CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761235Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761235
PDUFA Goal Date	January 28, 2022
OSE RCM #	2021-2029
Reviewer Name(s)	Carlisha Gentles, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	January 6, 2022
Subject	Evaluation of Need for a REMS
Established Name	Faricimab-svoa
Trade Name	Vabysmo
Name of Applicant	Genentech, Inc.
Therapeutic Class	Bispecific angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) inhibitor
Formulation(s)	6 mg/0.05 mL solution
Dosing Regimen	6 mg (0.05 mL) administered via intravitreal injection every for weeks for 4 doses, followed by 6 mg via intravitreal injections at intervals (b) (4)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vabysmo (faricimab) is necessary to ensure the benefits outweigh its risks. Genentech, Inc. submitted a Biologics Licensing Application BLA 761235 on May 28, 2021 for faricimab with the proposed indication for the treatment of neovascular (wet) age-related macular degeneration (nAMD), diabetic macular edema (DME), and diabetic retinopathy (DR). The clinical reviewer concluded that faricimab was effective in treating patients with neovascular (wet) age-related macular degeneration (nAMD) and diabetic macular edema (DME), (b) (4) The risks associated with faricimab include increases in intraocular pressure and arterial thromboembolic events. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Ophthalmology (DO) agree that a REMS is not necessary to ensure the benefits of faricimab outweigh its risks. The benefit for the treatment of neovascular (wet) age-related macular degeneration and diabetic macular edema was demonstrated by non-inferiority to aflibercept based on the change from baseline in Best Corrected Vision Acuity (BCVA). The risks associated with faricimab do not appear to exceed that of other products used in the treatment of nAMD and DME and are not unique to faricimab. The risks of increased intraocular pressure and arterial thromboembolic events will be addressed in section 5: Warning and Precautions of the labeling. Additionally, the risks of endophthalmitis and retinal detachments which are due to the intravitreal injection technique will also be addressed in Section 5. Likely prescribers of faricimab should be familiar with the monitoring and management of these risks. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vabysmo (faricimab) is necessary to ensure the benefits outweigh its risks. Genentech, Inc. submitted a Biologics Licensing Application (BLA) 761235 on May 28, 2021 for faricimab with the proposed indication for the treatment of neovascular (wet) age-related macular degeneration, diabetic macular edema, and diabetic retinopathy in adults. This application is under review in the Division of Ophthalmology. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Vabysmo (faricimab), a new molecular entity (NME)[a], is a bispecific angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) inhibitor with a mechanism that acts through inhibition of Ang-2 and VEGF-A. VEGF A has been shown to cause neovascularization and leakage in models of ocular

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD and DME. Faricimab is proposed for the treatment of neovascular (wet) age-related macular degeneration.

Faricimab is supplied as 120 mg/mL solution. The proposed dosage regimen for both indications is 6 mg (0.05 mL of 120 mg/mL solution) administered via intravitreal injection every 4 weeks for the first 4 doses, (b) (4) Faricimab may be administered in both the outpatient and inpatient settings for nAMD and DME.[b] Faricimab is not currently approved in any jurisdiction. If approved, faricimab will make the 5th drug in the pharmacologic class of intravitreal VEGF inhibitors. None of the intravitreal VEGF inhibitors marked in the U.S. are approved with a Boxed Warning or REMS.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761235 relevant to this review:

- 05/28/2021: BLA 761235 submission for the treatment of neovascular (wet) age-related macular degeneration, diabetic macular edema, and diabetic retinopathy received.
- 09/18/2021: A Mid-cycle meeting was held with the Applicant. The Agency informed the Applicant that review of the safety database was ongoing; however, at this time, there were no safety issues that require a REMS for faricimab.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Age-related macular degeneration (AMD) is a disease that affects the macula (central part of the retina) that may result in the loss of central vision.[c] It is the leading cause of adult blindness in industrialized countries.[1] AMD is more common among older people, affecting more than 14% of white Americans age 80 and older (other races/ethnicities ~ 2%).[2] From 2000-2010, the number of people with AMD grew 18%, from 1.75 million to 2.07 million.[2] Neovascular AMD (nAMD) or wet AMD is characterized by the growth of abnormal vessels into the subretinal space and occurs in approximately 10% – 15% of patients with AMD.[d] nAMD results in significant morbidity as rapid distortion and loss of central vision occurs over a period of weeks to months.[1]

Diabetic retinopathy is one of largest causes of blindness worldwide and the primary cause of vision impairment among people from 25 to 74 years of age.[3] Diabetic retinopathy (DR) and diabetic macular

