object to the submission of only the first year of clinical trials in nAMD or DME, the specific design and variability of dosing schedules used in these trials introduce limitations in the conclusions that can be drawn from these trials. (b) (4)

The design elements in the AMD trials which introduce limitations include the unequal treatment of the study arms in the dosing schedule. Patients assigned to the aflibercept arm received three initial monthly intravitreal administrations of aflibercept followed by intravitreal injections every eight weeks (q8W) for the duration of the study. Patients assigned to the faricimab arm received four initial monthly intravitreal injections followed by an evaluation 8 weeks later. The difference at Week 12 with faricimab patients receiving an injection and aflibercept patients not receiving an injection, unmasked the treatment arms allowing patients and investigators to know which patients were in which group. This creates the potential analysis issue since the visual acuity endpoint is dependent on patient effort. If trials Lucerne and Tenaya had been the only trials supporting faricimab, it is unlikely that there would have been sufficient evidence to support approval.

In addition to the study arms being unmasked, the faricimab group was subdivided into three non-nonrandomized arms based on patient response at the visits on Week 20 and 24. The evaluation criteria used to subdivide the groups used changes in visual acuity, changes in central macular thickness and physician judgement. The aflibercept arm was not evaluated in the same manner and not subdivided. Because the schedule of injections differed between faricimab and aflibercept, there was not equivalent timepoint to perform this evaluation and no physician judgement of the condition to apply.

Based on the subgroup assignment, patients considered to have active disease at week 20 received an injection at week 20, 28, 36, 44 and 52. Patients considered inactive at week 20, but active at week 24, received an injection at week 24, 36, 48. Patients who did not receive an

injection at either week 20 or week 24, received injections at week 28 and 44, regardless of whether the disease was considered active at week 28 or not. Once the dose regimen was determined, injections were given on the scheduled days. As described in the Study Report for Lucerne and Tenaya, the PTI dosing regimen was not part of the primary analysis reported in the primary CSR.

The lack of randomization at the time of the subgroup assignment prevents these trials from being able to compare the effect of the three dosing regimens on the efficacy. Instead, it suggests that a response to the first four injections can be used to identify as subset of patients who will maintain their visual acuity level through week 48 with few if any additional injections. It does not address the question of whether patients who have a better response at Weeks 20 and 24, could have improved their visual acuities to a greater extent if they had received additional injection(s). (b) (4)

(b) (4)

The study did not demonstrate superiority of faricimab over aflibercept, but instead demonstrated non-inferiority of faricimab to aflibercept.

The design elements in the DME trials, although different from the AMD trials, also introduce limitations in supporting a particular dose of faricimab by including unequal treatment regimens in the study arms based on different dosing schedules. Patients assigned to the aflibercept arm received five initial monthly intravitreal administrations of aflibercept followed by intravitreal injections every eight weeks (q8W) for the duration of the study. Patients assigned to one arm of the faricimab (faricimab q8W) dosing received six initial monthly intravitreal administrations of faricimab followed by intravitreal injections every q8W for the duration of the study. Patients assigned to the other faricimab arm (faricimab variable) received at least four initial monthly intravitreal injections and if the central macular field thickness was less than 325 microns, the interval for the next injection could be modified. The Week 12 visit was considered the first visit that the interval could be changed. Patients at the time of the Week 12 injection could be scheduled to receive their next injection four or eight weeks later. Patients at the time of each subsequent injection in this group could be scheduled to receive their next injection at the same

interval as the last injection, at an interval four weeks longer than the last injection or at an interval four (or eight) weeks shorter than the last interval. The differences at Week 16, 20 and 24 with patients receiving or not receiving an injection, unmasked the treatment arms allowing patients and investigators to know which patients were in which group. This creates the potential bias issue since the visual acuity endpoint is dependent on patient effort. If trials Rhine and Yosemite had been the only trials supporting faricimab, it is unlikely that there would have been sufficient evidence to support approval.

In Rhine and Yosemite, the faricimab arm with every 8 week dosing after six monthly doses was non-inferior to aflibercept dosed every eight weeks after five monthly doses. In this comparison, faricimab was dosed one more time than aflibercept and the faricimab was non-inferior to aflibercept. Faricimab dosed every 8 weeks after six monthly doses in light of all of the other clinical trials conducted and submitted with application is considered supported despite the one additional dose of faricimab in these two trials.

(b) (4)

Although not ideal, stemming from the differences in dosing regimens between the proposed product and the control, the data in the clinical trials would be expected to be able to support a dosing regimen in which faricimab is administered with initial monthly dosing followed by dosing intervals between 4 and 12 weeks apart. This is based on the majority of faricimab doses administered in the clinical trials with dosing intervals between 4 and 12 weeks, inclusive in all four clinical trials. It is further supported by faricimab dosed every eight weeks being non-inferior, but not superior to aflibercept dosed every eight weeks in spite of the faricimab group receiving one more initial monthly dose than aflibercept. (b) (4)

(b) (4)

Established Pharmacologic Class (EPC)

The applicant proposed the following established pharmacologic class (EPC) in the Highlights Indications and Usage (I&U) heading of the faricimab-svoa labeling: "*bispecific angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) inhibitor.*" The pharmacology/toxicology, clinical pharmacology, and OBP review staff supported this based on the *in vitro* data, non-clinical data, possible role of Ang-2 in angiogenesis and the decline on aqueous humor Ang-2 levels after injection in patients. The clinical staff did not because the applicant had not provided the added clinical contribution of the Ang-2 inhibition while still acknowledging that there was an effect on Ang-2 levels. Clinical proposed that the EPC be *vascular endothelial growth factor inhibitor* similar to other approved anti-VEGF drugs for similar indications.

The applicant provided information suggesting that the Ang-2 inhibition may allow for less frequent dosing because of the extended depression of aqueous humor Ang-2 levels. They believe that their pivotal studies, by allowing for less frequent dosing in some patients in the faricimab arms up to Q16W, demonstrate a longer effect duration. They also identified three approved applications that had included the term "bispecific" in the EPC in the Highlight I&U heading of their labeling.

This issue was discussed with Eric Brodsky, M.D. and Paul Brown, Ph.D. Dr. Brown noted that the applicant wants to have structure and mechanism of action be combined in the EPC. He suggested another option: vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor. This would treat them as separate mechanisms of action (MOA) in the event that there are future approvals for products with an MOA of Ang-2 inhibitor alone. It is also important to note that the structure of the three approved anti-VEGF inhibitors is different, but they all have the same EPC. Dr. Brodsky also noted that there are many other EPCs examples that include the mechanism of action but do not include the structure for drugs with different structures and the same mechanism of action: e.g., the EPC for adalimumab, golimumab, and infliximab (all monoclonal antibodies); etanercept (fusion protein); and certolizumab pegol (Fab fragment) are all identical: "tumor necrosis factor (TNF) blocker."

Although there is a theoretical basis to think that Ang-2 inhibition may contribute to the effect, the applicant cannot point to clinical effectiveness data that supports this. Attempts to demonstrate the added clinical benefit of Ang-2 inhibition for these diseases have not been able to do this, but those attempts may be limited. The specific example involves nesvacumab, which was administered to patients with nAMD or DME, in combination with aflibercept but could not demonstrate an added clinical benefit when compared to aflibercept alone in clinical trials.[1]

[1] https://investor.regeneron.com/news-releases/news-release-details/regeneron-provides-update-eylear-aflibercept-injection-and

Nesvacumab has not been reviewed as part of this application but trial results available publicly raise questions about the contribution of Ang-2 inhibition when in combination with anti-VEGF inhibition.

The applicant has not demonstrated that there is durability (i.e., less frequent dosing) of effect because the study design did not allow for a fair comparison to aflibercept because an aflibercept arm using the same dosing regimen as the faricimab (i.e., dose determined by disease activity) was not included in the trials. They also used 6.0 mg of faricimab which is the higher of two tested concentrations; the 1.5 mg dose of faricimab appears to be effective in some of the trials. The studies simply showed that some patients are very responsive to anti-VEGF therapies and may be dosed less frequently which is already known from clinical practice.

