21 July 2022
EMA/687844/2022

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vabysmo

International non-proprietary name: faricimab

Procedure No. EMEA/H/C/005642/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
Ang-2	angiopoetin-2
AS	active substance
CCF	cell culture fluid
CH	heavy chain constant region
CHO	Chinese hamster ovary
COVID-19	coronavirus disease 2019
CPP	critical process parameter
CQA	critical quality attribute
DME	diabetic macular edema
DOE	Design of experiment
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
Fab	fragment antigen binding
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FcγR	Fc gamma receptors
FDA	U.S. Food and Drug Administration
FP	Finished product
g/L	grams per liter
GMP	Good Manufacturing Practice
HC	heavy chain
HC1	VEGF heavy chain
HC2	Ang-2 heavy chain
HMW	high molecular weight
IgG1	immunoglobulin G1
IPC	in-process control
IPPL	in-process pool limit
LC	light chain
LC1	VEGF light chain
LC2	Ang-2 light chain

LIVCA	limit of in vitro cell age
LMW	low molecular weight
MAA	Marketing Authorisation Application
MCB	master cell bank
nAMD	neovascular age-related macular degeneration
PD	pharmacodynamics
PDR	proliferative diabetic retinopathy
PHCCF	preharvest cell culture fluid
PK	pharmacokinetics
PC	polycarbonate
PP	Process Parameter
PPQ	process performance qualification
QAs	Quality Attributes
RRF	Risk Ranking and Filtering
SDM	Scale – down Model
TCID50	median tissue culture infective dose
UFDF	ultrafiltration and diafiltration
UV	ultraviolet
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor-A
WCB	working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 28 May 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Vabysmo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Vabysmo is indicated for the treatment of adult patients with:

- neovascular (wet) age-related macular degeneration (nAMD),
- visual impairment due to diabetic macular oedema (DME).

1.2. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Articles 7 and 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions CW/0001/2015 and CW/0001/2011 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance faricimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 May 2017	EMEA/H/SA/3552/1/2017/II	Dr Jens Reinhardt and Prof. Markku Pasanen
14 December 2017	EMEA/H/SA/3552/2/2017/II	Dr Kerstin Wickström and Dr Karl-Heinz Huemer
14 December 2017	EMEA/H/SA/3552/3/2017/II Treatment of neovascular (wet) age-related macular degeneration	Dr Kerstin Wickström and Dr Karl-Heinz Huemer
20 September 2018	EMEA/H/SA/3552/1/FU/1/2018/I	Mr Nicolas Beix and Prof. Markku Pasanen
18 October 2018	EMEA/H/SA/3552/3/FU/1/2018/II	Dr Kerstin Wickström and Mr Christian Gartner
28 May 2020	EMEA/H/SA/3552/1/FU/2/2020/I	Ms Rosalia Ruano Camps and Dr Finbarr Patrick Leacy
17 September 2020	EMEA/H/SA/3552/3/FU/2/2020/II Treatment of neovascular macular degeneration	Dr Kerstin Wickström and Dr Stephan Lehr
17 September 2020	EMEA/H/SA/3552/2/FU/1/2020/II	Dr Kerstin Wickström and Dr Stephan Lehr

The Applicant received Scientific Advice on the development of Faricimab for treatment of choroidal neovascularisation secondary to age related macular degeneration and diabetic macular oedema from the CHMP on 18 May 2017 (EMEA/H/SA/3552/1/2017/II). The Scientific Advice pertained to the following quality and nonclinical aspects:

- Quality: feedback from CHMP on the potency assay approach
- Nonclinical: feedback from CHMP on the approach to address a novel pharmaceutical excipient for intravitreal

The Applicant received Scientific Advice on the development of Faricimab for treatment of diabetic macular oedema from the CHMP 14 December 2017 (EMEA/H/SA/3552/2/2017/II), and treatment of choroidal neovascularisation secondary to age related macular degeneration from the CHMP 14 December 2017 (EMEA/H/SA/3552/3/2017/II). The Scientific Advice pertained to the following clinical aspects:

- Clinical: feedback from CHMP on the design of the proposed Phase III study in patients with DME, including active comparators, non-inferiority margin, primary endpoints, duration, Endpoints for diabetic retinopathy severity scale
- feedback from CHMP on the design of the proposed Phase III nAMD, including active comparator, non-inferiority margin, primary endpoints.
- For both indications; feedback from CHMP on use of controlled data collected without sham after the primary endpoint, masking in the Phase III study design, absence of routine ECG

monitoring in Phase III, individualized dosing strategies, and overall development strategies for programs

The Applicant received Scientific Advice on the development of Faricimab for treatment of choroidal neovascularisation secondary to age related macular degeneration and diabetic macular oedema from the CHMP on 20 September 2018 (EMEA/H/SA/3552/1/FU/1/2018/I). The Scientific Advice pertained to the following nonclinical aspects:

- Non-clinical: feedback from CHMP on the overall nonclinical development program

The Applicant received Scientific Advice on the development of Faricimab for treatment of choroidal neovascularisation secondary to age related macular degeneration from the CHMP on 18 October 2018 (EMEA/H/SA/3552/3/FU/1/2018/II). The Scientific Advice pertained to the following clinical aspects:

- Clinical: Feedback from CHMP on Phase III pivotal study design including study population, dose and treatment regimens for RO6867461 and aflibercept active comparator arm, timing of disease activity assessment, definition and timing of the primary endpoint, proposed analysis plan, year 2 data, rescue therapy utilizing the assigned study treatment, analysis methods for the proposed extension in China, key aspects of the safety monitoring plan for the Phase III nAMD studies, sample size and safety database in nAMD, and development and Filing strategy.

The Applicant received Scientific Advice on the development of Faricimab inhibitor for treatment of diabetic macular oedema and neovascular macular degeneration from the CHMP on 28 May 2020 *(*EMEA/H/SA/3552/1/FU/2/2020/I*)*.
The Scientific Advice pertained to the following quality aspects:

- The approach to set commercial faricimab Sub Visible Particulate (SVP) limits in light of the current pharmacopoeial requirements

The Applicant received Scientific Advice on the development of Faricimab for treatment of diabetic macular oedema from the CHMP on 17 September 2020 (EMEA/H/SA/3552/2/FU/1/2020/II), and Treatment of neovascular macular degeneration (EMEA/H/SA/3552/3/FU/2/2020/II) from the CHMP on 17 September 2020 The Scientific Advice pertained to the following clinical aspects:

- Agreement was sought regarding the proposed plan for handling the impact of COVID-19 in the initial MAA.
- Acceptability to include additional eCRF to capture visual acuity assessments collected in a non-protocol-specified manner due to site limitations during the COVID-19 pandemic in the MAA dossier.
- Acceptability of the proposed approach for reporting COVID-19 related protocol deviations in the CSR.
- Acceptability of the proposed remote process for source verifying the pivotal study data (visual acuity) in case of limited access to study sites due to COVID 19.
- A question whether the target suppression data in aqueous humour in a subset of consenting patients can be used to support the description of the PD data in the faricimab label.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	28 May 2021

The procedure started on	17 June 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 September 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 October 2021
Clarification teleconference	18 November 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vabysmo on	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant has submitted an application for marketing authorisation for the following indications for the treatment of adult patients with:

- neovascular (wet) age-related macular degeneration (nAMD)
- visual impairment due to diabetic macular oedema (DME).

Age-related macular degeneration (AMD) is a chronic, progressive, multifactorial disease of the macula and a leading cause of central vision loss among people over the age of 50 years. nAMD (also known

as macular or choroidal neovascularisation [CNV] secondary to AMD) is a form of advanced AMD that causes rapid and severe vision loss. It is characterised by the abnormal proliferation of new blood vessels within the retina, or in the subretinal or sub-retinal pigment epithelium (RPE) spaces.

These neovascular membranes leak fluid, lipids, and blood into the outer retina often causing severe, irreversible loss of central vision if left untreated.

DME is the most common complication as well as a leading cause of central vision loss in patients with Diabetic retinopathy (DR) and can develop at any stage of DR severity, with increasing frequency as the underlying disease worsens. DME and DR are forms of the same underlying pathophysiological processes subsequent to microvasculopathy that is driven by hyperglycemia in patients with diabetes.

Approximately half of patients with DME will lose two or more lines of visual acuity within 2 years if left untreated.

2.1.2. Epidemiology

nAMD

The prevalence of nAMD increases with age, with estimates in the United States in 2011 ranging from 0.5% among people 65-69 years old to 14.6% among those 90 years old or older (Rudnicka et al. 2012). Of the estimated 253 million people worldwide with visual impairment, more than 10 million (4.1%) were caused by AMD.

In the future, the global population aged 60 years and older is projected to increase dramatically, resulting in a significant increase in the prevalence of nAMD from 23.47 million in 2010 to 80.44 million by 2050.

Diabetic Macular Edema (DME)

DME affects 21 million people around the world, including 12% of people with Type 1 diabetes and 28% of those with Type 2 diabetes. In patients diagnosed with insulin-dependent diabetes before the age of 30, the prevalence of DR reaches 97% when diabetes duration exceeds 15 years.

Eventually, nearly all patients with diabetes will develop some form of retinopathy (ADA 2013; Postel et al. 2013). In 2019, the worldwide population of people living with diabetes was approximately 463 million, and this is estimated to grow to 548 million by 2045 (Saeedi et al. 2019). The global burden of DME and DR is expected to increase significantly with considerable public health, socioeconomic, and quality-of-life consequences due to the combined impact on patients, caregivers, family members, and HCPs.

2.1.3. Aetiology and pathogenesis

Age-related macular degeneration (AMD) is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision. AMD can be classified as dry or wet (neovascular AMD). Dry AMD progressed to nAMD in a minority of patients.

Neovascular age-related macular degeneration (nAMD) (also known as choroidal neovascularisation or wet AMD) causes rapid and severe visual loss. It is a leading cause of visual impairment in older people. Several biochemical and biological processes, including angiogenesis, oxidative stress and inflammation are known to play a role in the pathogenesis of nAMD, which is characterised by the abnormal growth of new blood vessels in the subretinal space usually from the choroidal circulation. These new vessels leak leading to collections of subretinal fluid or blood.

nAMD can be subcategorized, based upon the pattern of choroidal neovascularisation seen in fluorescein angiography, into classic, occult, or fibrous lesions. Lesions that are predominantly classic typically progress more rapidly.

Diabetic Macular Edema (DME)

Diabetic retinopathy (DR) is regarded as the most common microvascular complication of diabetes and can occur as a complication of both Type 1 and Type 2 diabetes. Diabetic macular oedema (DME) is the most common complication of DR and is a leading cause of central vision loss in DR patients. DME can develop at any stage of DR severity, with increasing frequency as the underlying disease worsens. Approximately half of patients with DME will lose two or more lines of visual acuity within 2 years if left untreated.

The underlying pathophysiological process of DME and DR is a loss of pericytes, development of retinal micro-aneurysms, dilated capillaries and vascular inflammation which lead to an increase in vascular permeability.

The diagnosis of DR is based on the detection and clinical manifestations of microvascular abnormalities in the retina. DME is characterised by intraretinal fluid in the macular area. NPDR is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fibre layer infarcts and, in more severe cases, venous beading and intraretinal microvascular abnormalities. PDR is characterised by neovascularisation that can be detected anywhere on the retina, optic disc or in the anterior segment.

The excess of Ang-2 and VEGF in the vitreous of patients with diabetic eye disease was shown to correlate with disease severity, and is thought to mediate vessel destabilisation, vascular leakage, inflammation and, in later stages of disease, neovascularisation.

2.1.4. Clinical presentation, diagnosis

nAMD

Patients with nAMD usually present with a visual impairment and can have sudden changes in vision. The condition is diagnosed based on results of a slit lamp examination, fluorescein angiography and optical coherence tomography (OCT).

The symptoms of nAMD include central vision loss characterized by metamorphopsia, scotomas, and blurriness, which negatively affect reading, driving, patient mobility, face recognition, and other daily activities, including self-care. The diagnosis of nAMD is made clinically by ophthalmoscopy and multimodal retinal imaging techniques, which include optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). The clinical manifestation of nAMD includes the presence of subretinal fluid (SRF) and/or intraretinal fluid (IRF), retinal and subretinal hemorrhage, retinal thickening, and pigment epithelial detachment. Without treatment, progression of the disease results in the formation of a fibrous scar and consequently severely reduced vision.

DME

On a molecular level, DME and DR are characterized by hypoxia-mediated release of pro-angiogenic, hyperpermeability, and pro-inflammatory mediators in the retina, with Ang-2 and VEGF-A playing the key role.

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The diagnosis of DR is based on the detection and clinical manifestations of microvascular abnormalities in the retina. NPDR is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fibre layer infarcts and, in more severe cases, venous beading and intraretinal microvascular abnormalities. PDR is characterized by neovascularization that can be detected anywhere on the retina, optic disc or in the anterior segment.

2.1.5. Management

nAMD

The major goal of treatment is to avoid or recover lost vision and subsequently maintain vision in nAMD patients over time. Previously, laser photocoagulation therapy and photodynamic therapy with verteporfin were the standard of care and were shown to stabilize, but not recover, vision.

The introduction of anti-VEGF therapies has markedly improved vision outcomes and changed the management of nAMD.

The anti-VEGF therapies ranibizumab (Lucentis), aflibercept (Eylea), and brolucizumab (Beovu) are approved and used for the treatment of nAMD in the United States and European Union.

The introduction of anti-VEGF therapy has resulted in an improvement of vision outcomes in patients with nAMD. However, for most patients, the current treatment paradigm involves frequent health care provider (HCP) visits and intravitreal injections in order to maintain vision gains (Heier et al. 2012; Maguire et al. 2016). This imposes a considerable burden on patients, their families, caregivers, and the healthcare system (Jaffe et al. 2018).

Real-world data show that many patients with nAMD do not receive treatment as the perlabel recommended frequency, and the under-treatment in clinical practice may result in lower visual acuity gains compared with those observed in the clinical trials.

Although anti-VEGF therapy is the current mainstay of treatment, nAMD is a multifactorial disease with VEGF being only one of the key drivers; sustained efficacy over time with fewer injections may be achievable by targeting additional drivers of angiogenesis such as Ang-2. In addition, nAMD has an inflammatory component not completely addressed by anti-VEGF treatments alone. New and more durable treatments that target additional pathways to those mediated by VEGF are therefore required, in order to provide visual acuity outcomes with less frequent dosing that are at least as good as those achieved with more frequent anti-VEGF monotherapy regimens.

DME

The primary treatment goals in DME are improving or maintaining visual acuity, reducing retinal fluid, improving the underlying diabetic retinopathy and preventing irreversible damage to the macula. One of the factors found to be elevated in intraocular fluids in animal models of diabetic eye disease and in patients with diabetic eye disease is VEGF, a key mediator of both vascular leakage and growth of new vessels.

Macular laser used to be the standard of care for treatment of DME, however the development of anti-VEGF therapy in the last decade has led to dramatic improvements in visual outcomes for patients with DME. Other available approved options for the treatment of DME include periocular or intravitreal steroids and steroid implants which have the limitations of severe side effects such as cataract and glaucoma.

The availability of intravitreal anti-VEGF treatments enabled robust improvements in visual outcomes accompanied by robust improvements in the underlying DR severity in patients with DME and DR severity improvements with anti-VEGF treatments were enabled also in patients with DR, with or without DME (Antoszyk et al. 2020). Ranibizumab (Lucentis) is approved for the treatment of visual impairment due to DME and the treatment of patients with PDR (with or without DME) in the European Union. Aflibercept (Eylea) is approved for the treatment of visual impairment due to DME in the European Union. Although intravitreal anti-VEGF therapies for the treatment of patients with DME and DR represent major advances, there is still an unmet need for improved therapies in these diseases.

In the real world, a significant proportion of DME patients treated with approved therapies do not experience clinically meaningful improvements in vision or are unable to maintain their initial vision gains long-term due to a need for frequent HCP visits for injections or monitoring (Souied et al. 2015; Stefanickova et al. 2018; Shimura et al. 2020; Naujokaitis and Balaciuniene 2021).

Given the multifactorial pathogenesis of DME and DR, treatments targeting additional pathways beyond VEGF are needed to comprehensively address the underlying pathology and to provide more durable efficacy which could reduce the burden of frequent HCP visits and intravitreal injections in these patients.

2.2. About the product

2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 120 mg/ml of faricimab as active substance. Each vial contains 28.8 mg faricimab in 0.24 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab.

Other ingredients are: L-histidine, acetic acid, L-methionine, polysorbate 20, sodium chloride, D-sucrose, water for injections.

The product is available in vial with a coated rubber stopper sealed with an aluminum cap with a yellow plastic flip-off disk and it is co-packaged with a blunt transfer filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm). Pack size of 1 vial and 1 transfer filter needle. The user is instructed to transfer the finished product from the vial into a disposable injection syringe, which is not included in the package.

2.2.2. Active substance

2.2.2.1. General Information

The active substance (INN faricimab) is a recombinant bispecific antibody produced in Chinese hamster ovary (CHO) cells and consists of two different heavy chains (452 amino acid residues and 462 amino acid residues) and two different light chains (214 amino acid residues and 213 amino acid residues) with inter- and intra-chain disulfide bonds, that are typical for IgG1 antibodies plus an additional disulfide bridge in the CH3-CH3 interface.

To enforce heterodimerisation of the two different heavy chains, several point mutations were introduced (“knobs into holes”). Exchange of CH1 and CL domains in the Ang-2 binding Fab promotes the correct assembly of the two different light chains, known as the “CrossMAb approach”.

Modification of faricimab neonatal Fc receptor (FcRn) and Fc gamma receptor (FcγR) binding sites disables the antibody's Fc-mediated effector functions.

The Fc domain of each heavy chain contains one N-linked glycosylation site at the conserved Asn297 according to Kabat et al. 1991, at Asn303 for HC1 and Asn313 for HC2, respectively, according to the faricimab amino acid sequence numbering.

Faricimab is a next generation antibody with a dual action that targets not one but two pathways involved in angiogenesis/vascularisation/inflammation and retinal vessel destabilisation in the eye. Faricimab selectively binds with high affinity to VEGF-A and Ang-2 thereby preventing binding of VEGF-A and Ang-2 to its receptors. Binding of VEGF-A and Ang-2 to their receptors results in retinal vessel destabilization, inflammation, endothelial cell proliferation, neovascularisation and vascular leakage, which mediate onset and progression of neovascular form of age-related macular degeneration (nAMD), diabetic retinopathy and diabetic macular oedema (DME). The mechanism of action of faricimab works through the interference with the ligand-receptor binding process in Ang-2 and VEGF pathways that play a key role in these retinal diseases.

2.2.2.2. Manufacture, process controls and characterisation

The active substance is manufactured by Roche Diagnostics GmbH, Penzberg, Germany.

The active substance manufacturing site, testing sites, cell bank preparation, testing and storage sites are listed in the application. Valid manufacturing authorisations and/or Good Manufacturing Practice (GMP) certificates are available for all active substance manufacturers.

Description of manufacturing process and process controls

Faricimab is produced using a suspension-adapted CHO cell line. *Up-stream* manufacturing of faricimab active substance starts with thawing of 1 vial of working cell bank (WCB) followed by serial culture expansion from agitated flasks through 1) seed train bioreactors and 2) inoculum train cultures to the 3) production bioreactor. The seed train culture is used to provide a continuous source of cells for the production of multiple batches from a thaw of the WCB.. The production culture is harvested by separating the secreted molecule in the cell culture fluid (CCF) from cells and cell debris by centrifugation and filtration. The filtered harvest cell culture fluid (HCCF) hold time and conditions are properly validated. From each production run, a single batch of HCCF is produced, which can be traced back to the WCB thaw used to initiate the manufacturing process. Critical process parameters (CPPs) and non-CPPs with acceptance ranges are determined and summarised, in-process control (IPC) output parameters and acceptance/action limits are indicated.

The faricimab purification process consists of chromatography steps and additional steps for removal and inactivation (low pH and viral retention filtration) of potential viral contaminants. The final step in the active substance purification process is concentration of the product and buffer exchange using ultrafiltration and diafiltration (UFDF). Protein concentration and buffer composition are adjusted to the active substance specification by addition of a stock solution containing histidine/acetic acid buffer, sodium chloride, sucrose, methionine and polysorbate 20. The active substance solution is filtered into appropriate storage containers.

Faricimab is fully formulated at active substance level, no further formulation takes place during finished product manufacture.

CPPs/non-CPPs and IPCs were determined based on defined quality target product profile and critical quality attributes, process characterization, and criticality assessment of process parameters and attributes. The classification of the process parameters and their acceptable ranges are adequately justified. IPCs with action limits or acceptance criteria are implemented at critical steps. In conclusion,

the process parameters and IPCs in combination with the other control measures appear appropriate to ensure quality and safety of faricimab as well as to monitor process consistency. Batch numbering system allows proper traceability of the manufacturing process of the active substance.

Pre-harvest Cell Culture Fluid (PHCCF) is sampled for appropriate IPCs for microbial control; appropriate microbial safety tests are performed throughout the purification process, with appropriate action/acceptance limits.

Chromatography processes are described sufficiently. Number of cycles needed for processing one batch is stated, critical and non-critical process parameters with acceptable ranges are determined. Resin reuse limits are determined, and the selected validation approach is acceptable. Materials and types of UFDF membranes are listed. Appropriateness of the sanitisation, regeneration and storage procedures have been demonstrated. There are multiple filtration steps using 0.2 µm filters in the purification process. Reprocessing conditions are specified in the dossier. Refiltration has been appropriately validated. Type of the virus filter is stated and the filter is tested for integrity prior to and after use. Information about the integrity test method and the acceptance criterion is provided. Actions taken in case of failure are described in the Applicant's quality system.

Hold times have been established for the in-process pools based on biochemical and microbial hold time studies. Defined hold times are adequately justified by hold time studies.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. There are no raw materials of human/animal origin or any directly derived non-animal biological material used in the manufacturing process.

The generation of the production cell line and the expression vectors has been described in detail. Faricimab is manufactured in a Chinese Hamster Ovary (CHO) cell line which is regarded as well established. Sufficient details have been provided on the source and history of the cell substrate. The preparation of the expression constructs for the different antibody chains has been appropriately described and vector maps have been provided.

Cell line development, clonality, source, history, generation and composition of the Cell Substrate is described adequately. The cell bank system is composed of the MCB and the WCB and is appropriately qualified by characterization and testing according to relevant guidelines Test methods performed to confirm identity, microbial, viral and retroviral safety as well as genetic stability of master cell bank (MCB), WCB and Cells at limit of in vitro cell age (LIVCA) are described. Results demonstrate that no changes to the faricimab DNA sequences have occurred during the establishment of the cell bank system and the production process. Cell viability and MCB and WCB stability are suitably addressed.

Control of critical steps and intermediates

IPC tests and limits applied to the cell culture and purification process steps are summarized in tabular format. Depending on criticality, IPCs are tested against defined action limits or acceptance criteria. Appropriate IPC tests including for microbial control are conducted throughout the manufacturing process with action limits. Acceptance criteria is determined for safety relevant parameters where conformance is required for release.. The IPCs and their acceptance criteria/action limits are considered adequate.

No intermediates are defined for the faricimab active substance manufacturing process.

Process validation

The process validation/characterisation approach described in the dossier includes: 1. A process impact assessment (based on the outcome of the scale-down model (SDM) studies, linkage studies, large scale data from manufacturing scale runs, and hold time studies a process risk score is defined for CQAs), 2. PPQ batches, 3. Small-scale studies (Design of experiment (DOE) studies to identify CPPs, non-CPPs and acceptable ranges), 4. Qualification of scale-down models, 5. Process linkage studies for reduction/clearance of impurities/variants, 6. Validation of hold times, 7. Evaluation of raw material removal and leachables, 8. Validation of re-use of chromatography resins and ultrafiltration membranes, 9. Shipping qualification studies, 10. Validation of active substance re-filtration.

An appropriate number of consecutive batches from independent thaws of the WCB were manufactured at the commercial active substance manufacturing site in accordance with pre-approved protocols and according to the commercial process, scale, and control procedures. A subset of batches were manufactured at the limit of in vitro cell age.

For the at scale qualification, Quality Attributes (QAs) were assessed. PPQ results are provided for all individual process steps and phases for process parameters as well as for process attributes/IPCs and for release testing. All process validation data are within the pre-defined ranges/acceptance criteria/specifications, including the critical parameters and attributes (CPPs, CPAs and CQAs). For the product related impurities, data show consistent reduction throughout the purification steps across all batches.

Process Parameter (PP) Ranges for the upstream and downstream manufacturing steps, like chromatography steps and additional steps for removal and inactivation of potential viral contaminants, were evaluated in small scale studies.. PP Acceptable Ranges were set to ensure that each CQA is within the in-process pool limit (IPPL). A Risk Ranking and Filtering (RRF) assessment (based on development data and prior knowledge) was completed for each unit operation to assess the criticality of all PPs. Based on the outcome of the RRF, multifactor and single-factor studies were planned and evaluated using DOE concepts in the determination of CPPs. The SDMs were suitably qualified.

In-process hold time validation includes microbial and biochemical validations. Validation is ongoing. Upon completion of the hold time validation, the Applicant intends to submit a corresponding Type IB variation.

Resin lifetime and re-use studies are ongoing and have been verified at manufacturing scale. The small-scale data and the available data from large-scale manufacture support the proposed lifetimes and regeneration/sanitisation procedures for resins.

Shipment of faricimab active substance from Roche Penzberg, Germany for long-term storage and to the finished product manufacturing site has been validated.

Overall, the process validation results demonstrate that the process performed consistently and removal of impurities is generally considered adequately demonstrated.

Manufacturing process development

During development, different versions of the faricimab active substance manufacturing process were used.. Process steps/process parameters of the different processes are compared in tabular format, and rationale of the changes are provided and are deemed sufficient. All phase III clinical and the PPQ batches were manufactured at the commercial active substance manufacturing facility at commercial scale,. The potential impact of the manufacturing changes on product quality was assessed in an extensive comparability program that included routine analytical and extended characterisation of the biological and physicochemical properties of faricimab active substance as well as comparative

stress stability studies. The earlier developmental batches were also tested for comparability. Routine analysis results show that batches are consistent in terms of purity, potency, identity, and that all process versions have sufficient clearing capacity of impurities.

The same production cell line was used throughout development,

In conclusion, the process comparability exercise performed on the different developmental batches confirms that neither the process changes introduced during clinical development nor the changes introduced between the phase III clinical and PPQ batches are expected to adversely affect the activity and safety of the post-change materials.

Characterisation

Faricimab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a IgG1-type antibody derived from CHO cells.

Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities.

The approach to confirm the primary structure of faricimab is acceptable. Molecular mass figures corresponded with the expected mass figures of the main glycoforms, mass figures obtained showed close correspondence with the expected heavy- and light- chain masses. Peptide map analysis confirmed the theoretically expected amino acid sequences for each of the four different polypeptide chains. N-and C-terminal variants were quantitated by the peptide map analysis. The Applicant conducted peptide map analysis to detect sequence variants. The expected disulphide bonds were identified.

A study of active substance steric structure was conducted. Taken together the data in the original MAA and in the response, it may be reasonably assumed that faricimab is similar to the known IgG1 type mAbs by overall structure.

The N-glycosylation analysis presented is considered satisfactory; the glycosylation pattern is similar to that of other CHO-derived mAbs. Non-human carbohydrate structures have not been identified.

Stress studies were used to gain an insight into post translational modifications such as oxidation, deamidation.

Analysis of the active substance revealed a low abundance of high molecular weight (HMW) and low molecular weight (LMW) components. The formation of HMW and LMW components was found to impact biological activity. Charge variants have been analysed and been assigned to structural variants by various techniques.

An isoelectric point figure has been determined.

An extinction coefficient was also determined for faricimab.

Functional characterisation of faricimab included an assay to measure the anti-Ang-2 potency and a reporter gene assay to measure anti-VEGF potency. Both the assays are part of active substance as well as finished product release specification. A full description of the assays as well as justification of method choice have been provided. The faricimab treatment of ophthalmopathic patients is aimed at inhibiting vascular proliferation, therefore the anti-proliferation capacity of the active substance is to be explored.

Size -, and charge-related variants as well as stressed samples (the preparation of stressed samples was described) were assessed for functional activity.

Characterisation: assessment of critical quality attributes (CQAs)

A separate sub-section has been devoted to the definition of CQA-s within S.3. QAs have been reviewed to decide whether CQA-assessment is applicable.. Criticality was assessed by a procedure called risk ranking and filtering (RRF). In this procedure, impact and uncertainty scores were assessed on bioactivity, pharmacokinetics, immunogenicity and safety, taking clinical and non-clinical experience, physicochemical and biological characterisation, general knowledge on antibodies and published literature into account.

No high or medium impact attribute was identified for immunogenicity. The Applicant used clinical data for justification, namely the lack of finding ADAs with an impact on PK, efficacy or safety.

Based on the favourable safety profile of faricimab recorded during phase II and phase III clinical studies, no high or medium impact attribute was identified with respect of safety.

The potential synergistic effects of quality attributes as well as interactions that have been associated with potential stability issues have also been addressed.

In general, the definition of CQAs is considered approvable.

Impurities

The Applicant did not distinguish between product-related substances and product-related impurities referring to difficulties in isolating the individual variants. Nevertheless, in certain cases) a low biological activity was reported for some variants. These ones might have been identified as impurities. As CQAs have been defined for the variants with defective potency, they are controlled.

Concerning process-related impurities, characterisation and removal of these impurities are described.

Elemental impurities are discussed in connection with the active substance container-closure system. Only acetic acid is discussed as residual solvent, its removal is also described. Ethanol levels found in the PPQ batches are well below the acceptable limit. For control of potential contaminants (adventitious agents) refer to section below.

2.2.2.3. Specification

The active substance release specification includes general tests, test for identity, purity and impurity tests, test for protein content, potency by bioassays(anti Ang-2 assay and anti VEGF reporter gene assay) , polysorbate 20, including appropriate microbial safety tests.

Tightening of some criteria in the specification was undertaken during the procedure.

Analytical methods

Description of the analytical tests as well as their validation and the justification of specification is found in section P.5

Two bioassays serve as quantitative *in vitro* assays to determine potency of faricimab active substance and finished product. The anti-Ang-2 functionality of faricimab is measured in a cell-based assay. The anti-VEGF functionality of faricimab is measured in a cell-based VEGF reporter gene assay.

Batch analysis

Data for all the available active substance batches has been provided. Genealogy of the batches starting from the cell bank origin is presented. Results on all the batches meet the specification in

effect by the time of testing. Test results on the four PPQ batches meet the proposed commercial release specification criteria as well.

Reference materials

The same Reference Standards were used for active substance and finished product. Refer to the respective finished product section.

Container closure system

The active substance is stored in specified bags. A description of the active substance container, closure component (cap/seal), and technical drawing of the container are presented. Vendor certificate and irradiation certificate have been provided. . The active substance storage container is in compliance with Ph. Eur. 3.1.7.

Extractables study has been conducted by the vendor, the results are briefly summarised. A leachables study has been initiated and continued throughout the active substance shelf life..

So far, the study did not reveal any leachable posing a potential risk. The Applicant committed to submit full results of the study upon completion (recommendation 1).

2.2.2.4. Stability

A shelf life and storage conditions were proposed for the active substance.

The long term stability study results include data on an appropriate number of clinical and PPQ batches.. All the results are within specification. The comparability of the clinical batches to the PPQ batches has been demonstrated. In view of the storage conditions and the stability profile of faricimab active substance, the claimed shelf life can be granted.

Accelerated stability study revealed an increase in the HMW species as well as an increase in thebasic component.

The Applicant committed to include at least one commercial active substance batch per year if commercial production occurs during the calendar year.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Faricimab finished product is provided as a sterile, colourless to brownish-yellow solution for injection. The finished product is formulated as 120 mg/mL faricimab. Each single-use vial contains 28.8 mg of faricimab at target pH 5.5, and it is designed to deliver 6 mg of faricimab. The manufacturing fill parameters were selected so as to deliver the net quantity (nominal fill volume) declared on the label.

The container closure system consists of a Type I glass vial with a fluororesin-laminated butyl rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap.

The faricimab finished product is co-packaged with 1 blunt transfer filter needle (Becton Dickinson 18 G 1 × 1/2’’stainless steel transfer filter needle 5 µm; filter material: acrylic copolymer).

Formulation development

The finished product formulation is identical to the active substance formulation. L-histidine and acetic acid used for buffering, L-methionine as stabiliser, sodium chloride and D-sucrose are used as tonicity

agents, and polysorbate 20 used as surfactant as well as to minimise formation of aggregates. The formulation does not contain any preservatives. The rationale used to select the excipients was sufficiently described in the dossier. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Four different finished product formulation were used during faricimab development . Changes in formulation during development were sufficiently described. The rationale used to select the final composition has been described in the dossier. The proposed commercial finished product formulation is identical to the formulation used in phase III clinical trials. A multivariate formulation robustness study was performed, and it demonstrated that the formulation ensures the finished product stability during manufacture, storage, transportation and administration.

Considering that faricimab is an ophthalmologic product and developed for intravitreal injection, the number of particles is of special interest. No visible particles have been detected in finished product so far. The Ph. Eur does not set specific limits for subvisible particulates in ophthalmologic products. Faricimab finished product is intended to use with a transfer filter needle. The effectiveness of filter was demonstrated using polystyrene beads in formulation buffer, faricimab finished product and surrogate protein formulation. The use of filter needle is mandatory, and this is appropriately reflected in the SmPC. The filter needle is co-packed with the finished product. The control of subvisible particulates is considered acceptable.

The proposed commercial manufacturing process includes thawing and optional refreeze of active substance, pooling and mixing, bioburden reduction and sterile filtration, filling, stoppering, capping and crimping. The finished product is stored at 2°C-8°C.

Different finished product manufacturing processes were used during development. The manufacturing site was also changed. Processes used for manufacture of batches used during phase 3 pivotal studies and PPQ batches have been described.

A comprehensive comparability exercise was performed on finished product batches to account for changes between the development finished product process and the finished product proposed commercial process. The comparability exercise included quantitative comparison with predefined comparability acceptance criteria, qualitative comparability assessment of chromatograms and electropherograms, and stress stability studies. In general, the studies demonstrated comparable quality of materials. The results are in line with the finding of the active substance comparability exercise and demonstrate improved quality of the PPQ batches compared to phase III material with respect to main peak purity.

Overall, comparability data demonstrated that the material derived from the clinical trials and PPQ process- finished products were comparable.

The finished product does not contain any overages. Minimal fill volume was defined based on the results of user handling study. The minimum fill volume ensures that the appropriate dose (0.05 mL) can be withdrawn.

Compatibility of active substance with container closure system and devices used for administration was demonstrated. Extractable and leachable studies were conducted, and no risk was identified. Leachable studies are still ongoing. . The Applicant committed to provide data from ongoing leachables studies and any new leachables not previously identified will be reported to EMA (recommendation 2). In-use stability of finished product was assessed using representative injection syringes, equipped with transfer needle. The results demonstrated that finished product in simulated intravitreal administration is physically and chemically stable under the tested conditions.

2.2.3.2. Manufacture of the product and process controls

The finished product manufacture, release and stability testing sites are specified in the dossier. The finished product is released by Roche Pharma AG, Germany. GMP certificates were provided for the finished product sites. Batch formula is appropriately presented for minimum and maximum batch sizes.

The manufacturing process consists of thawing, pooling and mixing of active substance, bioburden reduction and sterile filtration, filling, stoppering and capping. The thawed active substance may be optionally refrozen. The vials are visually inspected before labelling and secondary packaging (including co-packaging with filter needle). The finished product is stored at 2-8°C. Vials and stoppers are sterilised by the finished product manufacturer. Manufacturing process is briefly described.