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug*.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

edema (DME) are major complications from diabetes and are a result of chronic damage to neurovascular structures of the retina.[4] DME is characterized by fluid leaking from vessels, due to DR, into the macula causing the macula to swell leading to blurred vision.[3,4] DR develops in approximately 75% of people with Type 1 diabetes and 50% of people with Type 2 diabetes.[4] DME affects approximately 35% of people with diabetes resulting in blindness and vision impairment.[4,e,f] DR and DME have been shown to contribute to the development of other diabetes-related complications including nephropathy, neuropathy and cardiovascular events significantly increasing morbidity.[5]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Neurovascular Age-related Macular Degeneration

Non-pharmacologic treatment of nAMD includes photodynamic therapy (PDT), thermal laser photocoagulation, surgery, and radiation therapy. With the advent of VEGF inhibitors, PDT and thermal laser photocoagulation are no longer considered first line therapies.[1] PDT is reserved for those who fail to respond to initial VEGF inhibitors. Thermal laser coagulation has the risk of scotoma and vision loss and is rarely recommended.[1] There are varying success rates with surgery and the long-term safety of radiation therapy is unknown.

Pharmacologic treatment of nAMD primarily consists of intravitreal VEGF inhibitors with differing mechanisms of actions. Ranibizumab, aflibercept, pegaptanib and brolucizumab are the four FDA approved intravitreal VEG-F inhibitors indicated for the treatment of nAMD. Ranibizumab, aflibercept, and brolucizumab are all associated with a risk of increased intraocular pressure and potential risk of arterial thromboembolic events. Although pegaptanib was the first FDA-approved drug for AMD, it is rarely used because the newer agents have more favorable adverse effect profiles. Bevacizumab, FDA-approved as an intravenous infusion for colorectal cancer, is frequently used off-label to treat nAMD and other ophthalmic conditions due to its lower cost and comparable efficacy and safety.[1] Additionally, supplementation with zinc and antioxidant vitamins (e.g. AREDS and AREDS2 nutritional supplement)[e] is recommended to prevent the likelihood of progression to late AMD.[6]

Diabetic Macular Edema

Non-pharmacologic treatment of DME includes focal laser photocoagulation and vitrectomy. Laser scars, paracentral scotomas, and subfoveal fibrosis are some of the complications that can occur with focal laser photocoagulation. Usage of vitrectomy may be limited by the following surgery complications that may occur: infection, bleeding, cataracts, retinal detachment, or loss of vision.[7]

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug*.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Pharmacologic treatment of DME is very similar to treatment for nAMD and consists of the following intravitreal VEGF inhibitors which are FDA-approved for DME: ranibizumab and aflibercept. Bevacizumab is also used off-label to treat DME as it is to treat nAMD. Please refer to the pharmacologic treatment section for nAMD above for risks associated with these treatments.
Use of faricimab will provide an option for patients who are unable to receive, tolerate, or adequately benefit from currently available therapies.

4 Benefit Assessment

Neurovascular Age-related Macular Degeneration

The efficacy and safety of faricimab for the treatment of nAMD is supported by two phase 3 pivotal trials, Study GR40306 (TENAYA - NCT03823287) and GR40844 (LUCERNE - NCT03823300). The studies were identical in design. Additional supportive safety evidence came from two phase 2 nAMD studies (CR39521 and BP29647), one phase 1 nAMD study (BP28936) and one safety study (JP39844).

Study GR40306 and Study GR40844 were 112-week randomized, multi-center, double-masked, active comparator-controlled studies to evaluate the efficacy and safety of faricimab in adults with nAMD. Patients were randomized in a 1:1 ratio to one of two treatment arms:

- Arm 1: faricimab 6 mg administered every 4 weeks for four monthly doses followed by faricimab 6mg every 16 weeks, every 12 weeks, or every 8 weeks based on an assessment of disease activity at Weeks 20 and 24 up to Week 108 or
- Arm 2: aflibercept 2 mg administered every 4 weeks up to Week 8, followed by aflibercept 2mg every 8 weeks up to Week 108.

For both studies, the primary efficacy endpoint was the mean change from baseline in Best Corrected Visual Acuity (BCVA)[g] when averaged over the visits for Week 40, 44, and 48 as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart[h].

Per the clinical reviewer, Study GR30406 and GR40844 demonstrated that faricimab was non-inferior to aflibercept based on the change from baseline in BCVA averaged over Weeks 40/44/48 in patients with nAMD.[8] Both studies had a comparable mean change from baseline in BCVA as the patients treated with aflibercept. Table 1 highlights the results of the primary endpoints for Study GR30406 and GR40844.

