Taiwan Food and Drug Administration

Assessment Report

Trade Name：羅視萌注射劑 / Vabysmo solution for intravitreal injection

Active Ingredient：Faricimab

License Number：MOHW-BI 001214

Applicant：羅氏大藥廠股份有限公司

Approval Date：111.12.26

Indication：

1. 血管新生型(濕性)年齡相關性黃斑部退化病變 (nAMD)
2. 糖尿病黃斑部水腫 (DME)

VABYSMO is indicated for the treatment of patients with:
1. Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
2. Diabetic Macular Edema (DME)

1. Background Information

Trade Name	羅視萌注射劑/ Vabysmo Solution for Intravitreal Injection
Active Ingredient(s)	Faricimab
Applicant	羅氏大藥廠股份有限公司
Dosage Form & Strengths	注射液劑 / 6 mg/0.05mL
Indication	1. 血管新生型(濕性)年齡相關性黃斑部退化病變 (nAMD) 2. 糖尿病黃斑部水腫 (DME)
Posology	請參閱仿單
Pharmacological Category **ATC Code**	S01LA09

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Faricimab is a humanized bispecific antibody that selectively binds vascular endothelial growth factor A (VEGF-A) and angiopoetin-2 (Ang-2), thereby preventing the binding of these angiogenic factors to their receptors and the modulation of the respective downstream signaling pathways leading to clinical efficacy.

The manufacturing process is sufficiently described. The in-process controls are acceptable. Control of raw materials, the manufacturing process and adventitious agents is considered adequate to ensure the safety of faricimab. The physiochemical and biological characterization of faricimab is considered sufficient. Process-related impurities and product-related impurities are well-controlled. The release tests for faricimab are acceptable. A two-tiered reference standard system has been established for commercial use. The container closure system is acceptable. The real time data provided are sufficient to support the proposed drug substance shelf life.

2.1.2 Drug product

Faricimab is the active ingredient in Vabysmo. Vabysmo is provided as a sterile, preservative-free, colorless to brownish-yellow solution intended for intravitreal injection. Each single-use vial is design to deliver 0.05 mL of solution containing 6 mg of faricimab. A 5 µm transfer filter needle is co-packaged with faricimab drug product for dose preparation to reduce subvisible particles.

Details of formulation development and manufacturing process development are provided. The drug product manufacturing process is sufficiently described and in-process controls are

considered adequate. The release and stability specifications for faricimab drug product are acceptable. The leachables studies demonstrate the primary packaging components are suitable and safe for use for the drug product. The stability data currently available for faricimab drug product are sufficient to support the proposed shelf life of 30 months when stored at 5±3°C, and protected from light.

In summary, the information on the drug substance and drug product is sufficiently provided and the quality of Vabysmo is considered to be acceptable when used in accordance with the conditions defined in the package insert.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Faricimab is designed to inhibit two distinct pathways involved in retinal diseases by blocking the actions of VEGF and Ang-2. In vitro, faricimab bound to both human VEGF-A and ANG-2, but not ANG-1, with high affinity and specificity, with K_D values for VEGF isoforms and ANG-2 in nM range. SPR experiments showed that faricimab could bind to both targets independently and simultaneously.

Based on the results of species cross-reactivity and the anatomical and functional similarities between the monkey and human eye, cynomolgus monkey was used as the relevant animal species for the nonclinical testing of faricimab. In a laser-induced CNV model in cynomolgus monkeys, faricimab significantly reduced the severity of laser-induced lesions more than ranibizumab (an anti-VEGF-A antibody) did at equimolar anti-VEGF binding sites, suggesting that faricimab's anti-ANG-2 activity contributes to the therapeutic efficacy.

Safety pharmacological endpoints were integrated into the repeated-dose toxicity studies performed up to a 6-month duration in cynomolgus monkeys, and no notable findings were found.