Summary of critical, non-critical process parameters, and hold times are presented. Acceptable ranges were defined for CPPs and non-CPPs. In-process controls include bioburden, bacterial endotoxin, filter integrity (for bioburden reduction filtration and sterile filtration), fill volume and visual inspection. Acceptance criteria or action limits were defined for in-process controls and are in compliance with guideline requirements and Ph. Eur.

The consecutive finished product PPQ batches were manufactured at the commercial manufacturing site.. PPQ results are provided for all individual process steps for both process parameters and in-process controls. All data comply with the pre-defined acceptance criteria. PPQ batches demonstrated that the finished product can be consistently manufactured within predefined processing parameters.

A risk assessment (RFF) was used to identify critical process attributes and parameters and to design the process design studies. The risk assessment and the scoring system is considered appropriate. Process design studies were performed to support the proposed process parameters, process and hold times. Process parameters were classified as CPPs or non-CPPs based on the observed impact on relevant CQAs in the process design studies and acceptable ranges were defined.. Aseptic filling has been validated. Hold times were justified from microbial perspective. All maximum hold times are sufficiently covered through either process design or PPQ studies.

In general, the PPQ batch data presented, in addition to the release and stability data of the PPQ batches along with the process design studies, confirm that all CQA met the acceptance criteria and the IPCs met their acceptance criteria or limits, respectively. All CPPs and non-CPPs were within their acceptable ranges and process performance was consistent between the PPQ batches. The finished product manufacturing process is considered thoroughly validated.

Supply chain and shipping system of finished product were sufficiently described. Several studies have been performed to ensure that shipment of faricimab finished product is adequate from a thermal and mechanical perspective. Validation for the depyrogenation and sterilisation of vials as well as for the sterilization of stoppers are described sufficiently and performed in accordance with EMA guideline.

2.2.3.3. Product specification

The finished product release specification includes general tests, test for identity , purity and impurity tests, test for protein content , test for polysorbate 20 content , potency by bioassays (anti Ang-2 assay and anti VEGF reporter gene assay) , as well as tests for safety, including entoxin and sterility .

Justification of active substance and finished product release and shelf-life specifications was provided. The Applicant used information from clinical experience, manufacturing history and stability studies for establishment of acceptance criteria.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

Finally, the nitrosamine risk assessment has been provided. The assessment has been carried out for the manufacturing process, active substance, excipients (including water for injections) and primary packaging materials, as required. It is agreed that the risk assessment shows that the risk of formation/introduction of nitrosamine impurities for the entirety of the finished product is negligible.

Analytical methods

The list of analytical methods is considered adequate.. Test method identification numbers are provided. The analytical procedures used in routine testing of active substance and finished product were described in sufficient details. Validation reports covering all the non-compendial methods have been submitted. Batch analyses results of all finished product batches were provided.

Batch analysis

All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch. In addition, all available release data from the finished product batches produced during the PPQ campaign meet the commercial release specification acceptance criteria.

Reference materials

A two-tiered reference system was prepared from the same active substance batch, using the same procedure for the primary (pRS) and the secondary (sRS) reference standard. This active substance batch was produced with a manufacturing procedure, which is considered representative of the commercial procedure. The secondary RS was appropriately characterized, including release methods as well as extended characterization. The same RS was used for the active substance and for the finished product. Potency of sRS is equivalent to former RSs.

The list of RSs used in clinical development is provided, along with their qualification history. Future RS will be prepared and characterized according to the defined protocol. In the response to day 120 questions, the Applicant committed that defined additional testsare going to be included in the testing panel when either a new primary reference standard or an updated RS testing protocol is going to be submitted for post marketing approval (recommendation 3).

Reference standard storage conditions are suitably defined.The stability of secondary RS is tested annually, which is adequate. After having the current secondary RS replaced, stability testing of the primary RS will be initiated (that far stability testing of secondary RS could stand for the primary RS as well).

Container closure system

The container closure system of faricimab finished product consists of a 2ml Type I glass vial closed with a fluororesin-laminated butyl rubber stopper and an aluminum seal with a plastic flip-off cap. The materials in contact with the finished product comply with Ph. Eur. requirements and appropriate for storage of the finished product. Specifications, drawing of elements and information on the dimensions of components are adequately provided.

The finished product is co-packaged with a transfer filter needle (BD 18G 1 x 1/2’’stainless steel transfer filter needle 5 µm; filter material: acrylic copolymer) and a leaflet in a carton folding box. The filter is CE-marked..

2.2.3.4. Stability of the product

A shelf life of 30 months when stored at 2-8°C is claimed for the finished product.

In general, stability studies were carried out in accordance with ICH Q5C. The protocol (including specification, methods, and test intervals) is provided and considered appropriate. Quality attributes (potency, purity, content) general attributes (pH, colour, clarity) and container closure integrity were addressed. The analytical methods used were demonstrated to be stability indicating..

Stability studies are being conducted under long-term (5°C), accelerated (25°C) and stress conditions (40°C). The stability batches are representative of the commercial finished product batches. The same containers were used in the stability studies as for marketing.

Additional stability data was provided in the response document.

Photostability study was performed in line with ICH Q1B. In summary, the results demonstrated that the faricimab finished product is photolabile, but the secondary packages provide adequate protection from light. The finished product should be kept in the original carton to protect from light, this issue is reflected in the SmPC.

The in-use stability studies were described. The results demonstrated that faricimab finished product is physically and chemically stable under the tested conditions. From a microbiological point of view, the prepared injection solution should be used immediately, as described in the SmPC.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

The commitment to put at least one finished product batch per year on long-term storage stability, using the proposed post approval stability protocol is endorsed.

2.2.3.5. Adventitious agents

Cell banks were suitably tested to demonstrate freedom from adventitious agents. The use of appropriate analytical methodology revealed no identifiable virus-like particles other than A-type and C-type retrovirus-like particles (RVLPs), which are intrinsic to the CHO cell line.

Preharvest cell culture fluid (PHCCF) is tested for adventitious viruses, mycoplasma and endotoxin. Additionally, endotoxin and bioburden is tested with action limits throughout the purification process. Tests methods are compendial, and are briefly described. Product specific verification has been performed, results are provided.

None of the materials (including raw materials and reagents) used in the faricimab active substance and finished product manufacturing process are derived from TSE/ BSE relevant species.

Small scale virus clearance studies (using model viruses) demonstrated that satisfactory log reduction values could be achieved by virus inactivation (low pH inactivation step) and removal (chromatography columns and small virus retention filter) in the faricimab purification process supporting the acceptable parameter ranges. Conditions of sanitisation and re-use of columns are reported and validated. The virus filter is a single-use filter and therefore a new filter was used for each validation experiment.

An appropriate retrovirus risk evaluation was also conducted. It can be concluded that the purification process provides sufficient capacity for retrovirus reduction.

Validity of small-scale models for the inactivation by low pH and removal by small-virus retentive filtration and chromatography steps is demonstrated.

Additionally, the common quantification median tissue culture infective dose ($TCID_{50}$) assay validation demonstrate the suitability of the $TCID_{50}$ to quantify the model viruses.

Overall, Faricimab is safe for use with regards to lack of risk for transmission of adventitious agents.

2.2.3.6. GMO

Not applicable

2.2.4. Discussion on chemical, and pharmaceutical aspects

Overall, the manufacturing process, process control, elucidation of structure and specifications for Faricimab active substance and finished product have been appropriately presented. Some additional information/clarification have been requested at day 120 regarding active substance heterogeneity, characterisation and validation results/criteria of certain analytical methods used for impurity testing; and further justification was required in some areas of the product control strategy including finished product release acceptance criteria. Additional stability data was provided to support the proposed active substance/finished product shelf life. Based on the extensive comparability studies it can be concluded, that the batches used in clinical trials are representative to the commercial product to guarantee that the latter will be the same as the clinical batches. All raised questions have been addressed and 3 recommendations are proposed related to submission upon completion of leachable studies and inclusion of defined additional tests of the RS.

A satisfactory overview on a nitrosamine risk assessment is included in the dossier.

The risk for transmission of adventitious agents seems adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

From the quality perspective, Faricimab is considered approvable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Vabysmo is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. To provide full leachable data for the active substance container closure system upon study completion (up to maximum 60 months). The study is foreseen to be completed in Q2 2025.

2. The long-term leachables study the finished product container closure system will be continued for at least up to 36 months covering the proposed finished product shelf life of 30 months, and any results that are above the toxicological thresholds or any new leachables not previously identified will be reported to EMA. Final results of the 36 months' time point will be available after study completion in October 2023.

3. To include defined additional tests when either a new primary reference standard or an updated protocol is submitted for post marketing approval.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Mechanism of action

Faricimab (RO6867461) is a humanized bispecific immunoglobulin G1 (IgG1) antibody generated by CrossMAb technology that selectively binds to and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). It is composed of two different heavy chains (HC) and two different light chains (LC). One arm of the antibody binds VEGF and the other arm binds Ang 2. The VEGF binding domain is a humanized fragment antigen binding (Fab) and is comparable to other anti VEGF molecules, e.g., ranibizumab. The Ang 2 binding domain is a human Fab derived from phage display. The constant part is based on a human IgG1 framework. The variable part contains heavy chain VH3 and light chain Vκ1 subgroup sequences (for the anti VEGF arm) and heavy chain VH1 and light chain Vλ3 (for the anti-Ang-2 arm), respectively. To enforce heterodimerization of the two different heavy chains, several point mutations were introduced ("knobs into holes"). Exchange of CH1 and CL domains in the Ang-2 binding Fab promotes the correct assembly of the two different light chains, known as the "CrossMAb approach".

The fragment crystallizable (Fc) portion was specifically engineered to reduce systemic exposure and reduce inflammatory potential. Mutations in the Fc domain of RO6867461 abolish binding to Fcγ receptors located on effector cells, and the neonatal Fc receptor (FcRn).

Faricimab has a total molecular weight of approximately 146 kDa and is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

Angiogenesis is implicated in the pathogenesis of intraocular neovascular syndromes (e.g. Age-related Macular Degeneration (AMD)). Targeting VEGF-A with monoclonal antibody is a state-of-art therapy in case of patients suffering from neovascular Age-related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME) (ranibizumab (LUCENTIS)). Ang-2 seems to be a complex regulator of vascular remodelling that plays a role in both vessel sprouting and vessel regression. Ang-2 causes vascular instability by promoting endothelial destabilization, pericyte loss, and pathological angiogenesis. The bispecific antibody targets both VEGF-A and Ang-2 mediated mechanisms.

In vitro studies

Primary pharmacodynamic studies used in vitro test systems to determine the specificity of faricimab to VEGF-A and Ang-2 and to exclude the possible binding to FCγRI, FCγRII, FCγRIIIa, C1q and to FcRn. These test systems on one hand were binding assays performed by Surface Plasmon Resonance and Isothermal Titration Calorimetry techniques. These experiments showed specific binding of faricimab to human VEGF-A and Ang-2 antigens, and no Ang-1 binding was observed. The KD value of faricimab binding to human VEGF-A121 And VEGF-A165 was 3 nM investigated by Isothermal Titration Calorimetry. Based on surface plasmon resonance (SPR) experiments faricimab appears to bind to ANG-2 and VEGF-A both independently and simultaneously i.e., faricimab can bind to both ligands at the same time.

Table 6. Details about the different substudies reported under the number 1056781.

Type of Study	Test System	Formulation/Vehicle	Noteworthy Findings

Ang-2 affinity in solution	SPR	CM VEGF/Ang-2; HBS-P	Full length Ang-2 affinity: Human 20 nM, Cynomolgus 13 nM, Mouse 13 nM, Rabbit 11 nM; Ang-2-RBD-Fc affinity: Human 21 nM, Mouse 5nM, Rat 8nM
Ang-1/2 Interaction	SPR	CM VEGF/Ang-2; HBS-P	Human: No binding to Ang-1
VEGF-A121 Affinity	SPR	CM VEGF/Ang-2; HBS-P	Human: kinetic affinity 1 nM, solution affinity 0.5 nM, Rat 14 nM kinetic affinity, Mouse No binding
VEGF-A121 Affinity	ITC	CM VEGF/Ang-2; HBS-P	Human: 3 nM
VEGF-A165 Affinity	ITC	CM VEGF/Ang-2; HBS-P	Human: 3 nM
Binding to FcγRI, FcγRIIa and FcγRIIIa (V158)	SPR	CM VEGF/Ang-2; HBS-P	FcγRI: No binding, FcγRIIa: No binding, FcγRIIIa (V158): No binding
Human, Cynomolgus, and Murine FcRn Binding	SPR	CM VEGF/Ang-2; HBS-P	Human: No binding Cynomolgus: No binding Murine: No binding

SPR: Surface Plasmon Resonance; ITC: Isothermal Titration Calorimetry; HBS-P (10 mM HEPES buffered saline including 0.05% Tween20) pH 7.4

Genetic modification was carried out on the molecule to inhibit the Fc arm binding. These modifications of faricimab neonatal Fc receptor (FcRn) and Fc gamma receptor (FcγR) binding sites (located in the CH3 domains) disable the antibody's Fc mediated effector functions: The "PG-LALA" mutation abrogates the binding to FcλRs and C1q. Additional point mutations ("TripleA") located in the CH3 domains of the Fc region of faricimab disable the functional binding to the FcRn. According to the binding measurements, these modifications were effective, and no binding was observed to FcγRI, FcγRIIa, FcγRIIIa and FcR receptors. These experiments exclude the possible Fc fragment-mediated unwanted effects.

The Applicant provided additional data in the amended report. These sensogram data clearly show the binding affinities for FCγ, FCγRIIA, FCγRIIIA and FcRn binding sites. In case of "no binding", positive and negative binding controls were applied to ensure the suitability of the assay.

Cell based in vitro assays

For pivotal clinical studies, mode of action-reflective cell-based assays were selected and validated to be used as potency assays. Considering that both faricimab functionalities have independent biological

effects related to clinical efficacy, two independent cell-based assays, each addressing one of the two faricimab functionalities, were used in conjunction with two independent potency specifications.

Tie-2 Phosphorylation Assay: Tie-2 is the main receptor for Ang-2, downstream effects (e.g. proliferation) are mediated via Tie-2 receptor activation. The best characterized in vitro system to monitor Ang-2 function is to measure its agonistic function on Tie-2 phosphorylation in the absence of Ang-1. Tie-2 phosphorylation assay was shown to be sensitive to the neutralisation of the Ang-2 ligand by faricimab (HEK293 cell lines (VEGFR2, Tie-2).

VEGF Reporter Gene Assay: Faricimab dose-dependent inhibition of the NFAT-Luciferase reporter gene expression is quantified by measuring luminescence after addition of a luminescent Luciferase substrate.

Human umbilical vein endothelial cell (HUVEC) anti-proliferation assay: Faricimab dose-dependent inhibition of VEGF-induced HUVEC cells proliferation is quantified using a luminescence substrate after 3 days incubation at 37°C.

The results of all of the three cell-based in vitro experimental setup show effectiveness of faricimab in vitro in a dose-dependent fashion.

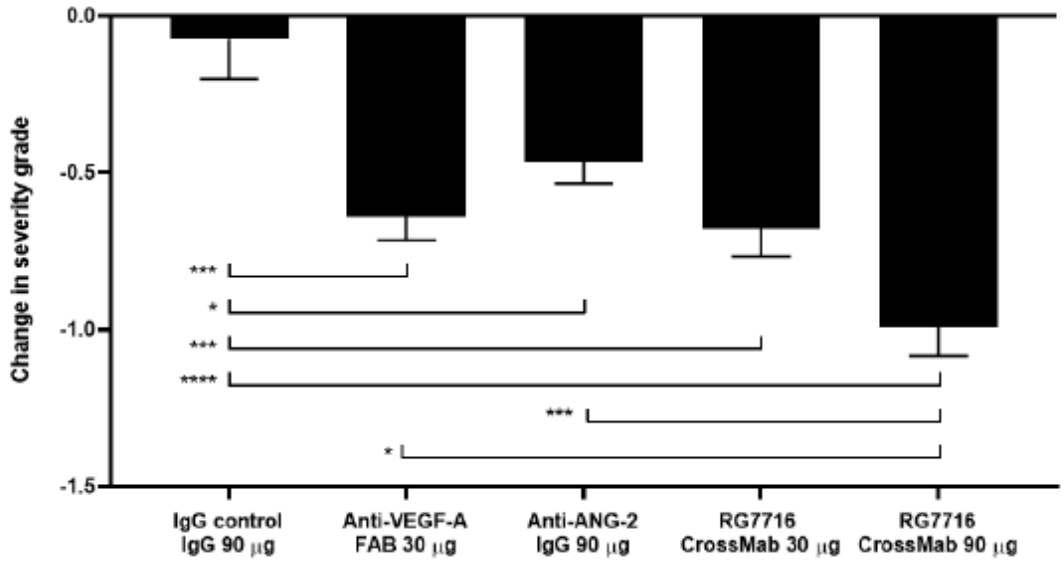
Simultaneous binding events were detected by measuring the sequence of binding by first adding Ang-2 followed by VEGF-A and first adding VEGF-A followed by Ang-2.

In vivo studies

The PD and PK of faricimab was tested on the eyes of Cynomolgus monkeys in vivo, pre-treated by laser beam to induce damage, leakage and neovascularization in the retina as a model of wet Age-related Macular Degeneration (nAMD). Ranibizumab, the VEGF-targeting mAb was investigated simultaneously with other mAbs as active controls.

The intravitreal administration of faricimab showed effectiveness dose dependently and in the dose of 30 µg proved to be equally effective to ranibizumab (Lucentis 30 µg). The higher (equimolar) dose of faricimab 90 µg reduced the damage severity (Fig.10) and the Grade-4 lesions (Fig.11) in the retina substantially better than ranibizumab in the dose of 30 µg ((0.91 vs 0.55, respectively, p=0.0039). (Of note faricimab has three times higher molecular weight - 146,157 Da than ranibizumab - 48,350 Da).

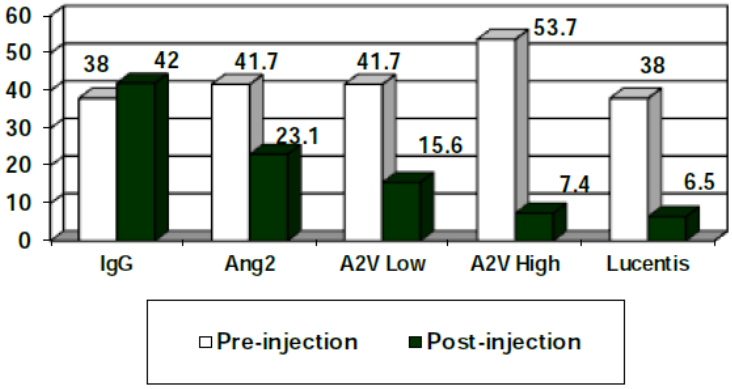
Figure 10. Effect of Anti-VEGF-A/ANG-2 (RG7716) Antibody in a Laser-Induced In Vivo Model of Choroidal Neovascularization



IgG = immunoglobulin; FAB = fragment antigen binding; IVT = intravitreal;
RG7716 CrossMab = faricimab (anti-VEGF-A/ANG-2 antibody); VEGF = vascular endothelial growth factor.

Inhibition of neovascularization measured in severity grades, change of severity from baseline is shown for each treatment; all treatments significantly reduced the severity grade compared to IgG control.
In addition, efficacy of RG7716 (150-kDa molecule at 90 µg/50 µl injected IVT) was significantly better at equal molar concentration of binding sites than anti-VEGF-A (ranibizumab, 50-kDa molecule at 30 µg/50 µl injected IVT) and anti-ANG-2.
Error bars show SEM of n = 12 eyes from 6 cynomolgus monkeys and 9 spots per eye in the groups treated with anti-VEGF-A, anti-ANG-2, and RG7716 CrossMab 90 µg, and SEM of n = 10 and n = 9 eyes from 6 and 5 cynomolgus monkeys and 9 spots per eye in the groups treated with RG7716 CrossMab 30 µg and IgG control, respectively.
The symbol "*" denotes significance after one-sided ANOVA and Tukey's multiple *t*-test.
IgG control is significantly different from anti-VEGF-A (***, $P = 0.0002$), anti-ANG-2 (*, $P = 0.0262$), RG7716, 30 µg (***, $P = 0.0001$), and RG7716, 90 µg (****, $P < 0.0001$).
Furthermore, RG7716, 90 µg is significantly different from anti-ANG-2 (***, $P = 0.0002$) and anti-VEGF-A (*, $P = 0.0319$).

Figure 11. Grade 4 lesion severity reductions after single dose of omalizumab (IgG), RO5485202 (Ang2), faricimab in the dose of 30 µg (A2V Low), faricimab in the dose of 90 µg (A2V High) and ranibizumab (Lucentis). The values are expressed in percentage.



- 9 laser burns in each eye (108 lesions per group, unless inflammation obscured grading)
- Grade 4 lesions developed in 38-53% of the laser sites at 2 weeks following laser injury.
- A single intravitreous injection resulted in reduction of grade 4 lesions from 53.7% to 7.4% in A2V (90ug) at day 28.
- The corresponding reduction with Lucentis was from 38.0% to 6.5%.

The CHMP noted that the Applicant presented the *in vivo* experimental model only for nAMD and not for DME, in contrast with the intended indications of faricimab. Hence, the Applicant was requested to justify the scientific (pathological, molecular) basis of intended use in other indications. In response, the Applicant explained that in diabetic macular edema (DME), Ang-2 is up-regulated due to chronic hyperglycemia, which increases vascular destabilization and sensitivity to VEGF similar to the situation in nAMD. An alternative rodent model for DME was not tested because the antibody in question reacts with human VEGF-A antigen and not with rodent, so classical animal models of diabetes could not work according to the applicant. However, it might have been possible to test the effect of faricimab in cynomolgus monkeys with spontaneous diabetes (Sun et al. 2020), as this bispecific Ab works in this species, similarly to ranibizumab used across the studies in this application. This is however not a blocking issue.

There was no apparent safety pharmacology signal in the submitted documentation of faricimab in Cynomolgus monkeys.

In summary the effectiveness of faricimab was tested on the eyes of Cynomolgus monkeys in vivo, pre-treated by laser beam to induce damage, leakage and neovascularization in the retina as a model of wet Age-related Macular Degeneration (nAMD). The intravitreal administration of faricimab showed effectiveness dose dependently and in the dose of 30 µg proved to be equal effective as ranibizumab (Lucentis) (30 µg). The higher dose of faricimab (90 µg) reduced the damage severity grade in the retina significantly higher than ranibizumab in the dose of 30 µg.

The primary characteristics of faricimab as a VEGF-A and ANG-2 neutralizing antibody have been demonstrated in in vitro pharmacology studies. The in vitro and in vivo assays seem to support the binding affinity, specificity, and biological activity of the bispecific monoclonal antibody faricimab on the target structures VEGF-A and Ang-2 and the Applicant provided evidence on lack of unwanted bindings to other similar binding sites; with elimination of binding to FcRn to limit systemic plasma residence time.

2.3.3. Pharmacokinetics

Nonclinical *in vivo* pharmacokinetic (PK) studies have been conducted to assess the pharmacokinetics of faricimab (also termed RO6867461 and mAb<Ang2/VEGF>) in rabbits and Cynomolgus monkeys following intravitreal (IVT) administration, the intended administration route in clinical studies. The PK parameters after a single-dose administration of faricimab were investigated via IVT and intravenous (IV) routes in rabbits and monkeys and after multiple-dose administration of faricimab as part of the toxicokinetic studies. The repeat dose pharmacokinetics of faricimab were evaluated following multiple IVT and IV doses in 2-week non-GLP tolerance studies in rabbits and cynomolgus monkeys, and in 2-month and 6-month GLP toxicology and pharmacokinetic studies in cynomolgus monkeys.

The pilot PK and toxicology studies in rabbits demonstrated that the rabbit is not an appropriate species for the safety evaluation of IVT administered faricimab.

2.3.3.1. Methods of analyses

Serum, aqueous, and vitreous humor samples were analyzed for faricimab concentration with ELISA methods. Several methods were developed, but only methods used for the determination of faricimab in Cynomolgus monkey serum in the pivotal GLP toxicology studies were validated. An ELISA method was developed for the determination of faricimab in Cynomolgus monkey plasma, but it was used only to analyze monkey serum samples in a pharmacological study.

The ELISA method used for the determination of faricimab in Cynomolgus monkey vitreous humor assays in a pivotal GLP toxicology study was qualified.

ADAs were analyzed using a one-step bridging ELISA format. The method used for the determination of ADA against faricimab in Cynomolgus monkey serum in the pivotal GLP toxicology studies were validated.

2.3.3.2. Absorption

The Fc region of faricimab has been engineered to abolish binding interactions with the FcRn, which, after entering into systemic circulation via either the choroidal vasculature and/or uveal blood flow following distribution in aqueous humor, leads to rapid systemic elimination. Following single IVT administration of 1.5 mg/eye faricimab in cynomolgus monkeys, absorption-rate limited elimination resulting in flip-flop pharmacokinetics (slow elimination from the eye to systemic circulation as rate limiting factor for elimination from the systemic circulation [as shown after IV injection with a clearance of 0.0107 mL/min/kg]) was observed with a strong correlation between exposure in vitreous humor, aqueous humor, and systemic circulation.

Following single IV administration, faricimab exhibited fast systemic clearance, which was associated with a short elimination half-life ($t_{1/2}$) when compared with wild-type IgG, consistent with the engineered reduction in affinity for FcRn.

In the toxicology studies in Cynomolgus monkeys, there was a dose-proportional increase in the mean values for maximum observed serum concentration (C_{max}) and area under the concentration-time curve (AUC) following both IVT and IV administration of faricimab. A correlation between ADA development and reduced systemic exposure was observed in both 2- and 6-month GLP toxicology studies; this did not compromise the overall readout of the studies because there was still sufficient exposure in ADA-positive animals.

2.3.3.3. Distribution

No specific distribution study was performed to characterize the distribution of faricimab.

Following IVT administration in cynomolgus monkeys, faricimab was distributed into aqueous humor (about 30% of vitreous humor $AUC_{0-\infty}$) and systemic circulation (approximately 1.3% of vitreous humor $AUC_{0-\infty}$). Faricimab was not detected in the untreated eye at any of the measured time points.

Following IV administration in cynomolgus monkeys, faricimab was mainly distributed in the serum, with a mean volume of distribution under steady-state conditions value of 0.025 L/kg. This distribution pattern is similar to that of endogenous IgG.

2.3.3.4. Metabolism

As the metabolism/catabolism of antibodies generally involves degradation to smaller peptides and amino acids, classical biotransformation studies were not conducted.

2.3.3.5. Excretion

No specific excretion study was performed to characterize the excretion of faricimab.

As described in Section 3.2.2.4, the elimination of faricimab is expected to occur via cleavage to small peptides and amino acids, which may be excreted renally, in a similar manner to the elimination of endogenous IgG.

2.3.3.6. Pharmacokinetic drug interaction

No PK drug interaction studies (e.g., cytochrome P450 interaction) were performed with faricimab. There was no evidence of faricimab-mediated specific cytokine release within the range of 0.1-100 µg/mL, thus no interaction via cytochrome P450 is expected. Additionally, faricimab is not expected to interact with other small molecule drugs because the clearance pathways of IgG molecules are distinct from those of small molecules.

2.3.4. Toxicology

The toxicology program for faricimab has been designed to evaluate the non-clinical safety profile of faricimab and to support intravitreal (IVT) dosing in patients.

Consistent with ICH S6 (R1) guidance the rabbit and cynomolgus monkey were chosen as the test species for the in vivo safety evaluation with faricimab on the basis of their superior suitability for intravitreal (IVT) administration, their ocular anatomy being most comparable to human, and their overall pharmacological relevance as responders compared with rodent species, which were shown to be not fully cross-reactive.

Repeat-dose toxicity studies of up to 2 weeks in rabbits and up to 6 months in cynomolgus monkeys have been conducted. In addition, a GLP embryofetal development study in pregnant cynomolgus monkeys, a non-GLP and a GLP tissue cross-reactivity study, and in vitro whole blood cytokine release assays have been conducted.

Based on an initial exploratory study in rabbits, the severity of the ADA-related immune-mediated adverse ocular and systemic effects precluded using rabbits as a second species in subsequent GLP toxicology studies. The GLP general toxicology and safety pharmacology investigations were conducted only in cynomolgus monkeys, in which the animal immunogenicity-related findings were less impacting feasibility.

All in vivo repeat-dose toxicology studies were conducted using the IVT route of administration, which is the administration route in humans. In addition, intravenous (IV) administration was used in 2-week pilot toxicity studies, 2-month pivotal toxicity study and reproductive toxicity studies to investigate any possible systemic toxic effects of faricimab.

The test material used in pivotal GLP non-clinical safety studies and the test material used in clinical trials and planned to be used for commercialization were considered comparable on the basis of analytical and biological comparability. All excipients of the IVT clinical Phase III and market formulation were included in the faricimab formulation used in the regulatory toxicology studies (except methionine). The safe use of methionine as novel pharmaceutical excipient for intravitreal use in humans was justified by appropriate toxicology and literature data in the Quality module.

Toxicokinetics

Toxicokinetic evaluation was performed in all general toxicology studies as well as in the embryo-fetal development study in Cynomolgus monkeys. Although NOAEL doses were 1.5 and 0.5 mg/eye/dose for IVT administered faricimab in 2-month and 6-month pivotal toxicology studies in Cynomolgus monkeys, the approach to calculate systemic exposure margins with the highest doses used in the pivotal toxicological studies due to the lack of ocular immune-mediated effects in the clinical trials is reasonable. Accordingly, systemic exposure margins were 8-10-fold (IVT) and more than 80-fold (IV) the faricimab human steady-state systemic exposure estimates in patients with nAMD or DME. Serum exposure (C_{max}) at the high dose of 3 mg/kg in the embryo-fetal development study was more than

500-fold greater than faricimab human steady-state systemic exposure estimates in patients with nAMD or DME.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, faricimab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In the pathomechanism of neovascular Age-related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME) at least two factors are relevant. Angiopoietin-2 (Ang-2) was described as a unique factor serving essential role in vascular leakage and plays a role in both vessel sprouting and vessel regression and pathological angiogenesis. The other factor is a homodimeric glycoprotein Vascular Endothelial Growth Factor (VEGF), which plays a pivotal role in mediating active intraocular neovascularization in patients suffering from diabetic retinopathy and retinal-vein occlusion. Targeting VEGF-A with monoclonal antibody (e.g. IVT ranibizumab) is a state-of-art therapy in patients with nAMD or DME.

The present application is a new invention concerning the antibody construction technique combining two different Fab sequences together to target VEGF-A and Ang-2 in one molecule, thus this construct is the main virtue of this drug development. Modifications in the sequence of this bispecific antibody resulted in elimination of binding to FcRn (TripleA) and to FCγRI, FCγRII, FCγRIIIa, C1q (PG-LALA).

Faricimab binding to human VEGF-A and to Ang-2 was determined with Surface Plasmon Resonance (SPR) and Isothermal Titration Calorimetry (ITC) in vitro, while no binding was observed to human Ang-1, FcRn, FCγRI, FCγRII, FCγRIIIa, C1q excluding the possibility of potential adverse events. Cell-based in vitro experiments like Tie-2 Phosphorylation Assay, VEGF reporter gene assay and Human umbilical vein endothelial cell (HUVEC) anti-proliferation assay were carried out with a limited number of data presented and found in the Quality module.

The *in vitro* binding was supported by additional figures for the SPR and ITC assays. The Applicant has demonstrated that double binding occurs regardless of which antigen the antibody binds first as it was demonstrated in the publication of Regula, 2016, 2017, 2019.

The effectiveness of faricimab was tested on the eyes of Cynomolgus monkeys *in vivo*, pre-treated by laser beam to induce damage, leakage and neovascularization in the retina as a model of nAMD. The intravitreal administration of faricimab showed effectiveness dose dependently and in the dose of 30 µg proved to be equal effective to ranibizumab 30 µg. The higher dose of faricimab (90 µg) reduced the damage severity grade in the retina substantially better than ranibizumab in the (equimolar) dose of 30 µg. Concentration of faricimab was determined in the aqueous humour, in the tear and in the plasma. Data provided in tables about the individual cases show decline in concentration versus time in all of the examined sample source.

In pregnant Cynomolgus monkeys, IV injections of faricimab resulting in serum exposure (Cmax) more than 500-times of the maximum human exposure did not elicit developmental toxicity or teratogenicity and had no effect on weight or structure of the placenta, although, based on its pharmacological action faricimab should be regarded as potentially teratogenic and embryo-/fetotoxic biological.

Drug-drug interactions are not expected as faricimab is given alone intravitreally and the resulting plasma concentrations have been considered to be very low.

There was no apparent safety pharmacology signal in in Cynomolgus monkeys.

Toxicology

In the 2-week non-GLP study in cynomolgus monkeys, no ocular or systemic effects related to faricimab were observed following two applications of 1.5, 3, or 6 mg/right eye/dose (the maximum feasible dose) IVT or 3 and 10 mg/kg IV administered 14 days apart. The no observed adverse effect level (NOAEL) was established at the highest doses of 6 mg/right eye/dose for IVT and 10 mg/kg for IV. One half of the treated animals were confirmed positive for ADA formation against faricimab, however, there was no reduction in systemic exposure of RO6867461.

In 2- and 6-month GLP studies, cynomolgus monkeys received up to 3 monthly doses of 1.5, 3, or 6 mg/right eye/dose IVT and up to 7 monthly doses at 0.5, 1.5, or 1.5/3 mg/right eye/dose IVT, respectively, with the high-dose group in the 6-month study receiving 1.5 mg/right eye/dose for the first IVT dose only followed by 3 mg/right eye/dose for subsequent doses. In the 2- and 6-month GLP study, the NOAEL was 1.5 mg/right eye/dose and 0.5 mg/right eye/dose, respectively. The effects of monthly IV doses of faricimab at 5 mg/kg were evaluated in the 2-month GLP study. The majority of animals in both studies were confirmed positive for ADA formation against faricimab.

In the 2- and 6-month GLP studies, animal immune-mediated ocular inflammatory cell infiltration and clinical signs of ocular inflammation occurred in faricimab-treated eyes following IVT administration every 4 weeks at doses of 3 and 6 mg/right eye/dose or 1.5 and 1.5/3 mg/right eye/dose, respectively. Ocular findings generally correlated with the systemic presence of ADAs against faricimab and exposure loss in the serum of animals. In addition, immunohistochemistry confirmed the presence of immune-complex deposits in affected eyes of faricimab-treated animals. No clinical ocular findings were observed in recovery animals after a 4- or 13-week treatment-free recovery period in the 2- and 6-month study, respectively. Inflammatory mononuclear cell infiltration was the only histopathological finding at the end of recovery in the 6-month study at 1.5 and 1.5/3 mg/right eye/dose. There were no relevant findings in the vehicle-treated eyes up to 6 months of treatment.

Faricimab did not induce any systemic effects in general toxicology studies up to 6 mg/eye IVT and up to 10 mg/kg IV, except for animal immune-mediated minimal mixed-cell inflammation in the aortic root of the heart observed in 2 animals at the end of the 4-week recovery period in the 2-month GLP study. Systemic presence of ADAs against faricimab was confirmed in 1 animal, and immunohistochemistry confirmed immune-complex formation and deposition in both animals at the aortic root. No extra-ocular findings were observed in the 6-month study in monkeys.