After taking all the information into account, the EPC in the Highlights I&U heading should mention the Ang-2 inhibition in addition to the VEGF inhibition for the following reasons:

- Ang-2 inhibitors are being studied for other diseases. If a drug/biologic with only Ang-2 inhibition is approved, Ang-2 inhibitor would be a separate EPC and it would be important for clinicians to know that faricimab also inhibits Ang-2.
- Ang-2 inhibition is a new pharmacologic effect, and it is important that clinicians know that it is present in faricimab for safety and efficacy reasons. There is limited long term safety data and outcome data available for the product and dosing for several years may identify new issues related to this therapy. By knowing that this product is different from the current VEGF inhibitors, it may prompt clinicians to report potential issues that may not be present with other anti-VEGF inhibitors.
- Section 12 in the label identifies the Ang-2 inhibition. So, for consistency, it is reasonable to acknowledge it under the Highlights I&U heading of the label.
- Section 12 will also state: "The contribution of Ang-2 inhibition to the treatment effect and clinical response for nAMD and DME has yet to be established."
- Section 11 and 12 will state that faricimab is a bispecific antibody.

Number of Doses and Timing of Doses in the Q16W Dosing Cohort in Tenaya/Lucerne

An analysis was done to see whether the protocol was followed as it relates to the Q16W dosing, specifically did they get the correct number of doses at the specified weeks. Patients in the post-randomization Q16W cohort should have received 6 doses by week 52. The protocol did not specify that rescue doses could be provided so the Q16W patients should have received no more than six doses. After the 4 initial doses at week 0, 4, 8, and 12 weeks, q16W dosing regimen was administered at week 28 (5th dose), week 44 (6th dose) and week 60 (7th dose). Most patients did not exceed the number of doses at 52 weeks suggesting that few investigators opted to increase the number of doses and followed the protocol. Two subjects received seven doses within 52 weeks.

- *Subject* (b) (6) *in Lucerne*: 5th dose received on week 28 (as planned), 6th dose received at week 40 (12 weeks later rather 16 weeks) and then a 7th dose at week 48 (3rd dose in q16W cohort should be dose at week 60).
- *Subject* (b) (6) *in Tenaya*: 5th dose received on week 28 (as planned), 6th dose received dose at week 40 (12 weeks) and then a 7th dose at week 52 (12 weeks after 2nd dose).

Patients in the Q16W cohort should have received doses at week 0, 4, 8, 12, 28 and 44. The information below supports that the study protocol was followed for the Q16W cohort. The reason for the deviations was not explored further but may have been a result of COVID influencing when a patient could be evaluated. See results below.

Lucerne Study

- 141 patients met Q16W disease activity criteria
- 11 did not receive a dose at week 28
    - 6 received 5th dose on week 32 then 6th dose on week 48
    - 2 received 5th dose on week 36 then 6th dose on week 52
    - 2 received 5th dose on week 48 then 1 received 6th dose on week 64 and one patient received no more doses
    - 1 withdrew at week 24

Tenaya Study

- 148 patients met the disease activity criteria
- 15 did not receive a dose at week 28
    - 8 received 5th dose on week 32 then 6th dose on week 48 or 52
    - 4 received 5th dose on week 36 then 6th dose on week 52
    - 2 received 5th dose on week 40
    - 1 received 5th dose on week 56

Patients were not to receive other anti-VEGF therapy or steroids. Ten patients did however receive prohibited anti-VEGF or steroid therapy in addition to their randomized therapy.

Pivotal Trial Design Issues and Dosing Interval Labeling

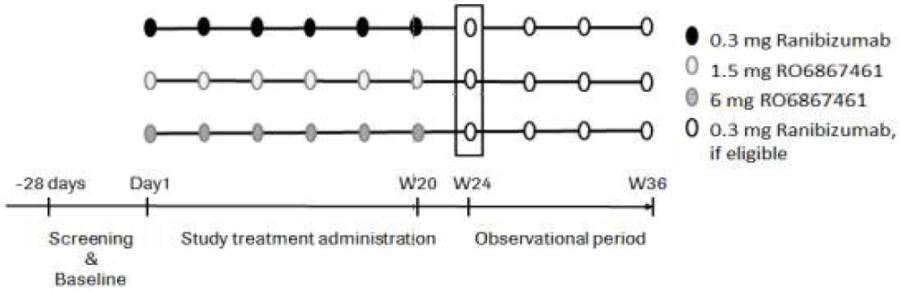
As noted in the reviews, the trial design in the AMD and the DME/DR studies included faricimab arms that allowed for post-randomization adjustment of the faricimab dose interval. An assessment of disease activity using pre-specified criteria directed the investigator to determine whether patients received faricimab dosing at Q8W, Q12W or Q16W intervals. The trials did not include a similar aflibercept arm that followed the same dosing adjustment post-randomization.

In the AMD trials, approximately 80% of the faricimab patients received dosing at the Q12W or Q16W dose interval. The applicant has taken those results to mean that there is a longer duration of effect with faricimab because the faricimab results for the BCVA endpoint included all faricimab patients who received dosing up to Q16W whereas the aflibercept patients received Q8W dosing after the initial monthly dosing. For all of the studies, the noninferiority comparison to aflibercept was met. This gives the impression that you can achieve a similar response to aflibercept with less frequent dosing. This is misleading because aflibercept was not dosed similarly to faricimab. Had aflibercept undergone post-randomization adjustment of the dosing interval, similar numbers of aflibercept patients may have been observed. For example, the Boulevard study suggests that ranibizumab maintains effectiveness when given less frequently to some patients.

Boulevard randomized DME patients (enrolled 229) to one of three arms: 0.3 mg ranibizumab, 1.5 mg faricimab or 6 mg faricimab every 4 weeks from day 1 to week 20 (week 0, 4, 8, 12, 16, 20). After week 20, the patients were followed and not dosed for 16 weeks unless rescue was needed. (see figure below)

Boulevard Study Dosing and Observation Period Off Drug

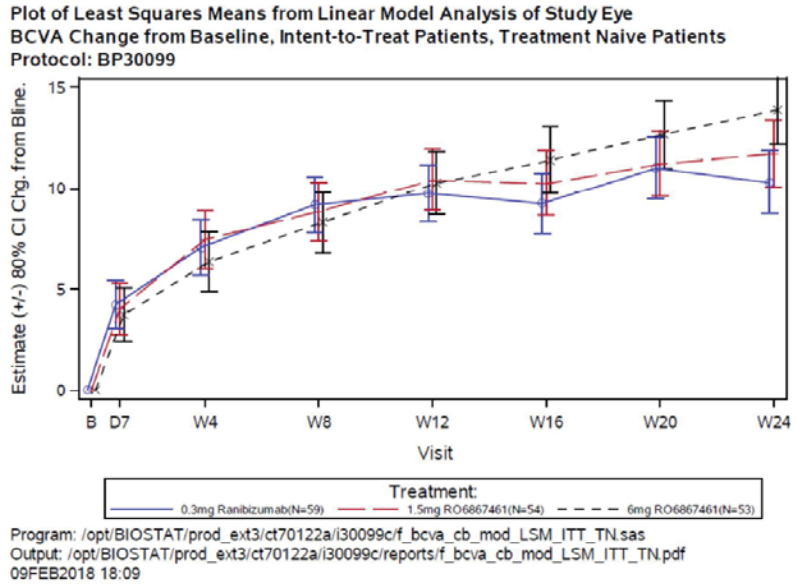
Figure 1 Study Design



The figure below shows that the change in BCVA is similar for all treatment arms. Note that the change in BCVA for 6 mg faricimab dose was similar to 1.5 mg faricimab.