In GLP repeated-dose studies up to 6 months duration in cynomolgus monkeys, IVT or IV administration of faricimab Q4W resulted in ADA formation in most faricimab-treated animals. The species-related, immune-mediated ocular inflammation was observed in the faricimab-treated eyes following IVT administration at higher doses and was partially to fully reversible. The ocular findings were generally correlated with the presence of ADAs and reduced serum exposure. The systemic exposure at the NOAEL values in the GLP monkey studies were approximately 0.3- to 4-fold the systemic exposure (AUC) in patients with nAMD or DME. No faricimab-related systemic effects were observed following IVT or IV administration at doses up to 6 mg/eye or 5 mg/kg, respectively, except for the IHC-confirmed, species-related immune-mediated minimal mixed-cell inflammation in the aortic root was observed in a few animals following IV dosing. Local tolerance for the

administration of faricimab via IVT and IV routes was also evaluated in the repeated-dose toxicity studies, and no faricimab-related local effects were observed at the injection sites.

Genotoxicity and carcinogenicity studies of faricimab were not conducted. The results of nonclinical and clinical studies and the weight of evidence did not suggest any significant concerns for the lifetime risk of cancer in patients.

No potential risks of faricimab on male or female fertility were identified in the monkey GLP repeated-dose toxicity studies up to a 6-month duration. In a GLP EFD study in cynomolgus monkeys, no maternal or developmental toxicity and no evidence of teratogenicity were noted except for a non-dose dependent increase in fetal loss in all groups. The systemic exposure (C_{max}) at the NOAEL in the monkey EFD study was more than 500-fold the estimated systemic exposure in patients with nAMD or DME. Despite the facts mentioned above, the mechanism-wised, potentially harmful effects of all anti-angiogenic agents, including faricimab, on female reproductive system and the teratogenic potential of the fetus cannot be ruled out.

Lastly, in vitro studies showed no unexpected cross-reactivity in normal human tissues. Also, no evidence of potential risk of cytokine release syndrome or adverse impacts to the immune cells was found to be associated with the treatment of faricimab.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Faricimab is administered directly into the vitreous to exert local effects in the eye and is cleared from the vitreous through the AH, then plasma. Following administration of faricimab 6 mg Q4W followed by Q8W, maximum faricimab plasma concentrations are estimated to occur approximately 2 days post-dose. Mean free faricimab (unbound to VEGF-A and Ang-2) plasma C_{max} are estimated to be 0.23 and 0.22 μg/mL in the nAMD and DME populations. No accumulation has been observed in plasma when faricimab has been administered as repeat doses in the vitreous.

Metabolism of faricimab has not been fully characterized. However, free faricimab is expected to undergo metabolism via proteolysis. Faricimab vitreous elimination is slow, with an estimated $t_{1/2}$ of 7.5 days based on the population PK analysis. The estimate of the plasma CL/F was 2.33 L/day, corresponding to a rapid $t_{1/2}$ of approximately 0.44 days.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted. Faricimab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are

substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

2.3.3 Special Populations

In the four Phase III clinical studies, approximately 60% of patients randomized to treatment with faricimab were ≥ 65 years of age. Population PK analyses showed that the covariates affecting faricimab vitreous disposition were age, while the covariates affecting plasma disposition were body weight and sex. However, the effects of these covariates are not considered clinically meaningful.

Faricimab has not been studied in patients with renal and hepatic impairment. There were 64% patients with renal impairment in 9 clinical studies (38% mild impairment of CRCL 60-89 mL/min, 24% moderate impairment of CRCL 30-59 mL/min, 2% severe impairment of CRCL 15-29 mL/min). Based on population PK analysis, renal impairment doesn't affect the faricimab PK parameters, thus no dose adjustment is suggested by renal impairment. Meanwhile, there were 5.4% patients with hepatic impairment according to the NCI-ODWG criteria in 9 clinical studies (5.2% mild hepatic dysfunction, 0.2% moderate hepatic dysfunction). Considering the population PK analysis results, the metabolism pathway through proteolytic catabolism and low systematic exposure, no dose adjustment is suggested by hepatic impairment.

In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 13.8% and 9.6% of patients with nAMD and DME respectively.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provides two pivotal studies [TENAYA] and [LUCERNE] to support the nAMD indication. Also, the sponsor provides two pivotal studies [YOSEMITE] and [RHINE] to support the DME indication.