Although the systemic exposure margins of the highest tested doses in the repeat-dose toxicity studies appear sufficiently high compared to expected human dose (around 10-fold for 1.5 / 3 mg/eye/dose), the exposure margin at the NOAEL of 0.5 mg/eye/dose (based on the animal immune mediated ocular effects in the 6 month monkey study) with mean AUC(0-72h) = 20200 ng•hr/mL and a mean Cmax = 220 ng/mL on Day 141, is only around 1 when compared to values of human exposure listed and used for calculation by the applicant. This should be kept in mind when interpreting these results. The ocular immune-mediated effects observed in animal studies were not recorded in the completed clinical development program with faricimab.

Moreover, some (slight) deviations between control and high dose group were observed in the ECG after IVT administration to the right eye in the male recovery group, e.g. decrease in QT and QTc interval and increase of QRS duration at Day 87 of recovery in the male treatment group. The Applicant stated that 'Electrocardiograms (ECGs) using jacketed external telemetry (JET) procedures were collected during the pre-dose phase, on dedicated days of the dosing phase, and during the

recovery phase in conscious animals. In both studies, heart rate and ECG endpoints, including QT and QTc, were comparable between control and faricimab-dosed groups.' The Applicant was able to provide a plausible explanation for the deviations in the recovery phase by to the small number of animals, compared to all other days in the "inlife phase", biasing the mean ECG data in the recovery phase to these few animals.

No dedicated local tolerance studies were conducted. Tolerability for application of faricimab following the IVT and IV route was established in the repeat-dose toxicity studies in rabbits and monkeys.

Consistent with ICH S6 (R1) guidance no genotoxicity studies have been conducted; faricimab is a biotechnology-derived pharmaceutical that is not expected to directly interact with DNA or other chromosomal material.

Faricimab is a biotechnology-derived pharmaceutical, and the need for animal studies for carcinogenic potential of faricimab has been assessed, consistent with ICH S6 (R1) guidance. No standard rodent carcinogenicity studies have been conducted as faricimab is not fully cross-reactive in rodents. The intended anti-angiogenic effects of faricimab and the weight of evidence do not suggest a carcinogenic potential of faricimab.

No effects of faricimab on male or female fertility were observed following 7 monthly IVT doses of 1.5/3 mg in the chronic 6-month study in sexually mature cynomolgus monkeys.

An embryofetal development study in cynomolgus monkeys did not reveal any effects of faricimab on the course and outcome of pregnancy or fetal viability following 5 weekly IV injections starting on gestation day 20 (GD20) at up to 3 mg/kg. A pre- and postnatal development study could not be conducted in cynomolgus monkeys due to ADA formation and exposure loss observed in general toxicology studies preventing sufficient systemic exposure with faricimab in such a study.

No adverse findings in RDT and EFD studies after IV Faricimab administration (at sufficiently high exposure) were somehow surprising with regard to the known class effect of VEGF inhibitors, however the Applicant covered this already known class effect accordingly in the SmPC under 5.3. '*In pregnant cynomolgus monkeys, IV injections of Vabysmo resulting in serum exposure (Cmax) more than 500-times the maximum human exposure did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, although, based on its pharmacological effect Vabysmo should be regarded as potentially teratogenic and embryo-/foetotoxic.*' Thus, no further action/studies are required as (expected) adverse findings in such studies would result in the same outcome, i.e. appropriate depiction in the SmPC.

No unexpected tissue binding of faricimab was observed in cross-reactivity studies of normal human tissues. The results of in vitro cytokine release assays in human cells indicated no substantial risk of cytokine release syndrome, direct complement activation, or peripheral immune-cell depletion with administration of faricimab.

2.3.7. Conclusion on the non-clinical aspects

Pharmacology

The *in vitro* binding- and cell-based assays seem to support the binding affinity, specificity, and biological activity of the bispecific monoclonal antibody faricimab on both of the target structures VEGF-A and Ang-2 and Applicant provided evidence on lack of unwanted bindings to other binding sites.

The effectiveness of faricimab was demonstrated *in vivo* on laser beam induced damage model for nAMD in Cynomolgus monkeys. IVT administered faricimab substantially and dose dependently diminished the severity of retinal damage, and this efficacy seems to be superior to the comparator ranibizumab, one of the widely used VEGF inhibitors.

No specific safety signals have emerged during the studies.

Pharmacokinetics

Intravitreal administration is the established clinical route for faricimab. Faricimab administered IVT distributes mainly in the eye, but it also reaches the systemic circulation. The elimination is slow from the eyes. Due to absorption-rate limited elimination, the elimination is also slow from the serum.

After IV administration, faricimab exhibits fast systemic clearance.

In the toxicology studies in cynomolgus monkeys, there was a dose-proportional increase in the mean values for maximum observed serum concentration and area under the concentration-time curve following both IVT and IV administrations of faricimab.

Toxicology

In summary, no target-related toxicological changes were observed up to the highest doses tested with faricimab including the evaluation of repeat-dose toxicity, male and female fertility, and embryofetal development using cynomolgus monkeys, the only feasible species cross-reactive to faricimab. Ocular and systemic changes observed in general toxicology studies mainly at higher doses were related to an animal immune-mediated response to faricimab.

There seems to be no safety margin at IVT administration as ocular inflammation was observed in some monkeys in case of the medium, 1.5 mg/eye dose used in 6-month repeat dose study. The high IVT dose of 3 mg/eye used in the 6-month repeat dose monkey study provides exposure coverage for the 6 mg clinical dose of faricimab based on the difference in vitreous volume. Inflammatory ocular reactions observed at higher doses in the 6-month study were animal immune-mediated responses to the administration of a humanized protein like faricimab. .

The ocular inflammations were mild to moderate and were reversible after recovery phase, therefore this toxic effect is not expected to impact the final Benefit/Risk conclusion, taking into consideration the serious target indication, treatment of progressive eye sight loss secondary to nAMD and DME.

Animal immune-mediated responses were also observed in studies with ranibizumab, an anti-VEGF Fab, and lampalizumab, an anti-factor D antibody. Ocular immune-mediated effects observed in animal studies were not recorded in the completed clinical development program with faricimab.

Faricimab can be considered a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, faricimab is not expected to pose a risk to the environment.

The systemic exposure margins were 8-10-fold (IVT) and more than 80-fold (IV) the faricimab human steady-state systemic exposure estimates in patients with nAMD or DME. Serum exposure at the high dose of 3 mg/kg in the embryo-fetal development study was more than 500-fold greater than faricimab human steady-state systemic exposure estimates in patients with nAMD or DME.

In conclusion, also in light of the responses to the questions formulated during the assessment, the toxicological evaluation can support the application for approval of faricimab as a new therapeutic option for treatment of the proposed indications at the intended dose via IVT administration.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1 Biopharmaceutic Studies								
No studies conducted.								
5.3.3 Human PK Studies								
BP28936	5.3.3.2 Final CSR Report Synopsis 1058993, p. 15 Final CSR Report 1058993	Safety, Tolerability, PK, PD	Phase I, Multiple Center, Single-and Multiple Ascending-Dose, Non-Randomized, Open-Label	Part A: (Single Doses): 0.5 mg, 1.5 mg, 3 mg, or 6 mg faricimab intravitreal injection Part B: (Multiple Doses): 3 mg or 6 mg faricimab intravitreal injection Q4W (3 doses)	Total = 24	Patients with nAMD previously treated with anti-VEGF	Part A: N/A Part B: 8 weeks	Completed/ Full Report
JP39844	5.3.3.2 Final CSR Report Synopsis 1106179, p. 2 Final CSR Report 1106179	Safety, Tolerability, PK and PD	Phase I, Non-randomized, Open-label, Multiple Ascending Dose Study	Intravitreal administration of either 1.5 mg or 6 mg faricimab dose Q4W (3 doses)	Total = 12 8 with DME 4 with nAMD	Patients with nAMD and DME [a]	12 weeks	Completed/ Full Report (English translation)
5.3.4 Human PD Studies								
No studies conducted.								

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Efficacy and Safety Studies (nAMD)								
TENAYA (GR40306) LUCERNE (GR40844)	5.3.5.1 Primary CSR Report 1102954, Synopsis Primary CSR Report 1102954 Primary CSR Report 1102955, Synopsis Primary CSR Report 1102955	Efficacy, Safety, durability, PK and PD	Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, 112-week Study	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to Week 108 Patients will return for a final visit at Week 112	**Total randomized** = 1329 **Intent-to-Treat** TENAYA = 671 Faricimab=334 Aflibercept=337 LUCERNE = 658 Faricimab=331 Aflibercept=327	Treatment-naive patients with nAMD	48 weeks for the primary analysis and 108 weeks for the study	Ongoing / Full Reports

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
STAIRWAY (CR39521)	5.3.5.1 Final CSR Report 1085977, p. 13 Final CSR Report 1085977	Efficacy, Safety, PK	Phase II, Multiple Regimen, Randomized, Active Comparator-Controlled, Subject and Assessor Masked, Three Parallel Groups, 52-week Study	• Faricimab Q12W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q12W up to Week 48 • Faricimab Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q16W up to Week 48; patients assessed with active disease at Week 24 were switched to a Q12W regimen for the remainder of the study • Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 48 weeks	**Total randomized = 76** 6 mg faricimab Q12W = 29 6 mg faricimab Q16W = 31 0.5 mg ranibizumab Q4W = 16	Treatment-naive patients with nAMD	40 weeks for the primary analysis and 48 weeks for the study	Completed / Full Report

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
AVENUE (BP29647)	5.3.5.1 Final CSR Report 1083912, p. 21 Final CSR Report 1083912	Safety, Tolerability, PK, Efficacy	Phase II, Multiple Center, Multiple Dose and Regimen, Randomized, Active Comparator-Controlled, Double-Masked, Five Parallel Groups, 36-week study	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q8W (i.e., on Weeks 20 and 28) • 0.5 mg Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 32 weeks • 0.5 mg Ranibizumab Q4W + 6 mg Faricimab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W up to Week 8, followed by 6 mg faricimab intravitreal injections Q4W to Week 32	**Total randomized = 273** 1.5 mg Faricimab Q4W=47 6 mg Faricimab Q4W=42 6 mg Faricimab Q8W=47 0.5 mg Ranibizumab Q4W=68 0.5 mg Ranibizumab Q4W + 6 mg Faricimab Q4W=69	Treatment-naive patients with nAMD	32 weeks of treatment with primary analysis at Week 36	Completed / Full Report

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Efficacy and Safety Studies (DME)								
YOSEMITE (GR40349) RHINE (GR40398)	5.3.5.1 Primary CSR Report 1102956, Synopsis Primary CSR Report 1102956 Primary CSR Report 1102957, Synopsis Primary CSR Report 1102957	Efficacy, Safety, PK and PD	Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, Three Parallel Groups, 100-week Study	• Faricimab Q8W: 6 mg intravitreal faricimab injections Q4W to Week 20 followed by Q8W to Week 96 • Faricimab PTI [b]: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96	**Total Randomized**=1891 1482 – treatment-naive 409 – previously treated with anti-VEGF **Intent-to-Treat** YOSEMITE = 940 Faricimab Q8W = 315 Faricimab PTI = 313 Aflibercept Q8W =312 RHINE = 951 Faricimab Q8W = 317 Faricimab PTI = 319 Aflibercept Q8W =315	Patients with DME	56 weeks for the primary analysis and 96 weeks for the study	Ongoing / Full Reports

Protocol No.	Location of Synopsis Location of Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BOULEVARD (BP30099)	5.3.5.1 Primary CSR Report 1083913, p. 21 Primary CSR Report 1083913	Safety, Tolerability, PK, Efficacy	Phase II, Multiple Center, Multiple Dose, Randomized, Active Comparator-Controlled, Double-Masked, Three Parallel Groups, 36-week Study	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 20 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 20 weeks • 0.3 mg Ranibizumab Q4W: 0.3 mg ranibizumab intravitreal injections Q4W for 20 weeks • Followed by an observational period (up to 16 weeks); if eligible, patients received one injection of 0.3 mg ranibizumab then exited the study	**Total randomized** = 229 168 – treatment-naive 61 – previously treated with anti-VEGF	Patients with DME	20 weeks of treatment with primary analysis at Week 24	Completed / Full Report

DME=diabetic macular edema; ITT=intent to treat; N/A=not applicable; nAMD=neovascular age–related macular degeneration; PD=pharmacodynamic; PK=pharmacokinetic; PTI=personalized treatment interval (up to Q16W adjustable dosing in DME and DR); Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; VEGF=vascular endothelial growth factor.

a Study JP39844, sponsored by Japanese co-development partner Chugai Pharmaceutical Co., Ltd., enrolled 4 patients with nAMD. and 8 patients with DME.

b Study drug dosing for patients on the PTI is extended, reduced or maintained at study drug dosing visits using 4-week increments to a maximum of every 16 weeks (Q16W) or a minimum of every 4 weeks (Q4W) based on the relative change of the central subfield thickness (CST) and best corrected visual acuity (BCVA) compared with the patient's reference CST and reference BCVA.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

The present application seeks approval for faricimab, a bispecific IgG1 antibody, for the treatment of adult patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). The recommended dose of faricimab is 6 mg administered by intravitreal injection Q4W for the first 4 doses, followed by 6 mg at intervals of up to Q16W for both nAMD and DME.

The clinical pharmacokinetics of faricimab has been characterized in nine clinical studies in patients with nAMD and DME; 2 Phase I, 3 Phase II and 4 Phase III studies. A population PK analysis was also conducted. No dedicated clinical pharmacology studies were conducted in healthy volunteers.

Bioanalytical methods

Concentrations of faricimab (active drug), Ang-2, VEGF-A (biomarkers), ranibizumab, and aflibercept (active comparators) were measured in human aqueous humor and plasma, and anti-drug antibodies (ADAs) against faricimab in plasma samples. All available Phase III samples and faricimab and ADA samples obtained from Phase I and Phase II studies were analyzed using fully validated assay methods. The ADA assay strategy used a three-tiered approach.

Generally, both the pre-study and in-study validations were appropriate and well documented. The concentration ranges were appropriate for the clinical trials. The methods were demonstrated to be precise and accurate for the analysis of human samples. The assays were carried out within the validated long-term stability period (except of biomarker assays).

Population PK analysis of faricimab

The population PK analysis was performed using data from Phase I (BP28936, JP39844), Phase II (BP29647, CR39521, BP30099), and Phase III (GR40306, GR40844, GR40349, GR40398) studies, which included PK measurements of faricimab in plasma and aqueous humour (AH).

A total of 1095 AH observations from 284 patients and 8372 plasma observations from 2246 patients were available for the analysis. There were 1366 (60.8%) patients that had DME and 880 (39.2%) who had nAMD. Patients with nAMD (mean age 76.0 years, range 50-99 years; mean weight 75.2 kg, range 37.3-172 kg) were on average older and lighter than patients with DME (mean age 62.1 years, range 24-91 years; mean weight 86.8 kg, range 40.5-209 kg). ADAs were detected at least once after the start of faricimab administration in 218 (9.7%) patients.

This was a 3-compartment linear model, composed of the VH compartment, where the drug is injected, the AH compartment, and the plasma compartment with clearance (CL) and volume (Vc) (Figure 12). Bioavailability (F) was assumed to be 1. The volume of VH compartment (VVH) was fixed to the literature value of 0.0045 L (Hutton-Smith et al, 2016). The parameters of the final popPK model 051 are presented in Table 8.

Figure 12. Schematic of the Model for Ocular and Systemic PK of Faricimab

Figure 7. Schematic of the Model for Ocular and Systemic PK of Faricimab

V_H, V_A, and V_C are the volumes of the VH, AH, and plasma compartments, respectively.

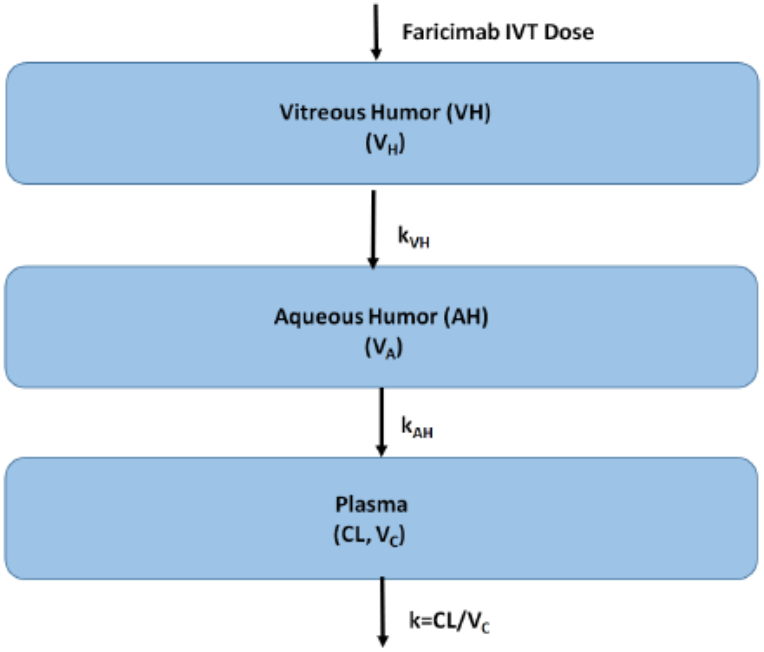


Table 8. Parameter Estimates of the Faricimab popPK Model 051.

Table 14. Parameter Estimates of the Faricimab Population PK Model 051 (Final Model)

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
V_A (mL)	θ_1	0.253	12.4	0.191 ; 0.315		
V_C (L)	θ_2	1.48	4.47	1.35 ; 1.61		
k_{VH} (1/day)	θ_3	0.0929	0.674	0.0917 ; 0.0941		
k_{AH} (1/day)	θ_4	15.6	12.9	11.6 ; 19.5		
CL (L/day)	θ_5	2.33	1.29	2.27 ; 2.39		
SD_{prop}	θ_6	0.414	1.44	0.402 ; 0.426		
SD_{PhaseI}	θ_7	0.614	5.28	0.55 ; 0.677		
$SD_{PhaseII}$	θ_8	0.788	2.61	0.748 ; 0.828		
$V_{C,WT}$	θ_9	1.00	10.6	0.795 ; 1.21		
CL_{WT}	θ_{10}	0.773	4.88	0.699 ; 0.847		
CL_{female}	θ_{11}	0.863	1.56	0.836 ; 0.889		
$CL_{formulation1}$	θ_{12}	0.816	1.71	0.788 ; 0.843		
$k_{VH,age}$	θ_{13}	-0.533	6.46	-0.6 ; -0.465		
$k_{VH,ADA}$	θ_{14}	1.30	1.5	1.27 ; 1.34		
$k_{AH,formulation1}$	θ_{15}	0.719	6.48	0.628 ; 0.81		
ω^2_{VC}	$\Omega(1,1)$	1.34	5.4	1.2 ; 1.48	CV=115.6%	60.5%
ω^2_{kVH}	$\Omega(2,2)$	0.087	2.33	0.083 ; 0.091	CV=29.5%	5.0%
R ω_{kVH} ω_{kAH}	$\Omega(2,3)$	0.0251	29	0.0108 ; 0.0394	R=0.174	
ω^2_{kAH}	$\Omega(3,3)$	0.24	9.11	0.197 ; 0.282	CV=48.9%	60.0%
R ω_{kAH} ω_{CL}	$\Omega(3,4)$	0.0311	21.1	0.0182 ; 0.0439	R=0.349	
ω^2_{CL}	$\Omega(4,4)$	0.0331	7.75	0.028 ; 0.0381	CV=18.2%	52.9%
ω^2_{ε}	$\Omega(5,5)$	0.086	7.03	0.0741 ; 0.0978	CV=29.3%	42.3%
σ^2_{AH}	$\Sigma(1,1)$	1	Fixed			10.6%
σ^2_{plasma}	$\Sigma(2,2)$	1	Fixed			17.5%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·abs(SE/PE); 95% CI: 95% confidence interval; SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

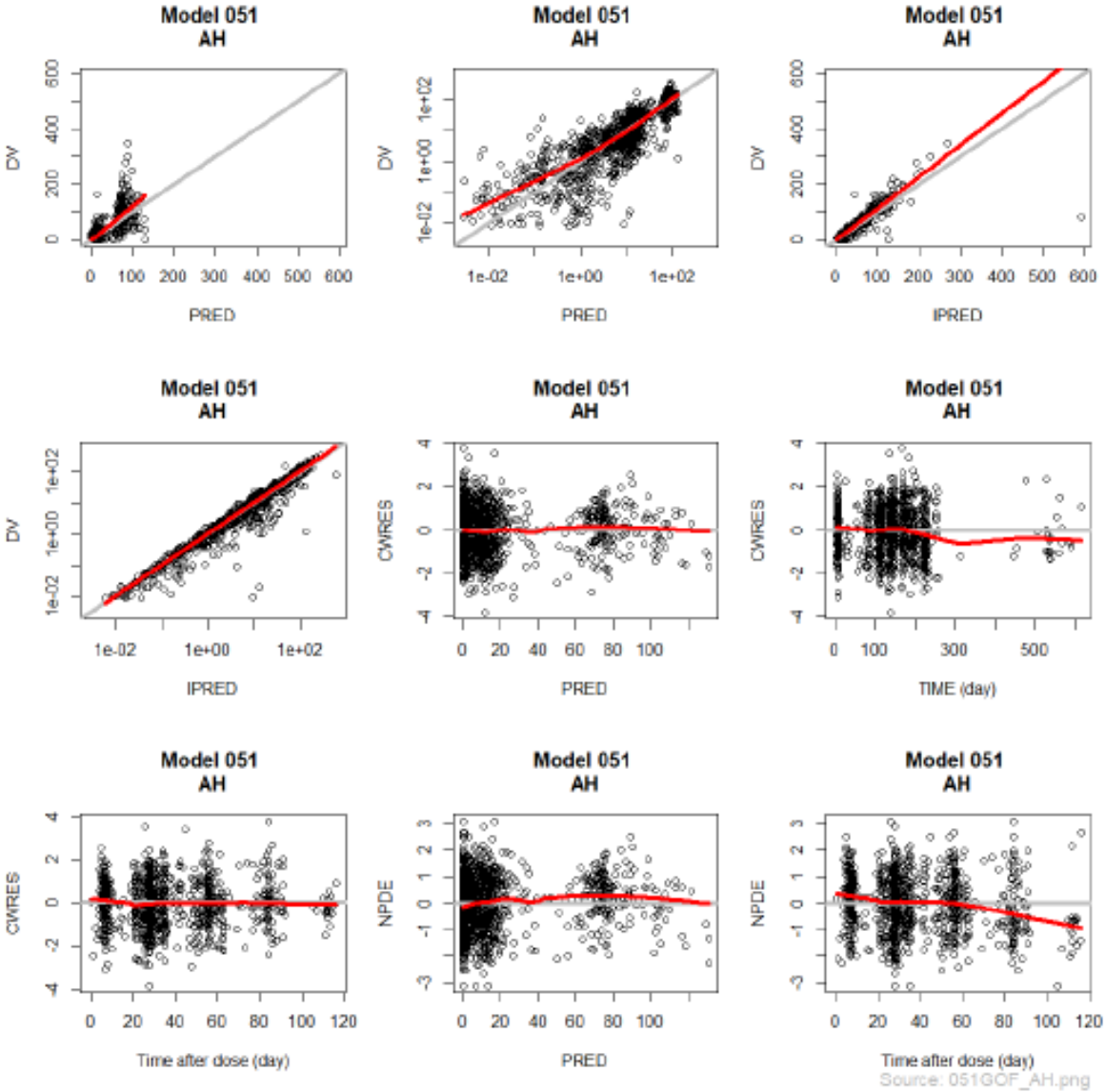
Source file: 051ParEst.csv (DiagnosticPlotsPK.R)

Figure 13 and Figure 14 show the goodness-of-fit plots for the final model for AH and plasma, respectively. The pcVPC for the final model is Figure 94.

Figures 13 and 14. Goodness-of-fit plots for the final model for AH (13) and plasma (14).

Figure 45. Goodness of Fit for Final Model 051: AH (All Patients)

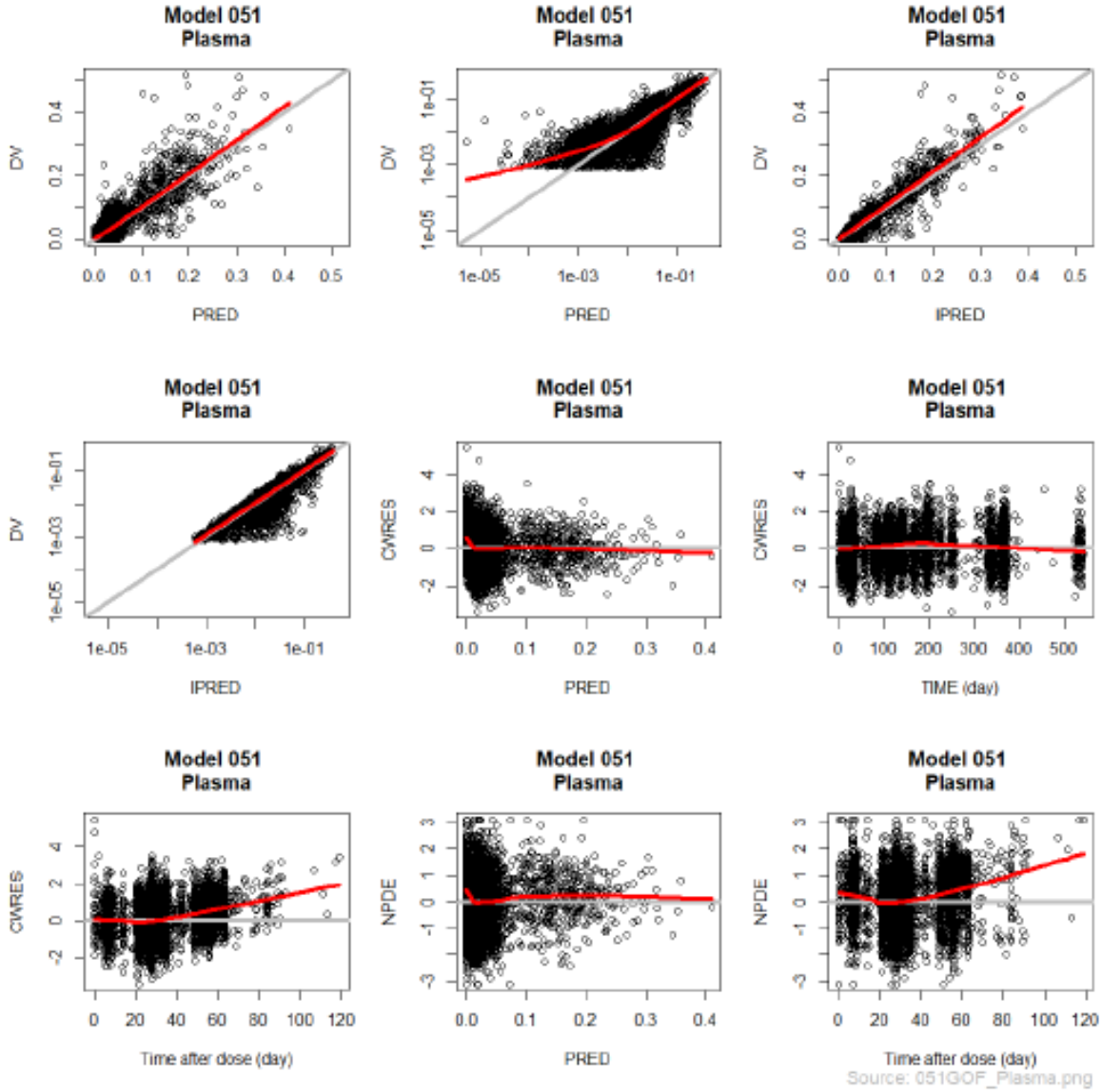
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **NPDE**: normalized prediction distribution errors; **TIME**: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. BQL data are not shown.



Source: 051GOF_AH.png

Figure 46. Goodness of Fit for Final Model 051: Plasma (All Patients)

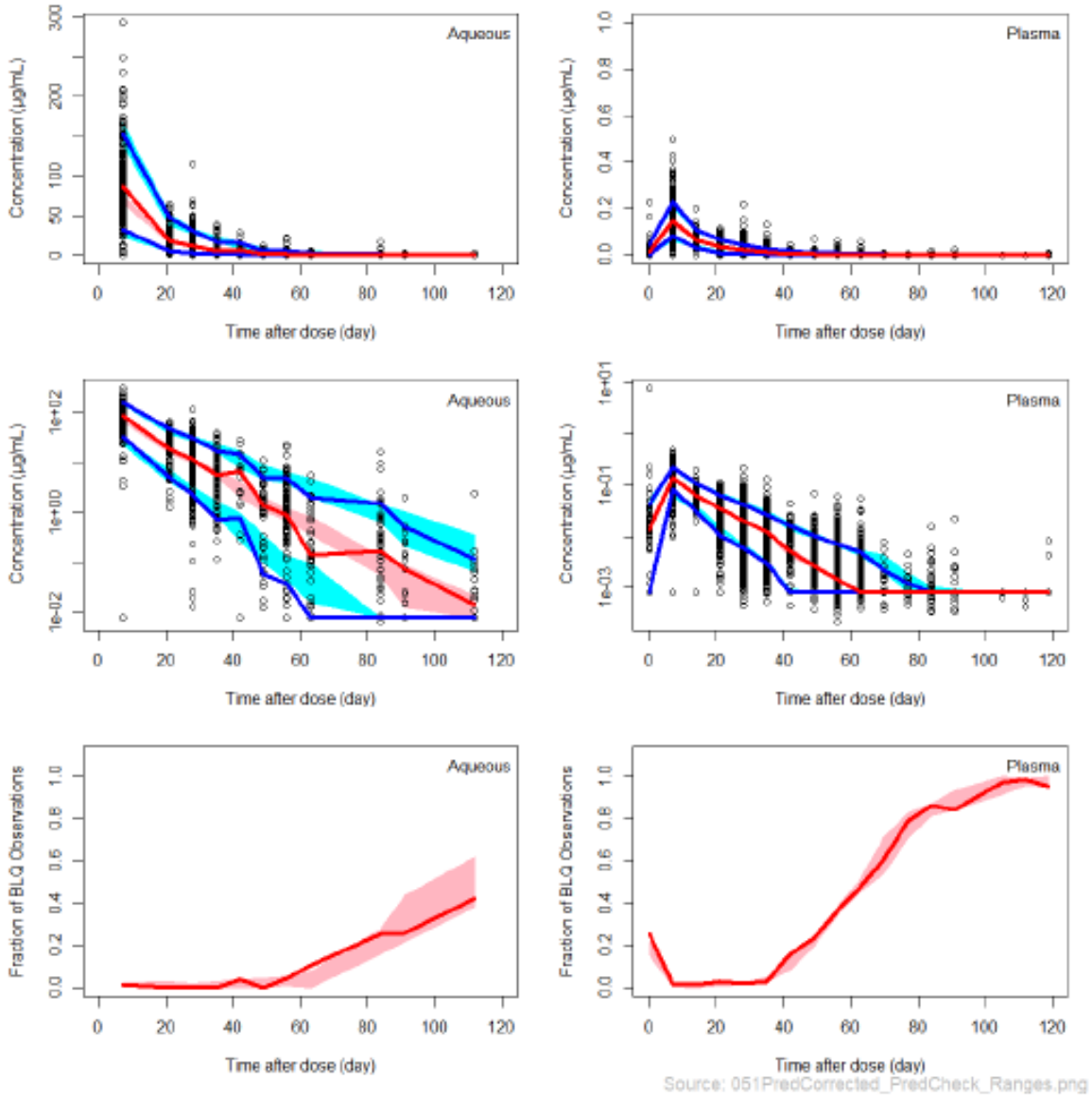
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **NPDE**: normalized prediction distribution errors; **TIME**: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines. BQL data are not shown.



Source: 051GOF_Plasma.png

Figure 94. Prediction-Corrected Visual Predictive Check for Final Model 051 (All Data)

The first and the second rows: The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. Third row: The red lines show fraction of the observed concentrations that are below the limit of quantification. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.



Source: 051PredCorrected_PredCheck_Ranges.png

Absorption

- **Bioavailability**

Phase I studies

Study BP28936

This was a SAD and MAD study in patients with nAMD (≥50years).

The study was divided in two parts:

- Part A where SADs were administered. 3 patients were enrolled at each dose level and the doses evaluated sequentially were 0.5 mg, 1.5 mg, 3 mg, and 6 mg (N=12).

- Part B, MAD where three doses were administered at Q4W intervals to 6 patients/dose. Part B was initiated only once the maximum tolerated dose was identified in Part A.

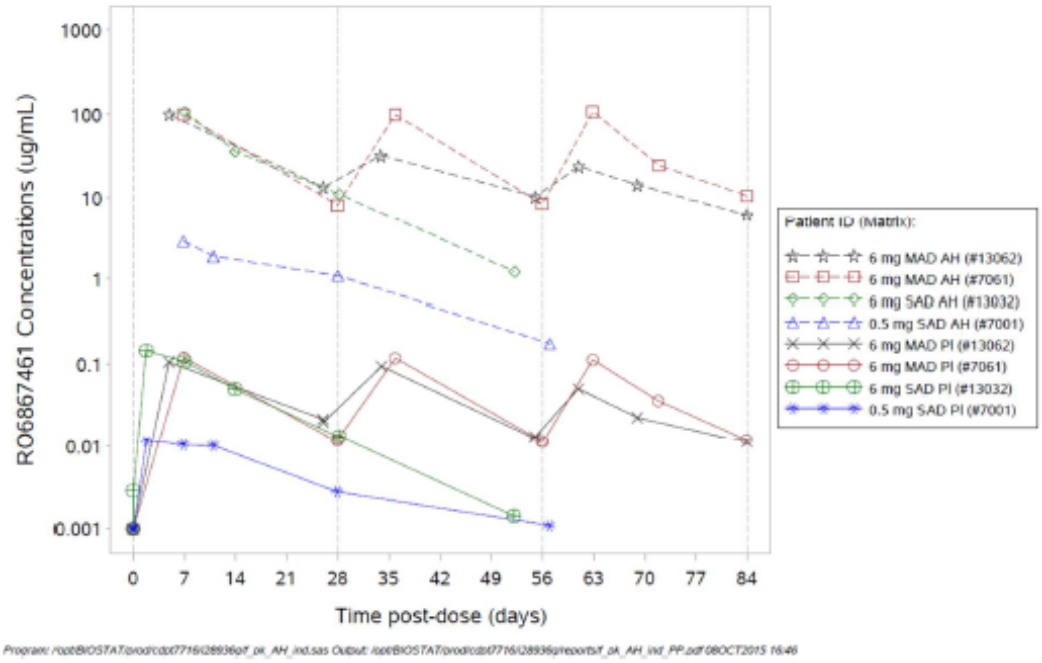
Plasma and optional AH samples were collected for measurement of faricimab and ADA.

Ocular and plasma pharmacokinetics

The individual concentration time profiles for the patients that had evaluable AH and plasma data are presented in Figure 15. For each patient, the AH concentration time profile declined in parallel to the profile in plasma and is consistent with flip flop kinetics, where the slowest rate, i.e., elimination from the vitreous, governs the overall elimination of faricimab from the body. The individual t1/2 in AH ranged from 6 to 13 days.

Figure 15. AH concentration time profiles

Figure 1 Study BP28936: Individual Faricimab Plasma and Aqueous Humor Concentration vs. Time Profiles for Patients with Available Aqueous Humor Samples (Semi-Log Scale)



AH=aqueous humor; MAD=multiple ascending dose; PI=plasma; SAD=single ascending dose
Source: CSR BP28936, Report 1058993, Figure 9

Plasma PK parameters derived using NCA are reported in Table 9. Based on Cmax, plasma faricimab concentrations were >100-fold lower than those in AH. The estimated apparent plasma t1/2 ranged from 5-15 days across SAD and MAD. The Tmax was either Day 3 or Day 7 in the SAD part, independent of dose.