Boulevard Study Change in Mean BCVA Change

Figure 3 Least Square Means from Linear Model Analysis of Study Eye (Treatment-Naive Patients)

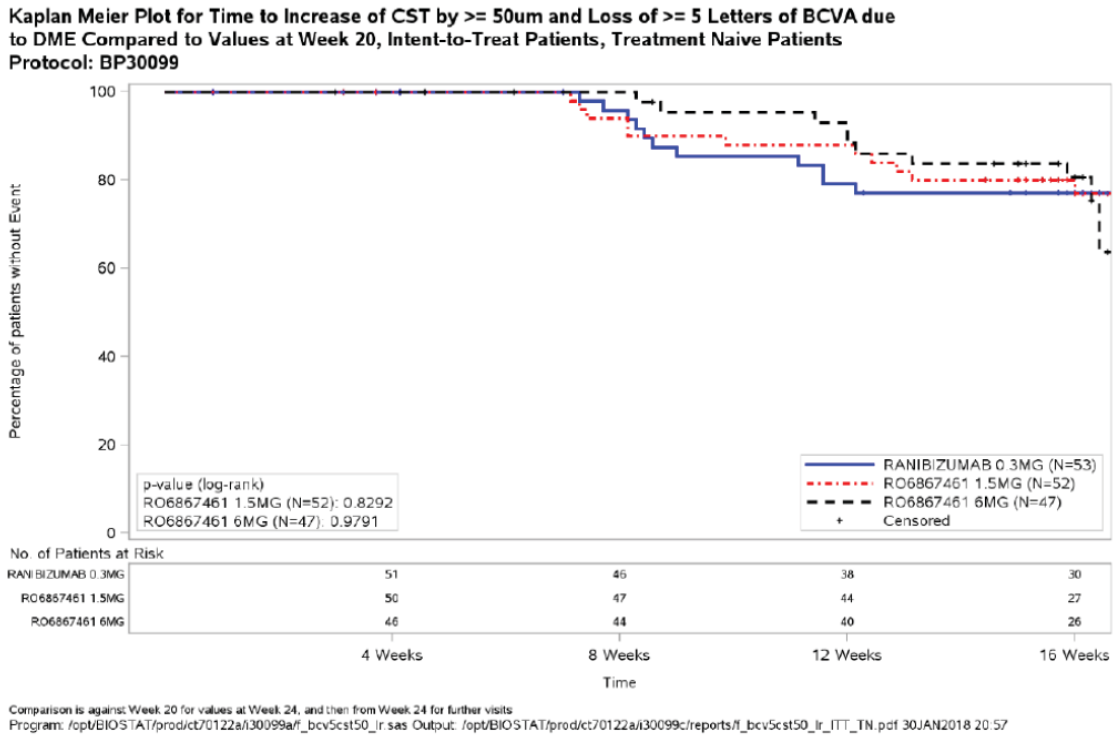


BCVA=best corrected visual acuity

The figure below shows the Kaplan Meier plot of the patients who did not achieve the disease activity criteria for active disease over the 16 week period after dosing ended. After 16 weeks with no treatment, almost 80% of ranibizumab patients, had not reached the active disease

activity criteria which was similar to the faricimab patients. This suggests that anti-VEGF therapy alone may have achieved similar results as faricimab.

Figure 17 Time to Disease Reactivation (Treatment-Naive Patients)



APPEARS THIS WAY ON ORIGINAL

BCVA=best corrected visual acuity; CST=central subfield thickness; DME=diabetic macular edema; VEGF=vascular endothelial growth factor

The applicant has emphasized that 80% percent of faricimab AMD patients in the Tenaya and Lucerne study were treated with Q12W or Q16W dosing. These results are uninterpretable without an aflibercept arm with similar dosing criteria to compare. The applicant has included this information in the label and FDA included language to explain the limitation of the trial design.

(b) (4)

The study design of the phase 3 studies allowed for post-randomization changes in the dose interval based in part on disease activity criteria. The percentage of patients in each dose interval cohort are not generalizable to a broader AMD and DME population for a variety of reasons. The inclusion/exclusion criteria limited enrollment to a select subset of AMD and DME patients and there is no empirical data that a similar magnitude would be observed if eligibility criteria

allowed for broader enrollment. The disease activity criteria, which was instrumental in determining dose frequency, is unvalidated. Stricter criteria would have changed how patients were treated resulting in different percentages of subjects in each dose interval cohort. There was not a similarly dosed aflibercept arm for comparison which makes the percentages difficult to interpret.

Contribution of Ang-2 Inhibition to Treatment

The contribution of Ang-2 inhibition to the treatment effect and clinical response for nAMD and DME has yet to be established. The applicant has suggested that it may contribute to the durability of effect, but it is not clear that the duration of effect with faricimab is different from aflibercept based on the results from the phase 3 trials. The lack of an aflibercept arm dosed similarly makes it difficult to interpret. If future studies sort out that there is a more prolonged effect, the reason may simply be that a higher dose of faricimab was administered (b) (4) Further study, possibly in different populations of patients and evaluating endpoints other than change in BCVA may better define any contribution.

(b) (4)

Corneal Endothelial Cell Health

The impact of faricimab on corneal endothelial health has not been evaluated. The safety profile of faricimab was otherwise similar to the safety profile of the approved anti-VEGF products. The most common adverse reaction (≥ 5%) reported in patients receiving faricimab was conjunctival hemorrhage (7%). Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, , sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

Combination Product

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including this product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER has primary jurisdiction over these products, including this product.

Benefit-Risk Assessment

NDA 215092 Benefit-Risk Integrated Assessment

The adequate and well controlled studies (GR40306 [TENAYA] and GR40844 [LUCERNE]) contained in this submission establish the efficacy of Vabysmo (faricimab-svoa) injection, 6 mg (0.05 mL of 120 mg/mL solution) for the treatment of neovascular (wet) age-related macular degeneration (nAMD) when the product is administered intravitreally every 4 weeks (approximately every 28 days, monthly) for the first four doses, and then as described in the proposed labeling. This demonstration of efficacy is based on non-inferiority in mean change from baseline in BCVA at Week 40 compared to aflibercept administered intravitreally.

The adequate and well controlled studies (GR40349 [YOSEMITE] and GR40398 [RHINE]) contained in this submission establish the efficacy of Vabysmo (faricimab-svoa) injection, 6 mg (0.05 mL of 120 mg/mL solution) for the treatment of diabetic macular edema (DME) when the product is administered as described in the proposed package insert. This demonstration of efficacy is based on non-inferiority in mean change from baseline in BCVA at Week 40 compared to aflibercept administered intravitreally.

(b) (4)

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

There is a favorable benefit-risk ratio of faricimab 6 mg (0.05 mL of 120 mg/mL solution) in the treatment of neovascular (wet) age-related macular degeneration (nAMD) and DME with some of the proposed dosing regimens.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide. • The neovascular form of AMD makes up about 10% of all AMD cases, but accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments. • The natural history of untreated wet AMD is that most eyes lose a letter of visual acuity each month. • Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus (DM). The pathology includes microvascular leakage followed by proliferation of abnormal vessels (PDR). • The most common cause of vision loss from DR is DME, which can occur at any stage of DR and is characterized by edema and retinal thickening.	The goal of treatment of wet AMD is the preservation of the central retina (macula) and the preservation of central visual acuity. The goal of treatment of DR and DME is to prevent or stop progression of DR and DME.
Current Treatment Options	• Lucentis, Eylea and Beovu have been shown to be safe and effective and are approved for the treatment of nAMD. The use of Avastin is supported by adequate and well controlled studies, but a BLA for its use intravitreally has never been submitted. • Lucentis and Eylea have been shown to be safe and effective and are approved to treat DME and DR in patients with and without DME.	Faricimab was non-inferior to Eylea (aflibercept) in the treatment of nAMD and DME. Faricimab would provide practitioners with an additional treatment option.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Studies TENAYA and LUCERNE demonstrate that faricimab was non-inferior to aflibercept in change from baseline in best-corrected visual acuity (BCVA) averaged over Weeks 40/44/48 in patients with nAMD. • Studies YOSEMITE and RHINE demonstrate that faricimab was non-inferior to aflibercept in change from baseline in best-corrected visual acuity (BCVA) averaged over Weeks 48/52/56 in patients with DME.	Adequate and well controlled studies support the efficacy of faricimab in patients with nAMD and DME. Use of the product led to patients maintaining stable visual acuity.
Risk and Risk Management	• The impact of faricimab on corneal endothelial health has not been evaluated. The safety profile of Vabysmo was otherwise similar to the safety profile of the approved anti-VEGF products.	The following phase 4 requirement will be required: Conduct a controlled trial to evaluate the corneal endothelial health of eyes treated with faricimab by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving faricimab.

2. Background

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

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

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

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

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

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

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

Faricimab has not been marketed in the U.S. Faricimab has not been approved for marketing in any other countries.
Following is a summary of regulatory activity for the product:

- IND 119225 received August 29, 2013
- Chemistry, manufacturing, and controls (CMC) Type C meeting held April 3, 2017

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

3. Product Quality

OPQ completed their integrated review of the original application on 12/15/2021.

Faricimab-svoa is a humanized bispecific IgG1 antibody that binds vascular endothelial growth factor A (VEGF-A) with one arm and angiopoetin-2 (Ang-2) with the other arm. It is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The antibody consists of two different heavy chains (VEGF-HC with 452 amino acid residues and Ang-2-HC with 462 amino acid residues) and two different light chains (VEGF-LC with 214 amino acid residues and Ang-2-LC with 213 amino acid residues). The CH2 domain of each heavy chain contains N-linked glycosylation at the conserved Asn site that is typical of those observed for CHO-produced antibodies. Faricimab-svoa has a total molecular weight of approximately 146 kDa (peptide chains only).