[g] Best-corrected visual acuity refers to the measurement of the best vision correction that can be achieved using glasses or contact lenses. The technique for determining this is the same as standard accuracy, but instead of using your regular eyesight, the score is determined when you are wearing corrective prescription lenses.

[h] The ETDRS chart is the most widely used outcome measure to assess changes in visual acuity from a therapeutic intervention. It is a modified version of the Snellen Chart and scores are based on the number of letters correctly read by a patient.

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Table 1. Primary Efficacy Endpoints in Studies GR40306 and GR40844*

	GR40306		GR40844	
	Faricimab N = 334	Aflibercept N = 337	Faricimab N = 331	Aflibercept N = 327
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	5.7 (4.4, 6.9)	5.1 (3.8, 63)	6.4 (5.2, 7.7)	6.6 (5.3, 7.8)
Difference in LS mean (95% CI)	0.6 (-1.2, 2.4)		-0.1 (-1.9, 1.6)	

*Modified table from Prescribing Information Draft as of November 26, 2021

The clinical reviewer concluded that the data from Studies GR40306 and GR40844 has established that faricimab is efficacious in the treatment of patients with nAMD.[8,i]

Diabetic Macular Edema

The efficacy and safety of faricimab for the treatment of DME is supported by two phase 3 pivotal trials, Study GR40349 (YOSEMITE - NCT03622580) and GR40398 (RHINE - NCT03622593). The studies were identical in design.

Study GR40349 and Study GR40398 were 96-week randomized, multi-center, double-masked, active comparator-controlled studies to evaluate the efficacy and safety of faricimab in adults with DME. Patients were randomized in a 1:1:1 ratio to one of three treatment arms:

- Arm 1 – Faricimab Q8W: faricimab 6 mg administered every 4 weeks for 6 monthly doses, then faricimab 6mg every 8 weeks thereafter,
- Arm 2 - Faricimab Variable: faricimab 6mg administered every 4 weeks for four monthly doses, then faricimab 6mg administered in progressively longer intervals at Week 4, 8, 12 or 16, based on an assessment of disease activity criteria, or
- Arm 3 – Aflibercept Q8W: aflibercept 2mg administered every 4 weeks for five monthly doses, then aflibercept 2mg every 8 weeks.

For both studies, the primary efficacy endpoint was the mean change from baseline in BCVA when averaged over the visits for Weeks 48, 52, and 56 as measured by the ETDRS letter chart.

[i] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Per the clinical reviewer, Study GR40349 and GR40398 demonstrated that faricimab was non-inferior to aflibercept based on the change from baseline in BCVA averaged over Weeks 48/52/56 in patients with DME.[8] Both studies had a comparable mean change from baseline in BCVA as the patients treated with aflibercept. Table 2 highlights the results of the primary endpoints for Study GR40349 and GR40398.

Table 2. Primary Efficacy Endpoints in Studies GR40349 and GR40398*

	GR40349			GR40398		
	Faricimab Q8W N = 315	Faricimab Variable N = 313	Aflibercept Q8W N = 312	Faricimab Q8W N = 317	Faricimab Variable N = 319	Aflibercept Q8W N = 315
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5% CI)	10.6 (9.3, 11.8)	11.5 (10.2, 12.7)	10.8 (9.6, 12.1)	11.7 (10.5, 12.9)	10.7 (9.5, 11.8)	10.2 (9.1, 11.4)
Difference in LS mean (97.5% CI)	-0.3 (-2.0, 1.5)	0.6 (-1.1, 2.4)		1.5 (-0.2, 3.1)	0.5 (-1.2, 2.1)	

*Modified table from Prescribing Information Draft as of November 26, 2021

The clinical reviewer concluded that the data from Studies GR40349 and GR40398 has established that faricimab is efficacious in the treatment of patients with DME.[8,j]

(b) (4)

[redacted]

5 Risk Assessment & Safe-Use Conditions

The safety database for faricimab is comprised of data from four phase 3 studies (Study GR40306, Study GR40844, Study GR40349 and Study GR40398) with 1926 participants. The most commonly reported

[j] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

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adverse events[k] (AEs) ≥ 1% of participants receiving faricimab in the safety database were conjunctival hemorrhage (7%), vitreous floaters (3%), retinal pigment epithelial tear (3%), increased intraocular pressure (3%), eye pain (3%), and intraocular inflammation (2%).

The serious adverse events of special interest associated with faricimab include increases in intraocular pressure (IOP), arterial thromboembolic events (ATEs), endophthalmitis and retinal detachments.[l] The risk of endophthalmitis and retinal detachments are considered potential complications of the intravitreal administration technique and are not related to the drug.