Table 9. Study BP28935, summary of plasma PK parameters.

Table 3 Study BP28936: Summary of Main Plasma Pharmacokinetic Parameters of Faricimab

Dose/schedule	N	C_{max} (µg/mL)	AUC (µg • h/mL)	$t_{1/2}$ (days)
0.5 mg SAD	3	0.0162 [0.00746-0.0409]	8.79,10.5 [a]	7.29, 15.4 [a]
1.5 mg SAD	3	0.0600 [0.0316-0.0701]	17.9 [16.4-22.3]	6.02 [5.06-12.6]
3.0 mg SAD	3	0.160 [0.0725-0.171]	51.1 [42.7-65.0]	7.41 [6.16-11.8]
3.0 mg MAD	6	0.152 (34) [0.0725-0.210]	36.5 (23) [24.8-46.3]	5.91 (51) [3.14-10.6]
6.0 mg SAD	2	0.126[b], 0.248 [a]	54.2 [43.6-64.7]	7.24 [6.76-7.71]
6.0 mg MAD	6	0.116 (37) [0.0734-0.176]	35.2 (31) [23.5-50.4]	7.34 (14) [6.50-9.29]

AUC = area under the concentration–time curve; AUC_{inf} = area under the concentration–time curve from Time 0 to infinity; AUC_{tau} = area under the concentration–time curve during one dosing interval (Day 0 to Day 28; C_{max} = maximum concentration observed; MAD = multiple ascending dose; SAD = single ascending dose; $t_{1/2}$ = half-life.

Notes: AUC_{inf} calculated for SAD; AUC_{tau} (0 to Day 28) calculated for MAD.

Median [range] reported for SAD if N > 2, Mean (CV%) [range] of third interval.

[a] individual values for 2 patients.

[b] Patient missed the Day 2 sample.

one patient in the SAD 6 mg was excluded because of undetectable plasma drug levels

Source: CSR BP28936, Report 1058993, Table 7

Study JP39844

This was a multiple dose study in Japanese patients (50-85 years) with nAMD or DME.

In Step 1, patients (N=6) received 1.5 mg intravitreal faricimab Q4W (for a total of up to three doses). Step 2 was initiated upon demonstration of safety in Step 1 and different patients (N=6) received 6 mg intravitreal faricimab every Q4W (for a total of up to three doses). Plasma samples were collected for measurement of faricimab and ADA. AH faricimab concentrations were not analysed because no patients consented to collection.

Plasma pharmacokinetics

Plasma PK parameters are summarized in Table 10. The mean plasma faricimab concentration peaked 2 days after administration with a monophasic elimination with a mean steady-state t1/2 of approximately 10 days at both dose levels. Consistent with the observed t1/2, the accumulation index was approximately 1, which is similar to the ratio in non-Asian patients observed in Study BP28936.

Table 10. Study JP39844: Mean Faricimab PK parameters.

Table 4 Study JP39844: Mean (SD) Faricimab Pharmacokinetic Parameters

Dose	C_{max} (µg/mL)	T_{max} [a] (day)	AUC [b] (day•µg/mL)	$t_{1/2}$ (day)
Single Dose				
1.5 mg	n = 6 0.196 (0.138)	n = 6 0.90 [1.82–7.89]	n = 5 2.23 (0.883)	n = 5 6.40 (2.48)
6 mg	n = 6 0.225 (0.0745)	n = 6 1.97 [1.88–8.11]	n = 4 3.53 (0.944)	n = 4 8.03 (3.75)
Multiple Dose				
1.5 mg	n = 6 0.0830 (0.0341)	n = 6 6.87 [4.87–7.85]	n = 6 1.03 (0.341)	n = 3 9.92 (2.42)
6 mg	n = 6 0.195 (0.0462)	n = 6 7.05 [1.90–8.89]	n = 6 3.15 (0.936)	n = 4 9.96 (3.25)

AUC = area under the concentration–time curve; $AUC_{0-\infty}$ = area under the concentration–time curve from time 0 to infinity; AUC_{tau} = = AUC from time 0 to the end of the dosing period; C_{max} = maximum concentration observed; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration.

[a] T_{max} values given as median [min–max]

[b] $AUC_{0-\infty}$ for single dose, AUC_{tau} for multiple dose

Source: CSR JP39844, Report 1106179, Table 11.4.1-1

Phase II studies

Study CR39521 (STAIRWAY)

This was a multiple dose 52-week study in patients with nAMD (≥50 years).

Eligible patients were randomized to one of three treatment arms:

- Faricimab Q12W: 6 mg faricimab Q4W by intravitreal injection up to Week 12 (4 injections), followed by 6 mg faricimab Q12W up to Week 48 (3 injections) (N=29).
- Faricimab Q16W: 6 mg faricimab Q4W by intravitreal injection up to Week 12 (4 injections), followed by 6 mg faricimab Q16W up to Week 48 (2 injections). A protocol-defined assessment of disease activity at Week 24 required patients with active disease to then receive a Q12W dosing interval for the remainder of the study (N=31).
- Ranibizumab Q4W (comparator arm): 0.5 mg ranibizumab Q4W by intravitreal injection for 48 weeks (13 injections) (N=16).

Ocular and plasma pharmacokinetics

Faricimab PK in AH are summarised in Table 11. AH samples (optional) were collected from only 14 faricimab-treated patients. Therefore, the data should be interpreted with caution.

Table 11. STAIRWAY – Summary of concentration in aqueous humor.

Table 6 Study STAIRWAY: Summary of Faricimab Concentrations in Aqueous Humor

Visit	Faricimab Q12W	Faricimab Q16W
4-Week Post-dose [a]		
N	8	3
Mean (SD), µg/mL	18.96 (14.91)	2.99 (1.14)
Median, µg/mL	14.35	2.87
8-Week Post-dose [b]		
N	11	3
Mean (SD), µg/mL	4.73 (4.52)	0.09 (0.13)
Median, µg/mL	4.24	0.024
12-Week Post-dose [c]		
N	11	3
Mean (SD), µg/mL	1.14 (1.24)	0.205 (0.0286)
Median, µg/mL	1.01	0.00391

BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q12W = once every 12 weeks.

[a] Corresponding to Week 28 for the Q12W and Week 32 for the Q16W group

[b] Corresponding to Week 32 for the Q12W and Week 36 for the Q16W group

[c] Corresponding to Week 36 for the Q12W and Week 24 for the Q16W group

Values BLQ were imputed with LLOQ/2 (0.00781 µg/mL/2).

Source: t_pk_blq_ah_PK_AH

Faricimab PK in plasma are summarised in Table 12. At Week 16 (i.e., 4 weeks following administration of the fourth Q4W faricimab dose), concentrations in plasma were similar in both groups. After Week 16, patients received faricimab either Q12W or Q16W. For the faricimab Q12W group, 4 weeks after administration of a previous dose, plasma concentrations were >580-fold lower than those in the AH.

Table 12. Study STAIRWAY: PK in plasma.

Table 7 Study STAIRWAY: Summary of Faricimab Pharmacokinetics in Plasma

Visit	Faricimab Q12W	Faricimab Q16W
4-Weeks Post fourth Monthly Dose (Week 16)		
N	34	18
Mean (SD), µg/mL	0.0322 (0.0176)	0.0306 (0.0211)
Median, µg/mL	0.0330	0.0301
8-Weeks Post-dose [a]		
N	30	15
Mean (SD), µg/mL	0.0045 (0.00450)	0.00363 (0.00387)
Median, µg/mL	0.00383	0.00203
12-Weeks Post-dose (Week 24)		
N	34	18
Mean (SD), µg/mL	0.00138 (0.00232)	0.00107 (0.00129)
Median, µg/mL	0.00040	0.00040

BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q12W = once every 12 weeks; Q16W = once every 16 weeks.

[a] Corresponding to Week 44 for the Q12W and Week 52 for the Q16W group

Values BLQ were imputed with LLOQ/2 (LLOQ=0.00781 µg/mL).

Source: t_pk_cb_blq_PK_PL

Study BP29647 (AVENUE)

This was a multiple dose 36-week study in patients with nAMD (≥50 years).

A total of 273 patients were randomized into five treatment arms and were administered study treatment by intravitreal injection from Day 1 to Week 32 according to the following schedule:

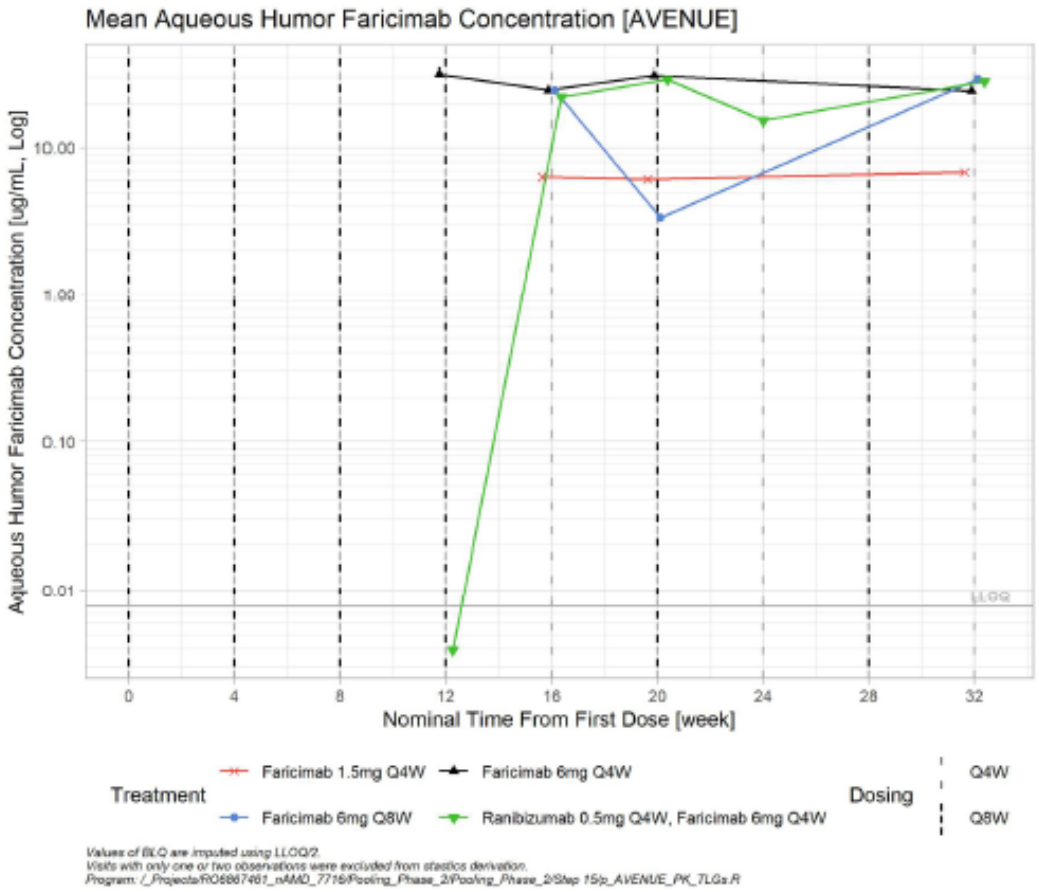
- Ranibizumab 0.5 mg Q4W (N=68)
- Faricimab 1.5 mg Q4W (N=46)
- Faricimab 6 mg Q4W (N=39)
- Faricimab 6 mg Q8W (N=46): 6 mg Q4W up to Week 12 followed by 6 mg Q8W
- Ranibizumab 0.5 mg Q4W followed by faricimab 6 mg Q4W (N=64): 0.5 mg ranibizumab Q4W up to Week 8 followed by 6 mg faricimab Q4W

<u>Ocular and plasma PK</u>

AH samples (optional) were collected in 10 patients randomized to faricimab 1.5 mg Q4W, 9 patients randomized to faricimab 6 mg Q4W, and 9 patients randomized to faricimab 6 mg Q8W. Mean faricimab concentration-time profiles in AH are presented in Figure 16.

Figure 16. Mean concentration-time profiles in AH

Figure 6 Study AVENUE: Mean Faricimab Concentration–Time Profiles in Aqueous Humor



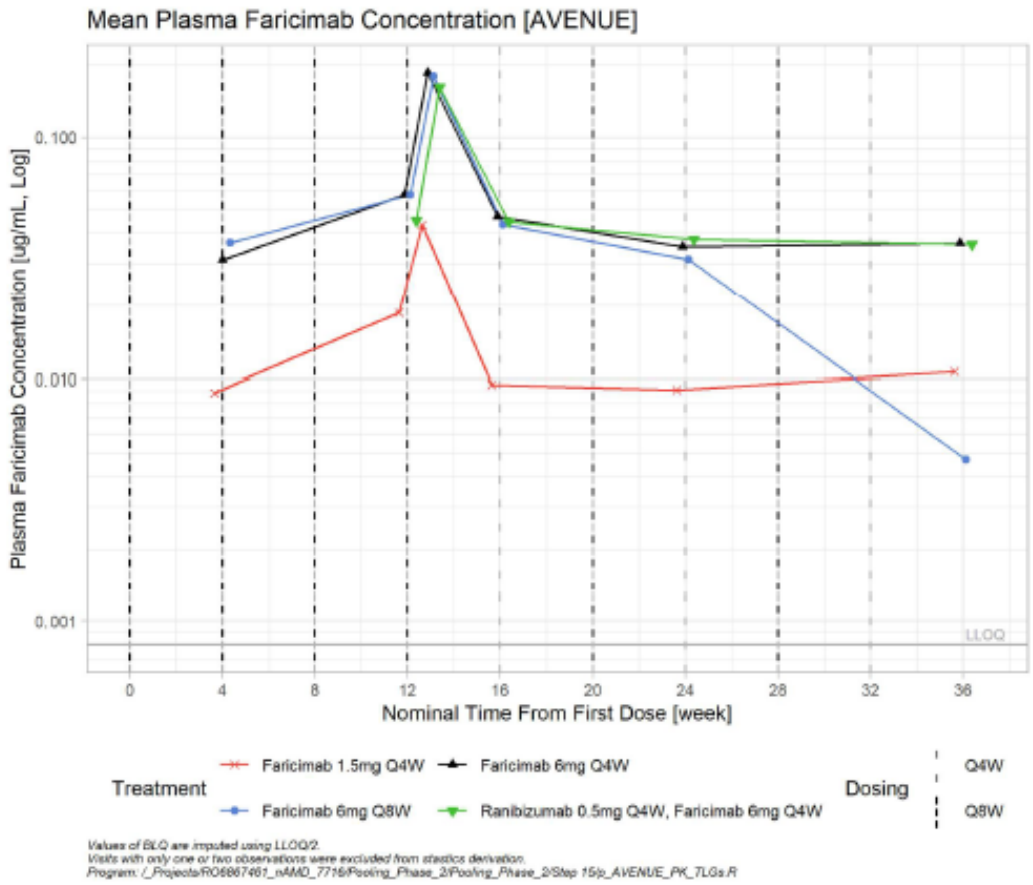
BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q4W = every 4 weeks; Q8W = every 8 weeks.

Source: t_pk_conc_AP

Mean faricimab concentration-time profiles in plasma are presented in Figure 17. For 6 mg Q8W, the Week 36 sampling time point represents the only 8 weeks post-dose assessment. Exposures at 8 weeks post-dose were about 10% that of exposures at 4 weeks post-dose (6 mg Q4W versus Q8W at Week 36). Based on the Week 12 concentrations, plasma concentrations were >400 times lower than those in AH.

Figure 17. Mean faricimab concentration-time profiles in plasma

Figure 7 Study AVENUE: Mean (SD) Faricimab Concentration-Time Profiles in Plasma



BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q4W = every 4 weeks; Q8W = every 8 weeks.

Source: t_pk_conc_AP

Study BP30099 (BOULEVARD)

This was a multi-dose study in patients with DME (≥18 years).

A total of 229 patients were randomized to one of the following treatment arms:

- Ranibizumab 0.3 mg Q4W, N=90
- Faricimab 1.5 mg Q4W, N=55
- Faricimab 6 mg Q4W, N=84

Study treatment was administered on Day 1 followed by Q4W for a total of 6 intravitreal injections.

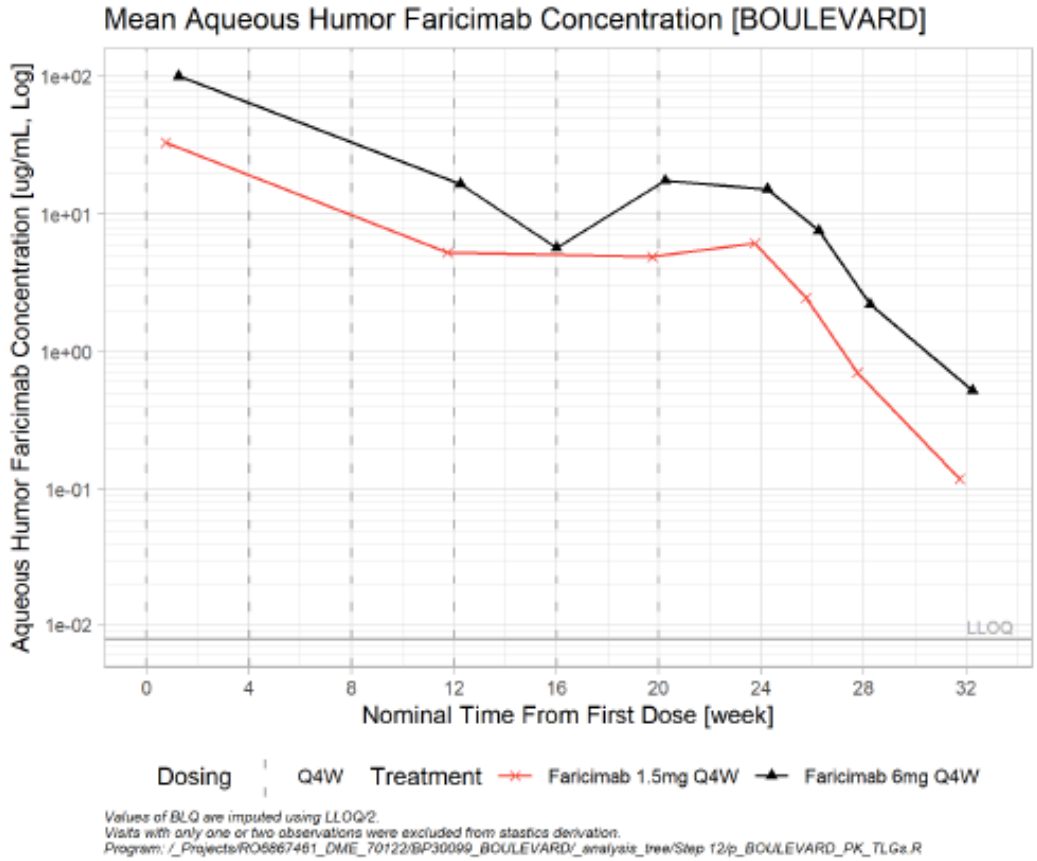
Ocular and plasma pharmacokinetics

Samples of AH were collected for 46 faricimab-treated patients (N=16 for 1.5 mg arm and N=30 for 6 mg arm).

Mean faricimab concentration-time profiles in AH are presented in Figure 18. Faricimab concentrations in AH remained stable with Q4W dosing. Following administration of the last dose (Week 20), faricimab concentrations in AH declined in parallel at both dose levels.

Figure 18 Study BOULEVARD – mean log-scale faricimab concentration-time profiles in aqueous humor

Figure 22 Study BOULEVARD: Mean Log-Scale Faricimab Concentration–Time Profiles in Aqueous Humor

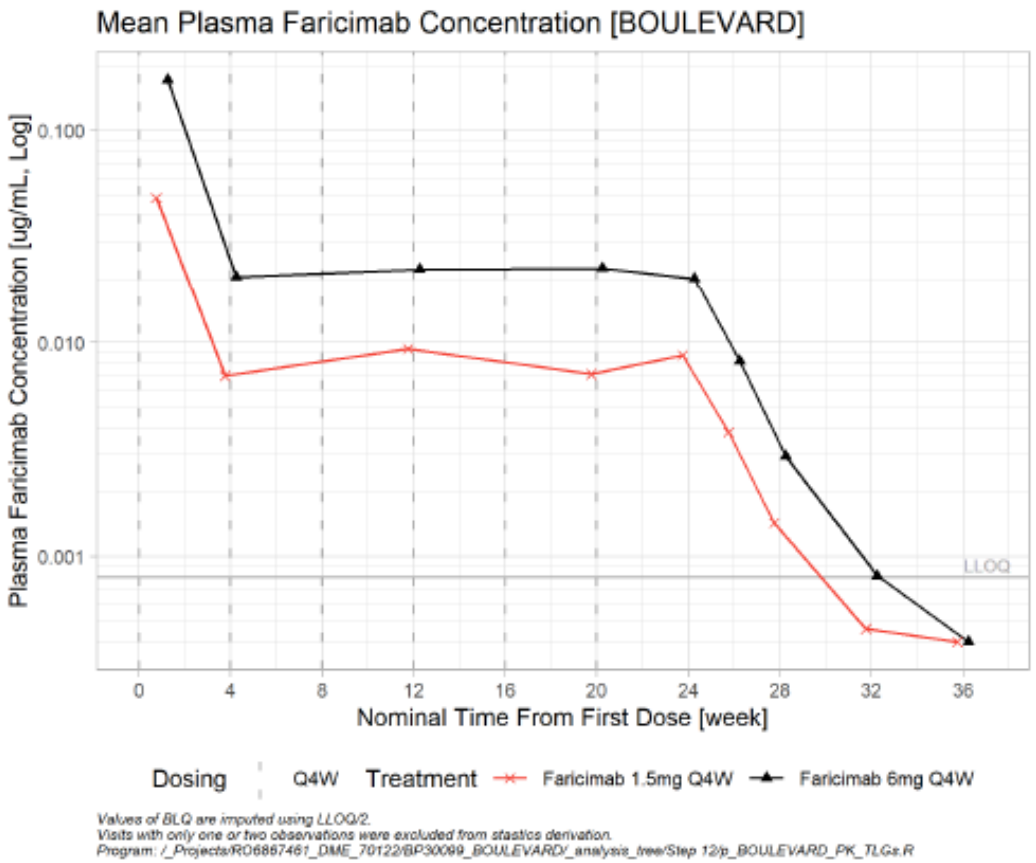


BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q4W = every 4 weeks.
Source: CSR BOULEVARD, Report 1083913, t_pk_conc_ITT

The mean faricimab plasma concentration-time profiles are presented in Figure 19. Plasma concentrations remained stable with subsequent Q4W doses at both dose levels. Plasma concentrations at later times postdose were lower as expected due to the exponential decrease after cessation of treatment. On Day 7, plasma concentrations were >580 times lower than those in AH.

Figure 19 Study BOULEVARD – mean log-scale faricimab concentration-time profiles in plasma

Figure 23 Study BOULEVARD: Mean Log-Scale Faricimab Concentration–Time Profiles in Plasma



BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q4W = every 4 weeks.
Source: CSR BOULEVARD, Report 1083913, t_pk_conc_ITT

- **Bioequivalence**

Three formulations were used in the clinical trials (F03, F04 and F06). F03 and F04 were used in the Phase I/II studies and only differed in concentration of the active ingredient. F06, the to-be-marketed formulation, was used in the Phase III studies.

A formal bioequivalence study between formulations was not conducted. Based on the final population PK model, the plasma exposure (steady-state AUC) was predicted to be 22.6% higher in Phase I-II studies compared to Phase III studies for a similar dose. This was caused by plasma clearance being 18.4% lower in Phase I-II studies. However, there were no differences in VH exposure between Phase I-II and Phase III studies and the safety profile of faricimab was consistent between studies. Since the formulation changed between Phase I-II and Phase III, it was not possible to differentiate the study effect from a formulation effect. Overall, the difference in plasma exposure observed between Phase II and Phase III studies is considered not clinically meaningful.

Distribution

In the population PK analysis, plasma Vc/F was 1.48 L, which is consistent with a limited distribution.

Elimination

Faricimab was engineered to abolish binding to the FcRn receptor, which is responsible for the recycling of immunoglobulin G (IgG) and the normally long terminal t1/2 of IgG of ~21 days. Without recycling, faricimab metabolism is through IgG proteolysis, which results in rapid elimination from the plasma. A summary of individual PK parameter estimates from the final population PK model (rate constants and corresponding half-lives for VH, AH and plasma) for Phase III study patients are summarised in Table 13.

Table 13. Individual estimates of faricimab PK parameters.

Table 17. Summary of Individual Estimates of Faricimab PK Parameters (Patients from Phase III Studies)

Subjects with ADA detected at any time post-baseline were assumed to have ADA at steady state.

Disease	N	k_{VH} (1/day)	$t_{1/2,kVH}$ (day)	k_{AH} (1/day)	$t_{1/2,kAH}$ (day)	$k=CL/V_C$ (1/day)	$t_{1/2,k}$ (day)	CL (L/day)	V_C (L)
Mean (Standard Deviation)									
DME	1221	0.104 (0.032)	7.26 (2.2)	15.8 (2.93)	0.0451 (0.00858)	1.46 (0.402)	0.611 (1.21)	2.35 (0.514)	1.99 (2.87)
nAMD	660	0.094 (0.029)	8.06 (2.4)	15.5 (3.04)	0.0463 (0.0104)	1.35 (0.485)	0.712 (0.759)	2 (0.446)	1.97 (2)
Median (95% Prediction Interval)									
DME	1221	0.1 (0.0565-0.178)	6.9 (3.89-12.3)	15.6 (11.1-21.1)	0.0443 (0.0329-0.0623)	1.53 (0.388-2.09)	0.453 (0.332-1.79)	2.31 (1.48-3.5)	1.56 (0.937-5.34)
nAMD	660	0.0891 (0.0507-0.164)	7.78 (4.23-13.7)	15.4 (10.6-20.5)	0.0449 (0.0338-0.0651)	1.39 (0.222-2.12)	0.498 (0.326-3.13)	1.95 (1.33-3)	1.42 (0.851-8.11)
Geometric Mean (Coefficient of Variation)									
DME	1221	0.0999 (0.3)	6.94 (0.3)	15.6 (0.174)	0.0444 (0.174)	1.37 (0.428)	0.505 (0.428)	2.29 (0.219)	1.67 (0.445)
nAMD	660	0.0898 (0.298)	7.71 (0.298)	15.3 (0.187)	0.0454 (0.187)	1.21 (0.542)	0.572 (0.542)	1.96 (0.215)	1.62 (0.527)

Source file: 051aucSim_ParameterSummary.csv (Simulations_PK_parameters_All_Q8W.R)

Since the estimated kVH is much lower than kAH (kAH/kVH = 168) and k (k/kVH = 16.9), the kinetics of faricimab are dominated by slow release from the VH. The estimated VH elimination half-life is 7.5 days, whilst the estimated plasma elimination half-life is 0.44 days.

Dose proportionality and time dependency

Faricimab doses tested in the clinical studies ranged from 0.5 mg to 6 mg.

In the Phase I study BP28936, based on single dose maximum concentration (Cmax) and area under the concentration-time curve (AUC), there was an approximate dose-proportional increase in faricimab plasma exposure up to 3 mg. There was no apparent increase in systemic exposure for the 6 mg dose group as compared to the 3 mg dose group. However, the apparent lack of systemic exposure increase from 3 mg to 6 mg should be interpreted with caution due the sparse sampling schedule. There was no apparent faricimab accumulation in plasma following multiple faricimab administration, as assessed with AUCtau and Cmax.

In the Phase II AVENUE study (nAMD), observed mean faricimab plasma concentrations at trough and at Week 13 (1 week after the last administration) were about 4-fold higher at 6 mg Q4W as compared to 1.5 mg Q4W. No plasma accumulation was observed following Q4W administration.

In the Phase II BOULEVARD study (DME), mean plasma Ctrough faricimab concentrations were approximately 2-4 times higher following administration of 6 mg compared with 1.5 mg. No plasma accumulation was observed following Q4W administration.

The popPK model described the single and multiple dose AH and plasma data. All transfer and elimination processes were first-order linear processes. No faricimab accumulation in the ocular or

plasma compartments was observed, with steady state reached by the end of the 12-week Q4W initiation dose period.

Inter-individual variability

In the Phase III TENAYA and LUCERNE studies (nAMD patients), high inter-patient variability was observed in faricimab AH concentrations (CV 40-394% and 51-245%, respectively) and plasma concentrations (CV 44-144% and 48-154%, respectively). Similarly, in the Phase III YOSEMITE and RHINE studies (DME patients), high inter-patient variability was observed in faricimab AH concentrations (CV 59-100% and 69-105%, respectively) and plasma concentrations (CV 45-199% for YOSEMITE; CV 52-184% for RHINE).

Pharmacokinetics in target population

Study GR40306 (TENAYA) and Study GR40844 (LUCERNE)

Studies TENAYA and LUCERNE are ongoing, 112-week, identically designed pivotal Phase III studies in patients with nAMD.

Patients were randomised in a 1:1 ratio to one of the following treatment arms:

- Faricimab: Patients received 6 mg of intravitreal faricimab Q4W up to Week 12 (4 injections). At Week 20, patients with active disease received faricimab at that visit and continued on a fixed-Q8W dosing regimen. At Week 24, following a second assessment of disease activity, patients with active disease (excluding those with active disease at Week 20) received faricimab at that visit, and continued on a fixed-Q12W dosing regimen. Patients who did not have active disease at Week 20 and Week 24 were treated with a fixed-Q16W dosing regimen. These fixed dosing regimens continued until Week 60.

From Week 60 onward, all patients are treated according to a personalized treatment interval (PTI) dosing regimen up to Week 108.

- Aflibercept: 2 mg of intravitreal aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of intravitreal aflibercept Q8W up to Week 108.

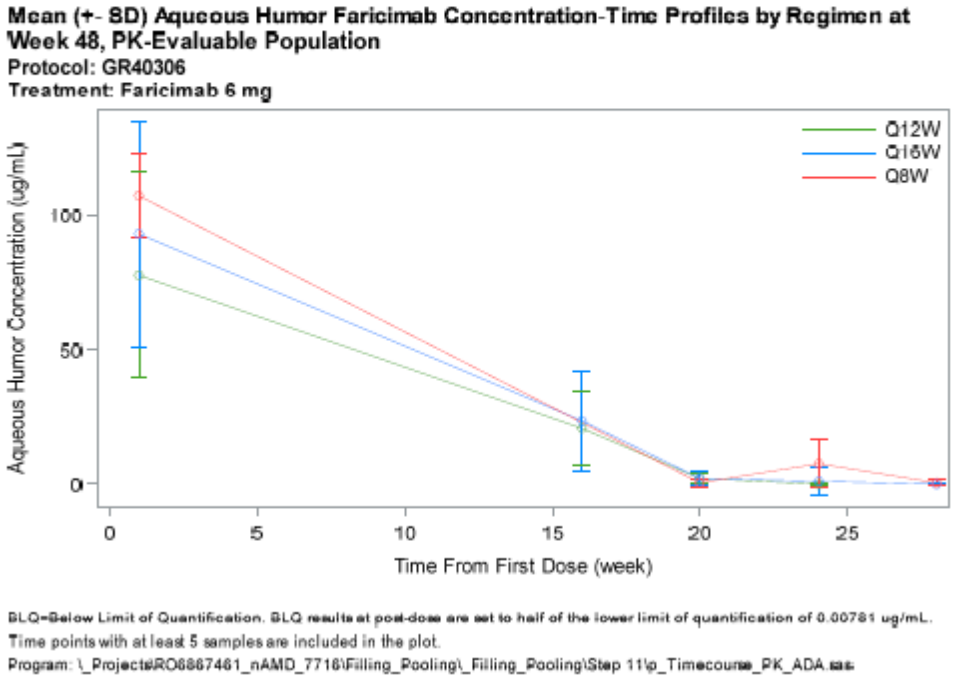
The primary analyses were performed when all patients had either completed the study through Week 48 or had discontinued from the study prior to Week 48.

<u>TENAYA ocular and plasma pharmacokinetics</u>

Faricimab concentrations in AH from 47 patients who consented to optional AH sampling were included in the PK data analysis. Mean faricimab AH concentration-time profiles are displayed in Figure 20. The maximum observed concentration [mean (SD) 92.5 (37.0) µg/mL] was 1 week post-dose (first timepoint following the first faricimab administration). At 12 and 16 weeks post-dose, approximately 13% and 26% of the samples were BLQ.

Figure 20. Mean aqueous humor faricimab concentration-time profiles

Figure 11 Mean (±SD) Aqueous Humor Faricimab Concentration-Time Profiles by treatment interval, PK-Evaluable Population (Linear and Semi-Log Scale)

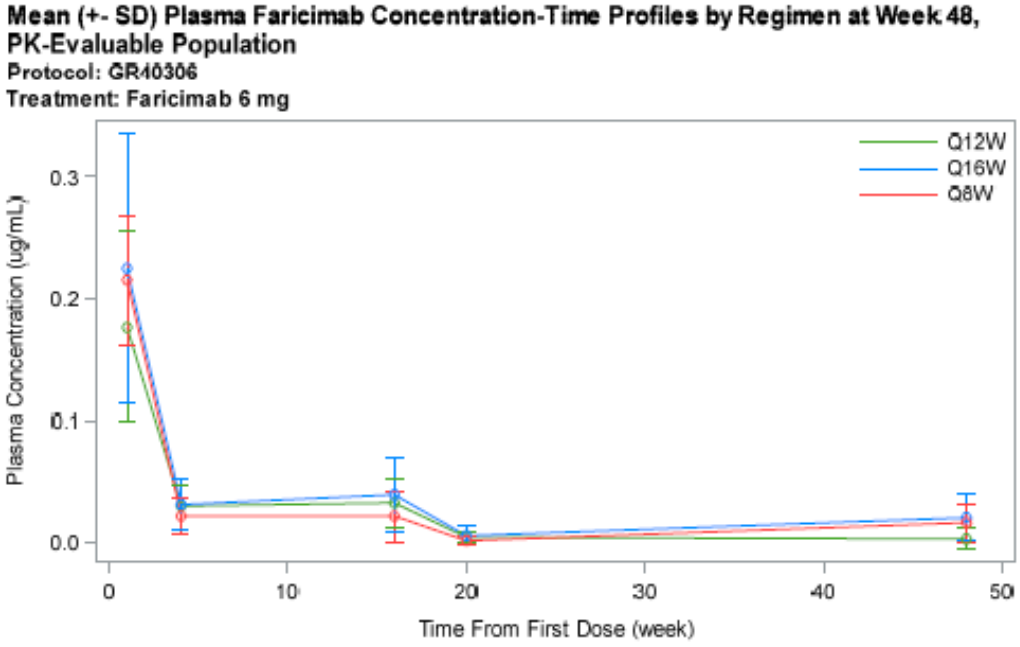


BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.00781 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: _Projects\RO6867461_nAMD_7716\Filling_Pooling_Filling_Pooling\Step 11\p_Timecourse_PK_ADA.sas

Faricimab plasma data from 333 patients were included in the PK data analysis. The mean plasma concentration-time profiles are shown in Figure 21. The maximum observed concentration [mean (SD) 0.207 (0.091) µg/mL] was 1 week post-dose (first timepoint following the first faricimab administration). Faricimab was measurable up to 8 weeks post-dose, where approximately 30% of the samples were BLQ. The ratio of faricimab AH to plasma on Day 7 was approximately 450.

Figure 21 . Mean Plasma Faricimab concentration-time profiles.