Faricimab-svoa is produced by expression of recombinant DNA encoding the faricimab-svoa nucleotide sequence in a CHO (b) (4) cell line using standard cell culture techniques. A two-tiered cell banking system was implemented. (b) (4)

Both the MCB and WCB were adequately tested to ensure product safety from adventitious agents and suitability for commercial manufacturing. The long-term stability of MCB and WCB will be assessed (b) (4)

3.1. Drug Substance Specification

Table S.4.1-1 Drug Substance Release Specification

Analytical Procedure	Acceptance Criterion
Color (Ph. Eur. Color Scale)	(b) (4)
Clarity/Opalescence (Ph. Eur. Opalescent Value) (NTU)	
pH	
Osmolality (mOsm/kg[b])	
Identity of Faricimab by Lys-C Peptide Mapping	
Purity by SE-UHPLC	
Main Peak (area%)	
Sum of HMW Forms (area%)	
Purity by NR-CE-SDS[a]	
Main Peak (%CPA)	
Sum of LMW Forms (%CPA)	
Purity by IE-HPLC	
Main Peak (area%)	
Acidic Region (area%)	
Acidic Peak 2 (area%)	
Basic Region (area%)	
Content of Protein by UV (mg/mL)	
Potency by Bioassay	
Anti-VEGF by VEGF-Reporter Gene Assay (% relative potency)	
Anti–Ang-2 by Tie-2 Phosphorylation Assay (% relative potency)	
Bioburden (CFU/10 mL)	
Bacterial Endotoxins (EU/mL)	
Content (b) (4) by HPLC (mg/mL)	

[a] NR-CE-SDS is also referred to as non-reduced CE-SDS in other parts of the dossier.
[b] mOsmol/kg and mOsm/kg are considered equivalent terms and are both used in the dossier.

Source: BLA 761235 Module 3.2.S.4.1

3.2. Drug Product Composition

Faricimab drug product is provided as a sterile, colorless to brownish-yellow solution for injection. It contains no preservatives.

Each single-use, 2 mL vial contains 6 mg (nominal) of faricimab at target pH 5.5. The drug product is formulated as 120 mg/mL faricimab, with the composition stated in the table below.
Each vial contains enough faricimab to adequately fill a syringe and deliver 6 mg of faricimab.

Table P.1-1 Composition of Faricimab Drug Product

Ingredient	Nominal Amount per Vial	Concentration	Function	Specification
Faricimab	6.00 mg	120 mg/mL	Active ingredient	Section S.4.1 *Specification*
L-Histidine	155 µg	20 mmol/L	(b) (4)	USP-NF/Ph. Eur./JP
Acetic Acid (b) (4)	QS to pH 5.5			Ph. Helv.[a]
L-Methionine	52.2 µg	7 mmol/L		USP-NF/Ph. Eur./JP
Sodium Chloride	73.1 µg	25 mmol/L		USP-NF/Ph. Eur./JP
D-Sucrose	2.74 mg	160 mmol/L		USP-NF/Ph. Eur./JP
Polysorbate 20	20.00 µg	0.4 mg/mL		USP-NF/Ph. Eur./JPE
Water for Injection	QS to 0.05 mL	—		USP-NF/Ph. Eur./JP

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

Source: BLA 761235 Module 3.2.P.1

3.3. Drug Product Specification

Table P.5.1-1 Drug Product Specification

Analytical Procedure	Release Acceptance Criterion	Stability Testing Acceptance Criterion
Physical State	Liquid	—
Color (Ph. Eur. Color Scale)	(b) (4)	
Clarity/Opalescence (Ph. Eur. Opalescent Value) (NTU)		
Extractable Volume (Ph. Eur./USP/JP) (mL/vial)		
Visible Particles	Practically free from particles[a]	Practically free from particles[a]
Subvisible Particles	(b) (4)	
Particles ≥ 10 µm per mL		
Particles ≥ 25 µm per mL		
Particles ≥ 50 µm per mL		
pH		
Osmolality (mOsm/kg[b])		
Identity of Faricimab by Lys-C Peptide Mapping	Positive identity	—

Source: BLA 761235 Module 3.2.P.5.1

The originally proposed Subvisible Particle (SvP) specification (see above) is (b) (4) times the USP limits described in USP<789>. The faricimab solution was evaluated without the use of the transfer filter needle for sample preparation. The applicant reported that for drug product manufactured for phase 3 and subsequently, subvisible particle counts during release testing and stability studies were sporadically above the USP <789> limits for ophthalmic solutions. In all cases, the subsequent stability time points demonstrated particle counts within the USP limits. An investigation including root cause analysis has been conducted. The inherent propensity of the protein to self-associate reversibly, analytical method variability was considered to be contributing factor. While the applicant claims that the filter needle will address any potential safety concern, the specification should be revised to test drug product which will actually be administered to the patient (i.e., after passing through the filter needle packaged with the drug product). A specification should be added to be consistent with the USP limits with the product prepared by passing it through the filter needle.

In response to a January 21, 2022, CMC Information Request regarding subvisible particle control strategy, the applicant the agreed to modify the control strategy for the subvisible particles. (b) (4) The acceptance criteria for this additional SvP test will comply with the USP<789> limits.

Table P.5.1-1 Drug Product Specification

Analytical Procedure	Release Acceptance Criterion	Stability Testing Acceptance Criterion
Physical State	Liquid	—
Color (Ph. Eur. Color Scale)	(b) (4)	
Clarity/Opalescence (Ph. Eur. Opalescent Value) (NTU)		
Extractable Volume (Ph. Eur./USP/JP) (mL/vial)		
Visible Particles	Practically free from particles[a]	Practically free from particles[a]
Subvisible Particles	(b) (4)	
Particles ≥ 10 µm per mL		
Particles ≥ 25 µm per mL		
Particles ≥ 50 µm per mL		
Subvisible Particles (b) (4)[b]		
Particles ≥ 10 µm per mL		
Particles ≥ 25 µm per mL		
Particles ≥ 50 µm per mL		
pH		
Osmolality (mOsm/kg[c])		
Identity of Faricimab by Lys-C Peptide Mapping	Positive identity	—

Table P.5.1-1 Drug Product Specification (cont.)

Analytical Procedure	Release Acceptance Criterion	Stability Testing Acceptance Criterion
Purity by SE-UHPLC	(b) (4)	
Main Peak (area%)		
Sum of HMW Forms (area%)		
Purity by NR-CE-SDS[d]		
Main Peak (%CPA)		
Sum of LMW Forms (%CPA)		
Content of Polysorbate 20 by HPLC (mg/mL)		
Purity by IE-HPLC		
Main Peak (area%)		
Acidic Region (area%)		
Acidic Peak 2 (area%)		
Basic Region (area%)		
Content of Protein by UV (mg/mL)		
Potency by Bioassay		
Anti-VEGF by VEGF-Reporter Gene Assay (% rel. potency)		
Anti–Ang-2 by Tie-2 Phosphorylation Assay (% rel. potency)		
Sterility, Final Container (Ph. Eur./USP/JP)		
Bacterial Endotoxins (EU/mL)		
Container Closure Integrity by Helium Leak Test		

[a] Visible particles release testing is based on AQL testing. Refer to Section P.3.4 *Controls of Critical Steps and Intermediates*. The result will be reported as practically free from particles if the AQL acceptance criteria are met.
[b] Subvisible Particles testing (b) (4) (b) (4)
[c] mOsmol/kg and mOsm/kg are considered equivalent terms and are both used in the dossier.
[d] NR-CE-SDS is also referred to as non-reduced CE-SDS in other parts of the dossier.

Source: BLA 761235 Module 3.2.P.5.1

3.4. Drug Product Container Closure

The container closure system consists of a (b) (4) glass vial with a (b) (4) rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap.

The faricimab drug product is co-packaged with a transfer filter needle ((b) (4) 18 G 1 x 1/2’’stainless steel transfer filter needle 5 µm; filter material: (b) (4)).

Table P.7-1 Container Closure Description

Component	Description	Manufacturer	Drug Master File No.[a]
Vial	[redacted]	(b) (4)	(b) (4)
Rubber Stopper			
Seal			Not applicable

[a] Refer to Module 1, Section 1.4.1 *Letters of Authorization*.