- **nAMD Indication**

[TENAYA] At Week 40/44/48, the adjusted mean change from baseline in BCVA was 5.8 and 5.1 letters in the Faricimab (N=334) and Aflibercept (N=337) arms, respectively; the difference between the Faricimab arm when compared with the Aflibercept arm at Week 40/44/48 was 0.7 letters (95% CI: -1.1, 2.5). The study met its primary endpoint of non-inferiority.

[LUCERNE] At Week 40/44/48, the adjusted mean change from baseline in BCVA was 6.6

and 6.6 letters in the Faricimab (N=331) and Aflibercept (N=327) arms, respectively; the difference between the Faricimab arm when compared with the Aflibercept arm at Week 40/44/48 was 0.0 letters (95% CI: -1.7, 1.8). The study met its primary endpoint of non-inferiority.

- **DME Indication**

[YOSEMITE] At Week 48/52/56 the adjusted mean change from baseline in BCVA was 10.7, 11.6, and 10.9 letters in the Faricimab Q8W (N=315), Faricimab PTI (N=313), and Aflibercept Q8W (N=312) arms, respectively. The difference in adjusted mean change from baseline in BCVA between the Faricimab Q8W and Faricimab PTI arms when compared with the Aflibercept Q8W arm at Week 48/52/56 was -0.2 letters (97.5% CI: -2.0, 1.6) and 0.7 letters (97.5% CI: -1.1, 2.5), respectively. The study met its primary endpoint of non-inferiority.

[RHINE] At Week 48/52/56 the adjusted mean change from baseline in BCVA was 11.8, 10.8 and 10.3 letters in the Faricimab Q8W (N=317), Faricimab PTI (N=319), and Aflibercept Q8W (N=315) arms, respectively. The difference in adjusted mean change from baseline in BCVA between the Faricimab Q8W and Faricimab PTI arms when compared with the Aflibercept Q8W arm at Week 48/52/56 was 1.5 letters (97.5% CI: -0.1, 3.2) and 0.5 letters (97.5% CI: -1.1, 2.1), respectively. The study met its primary endpoint of non-inferiority.

2.4.2 Safety Results

The safety profile of faricimab was otherwise similar to that of the approved anti-VEGF products. The most common adverse reactions of faricimab were conjunctival hemorrhage, vitreous floaters, intraocular pressure increased, eye pain, retinal pigment epithelial tear (nAMD only), and intraocular inflammation.

2.5 Bridging Study Evaluation

The population PK analysis (included Asian and non-Asian patients from phase III studies) showed that race was not identified as a significant covariate affecting the PK of faricimab in nAMD and DME patients. Besides, the Chinese (including Taiwanese) patients showed the similar PK results compared to Asian and non-Asian patients with nAMD and DME. No steep pharmacodynamic (effect-concentration) relationship is founded for both efficacy and safety in the range of the recommended dosage and dose regimen. Faricimab is administered by intravitreal injection, therefore, the impact on ethnic difference due to the high inter-subject variation in bioavailability of faricimab is limit. In conclusion, faricimab is considered to be none to minimally ethnically sensitive, therefore, the bridging study is recommended to be waived from PK aspect.

Clinical data from nAMD and DME phase III pivotal studies showed that faricimab

treatment had clinical improvement on BCVA in Asian patients, consistent with the improvement observed in the non-Asian population. The safety data indicated that faricimab was generally well tolerated in Asian patients, as evidenced by the low incidence of serious ocular AEs and AEs leading to study treatment withdrawal. The safety profile of Asian population was consistent with that of Non-Asian population. In conclusion, the ethnic difference of clinical efficacy and safety was minimal, and the bridging study could be waived.

2.6 Conclusion

Vabysmo as the treatment for patients with nAMD or DME demonstrates a favorable risk benefit profile to recommend regular approval. The recommended dose of Vabysmo is 6 mg every 4 weeks for the first 4 doses. The follow-on dosing interval should be individualized based on disease activity and may be extended up to every 16 weeks.

3. Post-Marketing Requirements

The report of the post-marketing controlled trial to monitor the density of corneal endothelial cells over a period of at least one year in at least 100 patients treated with Vabysmo at the request of USFDA should be submitted once completed.