Figure 12 Mean (±SD) Plasma Faricimab Concentration-Time Profiles by Treatment Interval, PK-Evaluable Population (Linear and Semi-Log Scale)



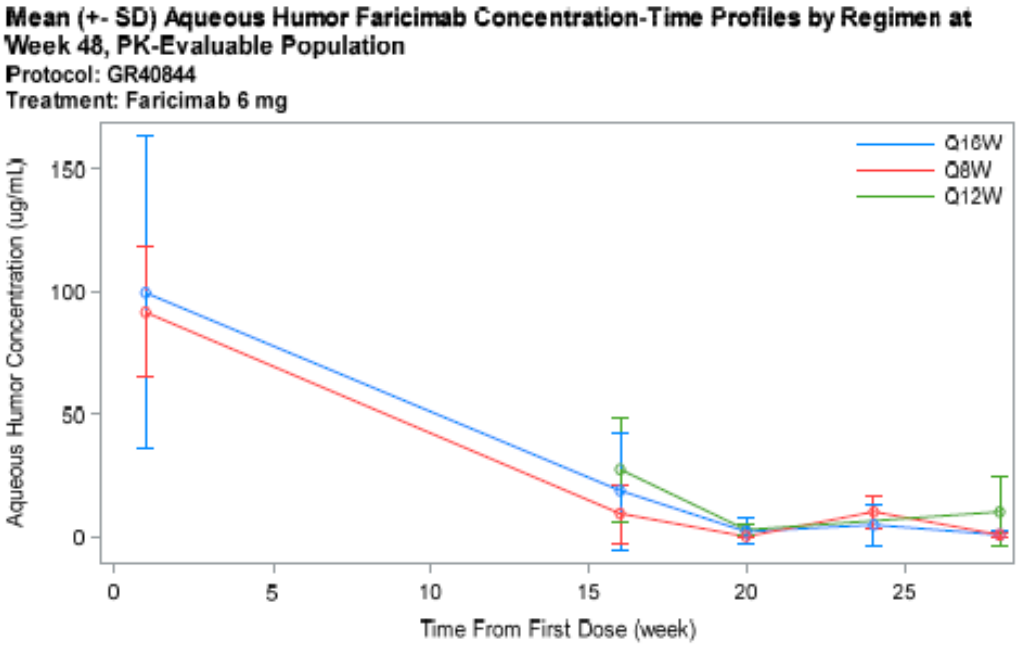
BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.0008 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: _Projects\RO6867461_nAMD_7716\Filling_Pooling_Filling_Pooling\Step 11\p_Timecourse_PK_ADA.sas

LUCERNE ocular and plasma pharmacokinetics

Faricimab concentrations in AH from 34 patients who consented to optional AH sampling were included in the PK data analysis. The mean faricimab AH concentration time profile is displayed in Figure 22. The maximum observed concentration [mean (SD) 101.2 (52.0) µg/mL] was 1 week post-dose (first timepoint following the first faricimab administration). At 12- and 16-weeks post-dose, approximately 21% and 58% of the samples were BLQ.

Figure 22. Mean Aqueous Humor Faricimab Concentration-time profiles.

Figure 11 Mean (±SD) Aqueous Humor Faricimab Concentration-Time Profiles by Treatment Interval, PK-Evaluable Population (Linear and Semi-Log Scale)

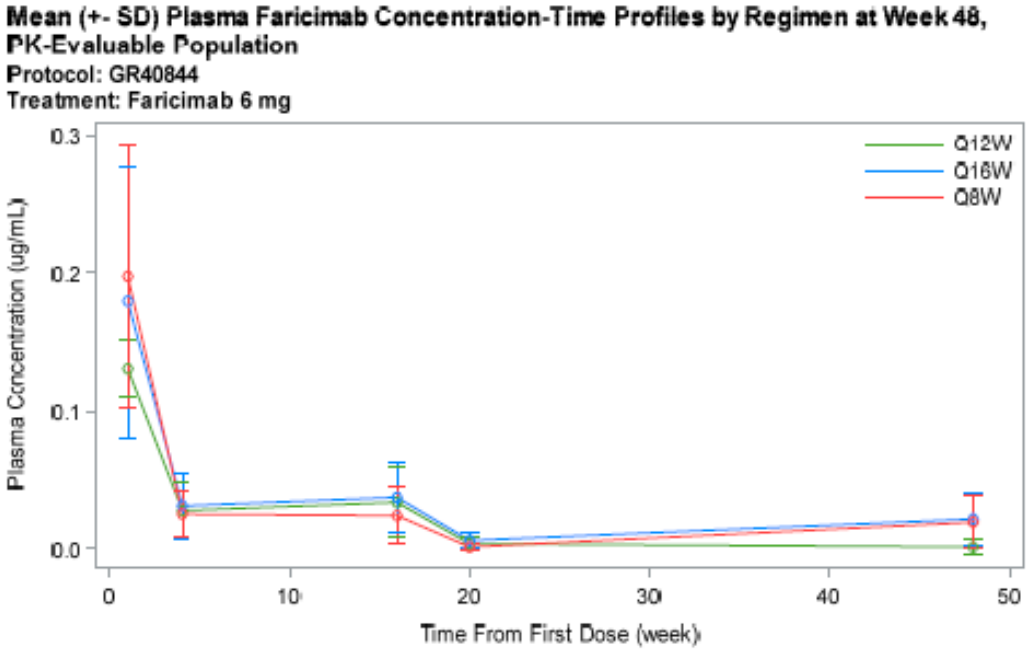


BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.00781 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: _Projects\RO6867461_nAMD_7716\Filling_Pooling_Filling_Pooling\Step 11\p_Timecourse_PK_ADA.sas

Faricimab plasma data from 331 patients were included in the PK data analysis. The mean plasma concentration-time profiles are shown in Figure 23. The maximum observed concentration [mean (SD) 0.180 (0.087) µg/mL] was 1 week post-dose (first timepoint following the first faricimab administration). Faricimab was measurable up to 8 weeks post-dose, where approximately 26% of the samples were BLQ. The ratio of faricimab AH to plasma on Day 7 was approximately 560.

Figure 23. Mean Plasma Faricimab Concentration-time profiles.

Figure 12 Mean (±SD) Plasma Faricimab Concentration-Time Profiles by Dosing Regimen, Treatment Interval, PK-Evaluable Population (Linear and Semi-Log Scale)



BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.0008 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: _Projects\RO6867461_nAMD_7716\Filling_Pooling_Filling_Pooling\Step 11\p_Timecourse_PK_ADA.sas

Study GR40349 (YOSEMITE) and Study GR40398 (RHINE)

Studies YOSEMITE and RHINE are 100-week, identically designed pivotal Phase III studies in patients with DME.

Patients were randomised in a 1:1:1 ratio to one of the following treatment arms:

- Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W to Week 20, followed by 6 mg faricimab injections Q8W to Week 96.
- Faricimab PTI: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI dosing of 6 mg faricimab intravitreal injections to Week 96.
- Aflibercept Q8W (comparator arm): 2 mg intravitreal aflibercept injections Q4W to Week 16, followed by 2 mg intravitreal aflibercept injections Q8W to Week 96.

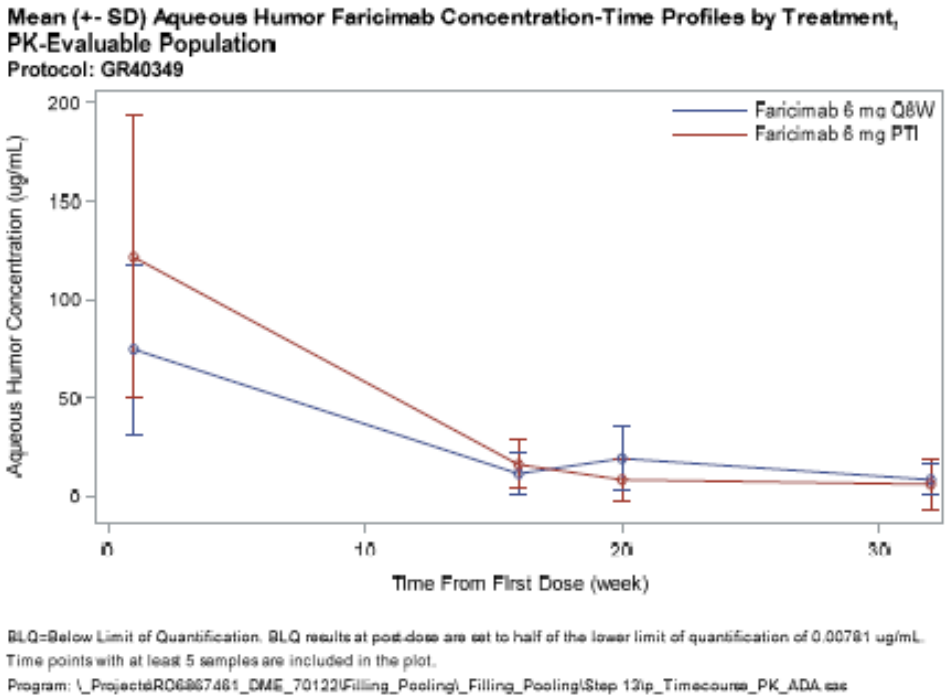
The primary analyses were performed when all patients had either completed the first year of the study through Week 56 or had discontinued from the study prior to Week 56.

<u>YOSEMITE ocular and plasma pharmacokinetics</u>

AH faricimab concentrations from 80 patients who consented to optional AH sampling were included in the PK analysis. The mean AH concentration-time profiles are shown in Figure 24. The maximum observed mean (SD) concentrations at Week 1 (1 week after the first administration) were 74 (43.3) and 121.6 (71.4) for the Q8W and PTI regimen, respectively. At 12 weeks post-dose, approximately 30% of the samples were BLQ.

Figure 24. Mean Aqueous Humor Faricimab concentration-time.

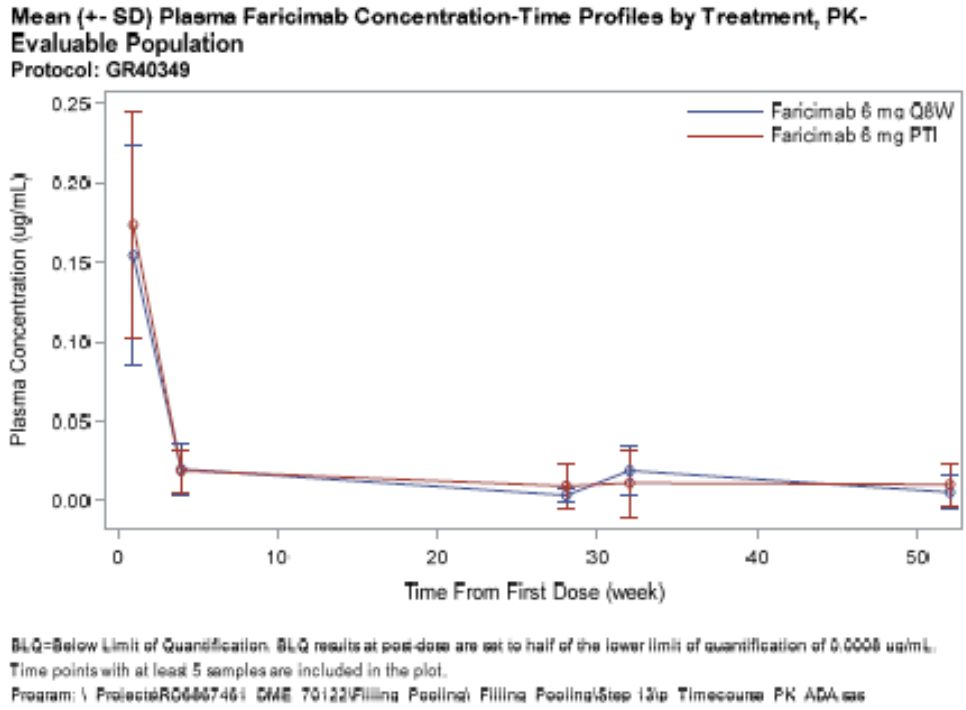
Figure 30 Mean (+/-SD) Aqueous Humor Faricimab Concentration-Time Profiles, PK-Evaluable Population (Linear and Semi-Log scale)



Plasma faricimab concentrations from 621 patients were included in the PK analysis. The mean AH concentration-time profiles are shown in Figure 25. The maximum observed mean (SD) concentrations at Week 1 (1 week after the first administration) were 0.154 (0.070 and 0.173 (0.071) for the Q8W and PTI regimen, respectively. Faricimab was measurable up to 8 weeks post-dose, where approximately 30-50% of the samples were BLQ. The faricimab AH to plasma ratio on Day 7 was approximately 480-700.

Figure 25. Mean Plasma Faricimab Concentration-time profiles

Figure 31 Mean (+/-SD) Plasma Faricimab Concentration-Time Profiles, PK-Evaluable Population (Linear and Log scale)



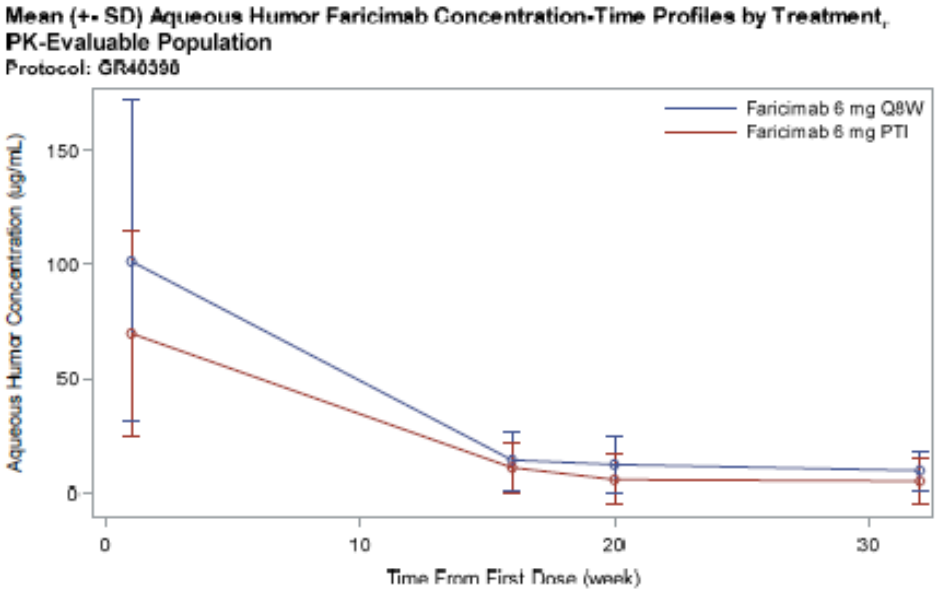
BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.0008 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: \ Projects\RO6867461 OME 70122\Filling Pooling\ Filling Pooling\Step 13\p Timecourse PK ADA.sas

RHINE ocular and plasma pharmacokinetics

AH faricimab concentrations from 44 patients consenting to optional AH sampling were included in the PK analysis. The mean faricimab AH concentration-time profiles are shown in Figure 26. The observed mean (SD) faricimab AH concentrations (µg/mL) at Week 1 (1 week after the first administration) were 101.5 (70.3) and 69.8 (45.1) for the Q8W and PTI regimen, respectively. At 12 weeks post-dose, approximately 40% of the samples were BLQ.

Figure 26. Mean Aqueous Humor Faricimab Concentration-Time profiles.

Figure 30 Mean (+/-SD) Aqueous Humor Faricimab Concentration-Time Profiles (PK-Evaluable Population; Linear and Semi-Log scale)

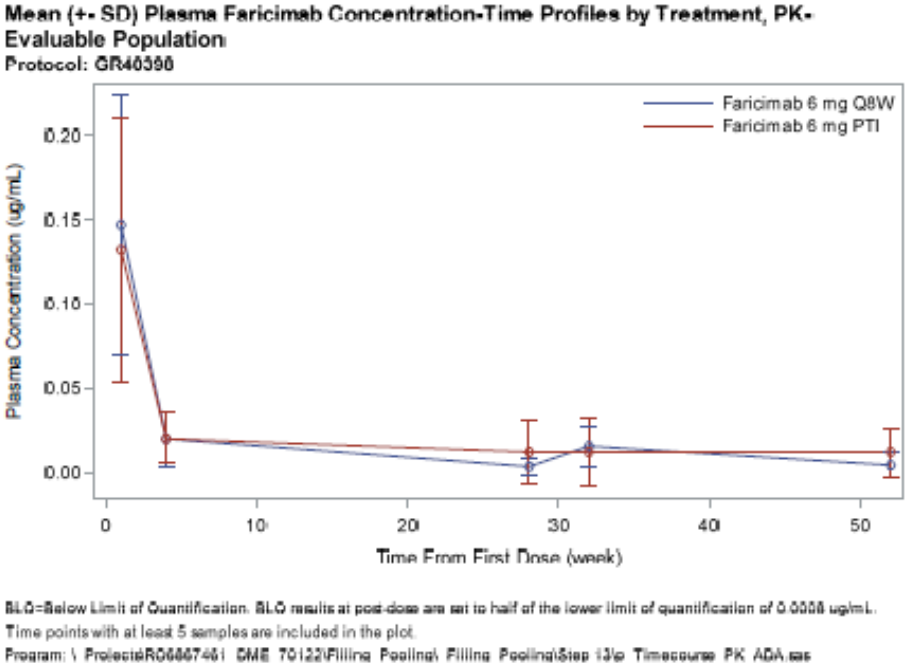


BLQ=Below Limit of Quantification. BLQ results at post-dose are set to half of the lower limit of quantification of 0.00781 ug/mL.
Time points with at least 5 samples are included in the plot.
Program: \ Projects\RO6867461 DME 70122\Filling Pooling\ Filling Pooling\Step 13\p Timecourse PK ADA.sas

Plasma data from 630 patients were included in the PK analysis. The mean plasma concentration-time profiles are shown in Figure 27. The observed mean (SD) faricimab plasma concentrations (µg/mL) at Week 1 (1 week after the first administration) were 0.147 (0.077) and 0.131 (0.078) for the Q8W and PTI regimen respectively. Faricimab was measurable up to 8 weeks post-dose, where approximately 40% of the samples were BLQ. The faricimab AH to plasma ratio on Day 7 was ~530-700.

Figure 27. Mean Plasma Faricimab Concentration-Time profiles.

Figure 31 Mean (+/-SD) Plasma Faricimab Concentration-Time Profiles (PK-Evaluable Population; Linear and Log scale)



Faricimab exposure predictions based on the population PK model

Individual PK parameters estimated from the final population PK model were used to simulate individual faricimab concentration-time courses in plasma, AH, and VH for nAMD patients from Phase III studies GR40306 and GR40844 and DME patients from Phase III studies GR40349 and GR40398. The individual estimates of the steady-state exposure parameters following 6 mg Q8W doses (the highest proposed maintenance dose regimen) are summarised by disease type in Table 14. For a reference male patient with DME or nAMD (80 kg body weight, 65 years old, treated with the Phase III formulation and without ADAs), maximum free faricimab concentrations in plasma are predicted to be approximately 600 and 6000-fold lower than in aqueous and vitreous humour, respectively.

Table 14. Steady state exposure estimates.

Table 13 Faricimab Steady-State Exposure Estimates Following 6 mg Q8W Dosing (Patients from Phase III Studies)

Disease	Compartment	N	AUC_{Q8W} (µg/mL*day)	C_{max} (µg/mL)	C_{Q8W} (µg/mL)	T_{max} (day)
			Median (95% Prediction Interval)			
nAMD	VH	660	15000 (8130-26300)	1340 (1330-1420)	9.15 (0.137-82.9)	0
	AH		1540 (1150-2230)	136 (89.7-219)	0.941 (0.023-6.21)	0.333 (0.248-0.475)
	Plasma		3.08 (2-4.51)	0.223 (0.125-0.407)	0.00208 ($7.34 \cdot 10^{-5}$-0.0121)	2.2 (1.44-6.8)
DME	VH	1221	13300 (7480-23600)	1340 (1330-1390)	4.82 (0.0618-58.8)	0
	AH		1520 (1120-2130)	149 (97.1-239)	0.563 (0.00903-4.78)	0.327 (0.236-0.454)
	Plasma		2.59 (1.72-4.06)	0.212 (0.116-0.385)	0.00102 ($1.97 \cdot 10^{-5}$-0.00818)	2.01 (1.4-4.81)

ADA = anti-drug antibody; AH = aqueous humor; AUC_{Q8W} = AUC at steady state during the 8 week dosing interval; C_{max} = maximum concentration observed; C_{Q8W} = through concentration at steady state for a Q8W dosing interval; DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; T_{max} = time to maximum concentration; VH = vitreous humor.

Subjects with ADA detected at any time post-baseline were assumed to have ADA at steady state.

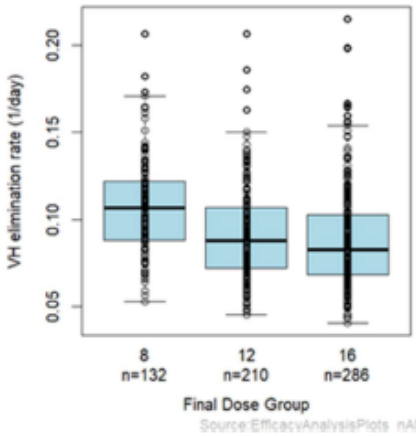
Source: popPK Report, Report 1105763, Table 16

The relationship between vitreous elimination rate constant and the frequency of drug administration was evaluated using the Phase III data. Figure 28 shows distribution of vitreous rate constant by dosing frequencies in the nAMD population treated with faricimab. Figure 29 shows distribution vitreous rate constant for each dosing frequency in the DME population treated with faricimab in the PTI arm.

Despite the overlap between the different dosing regimens, the figures indicate an overall trend for patients who were treated less frequently to have lower vitreous elimination rate constants and, therefore, longer vitreous half-lives.

Figure 28. Distributions of Kvh Values by Dose groups for nAMD studies.

Figure 39 Distributions of k_{VH} Values by Dose Group for nAMD Studies TENAYA and LUCERNE (Arms A)



IRQ = inter-quartile range; nAMD = neovascular age-related macular degeneration; VH = vitreous humor.

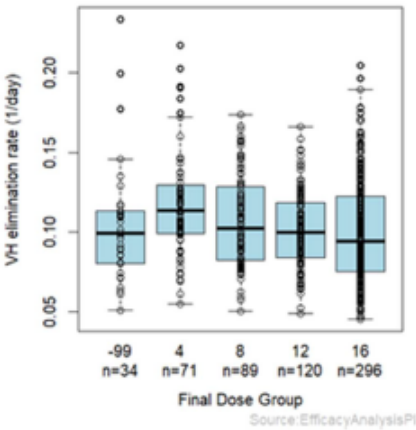
The individual values are plotted by dose group using box and whisker plots. Median values are designated by black lines in the center of the boxes. Boxes indicate the IQR. Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

Ocular elimination rate. Groups: 8: Q8W dosing; 12: Q12W dosing; 16: Q16W dosing.

Source: popPK Report 1105763, Figure 172

Figure 29. Distribution of Kvh Values by Dose groups for DME studies

Figure 40 Distributions of k_{VH} Values by Dose Group at Week 52 for DME Studies YOSEMITE and RHINE (Arms B)



DME = diabetic macular edema; IQR = inter-quartile range; k_{VH} = ocular elimination rate; PTI = personalized treatment interval; VH = vitreous humor.

The individual values are plotted by dose group using box and whisker plots. Patients from Arms B (PTI) of DME Studies YOSEMITE and RHINE are included. Median values are designated by black lines in the center of the boxes. Boxes indicate the IQR. Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

k_{VH}: Ocular elimination rate. Groups: -99: dropped out before Week 52; 4: Q4W dosing at Week 52; 8: Q8W dosing at Week 52; 12: Q12W dosing at Week 52; 16: Q16W dosing at Week 52.

Source: popPK Report 1105763, Figure 223

Immunogenicity

The overall incidence of treatment-emergent ADAs was low (ranging from 0-11%), based on Phase I and II, and remained low (8-10%), based on Phase III study results (Table 15).

In the Phase I and Phase II studies of faricimab in patients with nAMD and DME ≤11% of post-dose evaluable patients demonstrated treatment-induced or treatment-boosted ADA responses. In the pooled Phase III studies, 68/663 (10.4%) patients with nAMD and 105/1255 (8.4%) patients with DME showed treatment-induced or treatment-boosted ADA responses, which were persistent in 75-85% of the patients. The median time to onset of ADA response was 20 to 28 weeks. Titers ranged from 10-20480 in nAMD and 10-81920 in DME.

Table 15 Overall Summary of Immunogenicity Results by Study

Study	Indication	Baseline-ADA Evaluable Patients n	Baseline ADA Prevalence n (%)	Post-baseline ADA Evaluable Patients n	Treatment-Induced or Boosted ADAs n (%)
Phase I					
BP28936	nAMD	24	0 (0.0%)	24	0 (0.0%)
JP39844	nAMD/DME	12	0 (0.0%)	12	0 (0.0%)
Phase II					
AVENUE	nAMD	195	5 (2.6%)	195	22 (11.3%)
STAIRWAY	nAMD	55	0 (0.0%)	55	6 (10.9%)
BOULEVARD	DME	135	3 (2.2%)	135	10 (7.4%)
Phase III					
TENAYA	nAMD	322	10 (3.1%)	328	29 (8.8%)
LUCERNE	nAMD	318	2 (0.6%)	329	39 (11.9%)
YOSEMITE	DME	603	6 (1.0%)	619	62 (10.0%)
RHINE	DME	604	4 (0.6%)	624	43 (6.9%)
Pooled	nAMD	640	12 (1.8%)	657	68 (10.4%)
Pooled	DME	1207	10 (0.8%)	1243	105 (8.4%)

ADA = anti-drug antibodies; DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration.

Source: CSR JP38944, Report 1106179, Section 12.5.4; CSR BP28936, Report 1058993, Section 6.10.4, CSR BP30099; Report 1083913, Section 8.12.4; CSR BP26947, Report 1083912, Section 8.12.4; CSR CR39521, Report 1085977, Section 8 CSR GR40349, Report 1102956, Table 36; CSR GR40398, Report 1102957, Table 36; CSR GR40306, Report 1102954, Table 36; CSR GR40844, Report 1102955, Table 36; t_ada_base_IG_nAMD_HLS; t_ada_base_IG_DME_HLS

PopPK covariate analyses showed that plasma ADA had an effect on vitreous elimination t1/2. Patients with detected ADAs had 30.4% higher ocular elimination rate. As a consequence, ADA positive patients had 23.4% lower ocular exposure at steady state compared with ADA negative patients. Presence of plasma ADA had no effect on the plasma exposure.

The impact on ocular exposure was considered minor, and exposure-response analysis showed a similar response across the range of vitreous exposure in Phase III, confirming that the changes in vitreous exposure in ADA-positive patients are unlikely to be associated with a change in efficacy.

Based on all available data to date, no meaningful impact of ADA was observed on efficacy and on overall safety. Although a higher incidence of IOI was observed in ADA-positive compared with ADA-negative patients, this observation is not considered to be clinically relevant (see Safety section for further details).

Special populations

- **Impaired renal and hepatic function**

No specific studies in patients with renal or hepatic impairment were conducted with faricimab. Both renal impairment and hepatic impairment were not identified as covariates influencing faricimab PK in the population PK analysis. No dose adjustment is necessary.

- **Gender**

Systemic faricimab clearance was 13.7% slower in females, while VH elimination rate (and thus, VH exposure) was independent of sex. This change is not expected to be clinically significant due to the small magnitude of the effect and the low incidence of systemic, non-ocular, AEs. No dose adjustment is needed.

- **Race**

In the popPK analysis, race was not identified as a clinically relevant covariate affecting either ocular or plasma faricimab disposition. Plasma PK data in Japanese patients from Study JP39844 were consistent with those in Study BP28936, which enrolled Caucasian patients. No dose adjustment is necessary.

- **Weight**

Plasma volume and clearance increased with body weight. As patients with DME were on average heavier (mean weight 86.8 kg versus 75.2 kg for patients with nAMD), this translates to approximately 10% lower systemic exposure (steady state AUC) in a typical patient with DME compared to a typical patient with nAMD.

Faricimab was well tolerated across the broad plasma exposure range with low incidence of systemic, non-ocular AEs; therefore, differences in plasma exposure by bodyweight are considered not clinically meaningful and no body-weight based dosing is needed.

- **Elderly**

In the four Phase III clinical studies, approximately 60% (1149/1929), 25% (486/1929) and 5% (95/1929) of patients randomised to faricimab were ≥65, ≥75 and ≥85 years of age, respectively.

Age was an important covariate that influenced faricimab vitreous disposition (the site of action). The population PK model indicated that kVH declined with age and, therefore, VH t1/2 increased with age. A typical 44 year old patient had a VH elimination half-life approximately 31% shorter than a typical 89 year old patient. This effect might be explained by changes in VH with age. As patients with DME were on average younger (mean age 62.1 years versus 76 years for patients with nAMD), this translates to approximately 10% shorter VH elimination half-life in a typical patient with DME compared to a typical patient with nAMD.

The resulting age-based difference in ocular exposure is not considered to be clinically meaningful in view of the flat exposure BCVA correlation. Therefore, no dose adjustment is needed in patients aged 65 years or above.

Interactions

Since faricimab is a monoclonal antibody, no drug-drug interactions are expected via cytochrome P450, other metabolizing enzymes, or transporters. Therefore, no formal drug-drug interaction studies were conducted for faricimab. In the population PK analysis, IOP lowering drugs did not have any effect on faricimab ocular PK.

2.4.2.2. Pharmacodynamics

The clinical pharmacodynamics of faricimab has been characterized in 8 clinical studies in patients with nAMD and DME; 1 Phase I, 3 Phase II and 4 Phase III studies. The PD markers of faricimab assessed in the clinical studies were angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). In addition, the relationships between efficacy endpoints (best-corrected visual acuity [BCVA] and central subfield thickness [CST]) and vitreous faricimab PK were assessed in exposure-efficacy analyses. Exposure-safety analyses evaluated the relationship between intraocular inflammation (IOI) and vitreous faricimab PK.

Mechanism of action

Faricimab is a humanized bispecific IgG1 antibody that acts through inhibition of two distinct pathways by neutralization of both Ang-2 and VEGF-A. Ang-2 and VEGF are two key mediators in the pathogenesis of nAMD and DME. Ang-2 causes vascular instability by promoting endothelial destabilization, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitizes blood vessels to the activity of VEGF-A resulting in further vascular destabilization. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularization.

Primary pharmacology

Phase I studies

Study BP28936

AH PD data were only available for 3 patients in the SAD part and 2 patients in the MAD part. Faricimab administration resulted in target engagement i.e., decrease in AH Ang-2 and VEGF.

Phase II studies

Study CR39521 (STAIRWAY)

AH samples (optional) were only available for 11 patients in the 6 mg faricimab Q12W arm and 3 patients in the Q16W arm. Therefore, the data should be interpreted with caution.

Data were not presented for Ang-2 since the majority of free Ang-2 levels in AH were BLQ.

Mean free VEGF-A levels in AH were <10% of the baseline levels at 4 weeks post-first dose. In the Q12W group, AH VEGF-A levels remained lower than baseline at 8 and 12 weeks post-dose (Weeks 32 and 36, respectively). The Q16W dose group suggested a trend for some VEGF-A suppression at 12 weeks post-dose (Week 24), while the VEGF-A concentrations were similar to baseline values at 16 weeks post-dose (Week 28).

Study BP29647 (AVENUE)

A large free Ang-2 suppression was observed for all faricimab treatment groups, assessed by either the proportion of BLQ or by mean values. Ang-2 was suppressed for at least 4 weeks, with 8 weeks being inconclusive due to lack of data.

Trough free VEGF levels were at <10% (median) of the baseline levels for both doses (1.5 mg and 6 mg faricimab) and both regimens (Q4W and Q8W; 4 and 8 weeks post-dose).

There was no apparent change from baseline in mean Ang-2 or VEGF-A plasma concentrations across treatment arms.

Study BP30099 (BOULEVARD)

A large free Ang-2 suppression was observed for all faricimab treatment groups assessed by either the proportion of BLQ or by mean values. After cessation of treatment, free Ang-2 levels increased in the faricimab treatment groups, starting at 6 to 8 weeks postdose at 6 mg, but did not reach baseline levels at the end of the observation period (12 weeks postdose).

Treatment with either 1.5 mg or 6 mg faricimab resulted in an almost complete free AH VEGF suppression at 1-week post dose and remained at ≤10% (median) of the baseline levels at trough. After cessation of treatment, free VEGF levels were close to the baseline levels at 6-8 weeks postdose for 1.5 mg faricimab, whereas for the 6 mg, VEGF levels were close to the baseline levels only at 12 weeks postdose.

No apparent changes in the Ang-2 and VEGF-A plasma profiles were observed at the 1.5 or 6 mg dose levels.

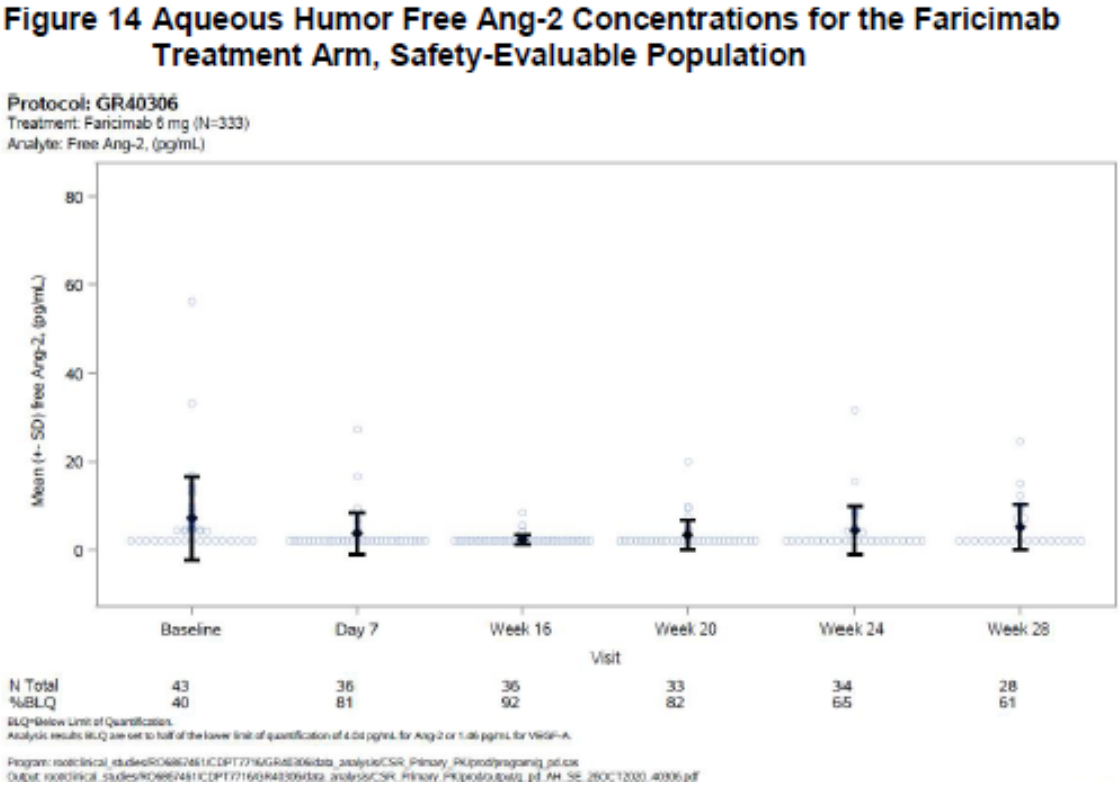
Phase III studies in nAMD patients

Study GR40306 (TENAYA)

High inter-patient variability was observed in AH Ang-2 (CV 36%-134%) and VEGF-A (CV 47%-270%) concentrations.