Source: BLA 761235 Module 3.2.P.7

3.5. Microbiology

The applicant has provided adequate sterility assurance. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

3.6. Establishment Information

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Roche Diagnostics GmbH (FEI 3002806560), proposed for DS manufacture. Following a review of requested manufacturing site records under Section 704(a)(4) for the drug substance manufacturing facility, a recommendation of approval was made for this facility. This document review is captured in both eNSpect 204599 and CMS WA 407375. Based on the records review, a post-approval inspection has been requested and this request includes the potential inspection items outlined in the Office of Biotechnology Products Review. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for F Hoffmann La Roche Limited (FEI 3003973536), proposed for DP manufacture. Based on the site's inspection history an inspection waiver was granted for the DP manufacturing site, and a recommendation of approval was made for this facility.

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Overall Recommendation: **Approval**					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, DS in-process control testing (including virus and mycoplasma testing), DS QC testing, DS release, DS stability testing, DS storage, preparation and storage of MCB and WCB	Roche Diagnostics GmbH, (Nonnenwald 2, 82377 Penzberg, Germany)	3002806560 / 323105205	704(A)(4) Assessment Performed with an approval recommendation	N/A	Approve based on 704(a)(4)
Additional site for virus and mycoplasma testing, additional storage site for part of the MCB	Genentech, Inc. (1 DNA Way, South San Francisco, CA 94080, United States)	2917293 / 080129000	Facility history assessment performed with an approval recommendation	N/A	Approved based on Previous History
Additional site for virus and mycoplasma testing	Genentech Inc. (Oceanside)	3006129086 / 146373191	Facility history assessment performed with an	N/A	Approved based on Previous History
	(1 Antibody Way, Oceanside, CA 92056, United States)		approval recommendation		
Additional site for DS storage	F. Hoffmann La Roche Ltd. (Grenzacherstrasse 124, 4070 Basel, Switzerland)	3002807200 / 482242971	Facility history assessment performed with an approval recommendation	N/A	Approved based on Previous History
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture (including filling/primary packaging), in-process control testing, QC release testing and stability testing except microscopic particle count test, DP release, DP storage, labeling and secondary packaging including co-packaging, release of finished DP	F. Hoffmann-La Roche Ltd. (Wurmisweg, CH-4303 Kaiseraugst, Switzerland)	3003973536 / 485244961	Facility history assessment performed which included a District File Review. An Inspection Waiver was issued with an approval recommendation.	N/A	Approved based on Previous History
QC release testing and stability testing of microscopic particle	(b) (4)		Facility history assessment performed with an	N/A	Approved based on Previous History

3.7. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps

None.

3.8. OPQ Recommendation

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761235 for VABYSMO (faricimab-svoa) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of VABYSMO (faricimab-svoa) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

4. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 11/18/2021:

Faricimab is a humanized bi-specific IgG1 monoclonal antibody directed against VEGF-A and Ang-2. The VEGF binding fragment (Fab) is identical to ranibizumab (Lucentis, BLA 125156, also Genentech). The Ang-2-binding Fab binds Ang-2 with high affinity. The Fc portion of the antibody has been altered so that it does not bind to Fc receptors. Faricimab is proposed to have anti-angiogenic activity by neutralizing VEGF-A and Ang-2 by binding to the receptor binding domains of each protein and inhibiting binding to its receptors.

The main adverse findings identified in the nonclinical studies were ocular inflammation and various findings in the heart in both rabbits and monkeys. The nonclinical data support the ocular findings are primarily related to development of an immunogenic response to faricimab and not a direct pro-inflammatory effect of faricimab. The animal data is insufficient to conclude whether the heart findings are a species-specific ADA response or a direct pro-inflammatory effect. However, together with the clinical data, the weight of data supports minimal clinical concern.

An embryofetal development (EFD) study in cynomolgus monkeys showed an increase incidence of abortions in faricimab treated monkeys at IV doses of 1 or 3 mg/kg administered weekly on gestation days 20 to 48. The increase was not dose dependent. No other maternal or fetal parameter showed a test article-related effect. Based on the increase incidence of the abortions, a test article related effect cannot be ruled out. Serum exposure (Cmax) in pregnant monkeys at the low dose of 1 mg/kg IV was 158 times the human exposure at the intended dose of 6 mg/eye.
Nonclinical Pharmacology/Toxicology recommended approval.

5. Clinical Pharmacology

From the original Clinical Pharmacology review dated 11/16/21:

The clinical pharmacology of faricimab was assessed in two Phase 1 studies (Study BP28936 in patients with nAMD and Study JP39844 in Japanese patients with nAMD and DME/DR), three Phase 2 studies (Studies CR39521 and BP29647 in patients with nAMD and Study BP30099 in patients with DME and DR), and four Phase 3 studies (Studies GR40306 and GR40844 in patients with nAMD and Studies GR40349 and GR40398 in patients with DME and DR). The to-be-marketed formulation was used in the Phase 3 studies.

The clinical pharmacology review was focused on the appropriateness of the proposed dosing regimen of 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W for nAMD, DME, and DR.

After review of the clinical pharmacology data submitted in support of BLA 761235 the Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) found the application acceptable to support approval from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on four randomized controlled Phase 3 trials (Studies GR40306, GR40844, GR40349, and GR40398) in patients with nAMD or DME and DR. Exposure-response analysis provided supportive evidence of effectiveness.
Proposed general dosing instructions	6 mg (0.05 mL) administered every 4 weeks (Q4W) for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to every 16 weeks (Q16W) for nAMD, DME, and DR; some patients may be dosed as frequently as Q4W.
Dosing in patients (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.
Labeling	The proposed labeling concepts are generally acceptable.
Pivotal or supportive evidence of effectiveness	The to-be-marketed formulation was used in the Phase 3 studies.

6. Clinical Efficacy

From the original Medical Officer Review dated 12/13/2021:

Clinical data for Studies TENAYA and LUCERNE were reviewed to support efficacy for the indication nAMD. Clinical data for Studies YOSEMITE and RHINE were reviewed to support safety and efficacy for the indications DME and DR.

Study GR40306 (TENAYA) Efficacy Results – Primary nAMD Endpoint

Table 6.1.2-6 Change from Baseline in BCVA, Study Eye Averaged over Week 40/44/48 *

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

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

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

Study GR40844 (LUCERNE) Efficacy Results – Primary nAMD Endpoint

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

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

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

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

Study GR40349 (YOSEMITE) Efficacy Results – Primary DME Endpoint

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

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

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

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

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

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

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(b) (4)

Study GR40398 (RHINE) Efficacy Results – Primary DME Endpoint

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

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

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

For the ITT, PP and TN populations, the confidence interval for the difference between the faricimab Q8W and aflibercept arms was greater than -0.7.

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

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

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(b) (4)

Efficacy Summary Statement

The data from two studies, GR40306 (TENAYA) and GR40844 (LUCERNE), contained in this submission establishes the efficacy of faricimab ophthalmic solution, 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 28 days x 4 and then as proposed in the package insert for the treatment of neovascular age-related macular degeneration.

The data from two studies, GR40349 (YOSEMITE) and GR40398 (RHINE), contained in this submission establishes the efficacy of faricimab ophthalmic solution, 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 28 days x 4 and then as proposed in the package insert for the treatment of diabetic macular edema.

(b) (4)

7. Safety

From the original Medical Officer Review dated 12/13/2021:

7.1. Safety Database

The safety database primarily consists of two nAMD studies GR40306 (TENAYA) and GR40844 (LUCERNE) and two DME/DR studies GR40349 (YOSEMITE) and GR40398 (RHINE). The clinical cutoff date (CCOD) for the safety update report was 09 April 2021.

AMD STUDIES

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

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

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

The mean number of intravitreal injections of active study treatment were 9 and 11 for the faricimab and aflibercept treatment groups, respectively.

DME/DR STUDIES

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

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

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

Through the safety update report clinical cutoff date, the mean number of intravitreal injections of active study treatment were 13, 12, and 13 for the faricimab Q8W, faricimab PTI (personalized treatment interval), and aflibercept Q8W treatment groups, respectively.