Deaths

For the nAMD studies, there were a total of 19 (2.9%) deaths in the faricimab group and 15 (2.3%) deaths in the aflibercept group through the safety update report clinical cut-off date. Additionally, there were 51 deaths (4.0%) in the pooled faricimab group (faricimab Q8W plus faricimab variable) and 22 deaths (3.5%) in the aflibercept group for the DME studies through the safety update report clinical cut-off date. Per the clinical reviewer, the deaths which occurred during the studies are consistent with the age and past medical history of the participants enrolled in the studies.[8]

5.1 ADVERSE EVENTS OF SPECIAL INTEREST

5.1.1 Increases in Intraocular Pressure

IOP increases are considered an adverse drug reaction (ADR) of intravitreal VEGF inhibitors including faricimab. Transient increases in the IOP were noted within 60 minutes of intravitreal injection with faricimab.[9] In the safety database, 3% of patients receiving faricimab 6 mg in the nAMD and DME studies experienced increased ocular pressure compared to 2% of patient receiving aflibercept 2mg in the nAMD and DME studies.

The clinical reviewer concluded that there were no clinically significant differences identified in adverse events between the faricimab and aflibercept arms.[8] The proposed label advises that both the IOP and perfusion of the optic nerve head be monitored and managed appropriately.[9]

5.1.2 Arterial Thromboembolic Events

ATEs were observed in the clinical trials program for the nAMD studies (faricimab 1% vs aflibercept 1%).[9,10] Additionally, ATEs were observed in the DME studies (faricimab 2% vs aflibercept 2%).[9,10]

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[k] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[l] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Overall, a low rate of ATEs were observed in the faricimab clinical trials program.

The clinical reviewer concluded that there were no clinically significant differences in adverse events identified between the treatment arms.[8] The proposed labeling notes that there is a potential risk of ATEs following use of VEGF inhibitors as is noted in the labeling for all VEGF inhibitors.

6 Expected Postmarket Use

The primary prescribers for faricimab are likely to be ophthalmologists who specialize in the treatment of nAMD and DME. Faricimab may be used in both the outpatient settings, such as outpatient surgery centers, and inpatient settings, where the drug product can be administered via intravitreal injection. Prescribers are likely familiar with the risks associated with intravitreal VEGF inhibitors like ranibizumab, aflibercept, pegaptanib and brolucizumab and faricimab does not pose any unusual risks.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or any risk management activities for faricimab.

8 Discussion of Need for a REMS

Faricimab is a bispecific angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) inhibitor proposed for the treatment of neurovascular (wet) age-related macular degeneration, diabetic macular edema, and diabetic retinopathy. (b) (4) Use of faricimab will provide an option for patients who are unable to receive, tolerate, or adequately benefit from currently available therapies.

nAMD and DME are both eye disorders impacting the retina and macula. AMD is the leading cause of adult blindness in industrialized countries with nAMD resulting in significant morbidity as rapid distortion and loss of central vision occurs over a short period of time. While DME affects approximately 35% of people with diabetes leading to vision impairment and blindness.[3,4] Common clinical manifestations of nAMD and DME include blurred vision and vision loss. The pivotal trials, Study GR40306, Study GR40844, Study GR40349 and Study GR40398, support the efficacy of faricimab as evidenced by non-inferiority to aflibercept based on the change from baseline in BCVA for both nAMD and DME with an acceptable safety profile.

Faricimab, along with the other intravitreal VEGF inhibitors, is associated with a risk of increased intraocular pressure, arterial thromboembolic events, endophthalmitis and retinal detachments. Of note, the risk of endophthalmitis and retinal detachments are considered potential complications of the intravitreal administration technique and are not related to the drug. The pivotal trials showed the presence of these risks; however, no clinically significant differences were identified among the faricimab or aflibercept treatment groups. The healthcare providers prescribing faricimab should be

familiar with monitoring and proper management of these risks. Labeling will be used to communicate these risks. As the risks associated with faricimab do not appear to exceed those of other approved products and are not unique to faricimab, this reviewer has concluded that based on available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9 Conclusion & Recommendations

The Clinical Reviewer has determined that the benefit/risk assessment for faricimab favors approval.

Based on the available data, the benefit-risk profile is favorable and a REMS is not necessary for faricimab to ensure the benefits outweigh the risks. At the time of this review, labeling discussions were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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/s/

CARLISHA C GENTLES
01/06/2022 01:11:57 PM

JACQUELINE E SHEPPARD
01/06/2022 01:28:29 PM

CYNTHIA L LACIVITA
01/06/2022 02:08:12 PM
Concur