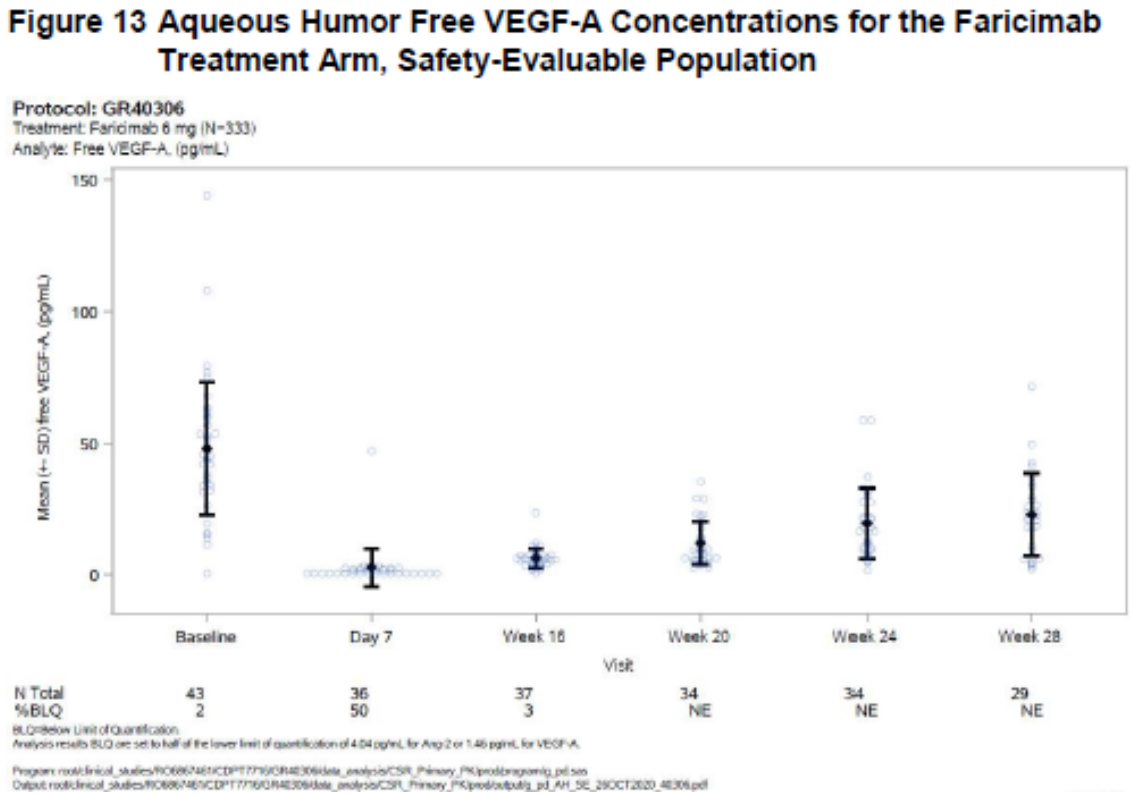
Rapid suppression of Ang-2 starting 7 days post-dose was observed and maintained at least up to Week 20, after which patients were assigned to a regimen based on disease activity. The percentage of Ang-2 levels measured BLQ decreased as the time from most recent dose increased. However, at 16 weeks post-dose, a higher proportion of samples continued to have Ang-2 concentrations measured BLQ compared to at baseline (Figure 30).

Figure 30. Aqueous Humor free Ang-2 Concentration.



Rapid suppression of VEGF-A was shown starting 7 days post-dose and remained suppressed at least up to Week 20, after which patients were assigned to different dosing regimens. VEGF-A levels increased as the sampling time from most recent dose increased and were approaching baseline values 16 weeks post-dose (Figure 31).

Figure 31. Aqueous Humor Free VEGF-A concentrations.



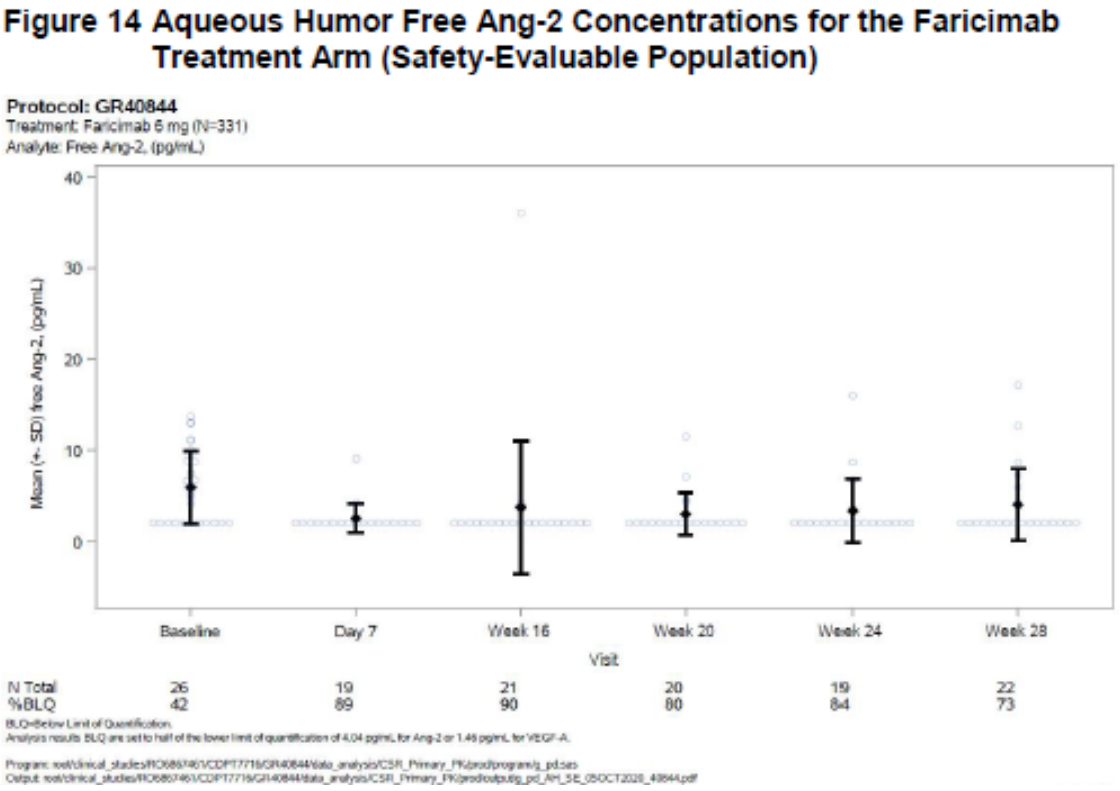
No change in plasma free Ang-2 or in free VEGF-A was observed post-dose as compared to baseline in any of the faricimab treatment arms.

Study GR40844 (LUCERNE)

High inter-patient variability was observed in AH Ang-2 (CV 35%-198%) and VEGF-A (CV 39%-103%) concentrations.

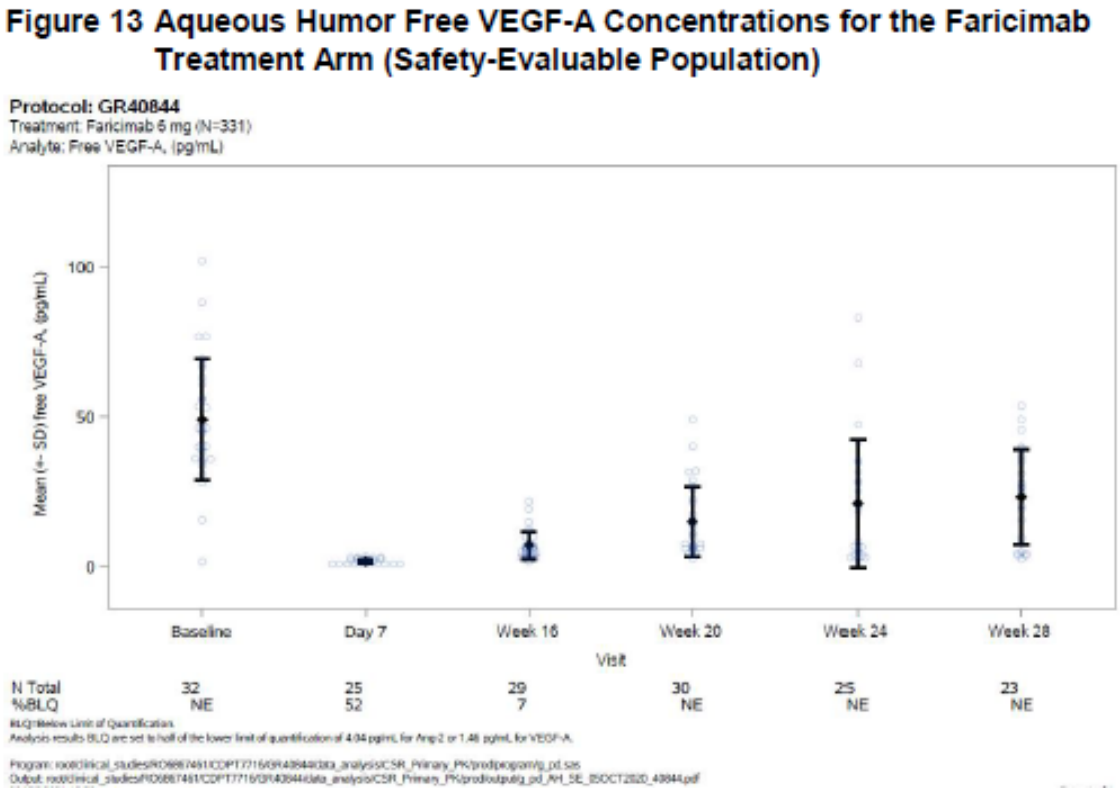
Rapid suppression of Ang-2 starting 7 days post-dose was observed and maintained at least up to Week 20, after which patients were assigned to a regimen based on disease activity. The percentage of Ang-2 levels measured BLQ decreased as the time from last-dose increased. However, at 16 weeks after last dose, a higher proportion of samples continued to have Ang-2 concentrations measured BLQ compared to baseline (Figure 32).

Figure 32. Aqueous Humor Free Ang-2 Concentrations.



Rapid suppression of VEGF-A was shown starting 7 days post-dose and remained suppressed at least up to Week 20, after which patients were assigned to different dosing regimens. VEGF-A levels increased as the sampling time from last-dose increased and were approaching baseline values 16 weeks after the last dose (Figure 33).

Figure 33. Aqueous Humor Free VEGF-A Concentrations.



No change in plasma free Ang-2 or in free VEGF-A was observed post-dose as compared to baseline in any of the faricimab treatment arms.

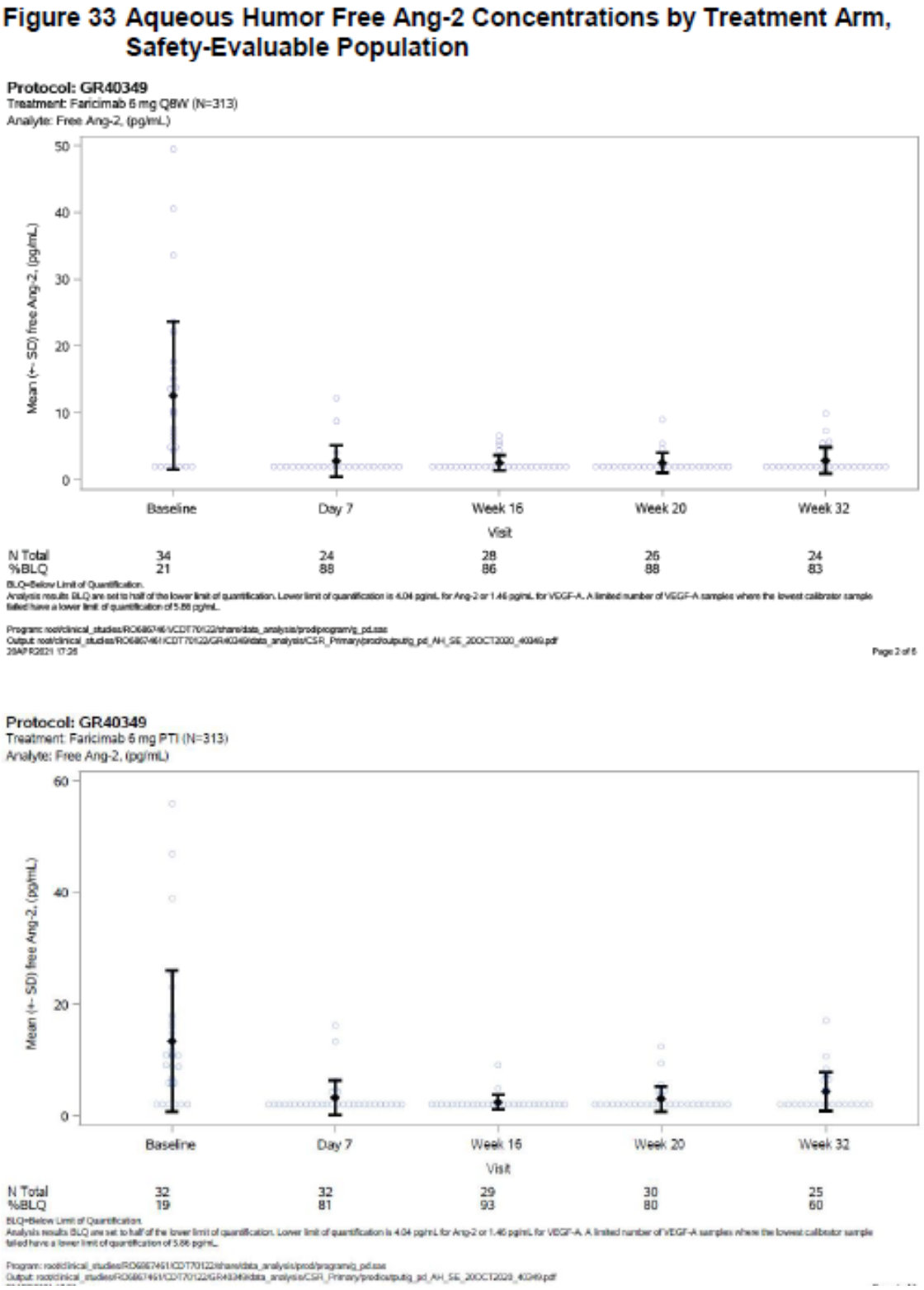
Phase III studies in DME patients

Study GR40349 (YOSEMITE)

High inter-patient variability was observed in AH Ang-2 (CV 51-89% in the Q8W arm) and VEGF-A (CV 80-222% in the Q8W arm) concentrations.

Both faricimab arms showed rapid suppression of Ang-2 starting 7 days post-dose and mean concentrations remained below mean baseline throughout the study (Figure 34).

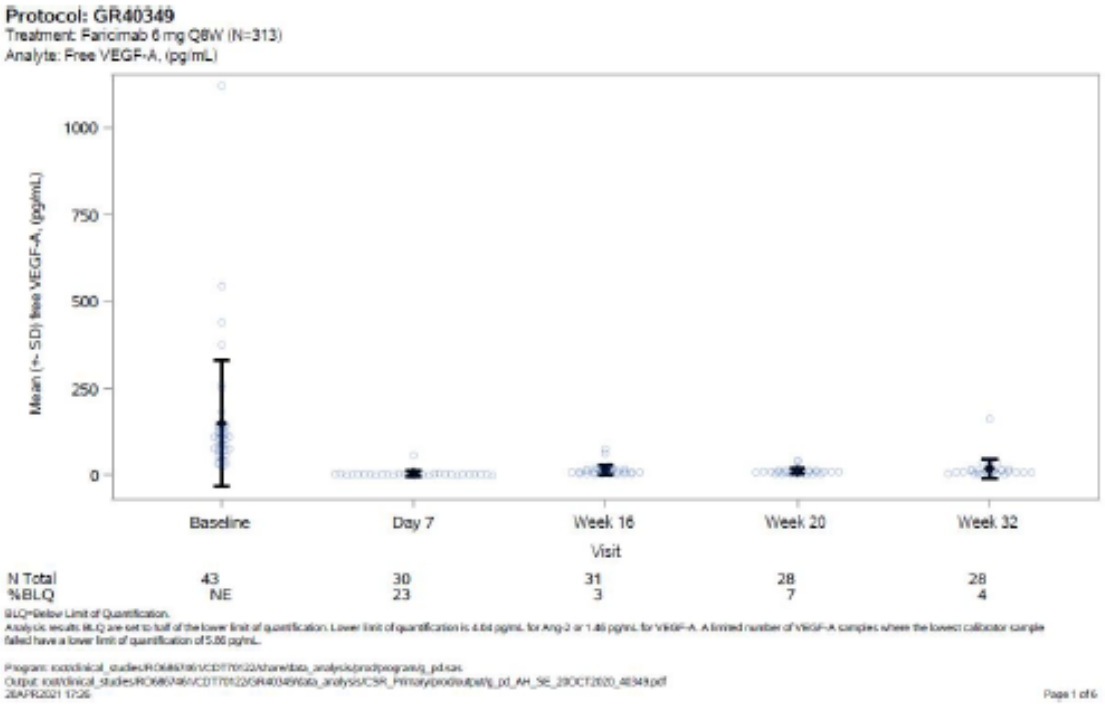
Figure 34. Aqueous Humor Free Ang-2 Concentrations

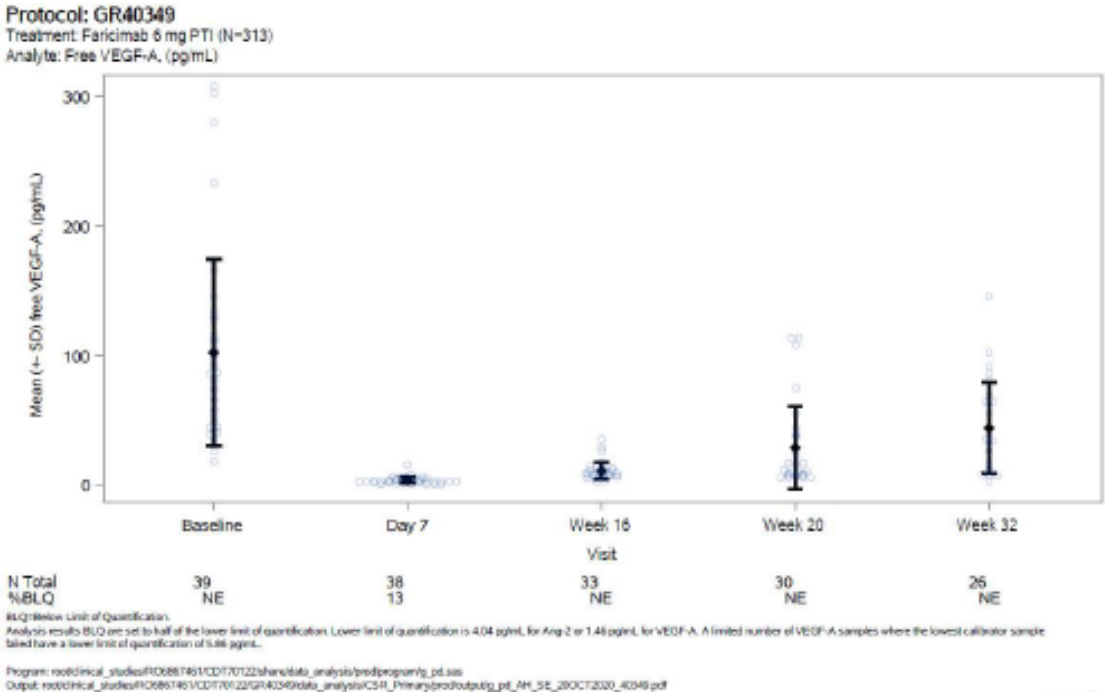


Both faricimab treatment arms showed rapid suppression of VEGF-A from day 7 onwards and thereafter sustained target suppression was observed in both arms. In the PTI arm, there was a trend for increased VEGF-A concentrations as sampling time from last dose increased (Figure 35).

Figure 35. Aqueous Humor Free VEGF-A Concentrations.

Figure 32 Aqueous Humor Free VEGF-A Concentrations by Treatment Arm, Safety-Evaluable Population





No change in plasma free Ang-2 or in free VEGF-A was observed post-dose as compared to baseline in any of the faricimab treatment arms.

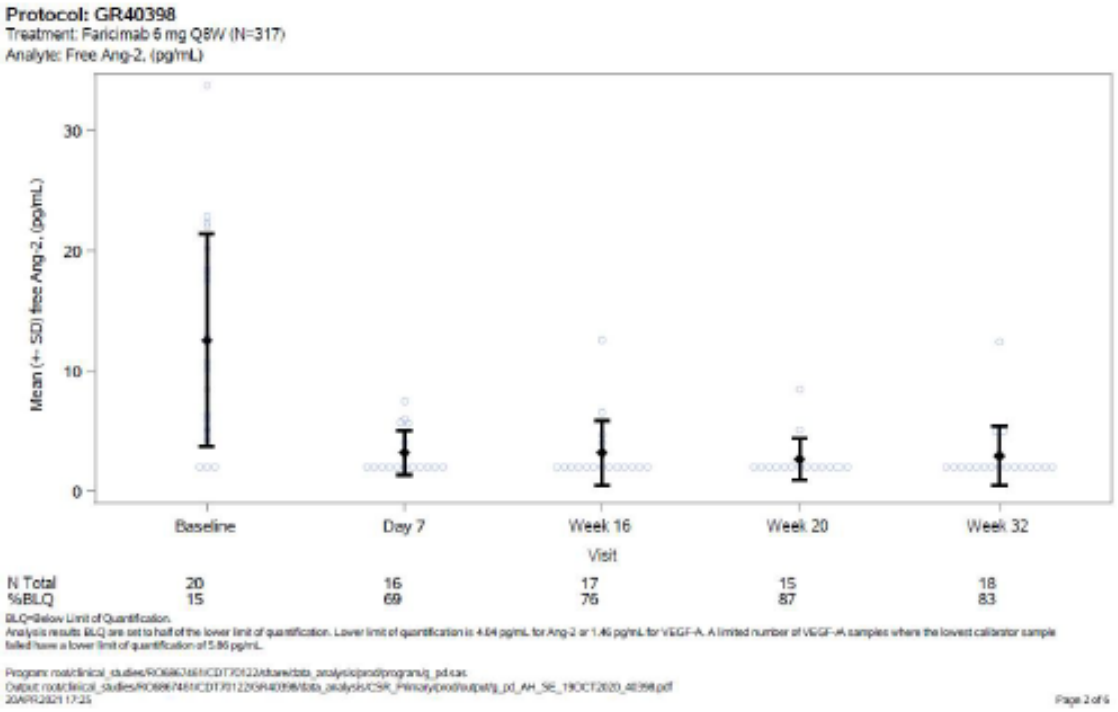
Study GR40398 (RHINE)

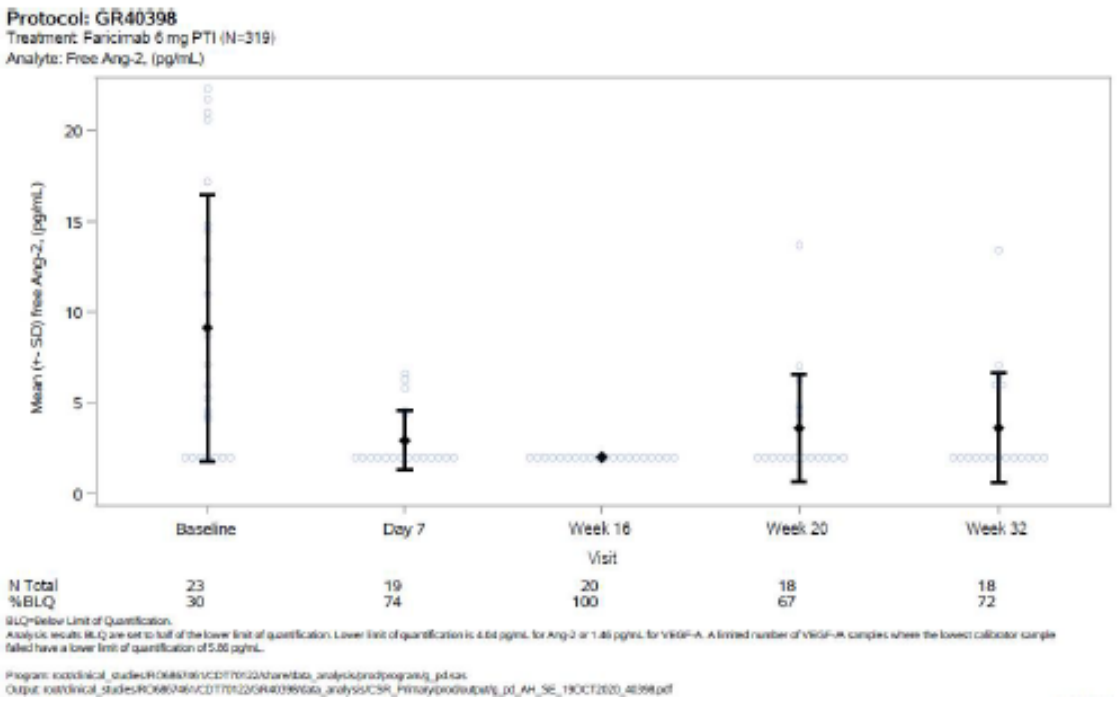
High inter-patient variability was observed in AH Ang-2 (CV 60-87% in the Q8W arm) and VEGF-A (CV 66-197% in the Q8W arm) concentrations.

Both faricimab arms showed rapid suppression of Ang-2 starting 7 days post-dose and mean concentrations remained below mean baseline throughout the study (Figure 36).

Figure 36. Aqueous Humor Free Ang-2 Concentrations.

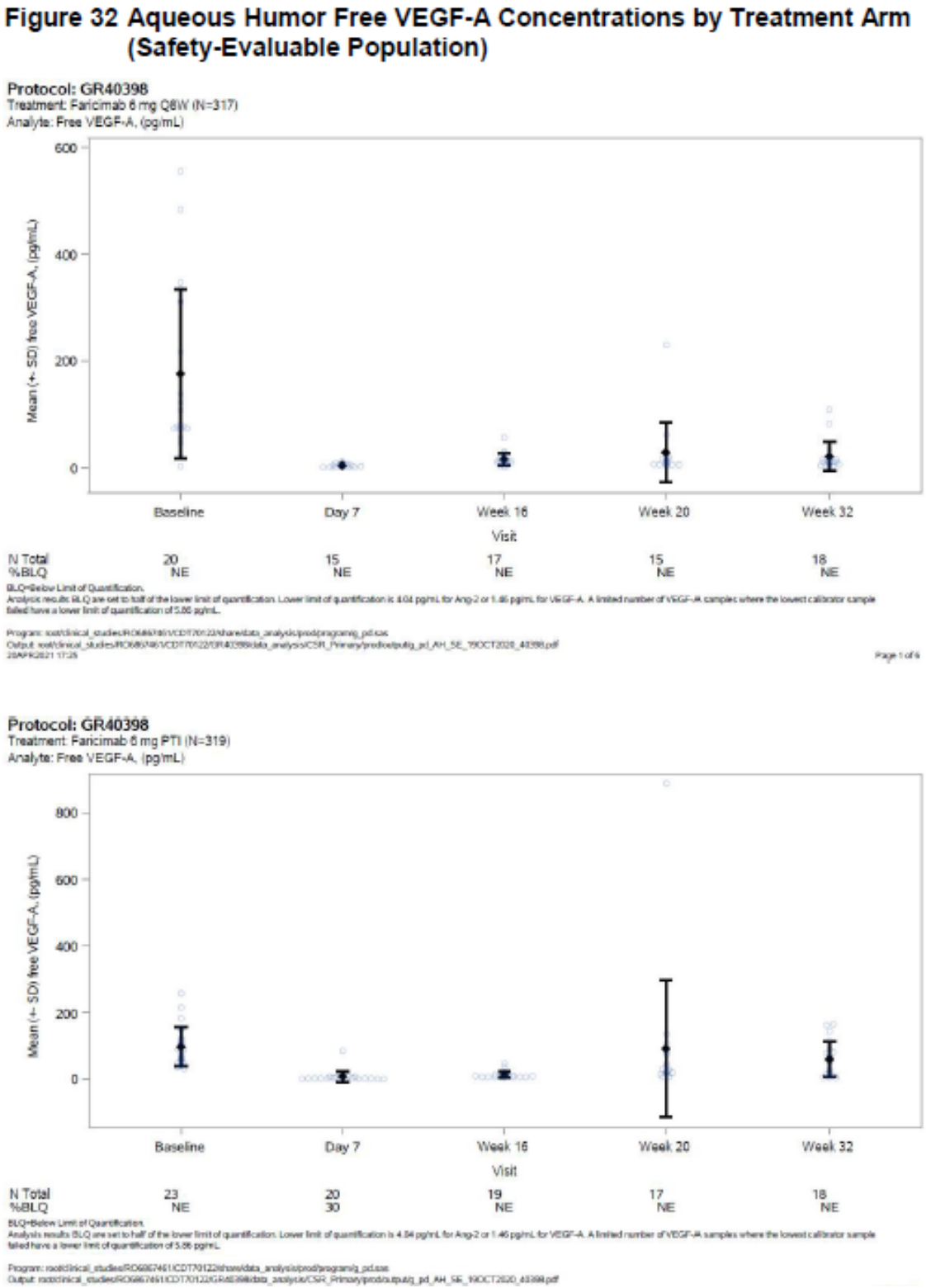
Figure 33 Aqueous Humor Free Ang-2 Concentrations by Treatment Arm (Safety-Evaluable Population)





Both faricimab treatment arms showed rapid suppression of VEGF-A from day 7 onwards and thereafter sustained target suppression was observed in both arms. In the PTI arm, there was a trend for increased VEGF-A concentrations as sampling time from last dose increased (Figure 37).

Figure 37. Aqueous Humor Free VEGF-A Concentrations.



No change in free Ang-2 or free VEGF-A was observed post-dose as compared to baseline in any of the faricimab treatment arms.

Secondary pharmacology

Cardiac physiology

No thorough QTc study has been performed with faricimab, as monoclonal antibodies are not known to cause QT prolongation, and faricimab plasma concentrations were low.

Information on obtained ECG data during the clinical development of faricimab is provided in the Safety section of this report.

Pharmacodynamic interactions

No PD interaction studies have been conducted.

Exposure-efficacy analyses

The analyses of exposure-efficacy relationships were performed by indication using the PK and efficacy data from Phase III studies in nAMD (GR40306 and GR40844) and DME (GR40349 and GR40398). The efficacy endpoints analysed were best-corrected visual acuity (BCVA), change from baseline in BCVA (dBCVA) and % change from baseline in BCVA (pdBCVA). Additional efficacy endpoints included, central subfield thickness (CST), change from baseline in CST (dCST) and % change from baseline of CST (pdCST). Different exposure metrics or predictors were used for inference between faricimab exposure and responses. The effect of relevant covariates (e.g. ADA) was assessed as appropriate.

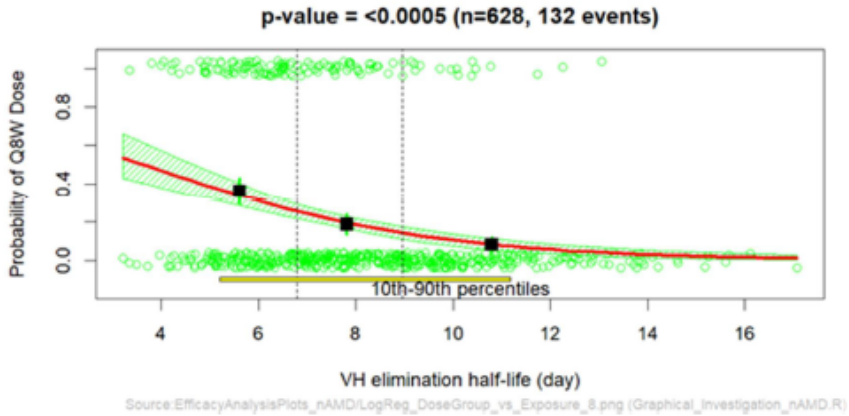
nAMD trials

For BCVA, dBCVA, and pdBCVA and for CST, dCST and pdCST, there were no marked differences in response between different groups of VH elimination half-life (t1/2,kVH). Similarly, none of the three dosing groups (Q8W, Q12W, and Q16W) showed marked differences in response between the VH exposure categories (VH Ctrough,ss). The linear regression analyses suggested flat relationships between half-life or exposure and responses to faricimab treatment, with no apparent trends noticeable.

The logistic regression analyses to assess the relationships between the probability of requiring a Q8W dose regimen and the probability of either a Q8W or Q12W regimen vs t1/2,kVH are presented in Figure 38 and Figure 39, respectively. Results showed that in patients with nAMD the probability of requiring a Q8W administration decreased with longer t1/2,kVH. The same trend was observed for the probability of receiving faricimab Q8W or Q12W.

Figures 38 and 39. Logistic regression analyses to assess the relationships between the probability of requiring a Q8W dose regimen and the probability of either a Q8W or Q12W regimen vs t1/2,kVH

Figure 41 Logistic Regression for Probability of Requiring a Q8W Dosing for nAMD Studies TENAYA and LUCERNE (Arms A)



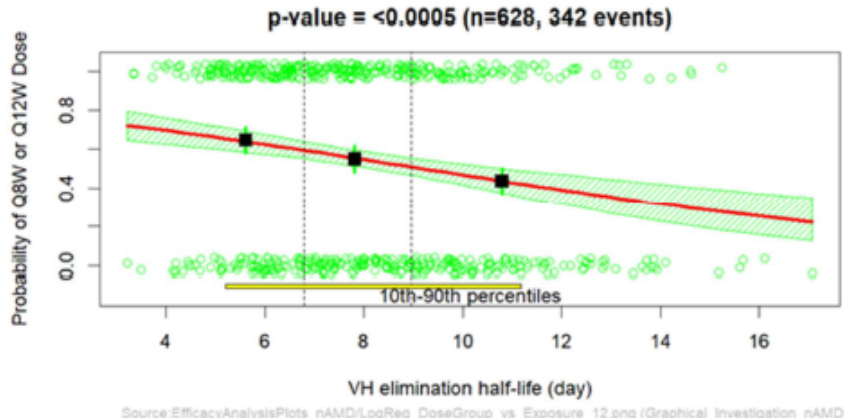
Source:EfficacyAnalysisPlots_nAMD/LogReg_DoseGroup_vs_Exposure_8.png (Graphical_Investigation_nAMD.R)

nAMD = neovascular age-related macular degeneration; Q8W = every 8 weeks; VH = vitreous humor.

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p = 1) and without events (p = 0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function.

Source: popPK Report, Report 1105763, Figure 173

Figure 42 Logistic Regression for Probability of Requiring Q8W or Q12W Dosing for nAMD Studies TENAYA and LUCERNE(Arms A)



Source:EfficacyAnalysisPlots_nAMD/LogReg_DoseGroup_vs_Exposure_12.png (Graphical_Investigation_nAMD.R)

nAMD = neovascular age-related macular degeneration; Q8W = every 8 weeks; Q12W = every 12 weeks; VH = vitreous humor.

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p = 1) and without events (p = 0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function.

Source: popPK Report, Report 1105763, Figure 174

The parameter estimates of the logistic regression final model are presented in Table 16. Probability of Q8W dosing was lower for ADA-positive patients, and it was higher for patients with higher baseline pigment epithelium detachment thickness (PEDT). No other covariates had a significant effect on probability of Q8W dosing.