7.2. Deaths

AMD STUDIES

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

Preferred Term	Week 48 Pooled TENAYA and LUCERNE (N=1326)		SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
Total number of deaths	9 (1.4)	8 (1.2)	19 (2.9)	15 (2.3)
Primary cause of deaths				
N	9	8	19	15
Cardiac failure	0	2 (25.0)	1 (5.3)	2 (13.3)
Fall	1 (11.1)	1 (12.5)	1 (5.3)	1 (6.7)
Acute kidney injury	0	1 (12.5)	0	1 (6.7)
Brain edema	1 (11.1)	0	1 (5.3)	0

Preferred Term	Week 48 Pooled TENAYA and LUCERNE (N=1326)		SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
Cardiac failure congestive	1 (11.1)	0	2 (10.5)	0
Cardiopulmonary failure	0	1 (12.5)	0	1 (6.7)
Cerebrovascular accident	1 (11.1)	0	1 (5.3)	0
Unknown cause of death	1 (11.1)	1 (12.5)	1 (5.3)	2 (13.3)
Glioblastoma multiforme	0	1 (12.5)	0	1 (6.7)
Ill-defined disorder	1 (11.1)	0	1 (5.3)	0
Metastases to liver	0	1 (12.5)	0	1 (6.7)
Multiple organ dysfunction syndrome	1 (11.1)	0	1 (5.3)	0
Pancreatic carcinoma	1 (11.1)	0	1 (5.3)	0
Pneumonia	1 (11.1)	0	1 (5.3)	1 (6.7)
Pneumonia bacterial	1 (11.1)	0	1 (5.3)	0
COVID-19 pneumonia	0	0	1 (5.3)	1 (6.7)
Bile duct cancer	0	0	0	1 (6.7)
Cardiac failure chronic	0	0	1 (5.3)	0
Colon cancer stage IV	0	0	0	1 (6.7)
Myocardial infarction	0	0	1 (5.3)	0
Plasma cell myeloma	0	0	1 (5.3)	0
Pulmonary embolism	0	0	0	1 (6.7)
Pulmonary edema	0	0	1 (5.3)	0
Respiratory failure	0	0	1 (5.3)	0
Subdural hemorrhage	0	0	1 (5.3)	0
Sudden death	0	0	0	1 (6.7)

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

The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.

DME/DR STUDIES

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

Preferred Term	SUR CCOD Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Faricimab 6 mg All (N=1262) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
Total number of deaths	25 (4.0)	26 (4.1)	51 (4.0)	22 (3.5)
Primary cause of deaths				
N	25	26	51	22
Death	2 (8.0)	4 (15.4)	6 (11.8)	1 (4.5)
Acute myocardial infarction	1 (4.0)	1 (3.8)	2 (3.9)	2 (9.1)
Myocardial infarction	2 (8.0)	2 (7.7)	4 (7.8)	4 (18.2)
Bladder cancer	2 (8.0)	0	2 (3.9)	0
Cardiac arrest	2 (8.0)	0	2 (3.9)	1 (4.5)
Cardiac failure	0	3 (11.5)	3 (5.9)	0
Adenocarcinoma of colon	0	0	0	1 (4.5)
COVID-19	2 (8.0)	2 (7.7)	4 (7.8)	1 (4.5)
Cerebral hemorrhage	1 (4.0)	1 (3.8)	2 (3.9)	0
Completed suicide	0	0	0	1 (4.5)
Coronary artery disease	0	0	0	1 (4.5)
Diabetic complication	1 (4.0)	0	1 (2.0)	0
Diabetic gangrene	0	0	0	0
Embolism	1 (4.0)	0	1 (2.0)	0
General physical health deterioration	1 (4.0)	0	1 (2.0)	0
Hypotension	0	0	0	1 (4.5)
Left atrial dilatation	1 (4.0)	0	1 (2.0)	0
Leukemia	0	1 (3.8)	1 (2.0)	0
Pneumonia aspiration	0	1 (3.8)	1 (2.0)	0
Sepsis	1 (4.0)	0	1 (2.0)	0
Type 1 diabetes mellitus	0	0	0	1 (4.5)
COVD-19 pneumonia	1 (4.0)	2 (7.7)	3 (5.9)	1 (4.5)
Pneumonia	1 (4.0)	1 (3.8)	2 (3.9)	0
Chronic kidney disease	1 (4.0)	0	1 (2.0)	1 (4.5)
Pancreatic carcinoma metastatic	0	1 (3.8)	1 (2.0)	1 (4.5)
Acute pulmonary edema	0	1 (3.8)	1 (2.0)	0
Acute respiratory failure	1 (4.0)	0	1 (2.0)	0
Anemia	0	1 (3.8)	1 (2.0)	0
Cardiac failure congestive	1 (4.0)	0	1 (2.0)	0
Coronavirus infection	1 (4.0)	0	1 (2.0)	0
Dyspnea	0	1 (3.8)	1 (2.0)	0

Preferred Term	SUR CCOD Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Faricimab 6 mg All (N=1262) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
Hemorrhage intracranial	0	1 (3.8)	1 (2.0)	0
Hemorrhagic stroke	1 (4.0)	0	1 (2.0)	0
Hernia obstructive	0	1 (3.8)	1 (2.0)	0
Ischemic stroke	0	1 (3.8)	1 (2.0)	0
Pulmonary fibrosis	0	1 (3.8)	1 (2.0)	0

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

The deaths that occurred during the studies are consistent with the age and past medical history of the subjects enrolled.

7.3. Serious Adverse Events

AMD STUDIES

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

Preferred Term	Week 48 Pooled TENAYA and LUCERNE (N=1326)		SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
OCULAR				
Total number of patients with ≥ 1 adverse event	11 (1.7)	13 (2.0)	17 (2.6)	23 (3.5)
Total number of events	15	13	22	26
Neovascular Age-related macular degeneration	2 (0.3)	3 (0.5)	3 (0.5)	6 (0.9)
Retinal epithelial tear	4 (0.6)	0	4 (0.6)	0
Uveitis	2 (0.3)	1 (0.2)	2 (0.3)	1 (0.2)
Viral uveitis	2 (0.3)	0	2 (0.3)	0
Vitritis	2 (0.3)	0	2 (0.3)	0
Age-related macular degeneration	0	1 (0.2)	0	1 (0.2)
Cataract	1 (0.2)	0	2 (0.3)	1 (0.2)
Cataract cortical	0	1 (0.2)	0	1 (0.2)

Preferred Term	Week 48 Pooled TENAYA and LUCERNE (N=1326)		SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
Chorioretinitis	1 (0.2)	0	1 (0.2)	0
Corneal abrasion	0	1 (0.2)	0	1 (0.2)
Corneal edema	0	1 (0.2)	0	1 (0.2)
Endophthalmitis	0	1 (0.2)	2 (0.3)	1 (0.2)
Eye allergy	0	1 (0.2)	0	1 (0.2)
Facial bone fracture	0	1 (0.2)	0	1 (0.2)
Intraocular pressure increased	1 (0.2)	0	1 (0.2)	1 (0.2)
Subretinal fibrosis	0	1 (0.2)	0	1 (0.2)
Vitreous hemorrhage	0	1 (0.2)	0	1 (0.2)
Visual acuity decreased	0	0	1 (0.2)	1 (0.2)
Cataract operation complication	0	0	0	1 (0.2)
Cataract traumatic	0	0	0	1 (0.2)
Hyphema	0	0	0	1 (0.2)
Non-infectious endophthalmitis	0	0	0	1 (0.2)
Retinal degeneration	0	0	0	1 (0.2)
Retinal rear	0	0	0	1 (0.2)
Retinopathy hemorrhagic	0	0	0	1 (0.2)
Rhegmatogenous retinal detachment	0	0	1 (0.2)	0
Tractional retinal detachment	0	0	1 (0.2)	0
Vitreous hemorrhage	0	0	0	1 (0.2)

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

Through Week 48, the incidence of ocular serious adverse event was 2% for the faricimab and aflibercept treatment groups. Through the safety update report clinical cutoff date, the incidence of ocular serious adverse event was 3% for the faricimab and 4% for the aflibercept treatment groups.

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

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

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

Through Week 48, the incidence of non-ocular serious adverse event was 10% for the faricimab and 12% for the aflibercept treatment groups. Through the safety update report clinical cutoff date, the incidence of non-ocular serious adverse event was 16% for the faricimab and 18% for the aflibercept treatment groups.

DME/DR STUDIES

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

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

Preferred Term	SUR CCOD Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Faricimab 6 mg All (N=1262) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
Visual impairment	0	2 (0.3)	2 (0.2)	0
Posterior capsule opacification	1 (0.2)	1 (0.2)	2 (0.2)	0
Cataract nuclear	1 (0.2)	0	1 (<0.1)	1 (0.2)
Diabetic eye disease	0	1 (0.2)	1 (<0.1)	0
Diabetic vascular disorder	0	1 (0.2)	1 (<0.1)	0
Macular edema	1 (0.2)	0	1 (<0.1)	0
Ocular ischemic syndrome	0	1 (0.2)	1 (<0.1)	0
Open angle glaucoma	0	1 (0.2)	1 (<0.1)	0
Posterior capsule rupture	0	1 (0.2)	1 (<0.1)	0
Swelling of eyelid	0	0	0	1 (0.2)

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

Through the safety update report clinical cutoff date, the incidence of ocular serious adverse event was 4% for the faricimab Q8W, 5% for the faricimab PTI (personalized treatment interval) and 3% for the aflibercept Q8W treatment groups.