Table 16. Logistic regression of Q8W dosing in nAMD

Table 30. Logistic Regression Final Model of Q8W Dosing Regimen (Arms A of Phase III nAMD Studies)

VH elimination half-life (day) was used as predictor variable. P-values below 0.01 are highlighted red.

Parameter	Coefficient	SE	RSE	95% CI	p-value	Group
Intercept	1.234	0.4613	37.39	0.3295;2.138	0.007	Q8W
VH half-life	-0.4365	0.06166	14.13	-0.5573;-0.3156	<0.0005	
PEDT	0.00305	0.00053	17.38	0.002011;0.004089	<0.0005	
ADA = Yes	-1.008	0.3514	34.86	-1.697;-0.3194	0.004	

Source file: nAMD_modelTableRed4.csv (Graphical_Investigation_nAMD.R)

DME trials

Arm A

The time courses of BCVA, dBCVA, and pdBCVA by exposure categories (VH Ctrough,ss) showed no marked differences in response between the exposure categories. There was greater CST reduction in patients with higher exposure. The linear regression analyses suggested flat relationships between exposure and response (BCVA and CST) to faricimab treatment.

Arm B

For BCVA, dBCVA, and pdBCVA, there were no marked differences in response between number of administered doses between week 12 and 56. All three measures were higher in the lowest t1/2,kVH tertile, lower in the highest tertile, and similar to the control group in the intermediate t1/2,kVH tertile. Results of the linear regression analyses, did not demonstrate a trend deviating strongly from a flat relationship between the endpoints and their predictors.

For CST, dCST and pdCST, there were no marked differences in response between number of administered doses between week 12 and 56. CST appeared to reach lower levels in patients with longer t1/2,kVH. Results of the linear regression analyses, did not demonstrate a trend deviating strongly from a flat relationship between the endpoints and their predictors.

Table 17 shows the number and percent of patients in different dosing groups (defined by dosing schedules at Week 52) by tertiles of t1/2,kVH. Patients who needed fewer doses (i.e groups with longer inter-dose interval) tended to have longer t1/2,kVH.

Table 17. Patients with different dosing regiments, by tertile of VH elimination half-life

Table 31. Fraction of Patients with Different dosing Regimens, by Tertile of VH Elimination Half-Life (Arms B of Phase III DME Studies)

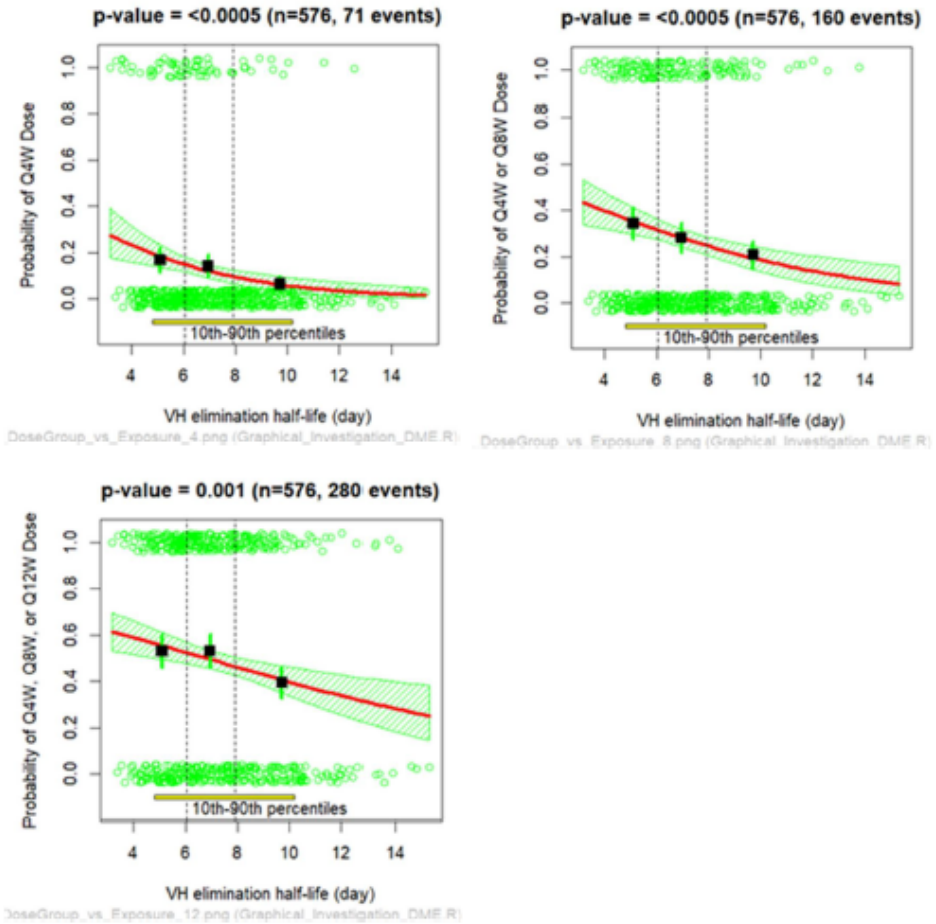
VH elimination half-life range (day)	N	Number of patients in the group (all patients are included)					Percent of patients (patients dropped out before Week 52 are excluded)			
		Drop	Q4W	Q8W	Q12W	Q16W	Q4W	Q8W	Q12W	Q16W
2.97-6.06	203	8	32	34	36	93	16.4	17.4	18.5	47.7
6.08-7.91	203	14	27	27	48	87	14.3	14.3	25.4	46.0
7.91-15.3	204	12	12	28	36	116	6.2	14.6	18.8	60.4

Source file: DME_tempTable_REG.csv (Graphical_Investigation_DME.R)

Logistic regression to assess the relationship between the dosing frequencies and the vitreous t1/2 is shown in Figure 40. The probability of Q4W regimen at Week 52 decreased with increasing vitreous t1/2. A similar trend was observed for the probability of a Q4W or Q8W regimen, as well as for a Q4W or Q8W or Q12W regimen.

Figure 40. Logistic regression for probability of Dosing Intervals at w56 for DME studies.

Figure 43 Logistic Regression for Probability of Dosing Intervals at Week 56 for DME Studies YOSEMITE and RHINE (PTI Dosing)



DME = diabetic macular edema; PTI = personalized treatment interval; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; VH = vitreous humor.

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function. Patients who dropped out before Week 56 were excluded from the analysis.

Source: popPK Report 1105763, Figure 225, Figure 226, Figure 227

Table 18 shows the parameter estimates of the final logistic regression models. Low CST at baseline and longer VH t1/2 decrease the probability of Q4W regimen. The probability of Q12W or Q16W regimens was higher in NAIVE patients with long VH elimination half-life and low CST. The probability of Q16W regimen was higher in patients with low CST, longer VH elimination half-life and in patients with no cataract surgery.

Table 18

Table 33. Logistic Regression Final Models (Arms B of Phase III DME Studies)
VH elimination half-life (day) was used as predictor variable. P-values below 0.01 are highlighted red.

Parameter	Coefficient	SE	RSE	95% CI	p-value	Endpoint
Intercept	-1.919	0.6759	35.22	-3.244;-0.5942	0.005	Q4W at W52
VH half-life	-0.2795	0.07552	27.02	-0.4275;-0.1315	<0.0005	
CST	0.003753	0.000946	25.2	0.001899;0.005606	<0.0005	
Intercept	-1.51	0.5421	35.89	-2.573;-0.4478	0.005	Q4W, Q8W at W52
VH half-life	-0.1777	0.05093	28.67	-0.2775;-0.07783	<0.0005	
CST	0.004783	0.000802	16.78	0.00321;0.006355	<0.0005	
NAIVE	-0.6854	0.2255	32.9	-1.127;-0.2434	0.002	
Intercept	-2.553	0.5194	20.34	-3.571;-1.535	<0.0005	Q4W, Q8W, or Q12W at W52
VH half-life	-0.1368	0.04337	31.7	-0.2218;-0.0518	0.002	
CST	0.006959	0.000892	12.82	0.005211;0.008707	<0.0005	
CATARACT	0.5062	0.1839	36.33	0.1457;0.8667	0.006	

Source file: DME_modelTableRed1.csv (2d endpoint), DME_modelTableRed2.csv (3d endpoint), DME_modelTableRed3.csv (1st endpoint) (Graphical_Investigation_DME.R)

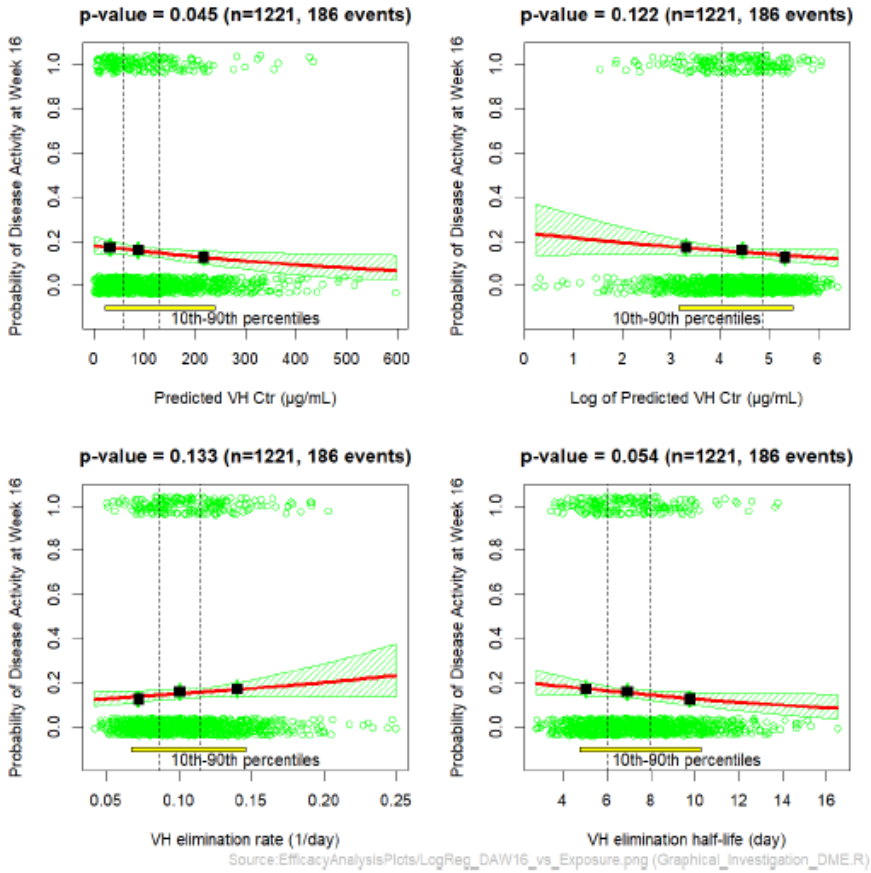
Arms A and B combined

Figure 41 illustrates the logistic regression models for the probability of disease activity at Week 16 (DAW16) versus Ctrough,ss following Q4W dosing and versus the other exposure parameters. The probability of DAW16 declined with increasing Ctrough,ss but the relationship was shallow. The logistic regression models for the probability of DAW16 versus VH elimination rate and VH t1/2 also indicated shallow dependencies.

Figure 41. Logistic regression for disease activity at w16

Figure 228. Logistic Regression for Disease Activity at Week 16 for DME Studies GR40349 and GR40398 (Arms A and B)

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function. Ctr: $C_{trough,ss}$ following Q4W dosing; k_{VH}: VH elimination rate.



Source:EfficacyAnalysisPlots/LogReg_DAW16_vs_Exposure.png (Graphical_Investigation_DME.R)

Graphical analysis of exposure-PD relationships

nAMD trials

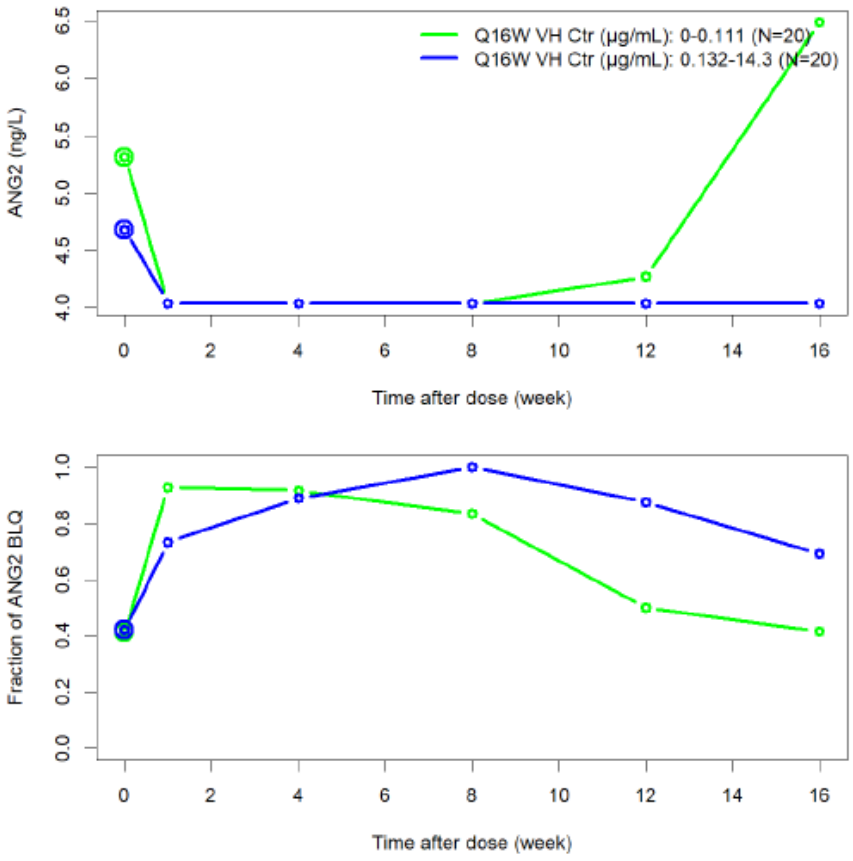
Ang-2

For the Phase III studies, the relationships of free Ang-2 vs time after dose by VH Ctrough,ss (only Q16W regimen shown) and by VH t1/2 are illustrated in Figure 42 and Figure 43, respectively. For the Phase II study, the relationship between Ang-2 vs time after dose by VH Ctrough,ss is illustrated in Figure 44. Overall, the results indicated that groups with higher VH Ctrough,ss and longer VH t1/2 have longer Ang-2 suppression and a higher fraction of BLQ observations.

Figure 42. Median and BQL fractions of free Ang-2 AH concentration over time

Figure 260. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for nAMD Studies GR40306 and GR40844 (Arms A Q16W Group)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 6 mg Q16W dosing. Values below quantification limit LLOQ = 4.04 ng/L were assigned LLOQ.

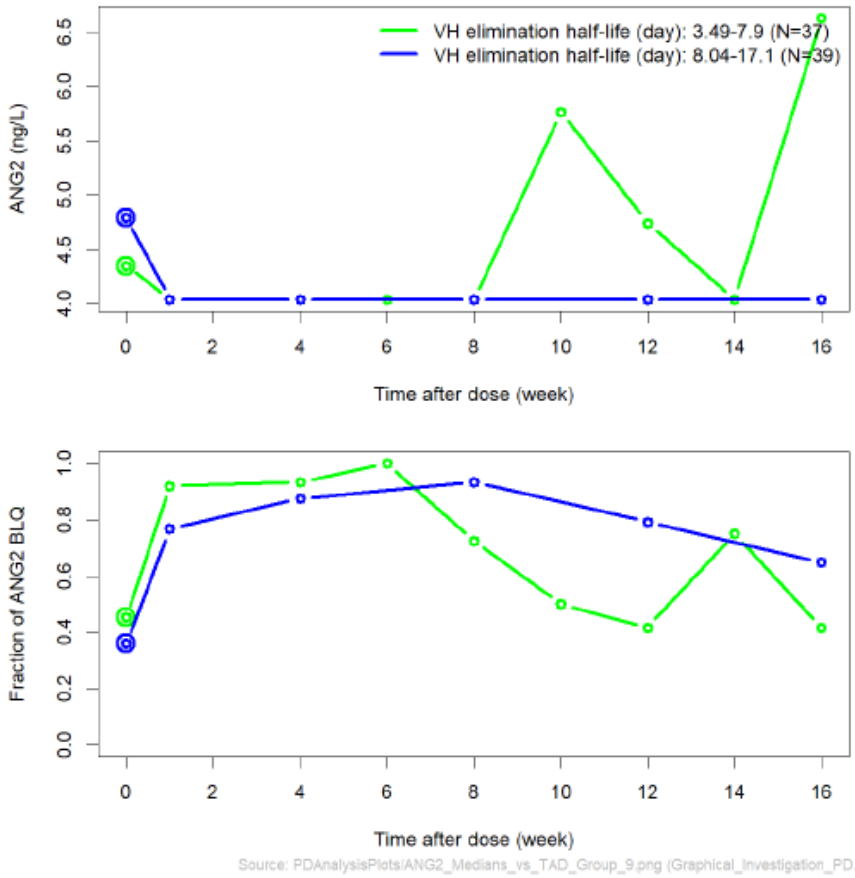


Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_7.png (Graphical_Investigation_PD.R)

Figure 43. Medians and BQL fractions of free ang-2 AH concentrations versus time after dose by VH elimination half-life for nAMD studies.

Figure 264. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH Elimination Half-life for nAMD Studies GR40306 and GR40844 (Arms A)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH elimination half-life. Values below quantification limit LLOQ = 4.04 ng/L were assigned LLOQ.

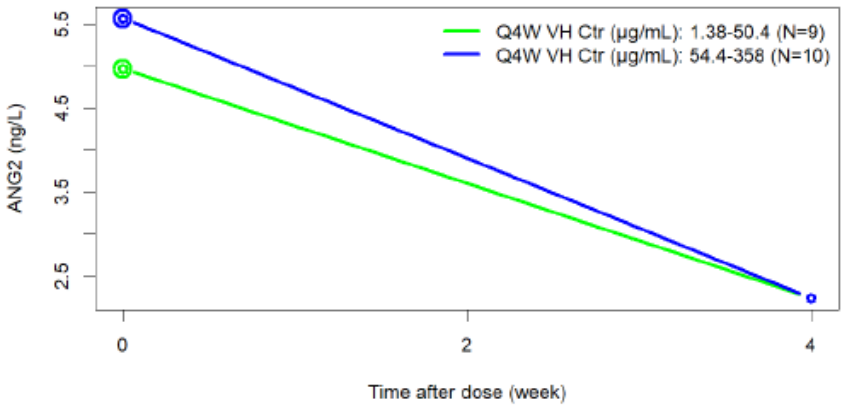


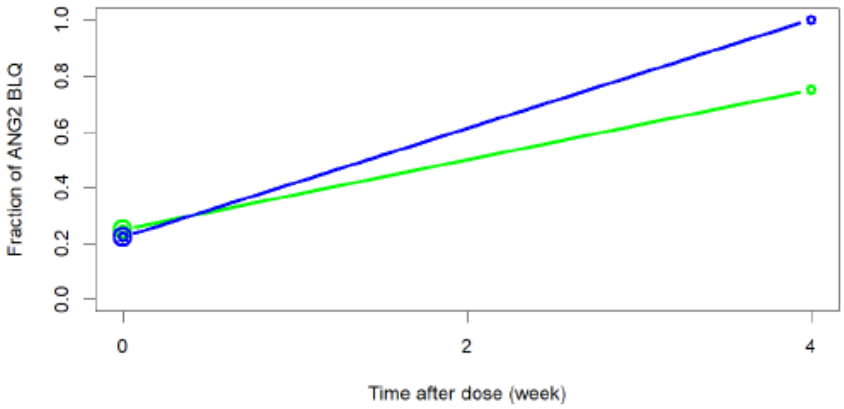
Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_9.png (Graphical_Investigation_PD.R)

Figure 44. Median and BQL fractions of free Ang-2 AH concentrations versus time after dose.

Figure 268. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for nAMD Study BP29647

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 1.5 mg or 6 mg Q4W dosing. Values below quantification limit LLOQ = 2.24 ng/L were assigned LLOQ.





Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_3.png (Graphical_Investigation_PD.R)

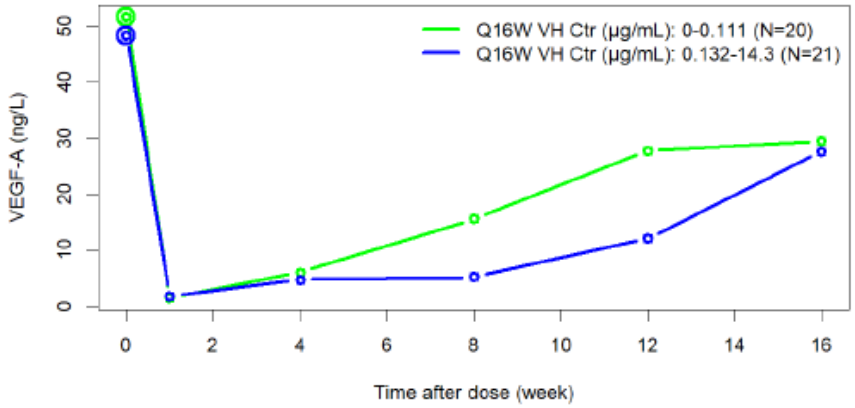
VEGF-A

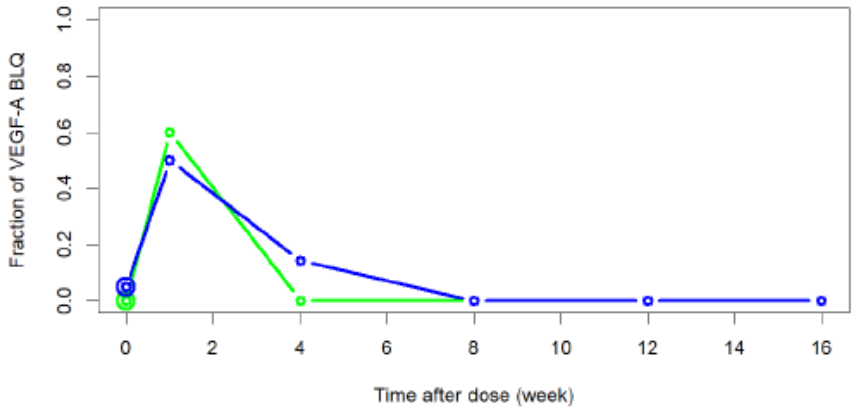
For the Phase III studies, the relationships of free VEGF-A vs time after dose by VH Ctrough,ss (only Q16W regimen shown) and by VH t1/2 are illustrated in Figure 45 and Figure 46, respectively. For the Phase II study, the relationship between VEGF-A vs time after dose by VH Ctrough,ss is illustrated in Figure 47. Overall, the results indicated that groups with higher VH Ctrough,ss and longer VH t1/2 have longer VEGF-A suppression and a higher fraction of BLQ observations.

Figure 45. Medians and BQL fractions of free VEGF-A AH concentration versus time.

Figure 240. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for nAMD Studies GR40306 and GR40844 (Arms A Q16W Group)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 6 mg Q16W dosing. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.



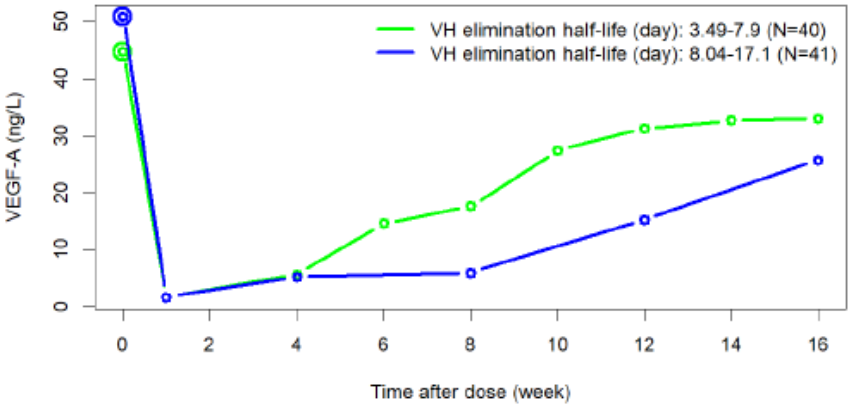


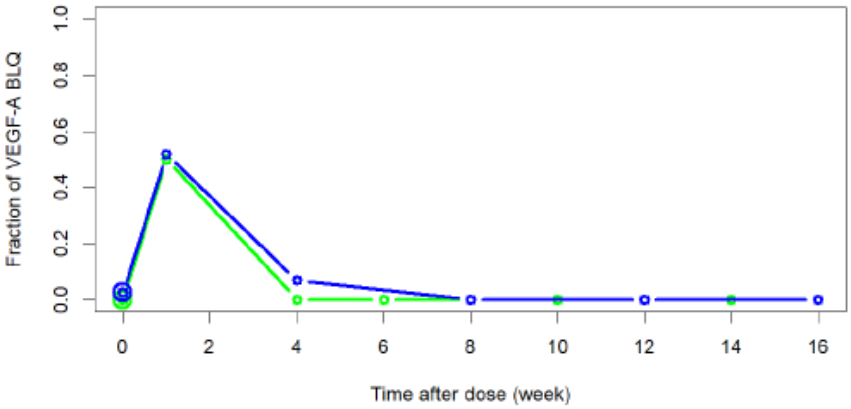
Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_7.png (Graphical_Investigation_PD.R)

Figure 46. Medians and BQL fractions of free VEGF-A concentrations versus time.

Figure 244. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH Elimination Half-life for nAMD Studies GR40306 and GR40844 (Arms A)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH elimination half-life. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.



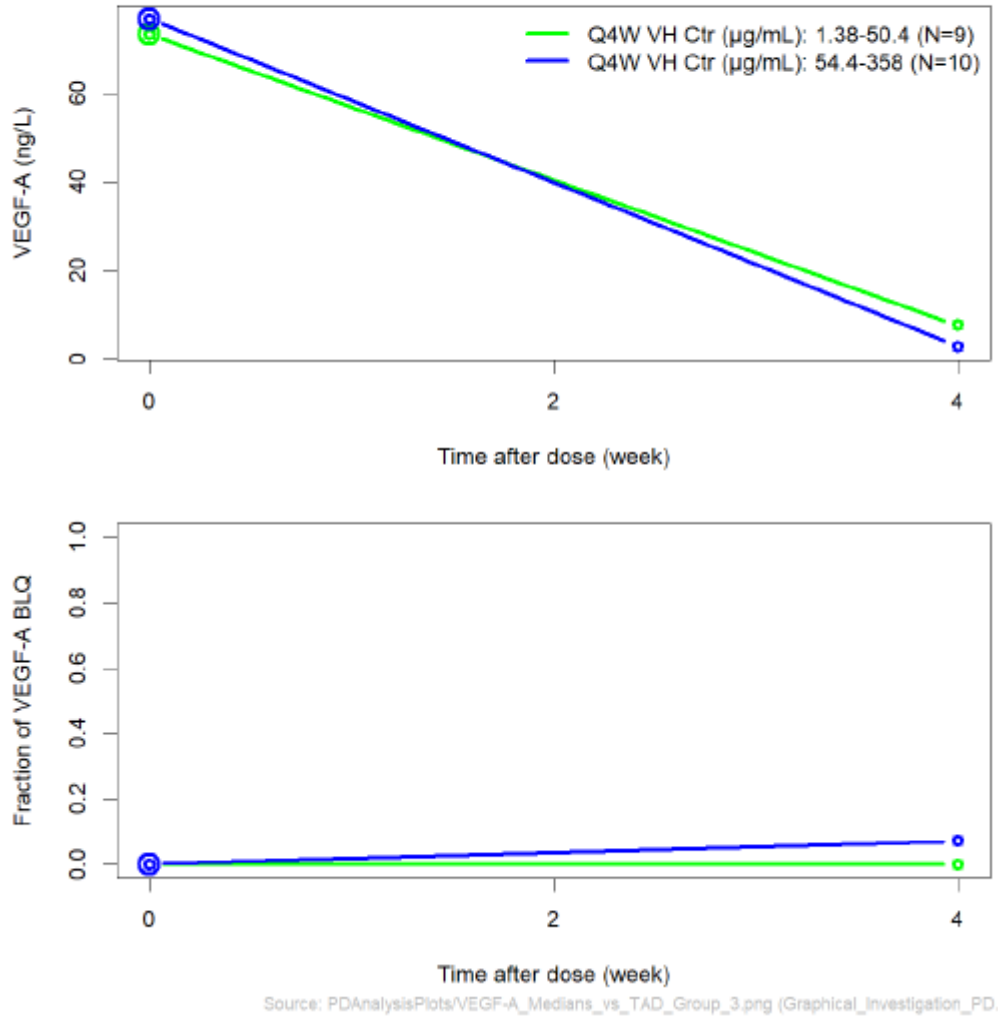


Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_9.png (Graphical_Investigation_PD.R)

Figure 47. Medians and BQL fractions of free VEGF-A AH concentration versus time.

Figure 248. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for nAMD Study BP29647

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 1.5 mg or 6 mg Q4W dosing. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.



Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_3.png (Graphical_Investigation_PD.R)

DME trials

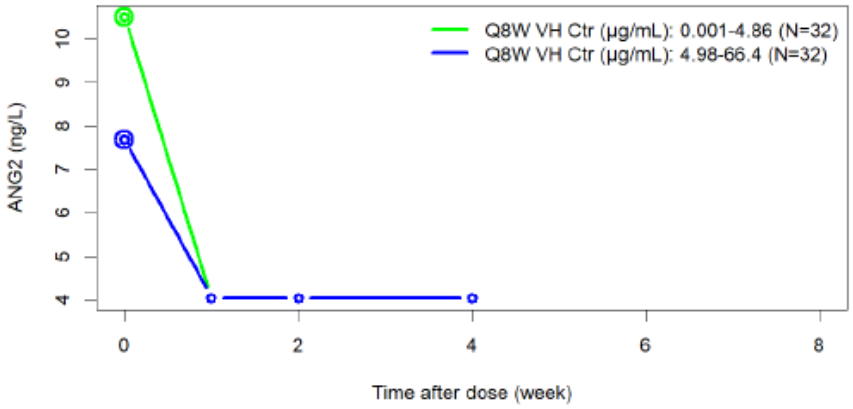
Ang-2

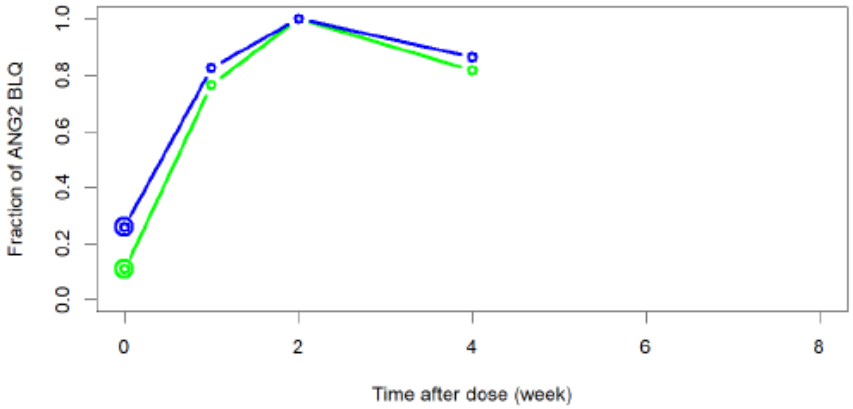
For the Phase III studies, the relationships between Ang-2 vs time after dose by VH Ctrough,ss following Q8W dosing (Arm A) and by VH t1/2 (Arm B, PTI) are illustrated in Figure 48 and Figure 49, respectively. For the Phase II study, the relationship between Ang-2 vs time after dose by VH Ctrough,ss is illustrated in Figure 50. No appreciable differences between patients with high and low VH exposure following 6 mg Q8W dosing were noticeable. In Arm B (PTI), patients with longer VH t1/2 had longer Ang-2 suppression and higher fractions of BLQ observations.

Figure 48. Medians and BQL fractions of free Ang-2 AH concentrations versus time.

Figure 284. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for DME Studies GR40349 and GR40398 (Arms A)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 6 mg Q8W dosing. Patients from Arms A of DME Studies GR40349 and GR40398 studies are included. Values below quantification limit LLOQ = 4.04 ng/L were assigned LLOQ.



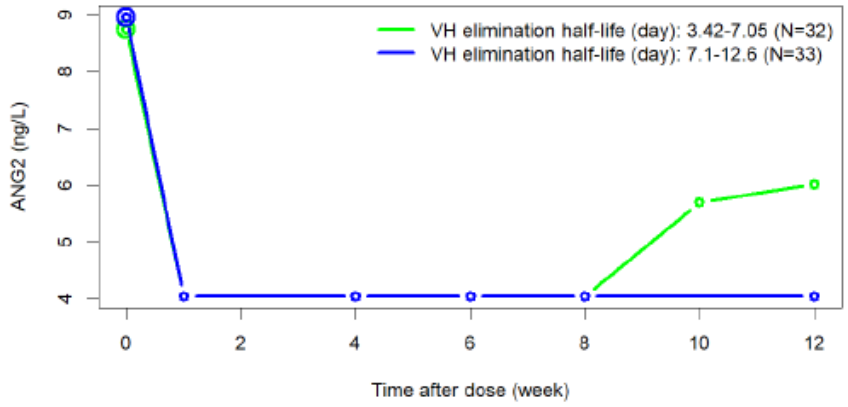


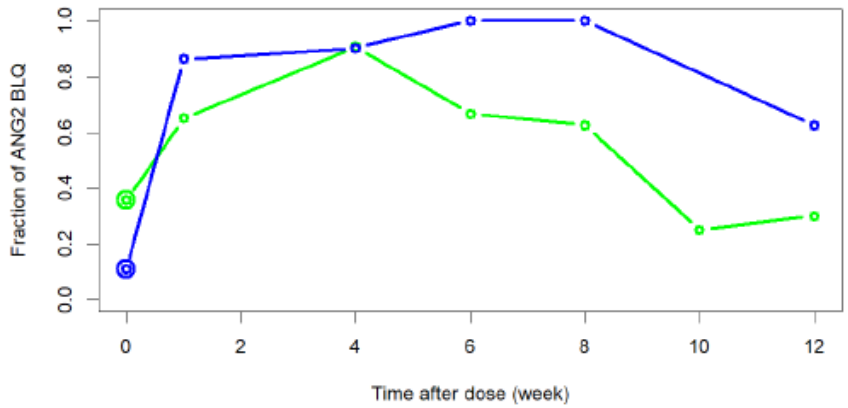
Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_2.png (Graphical_Investigation_PD.R)

Figure 49. Medians and BQL fractions of free Ang-2 AH concentrations versus time.

Figure 288. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH Elimination Half-life for DME Studies GR40349 and GR40398 (Arms B)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of halves of VH elimination half-life. Patients from Arms B of DME Studies GR40349 and GR40398 studies are included. Values below quantification limit LLOQ = 4.04 ng/L were assigned LLOQ.