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

	SUR CCOD Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Faricimab 6 mg All (N=1262) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
NON-OCULAR				
Total number of patients with ≥ 1 adverse event	456 (72.4)	462 (73.1)	918 (72.7)	462 (73.9)
Overall total number of events	1996	1846	3842	1795
Infections and infestations				
Total number of patients with ≥ 1 adverse event	256 (40.6)	234 (37.0)	490 (38.8)	258 (41.3)
Overall total number of events	443	381	824	464
Nasopharyngitis	58 (9.2)	44 (7.0)	102 (8.1)	66 (10.6)
Urinary tract infection	31 (4.9)	30 (4.7)	61 (4.8)	51 (8.2)

	SUR CCOD Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Faricimab 6 mg All (N=1262) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
COVID-19	31 (4.9)	43 (6.8)	74 (5.9)	25 (4.0)
Vascular Disorders				
Total number of patients with ≥ 1 adverse event	69 (11.0)	93 (14.7)	162 (12.8)	78 (12.5)
Overall total number of events	91	109	200	96
Hypertension	43 (6.8)	53 (8.4)	96 (7.6)	51 (8.2)
Injury, Poisoning and procedural complications				
Total number of patients with ≥ 1 adverse event	97 (15.4)	83 (13.1)	180 (14.3)	84 (13.4)
Overall total number of events	136	121	257	110
Fall	35 (5.6)	27 (4.3)	62 (4.9)	22 (3.5)

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

Through the safety update report clinical cutoff date, the incidence of non-ocular serious adverse event was 72% for the faricimab Q8W, 73% for the faricimab PTI (personalized treatment interval) and 74% for the aflibercept Q8W treatment groups.

7.4. Treatment Emergent Adverse Events and Adverse Reactions

AMD STUDIES

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

Preferred term	SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
OCULAR		
Total number of patients with ≥ 1 adverse event	319 (48.0)	308 (46.5)
Total number of events	768	708
Conjunctival hemorrhage	56 (8.4)	56 (8.5)

Preferred term	SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
Neovascular age-related Macular degeneration	53 (8.0)	50 (7.6)
Vitreous detachment	27 (4.1)	26 (3.9)
Eye pain	23 (3.5)	25 (3.8)
Dry eye	23 (3.5)	35 (5.3)
Cataract	38 (5.7)	27 (4.1)
Intraocular pressure increased	25 (3.8)	24 (3.6)
Vitreous floaters	25 (3.8)	14 (2.1)
Retinal pigment epithelial tear	19 (2.9)	10 (1.5)
Foreign body sensation in eyes	10 (1.5)	14 (2.1)
Punctate keratitis	12 (1.8)	16 (2.4)
Blepharitis	15 (2.3)	16 (2.4)
Posterior capsule opacification	15 (2.3)	14 (2.1)
Dry age-related macular degeneration	12 (1.8)	12 (1.8)
Lacrimation increased	6 (0.90	9 (1.4)
Photopsia	6 (0.9)	10 (1.5)
Eye irritation	11 (1.7)	4 (0.6)
Corneal abrasion	10 (1.5)	9 (1.4)
Ocular discomfort	8 (1.2)	4 (0.6)
Medication error	8 (1.2)	7 (1.1)
Ocular hypertension	9 (1.4)	5 (0.8)
Eye pruritus	8 (1.2)	5 (0.8)
Hordeolum	7 (1.1)	6 (0.9)
Iritis	7 (1.1)	2 (0.3)

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

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

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

Preferred term	SUR CCOD Pooled TENAYA and LUCERNE (N=1326)	
	Faricimab 6 mg (N=664) n (%)	Aflibercept 2 mg (N=662) n (%)
Non-OCULAR		
Total number of patients with ≥ 1 adverse event	439 (66.1)	448 (67.7)
Total number of events	1466	1526
Nasopharyngitis	48 (7.2)	52 (7.9)
Urinary tract infection	42 (6.3)	42 (6.3)
Hypertension	31 (4.7)	31 (4.7)
Upper respiratory tract infection	20 (3.0)	20 (3.0)
Arthralgia	31 (4.7)	25 (3.8)
Fall	31 (4.7)	33 (5.0)
Bronchitis	19 (2.9)	10 (1.5)
Headache	22 (3.3)	16 (2.4)
Sinusitis	19 (2.9)	15 (2.3)
Back pain	21 (3.2)	22 (3.0)
COVID-19	24 (3.6)	18 (2.7)
Cough	19 (2.9)	10 (1.5)
Dizziness	17 (2.6)	12 (1.8)
Basal cell carcinoma	16 (2.4)	8 (1.2)
Contusion	11 (1.7)	13 (2.0)
Atrial fibrillation	10 (1.5)	13 (2.0)
Diarrhea	9 (1.4)	14 (2.1)
Influenza	13 (2.0)	9 (1.4)
Pain in extremity	7 (1.1)	15 (2.3)
Pneumonia	8 (1.2)	13 (2.0)

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

Overall, there were no significant differences between groups in non-ocular adverse events in the nAMD studies.

DME/DR STUDIES

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

Preferred term	Pooled YOSEMITE and RHINE (N=1887)		
	Faricimab 6 mg Q8W (N=630) n (%)	Faricimab 6 mg PTI (N=632) n (%)	Aflibercept 2 mg Q8W (N=625) n (%)
Total number of patients with ≥ 1 adverse event	299 (47.5)	299 (47.3)	273 (43.7)
Total number of events	646	615	482
Conjunctival hemorrhage	50 (7.9)	42 (6.6)	40 (6.4)
Cataract	76 (12.1)	60 (9.5)	58 (9.3)
Vitreous detachment	31 (4.9)	26 (4.1)	25 (4.0)
Vitreous floaters	32 (5.1)	16 (2.5)	17 (2.7)
Intraocular pressure increased	31 (4.9)	21 (3.3)	16 (2.6)
Dry eye	29 (4.6)	26 (4.1)	16 (2.6)
Eye pain	13 (2.1)	20 (3.2)	21 (3.4)
Conjunctivitis	9 (1.4)	13 (2.1)	11 (1.8)
Cataract Cortical	8 (1.3)	11 (1.7)	9 (1.4)
Diabetic retinal edema	10 (1.6)	16 (2.5)	14 (2.2)
Medication error	9 (1.4)	9 (1.4)	6 (1.0)
Punctate keratitis	9 (1.4)	10 (1.6)	9 (1.4)
Posterior capsule opacification	12 (1.9)	7 (1.1)	11 (1.8)
Blepharitis	15 (2.4)	9 (1.4)	5 (0.8)
Vision blurred	7 (1.1)	3 (0.5)	7 (1.1)
Vitreous hemorrhage	5 (0.8)	1 (0.2)	3 (0.5)
Cataract nuclear	10 (1.6)	13 (2.1)	8 (1.3)
Diabetic retinopathy	4 (0.6)	13 (2.1)	7 (1.1)
Cataract subcapsular	19 (3.0)	14 (2.2)	9 (1.4)
Macular fibrosis	4 (0.6)	2 (0.3)	9 (1.4)
Sensation of foreign body	6 (1.0)	1 (0.2)	3 (0.5)
Ocular hypertension	2 (0.3)	8 (1.3)	2 (0.3)
Lacrimation increased	4 (0.6)	11 (1.7)	4 (0.6)
Eye pruritus	6 (1.0)	4 (0.6)	5 (0.8)
Eye irritation	6 (1.0)	3 (0.5)	6 (1.0)
Visual impairment	3 (0.5)	7 (1.1)	4 (0.6)
Corneal erosion	7 (1.1)	1 (0.2)	2 (0.3)
Hordeolum	2 (0.3)	3 (0.5)	8 (1.3)

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

In the DME studies, the overall ocular adverse event rates were similar between pooled faricimab Q8W, faricimab PTI (personalized treatment interval), and aflibercept treatment groups. The most common ocular adverse events for faricimab treated patients through the safety update report clinical cutoff date were cataract (12%) and conjunctival hemorrhage (8%).

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

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

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

Overall, there were no significant differences between groups in non-ocular adverse events in the DME studies.

7.5. Corneal Endothelium

Intravitreal injection of faricimab to the aqueous raises a question about health of the corneal endothelial cells. The applicant did not evaluate corneal endothelial cell in the clinical trials. Corneal endothelial cells are not visualized in typical eye examinations. If the number of corneal endothelial cells falls too low, corneal edema and loss of vision will occur. Without specific equipment to visualize the cells, a loss of cells would normally not be noticed until vision was lost.

The applicant will be required to conduct a controlled clinical trial in which the health of the corneal endothelial cells are evaluated by monitoring the number/density of corneal endothelial cells using specular microscopy over a period of at least one year in patients receiving faricimab.

Specifically, the PMR will state:

> Conduct a controlled trial to evaluate the corneal endothelial health of eyes treated with faricimab by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving faricimab.

Safety Summary Statement

The impact of faricimab on corneal endothelial health has not been evaluated. See Section 8.5 of this review regarding the need for a Post Marketing Requirement.

The safety profile of Vabysmo was otherwise similar to the safety profile of the approved anti-VEGF products. The most common adverse reaction (≥ 5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%). Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were vitreous hemorrhage, corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

8. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the BLA.

9. Pediatrics

The applicant has requested a full product specific waiver for all pediatric age groups (i.e., birth to < 18 years) for Neovascular (wet) age-related macular degeneration (nAMD), Diabetic macular edema (DME), and Diabetic retinopathy (DR) on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients.

The product triggers PREA as a new molecular entity and was presented at the Pediatric Review Committee (PeRC) on January 11, 2022. The PeRC agreed with granting full waiver for the Neovascular (wet) age-related macular degeneration (nAMD), Diabetic macular edema (DME), and Diabetic retinopathy (DR) indications.

10. BIOSTATISTICS

Per the original Biostatistics review dated 11/10/2021:

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.

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 study's 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. 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]).

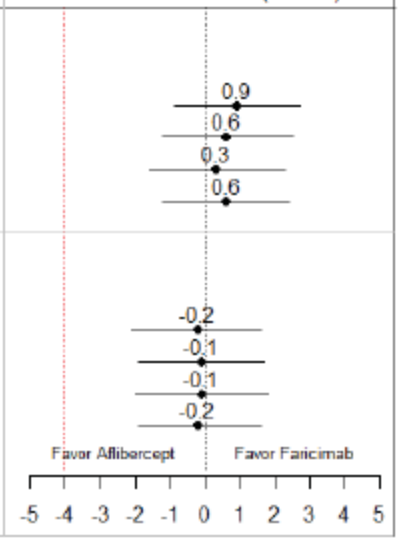
The main efficacy evaluation in both studies was based on BCVA assessed every 4-week through Week 112 as measured by the number of letters read at a starting distance of 4 meters. Although the total study duration of both studies is 112-week, this BLA was based on the first 48-week data with the remaining 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. The noninferiority margin was set at -4.0 letters.

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. 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 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.

Based on the collective efficacy evidence from the two adequate and well controlled trials of TENAYA/LUCENRE studies, the statistical reviewer concluded that the application for the nAMD indication provided substantial evidence for comparable efficacy benefit of faricimab.

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). 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 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.

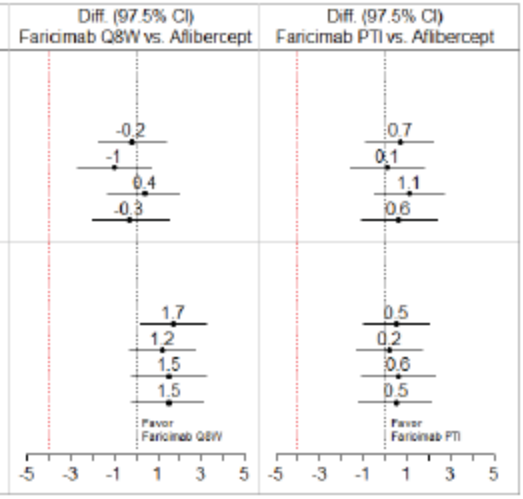
The primary efficacy endpoint in both studies was the change in BCVA from baseline averaged over Weeks 48, 52, and 56 (here after referred to as Week 48/52/56). The primary efficacy analysis was an evaluation of noninferiority of each dose of faricimab to aflibercept in the primary efficacy endpoint on the ITT population including all randomized subjects regardless of the occurrence of intercurrent events. 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)

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. 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 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 and in the ITT population were not established in both studies. (b) (4)

Based on the collective efficacy evidence from the two adequate and well controlled trials of YOSEMITE/RHINE studies, the statistical reviewer concluded 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.

11. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

Clinical Investigator Financial Disclosure
Review Template

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

Date of Review: October 25, 2021
Covered Clinical Studies (Name and/or Number):

GR40306 (TENAYA)
GR40844 (LUCERNE)
GR40349 (YOSEMITE)
GR40398 (RHINE)
BP29647 (AVENUE)
BP30099 (BOULEVARD)
CR39521 (STAIRWAY)

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

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

12. Study Integrity

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 12/6/2021:

The Applicant submitted this BLA to support the use of Vabysmo (faricimab-svoa), in the treatment of Neovascular (Wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

Inspections were requested for the following four protocols in support of this application:

1. **Protocol GR40306:** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-controlled Study to Evaluate the Efficacy and Safety of Faricimab In Patients with Neovascular Age-Related Macular Degeneration (Tenaya)

2. **Protocol GR40844:** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-controlled Study to Evaluate the Efficacy and Safety of Faricimab In Patients with Neovascular Age-Related Macular Degeneration (Lucerne)

3. **Protocol GR40349:** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of RO6867461 In Patients with Diabetic Macular Edema (Yosemite)

4. **Protocol Gr40398**: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-controlled Study to Evaluate the Efficacy and Safety Of RO6867461 in Patients with Diabetic Macular Edema (Rhine)

The clinical sites of Drs. Rich, Hu, Sheth, Wells, and Warrow were inspected in support of this NDA. Based on the results of these inspections, Protocols GR40306, GR40844, GR40349, and

GR40398 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indications.

13. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Vabysmo, and found the proposed name conditionally acceptable on 8/24/2021.

DEMPA finalized a review of the proposed suffix for the nonproprietary name, faricimab-svoa, and found the proposed suffix conditionally acceptable on 11/9/2021.

DMEPA finalized a review of the originally submitted labeling on 11/10/2021.

14. DRISK

The Division of Risk Management (DRM) in the Office of Medication Error Prevention and Risk Management (OMEPRM) completed a review of the application on 01/06/2021. Based on the available data, the concluded that a REMS is not necessary for faricimab to ensure the benefits outweigh the risks.

15. OPDP

The Office of Prescription Drug Promotion (OPDP) completed a review of the product labeling dated 01/04/2021.

16. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X □	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X □	Clinical outcome assessment (COA) data		Sec 6
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Sec 6
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			

		□ Input informed from participation in meetings with patient stakeholders	
		□ Patient-focused drug development or other stakeholder meeting summary reports	
		□ Observational survey studies designed to capture patient experience data	
		□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.		

17. Labeling

BLA 761235 Vabysmo (faricimab-svoa) injection, for intravitreal use will be approved for the treatment of patients with neovascular (wet) age-related macular degeneration (nAMD) and diabetic macular edema (DME) with the attached labeling at the end of this review (package insert submitted 1/27/22; carton/container labeling submitted 1/14/22).

18. Regulatory Action

BLA 761235 Vabysmo (faricimab-svoa) injection, for intravitreal use will be approved for the treatment of patients with neovascular (wet) age-related macular degeneration (nAMD) and diabetic macular edema (DME). There are no recommended post-marketing risk evaluation and management strategies (i.e., REMS) for this drug product. We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of corneal endothelial cell loss. Furthermore, the active post-market risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of corneal endothelial cell loss. Therefore, based on appropriate scientific data, FDA will require the following trial:

4214-1 Conduct a controlled trial to evaluate the corneal endothelial health of eyes treated with faricimab by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving faricimab.

The timetable submitted by the applicant on January 25, 2022 states that it will conduct this trial according to the following schedule:

Final Protocol Submission: 04/2022
Trial Completion: 12/2024
Final Report Submission: 04/2025.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
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WILEY A CHAMBERS
01/28/2022 01:52:16 PM

CHARLES J GANLEY
01/28/2022 02:23:51 PM