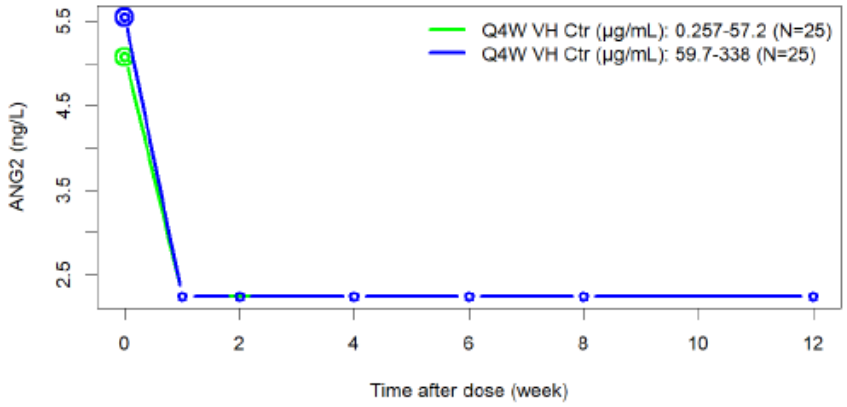


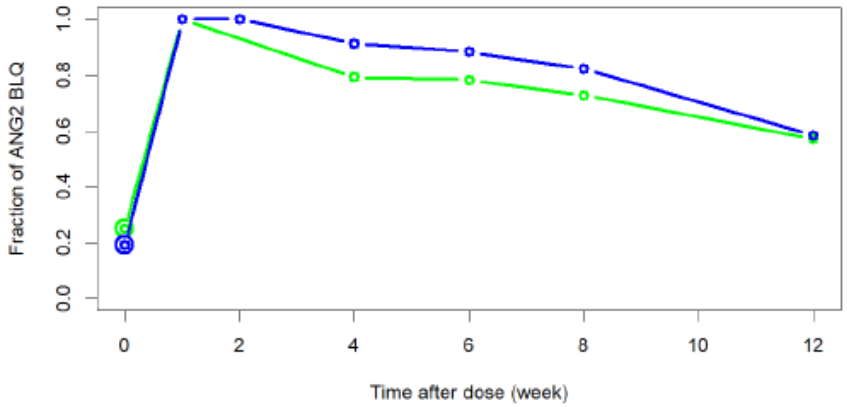
Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_8.png (Graphical_Investigation_PD.R)

Figure 50. Medians and BQL fractions of free Ang-2 AH concentration over time.

Figure 292. Medians and BQL Fractions of Free Ang-2 AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for DME Study BP30099

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 1.5 mg or 6 mg Q4W dosing. Values below quantification limit LLOQ = 2.24 ng/L were assigned LLOQ.





Source: PDAnalysisPlots/ANG2_Medians_vs_TAD_Group_4.png (Graphical_Investigation_PD.R)

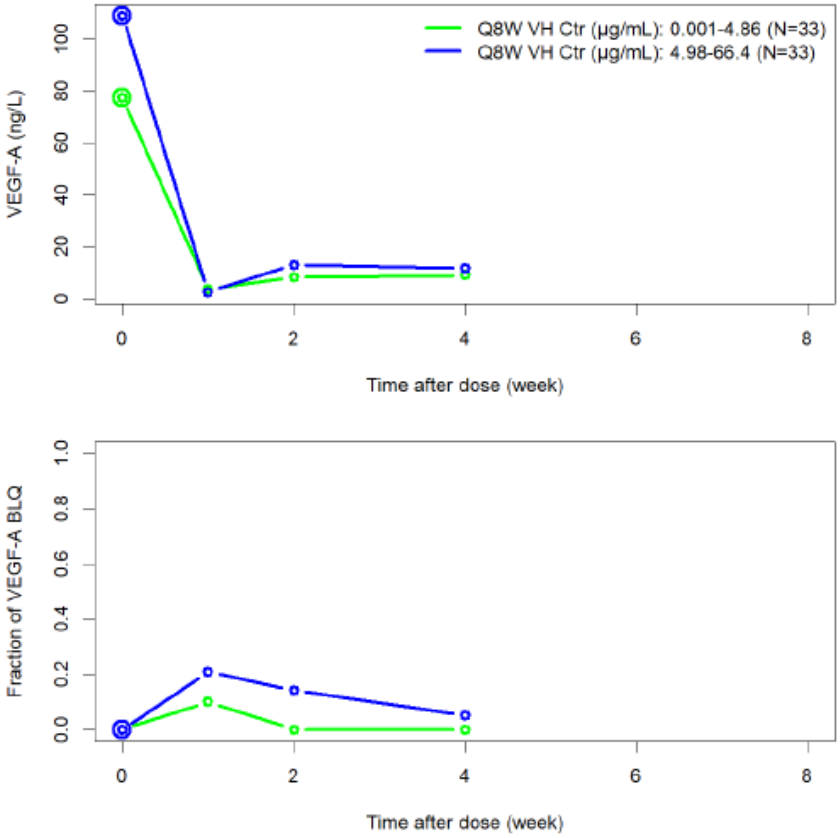
VEGF-A

For the Phase III studies, the relationships between VEGF-A vs time after dose by VH Ctrough,ss following Q8W dosing (Arm A) and by VH t1/2 (Arm B, PTI) are illustrated in Figure 51 and Figure 52, respectively. For the Phase II study, the relationship between VEGF-A vs time after dose by VH Ctrough,ss is illustrated in Figure 53. The results indicate that the groups with higher exposure and longer VH t1/2 tended to have longer VEGF-A suppression and a higher fraction of BLQ observations.

Figure 51. Medians and BQL fractions of Free VEGF-A AH concentrations over time.

Figure 272. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for DME Studies GR40349 and GR40398 (Arms A)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 6 mg Q8W dosing. Patients from Arms A of DME Studies GR40349 and GR40398 studies are included. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.

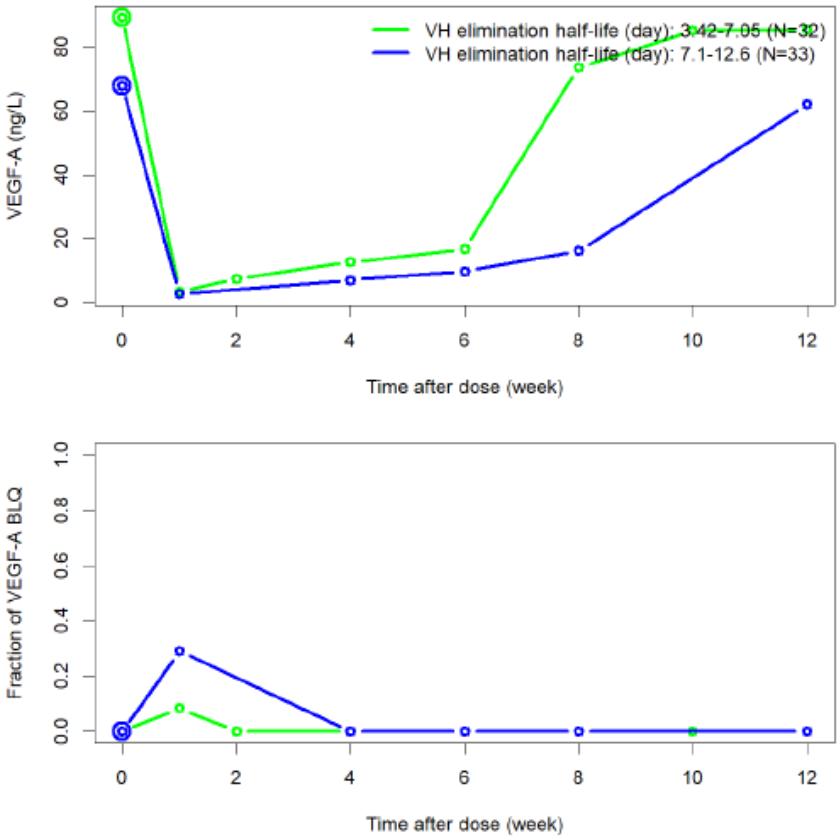


Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_2.png (Graphical_Investigation_PD.R)

Figure 52. Medians and BQL fractions of free VEGF-A AH concentrations over time.

Figure 276. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH Elimination Half-life for DME Studies GR40349 and GR40398 (Arms B)

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of halves of VH elimination half-life. Patients from Arms B of DME Studies GR40349 and GR40398 studies are included. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.

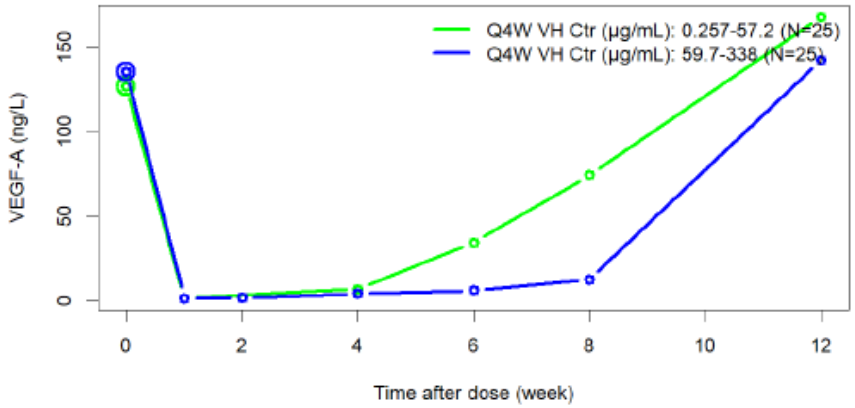


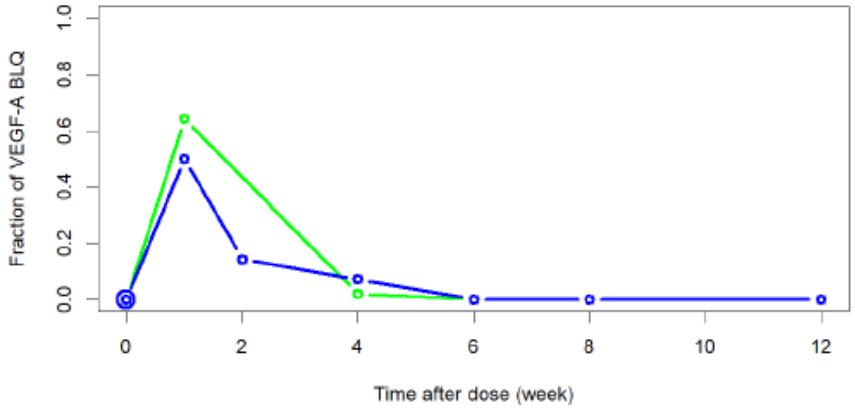
Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_8.png (Graphical_Investigation_PD.R)

Figure 53. Medians and BQL fractions of free VEGF-A AH concentrations over time.

Figure 280. Medians and BQL Fractions of Free VEGF-A AH Concentrations versus Time after Dose by VH $C_{trough,ss}$ for DME Study BP30099

The medians of individual values (**top**) and fraction of BLQ observations (**bottom**) are plotted versus time after dose by halves of VH $C_{trough,ss}$ following 1.5 mg or 6 mg Q4W dosing. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.





Source: PDAnalysisPlots/VEGF-A_Medians_vs_TAD_Group_4.png (Graphical_Investigation_PD.R)

Exposure-safety analyses

The analyses of exposure-safety relationships were performed by indication, using the data of patients receiving faricimab in Phase III studies. As the onset of the safety events (intraocular inflammation, IOI) occurred mostly during the initial Q4W dosing period, the VH Ctrough,ss following 6 mg Q4W dosing regimen was used as a metric of exposure. The individual PK parameters from the final population PK model were used to predict individual VH Ctrough,ss. In addition, log(VH Ctrough,ss), VH elimination rate constant (kVH), and VH t1/2 were used as potential predictors of response. IOI was defined as binary 0/1 variable, irrespectively of the severity of the event or the number of occurrences.

nAMD trials

Table 26 shows incidence rates of IOI by tertiles of VH Ctrough,ss. The logistic regression models for VH Ctrough,ss, log(Ctrough,ss), kVH, and t1/2,kVH indicated that the probability of IOI did not increase with faricimab exposure.

Table 26. Fraction of Patients with Intra-Ocular Inflammation, by $C_{trough,ss}$ (Phase III nAMD Studies)

$C_{trough,ss}$ is predicted VH steady-state C_{trough} for 6 mg Q4W dosing regimen

VH $C_{trough,ss}$		Number of		Percent of Patients with Events (%)
Exposure Group	Range (µg/mL)	Patients	Events	
Low	3.32-82.2	210	9	4.3
Mid	82.2-174	209	1	0.5
High	174-632	209	2	1.0
Total	**3.32-632**	**628**	**12**	**1.9**

Source file: nAMD_summaryTableDAW20_IOI_by_VCONC_Q4W.csv (Graphical_Investigation_nAMD.R)

DME Trials

Table 19 shows incidence rates of IOI by tertiles of VH Ctrough,ss. The logistic regression models for Ctrough,ss, log(Ctrough,ss), kVH, and t1/2,kVH indicated that the probability of IOI did not increase at higher exposures.

Table 19.

Table 27. Fraction of Patients with Intra-Ocular Inflammation, by $C_{trough,ss}$ (Phase III DME Studies)

$C_{trough,ss}$ is predicted VH steady-state C_{trough} for 6 mg Q4W dosing regimen

VH $C_{trough,ss}$		Number of		Percent of Patients with Events (%)
Exposure Group	Range (µg/mL)	Patients	Events	
Low	1.27-57.3	407	11	2.7
Mid	57.3-130	407	5	1.2
High	130-597	407	2	0.5
Total	**1.27-597**	**1221**	**18**	**1.5**

Source file: DME_summaryTableDAW16_IOI_by_VCONC_Q4W.csv (Graphical_Investigation_DME.R)

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Faricimab, Ang-2, VEGF-A, ranibizumab, and aflibercept (as active comparators) concentrations were measured in aqueous humor and plasma, and anti-drug antibodies (ADAs) against faricimab in plasma samples. All available Phase III samples and faricimab and ADA Phase II and Phase I samples were analyzed using fully validated assays. The ADA assay strategy used a three-tiered approach.

Generally, both the pre-study and in-study validations were appropriate and well documented. The concentration ranges were appropriate for the clinical trials. The methods were demonstrated to be precise and accurate for the analysis of human samples. The assays were carried out within the validated long-term stability period.

In the case of the aflibercept assays in Phase II and Phase III studies many plasma and aqueous humor samples were analyzed significantly outside the validated stability.

Population PK analysis of faricimab (RO6867461)

The population PK analysis of faricimab was based on aqueous humour (AH) and plasma concentrations collected from patients with nAMD and DME in two Phase I, three Phase II, and four Phase III studies. The methods used for model development and evaluation are acceptable. Data exclusions were well documented and are acceptable. Post-dose BLQ observations were appropriately handled using the M3 method.

Over the dosage range tested, a 3-compartment linear model, composed of the vitreous humour (VH) compartment, where the drug is injected, the AH compartment, and the plasma compartment adequately described faricimab concentration-time profiles. The VH volume was fixed to the literature value of 4.5 mL, which is considered acceptable.

All final model parameters were estimated with adequate precision. There was high shrinkage (~50-60%) of plasma CL and Vc as well as the AH elimination rate constant (K_{AH}). However, the reliability of AH and systemic faricimab PK parameters, as reported in the SmPC, were adequately justified by the applicant. Importantly, shrinkage of K_{VH} was low (5%). As such, predicted VH exposure and VH elimination half-life, which were used as predictors in the PK-PD analyses, can be considered reliable.

The goodness-of-fit diagnostic plots indicated that the final model described the observed data adequately. The visual predictive checks showed that the final model captured both the central tendency and the interindividual variability of faricimab PK in AH and plasma reasonably well. However, the model does show deviations at the later time points, starting from around day 50. The Applicant acknowledged these shortcomings and argued that this is mainly due to the increasing number of BLQ-values in the dataset. This can be followed. Nevertheless, respective simulations for later timepoints have to be interpreted with care.

The covariates found to influence faricimab ocular PK parameters were age, formulation, and presence of ADAs, while faricimab systemic PK parameters were influenced by sex, body weight, and formulation. However, the effects of these covariates were considered not clinically meaningful (see Section 2.1.9 [Special Populations] for further discussion of the impact of relevant covariates). No other covariates (including race, patient disease characteristics at baseline, prior medication or treatment, fellow eye treatment, concomitant administration of drugs lowering IOP, hepatic or renal impairment) affected the faricimab PK parameters.

Absorption

- **Bioavailability**

Phase 1 studies

In Study BP289936, following SAD and MAD dosing administered intravitreally to patients with nAMD, faricimab apparent t1/2 in AH ranged from 6-13 days, which is similar to the range of mean apparent t1/2 in plasma (6-15 days) and consistent with flip-flop kinetics. Faricimab concentrations in plasma were >100-fold lower than those in AH. Plasma faricimab exposure increased approximately dose-proportionally up to 3 mg faricimab. No plasma accumulation was observed following Q4W administration, which is consistent with the apparent t1/2.

In Study JP39844, following Q4W faricimab intravitreal administration at a dose of 1.5 or 6 mg for 3 doses to Japanese patients with nAMD or DME, faricimab systemic exposure was generally within the range of the data in non-Japanese patients, with higher plasma concentrations following administration of 6 mg compared with 1.5 mg. Plasma faricimab t1/2 was similar at both dose levels with values ranging from 6-10 days. No plasma accumulation was observed following Q4W administration, consistent with faricimab t1/2.

Phase II studies

In Study CR39521 (STAIRWAY) in patients with nAMD, faricimab concentrations in plasma were >580-fold lower than in AH.

In Study BP29647 (AVENUE) in patients with nAMD, faricimab exposure in both AH and plasma was dose linear. Compared with AH, faricimab plasma concentrations were >400-fold lower. No plasma accumulation was observed following Q4W administration.

In Study BP30099 (BOULEVARD) in patients with DME, faricimab concentrations in AH were around 3 times higher following administration of 6 mg compared to 1.5 mg, and at both dose levels, concentrations declined in parallel for both doses following administration of the last administration. Faricimab plasma concentrations were >580-fold lower compared to AH, and were approximately 2-4 times higher following administration of 6 mg compared to 1.5 mg.

- **Bioequivalence**

A formal bioequivalence study between the formulations used in the clinical trials was not conducted. This is considered acceptable since the to-be-marketed formulation was used in the pivotal Phase III studies.

Based on the population PK analysis, there was no difference in faricimab vitreous exposure between formulations. As such, a formulation effect on efficacy or safety would not be expected. It is agreed that the predicted difference in faricimab systemic exposure between the different formulations is unlikely to be of clinically relevance.

Distribution and elimination

The distribution of faricimab in the plasma is limited. The popPK estimate of apparent volume of distribution was 1.48 L.

As expected, faricimab plasma clearance is higher than typical for monoclonal antibodies, which is consistent with the effect of the abolished binding of faricimab to the FcRn receptor. Slow elimination from the VH dominates faricimab kinetics. The elimination rate from the plasma compartment is around 17 times faster than the VH elimination rate.

Dose proportionality and time dependency

Overall, faricimab exhibits approximately dose-proportional increases in exposure. Consistent with the PK and frequency of administration, there is minimal ocular or systemic accumulation of faricimab.

Intra- and inter-individual variability

Intra-individual variability was not assessed. High inter-individual variability was observed in both AH and plasma faricimab exposure in the pivotal Phase III studies in nAMD and DME patients.

Pharmacokinetics in target population

The AH and plasma PK of faricimab in the pivotal Phase III studies in patients with nAMD (TENAYA and LUCERNE) were similar and consistent with Phase II studies. In both studies, high inter-patient variability was observed in faricimab AH and plasma concentrations. Mean faricimab concentrations in plasma were approximately 450-fold and 560-fold lower than in AH in TENAYA and LUCERNE, respectively.

The AH and plasma PK of faricimab in the pivotal Phase III studies in patients with DME (YOSEMITE and RHINE) were similar and consistent with Phase III studies in patients with nAMD. In both studies, high inter-patient variability was observed in faricimab AH and plasma concentrations. Mean faricimab concentrations in plasma were approximately 480-700-fold and 530-700-fold lower than AH concentrations in YOSEMITE and RHINE, respectively.

The relationship between individual VH elimination rate estimates (K_{VH}) from the population PK model and dosing frequency of faricimab in the Phase III studies suggested that patients with slower K_{VH} and, hence, longer VH elimination half-life (longer retention of the drug in the VH) may need less frequent dosing. However, there was considerable overlap between the different dosing regimens. As such, variability in faricimab PK alone does not appear to fully explain the variability in response to faricimab treatment.

Immunogenicity

In the Phase I studies BP28936 and Study JP39844, no patients were ADA-positive at any time during either study.

In the three Phase II studies STAIRWAY, AVENUE and BOULEVARD, the incidence of treatment-induced or treatment boosted ADA was relatively low (10.9%, 11.3% and 7.3%, respectively). In each of the studies, there was no apparent effect of ADA response on PK, safety or efficacy outcomes. However, this is based on a limited number of ADA-positive patients in each study.

Consistent with Phase II studies, the incidence of faricimab ADAs was relatively low in the pivotal Phase III studies in patients with nAMD, TENAYA and LUCERNE; 8.8% and 11.9% of patients had treatment-emergent ADA respectively. No apparent influence of ADA on systemic exposure, overall safety or efficacy was observed based on the available data, acknowledging the limitation in the assessment due to the low number of ADA-positive patients.

Also consistent with other studies, the incidence of faricimab ADAs was relatively low in the pivotal Phase III studies in patients with DME, YOSEMITE and RHINE; 10.0% and 6.9%, respectively. In each study, there was no apparent influence of ADAs on systemic exposure, overall safety or efficacy. However, this observation was based on a low number of ADA-positive patients.

Special populations

Renal and hepatic impairment

Given that faricimab is eliminated by proteolytic catabolism, the lack of specific studies in patients with renal or hepatic impairment is acceptable. It is agreed that no dose adjustment of faricimab is warranted in patients with renal or hepatic impairment.

Gender

Plasma clearance of faricimab was slightly slower in females (~14%) compared to males. However, it is agreed that this difference is unlikely to be clinically relevant and, therefore, a dose adjustment of faricimab in terms of sex is not warranted.

Race

Race was not identified as a clinically relevant covariate in the population PK analysis. It is agreed that no dosage adjustment of faricimab is warranted in terms of race.

Weight

As with the majority of monoclonal antibodies, plasma clearance and volume of faricimab increased with increasing body. In DME patients, who are typically heavier than nAMD patients, the systemic faricimab exposure was ~10% lower compared to nAMD patients. It is agreed that this difference is unlikely to be clinically relevant and, therefore, a dose adjustment in terms of weight is not warranted.

Elderly patients

Age was identified as a significant covariate affecting the elimination rate from the VH, with VH half-life increasing with age. The VH half-life in a typical 44 year old patient had a VH half-life ~31% shorter than a typical 89 year of old patient. However, the age-related difference in the duration of faricimab VH exposure is not considered to be clinically relevant given the flat exposure relationship with BCVA. Therefore, it is agreed that a dose adjustment in elderly patients is not warranted.

Interactions

Since faricimab is a monoclonal antibody, the lack of formal drug-drug interaction studies is acceptable.

Pharmacodynamics

Primary pharmacology

Phase 1 studies

In Study BP289936, whilst limited by the small sample size, the data suggest inhibition of Ang-2 and VEGF-A in AH following faricimab administration in nAMD patients. Faricimab administration resulted in a minor increase in plasma Ang-2 at Week 1, with no changes seen in plasma VEGF-A. Improvement in BCVA was observed at all dose levels in the SAD part, but only for the 6 mg dose in the MAD part. Decrease in CST was observed with a larger decrease observed for the 6 mg dose in the MAD part.

Phase II studies

In Study CR39521 (STAIRWAY) in patients with nAMD, exploratory PD assessments of AH samples from a subset of patients demonstrated suppression of Ang-2 and VEGA-A treated with faricimab including up to 8 weeks post-dose. However, there was a high level of non-quantifiable Ang-2 levels at baseline, limiting the interpretation of Ang-2 suppression data.

In Study BP30099 (BOULEVARD) in patients with DME, Ang-2 and VEGF-A suppression was observed in AH with 1.5 mg and 6 mg Q4W regimens and remained below baseline for 8-12 weeks after the last administration of 6 mg. No apparent changes in the Ang-2 and VEGF-A plasma profiles were observed at the 1.5 or 6 mg dose levels.

Phase III studies

The PD of faricimab in both pivotal Phase III studies in patients with nAMD (TENAYA and LUCERNE) were similar. High inter-patient variability was observed in free Ang-2 and free VEGF-A AH and plasma concentrations. Suppression of Ang-2 and VEGF-A in AH was observed from Day 7 onwards in the faricimab treatment arms, which supports the proposed mechanism of action of faricimab. Suppression was maintained at least up to Week 20 after which patients were assigned to a regimen based on disease activity. Free VEGF-A and Ang-2 levels increased as the sampling time from most recent dose increased. No systemic target inhibition was observed.

The PD of faricimab in both pivotal Phase III studies in patients with DME (YOSEMITE and RHINE) were similar and consistent with the results of the Phase III studies in patients with nAMD. High inter-patient variability was observed in Ang-2 and VEGF-A concentrations. Suppression of free Ang-2 and free VEGF-A in AH was generally observed from day 7 onwards in faricimab treatment arms and free target concentrations remained below the average baseline at later visits. In the plasma, no change in the free Ang-2 and VEGF-A levels was observed after administration of Faricimab. This is in line with the low Faricimab levels observed in plasma.

Secondary pharmacology

No formal QTc study was performed with faricimab. This is acceptable since mAbs have a low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed. Please see the Safety section of this report for discussion of ECG data from the clinical trials.

Pharmacodynamic interactions

Pharmacodynamic interactions were not discussed by the Applicant. This is not unusual in clinical developments of monoclonal antibodies and is based on the argument that they are specific for their

ligand(s) and unbound molecules are rapidly degraded into pharmacologically inactive peptides and amino acids.

Exposure-efficacy analyses

In patients with nAMD, the analyses suggested comparable increases in BCVA across the range of predictors. Similar results were observed in terms of decreases in CST. This supports the dosing algorithm used in the clinical trials since patients seem to have been appropriately allocated to the regimen that would likely lead to an optimal response.

Results of the logistic regression analyses suggested that patients with longer VH t1/2 need less frequent dosing. This is as expected since patients with higher VH t1/2 will retain the drug longer in vitreous (the site of action). However, PK variability alone cannot fully explain the variability observed in response to treatment given the observed overlap in the distribution of VH t1/2 values between the different dosing regimens.

The final logistic regression model suggested that, in addition of the VH t1/2, size of PEDT and the presence of ADA influence the dosing regimen. The larger the size of PEDT (more severe disease) the higher the probability of Q8W regimen, whilst ADA-positive patients had a lower likelihood of Q8W dosing. However, the difference in probability between the two groups for the Q8W regimen was 3.7%, which is not considered to be of clinical relevance.

Consistent with patients with nAMD, the analyses in DME patients suggested comparable increases in BCVA and comparable decreases in CST across the range of predictors. This supports the dosing algorithm used in the PTI treatment arm since patients seem to have been appropriately allocated to the regimen that would likely lead to an optimal response. This was also evidenced in the Q8W treatment arm by the flat relationship between faricimab exposure and the clinical endpoints. Also consistent with nAMD patients, the results suggested that patients with longer VH t1/2 need less frequent dosing.

The probability of receiving different dosing regimens (Q4W, Q4W or Q8W, Q4W or Q8W or Q12W) was modelled using logistic regression and the VH t1/2. In addition to VH t1/2, the probability of receiving the Q4W regimen was influenced by the size of CST; the larger the size of CST the higher the probability of Q4W regimen. NAIVE patients had a lower probability to be in the Q4W or Q8W regimen compared to previously treated patients. The probability to be in the Q16W regimen was influenced by the size CST and cataract surgery; the smaller the size of CST and not having cataract surgery increased the probability of needing the Q16W regimen. However, the trials were not powered for assessment of such subsets within the PTI study and should only be considered as exploratory. The probability of less frequent dosing will likely be a multifactorial function of several patient-specific and disease-specific factors but also of previous treatments received. Therefore, additional data is required to prove or disprove the relationships between these patient characteristics and the durability of treatment effect.

The probability of disease activity at Week 16 declined with increasing faricimab exposure (from 17.2% among patients in the lower exposure tertile to 12.5% among patients in the upper exposure tertile). However, the relationship was shallow.

Graphical analysis of exposure-PD relationships

In patients with nAMD, observed concentrations of free Ang-2 in AH declined from the median value of around 5 ng/L to undetectable levels shortly after faricimab administration and then increased when faricimab VH concentrations decayed. In the lower exposure groups, they returned to baseline level by week 16 post-dose. In patients with higher exposure, Ang-2 levels remained lower than the baseline

level by week 16 post-dose. Patients with higher VH exposure and longer VH t1/2 had longer Ang-2 suppression.

Observed concentrations of free VEGF-A in AH declined from the median value of around 50 ng/L to nearly undetectable levels shortly after faricimab administration and rebounded when faricimab VH concentrations decayed. By week 16 post-dose, VEGF-A levels remained about half of baseline values. Patients with higher VH exposure and longer VH t1/2 had longer VEGF-A suppression.

The group of patients with longer half-life had their median VEGF-A level increasing to ~20 pg/ml at around 12 weeks post dose. This means that, if the dosing regimens were based on VEGF suppression time, then at most only 50% of the patients would reach the Q12W regimen, which is a much lower percentage than what was observed in the Phase III nAMD trials. This suggests that VEGF-A inhibition alone cannot explain the observed response to faricimab treatment.

In patients with DME, observed concentrations of free Ang-2 in AH declined from the median value of around 10 ng/L to undetectable levels shortly after faricimab administration and remained below quantification limit during Q8W dosing. No appreciable differences between patients with high and low VH exposure following 6 mg Q8W dosing were noticeable. This is explained by the fact that the Q8W regimen maintains the target maximally suppressed in all patients during the dosing interval and, therefore, no exposure-response is apparent. Among patients administered PTI dosing, patients with higher VH t1/2 had longer Ang-2 suppression.

Observed concentrations of free VEGF-A in AH declined from the median value of around 100 ng/L to nearly undetectable levels shortly after faricimab administration and rebounded when faricimab concentrations decayed. By Week 4 post-dose, VEGF-A levels remained about 10 times lower than at baseline. By Week 12 post-dose, VEGF-A levels returned to baseline values. Patients with higher VH exposure and longer VH elimination half-life had longer VEGF-A suppression. The group of patients with longer half-life had their median VEGF-A level increasing to ~60 pg/ml at around 12 weeks post dose. This means that, if the dosing regimens were based on VEGF suppression time, then at most only 50% of the patients would reach a Q12W regimen, which is a much lower percentage than what was observed in the Phase III DME trials. This suggests that VEGF-A inhibition alone cannot explain the observed response to faricimab treatment.

Overall, the results of the graphical analyses for Ang-2 and VEGF-A suggest a strong correlation between the lengths of time these biomarkers are suppressed and dosing regimens in both nAMD and DME patients.

Exposure-safety analyses

Overall, the analyses of exposure-safety relationships for nAMD and DME populations indicated that the total number of IOI events was low and the probability of IOI did not increase at higher vitreous faricimab exposures.

It is noted that a higher incidence of IOI was observed in ADA-positive compared with ADA-negative patients. However, the applicant does not consider this observation to be clinically relevant. Please see Safety section for further discussion.

2.4.4. Conclusions on clinical pharmacology

After considering the submissions from the Applicant – including responses to questions raised by the CHMP – the product is approvable from a clinical pharmacology point of view.

2.4.5. Clinical efficacy

The Applicant has sought the following indications for faricimab:

- treatment of adult patients with neovascular (wet) age-related macular degeneration
- treatment of adult patients with visual impairment due to diabetic macular oedema.

In support of the age-related macular degeneration indication, the Applicant has submitted two phase II studies AVENUE (BP29647) and STAIRWAY (CR39521), and two phase III studies TENAYA (GR40306) and LUCERNE (GR40844) which are similar studies.

For the diabetic macular oedema indication the Applicant has submitted one phase II study BOULEVARD (BP30099) and two phase III studies RHINE (GR40398) and YOSEMITE (GR40349) which are also similar studies.

The Applicant has confirmed that all studies were conducted under GCP conditions. However, during the compilation of this application, the Sponsor identified two breaches of GCP in the Phase III studies: 1) potential unmasking of 3 patients due to an internal software update to the safety database and 2) unconsented optional plasma samples or optional aqueous humor samples were collected from a total of 235 patients (TENAYA: 52, LUCERNE: 23, YOSEMITE: 69, and RHINE: 91). Internal audits by the Sponsor did not identify any critical findings for the phase III studies.

For the Phase II studies (STAIRWAY, AVENUE, and BOULEVARD), critical audit findings of non-compliance with GCP were identified at one site, and appropriate corrective and preventive actions were implemented.

Table 1 Summary of nAMD Studies Contributing to Efficacy Evaluation

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Pivotal Studies							
TENAYA (GR40306) **LUCERNE** (GR40844)	Global	A Phase III, Multicenter, Randomized, Double–Masked, Active Comparator-Controlled, 112-week Study	Treatment-naive patients with nAMD	Efficacy, Safety, PK and PD	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to Week 108 Patients will return for a final visit at Week 112.	**Total Randomized** =1329 **Intent-to-Treat (ITT)** TENAYA=671 LUCERNE=658 **Pooled** Pooled ITT =1329 Faricimab=665 Aflibercept=664	Ongoing Primary analysis at Week 40/44/48 [a] CCOD: TENAYA: 26 October 2020 LUCERNE: 5 October 2020 Analysis at Week 60 CCOD: TENAYA: 19 January 2021 LUCERNE: 28 December 2020
Supportive Studies							
STAIRWAY (CR39521)	U.S.	Phase II, Multiple Regimen, Randomized, Active Comparator-Controlled, Subject and Assessor Masked, Three Parallel Groups, 52–week Study	Treatment naive patients with nAMD	Efficacy, Safety, PK	• Faricimab Q12W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q12W up to Week 48 • Faricimab Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q16W up to Week 48. Patients assessed with active disease at Week 24 were switched to a Q12W regimen for the remainder of the study. • Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 48 weeks	**Total Randomized** =76	Completed

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	• Dose, Duration	No. of Patients	Study Status
Supportive Studies (cont.)							
AVENUE (BP29647)	U.S.	Phase II, Multiple Center, Multiple Dose and Regimen, Randomized, Active Comparator-Controlled, Double-Masked, Five Parallel Groups, 36-week study	Treatment-naive patients with nAMD	Safety, Tolerability, PK, Efficacy	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q8W (i.e., on Weeks 20 and 28) • 0.5 mg Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 32 weeks • 0.5 mg Ranibizumab Q4W + 6 mg Faricimab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W up to Week 8, followed by 6 mg faricimab intravitreal injections Q4W to Week 32	**Total Randomized** =273	Completed

CCOD=clinical cutoff date; IVT=intravitreal; nAMD=neovascular age-related macular degeneration; PD=pharmacodynamics; PK=pharmacokinetics; PTI=personalize treatment interval; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks

[a] The primary endpoint, change from baseline in BCVA, was averaged over Weeks 40, 44, and 48 (represented by 'Week 40/44/48').

5.3.5 Efficacy and Safety Studies (DME)								
YOSEMITE (GR40349) **RHINE** (GR40398)	5.3.5.1 Primary CSR Report 1102956, Synopsis Primary CSR Report 1102956 Primary CSR Report 1102957, Synopsis Primary CSR Report 1102957	Efficacy, Safety, PK and PD	Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, Three Parallel Groups, 100-week Study	• Faricimab Q8W: 6 mg intravitreal faricimab injections Q4W to Week 20 followed by Q8W to Week 96 • Faricimab PTI [b]: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96	**Total Randomized**=1891 1482 – treatment-naive 409 – previously treated with anti-VEGF **Intent-to-Treat** YOSEMITE – 940 Faricimab Q8W = 315 Faricimab PTI = 313 Aflibercept Q8W =312 RHINE – 951 Faricimab Q8W = 317 Faricimab PTI = 319 Aflibercept Q8W =315	Patients with DME	56 weeks for the primary analysis and 96 weeks for the study	Ongoing / Full Reports
BOULEVARD (BP30099)	5.3.5.1 Primary CSR Report 1083913, p. 21 Primary CSR Report 1083913	Safety, Tolerability, PK, Efficacy	Phase II, Multiple Center, Multiple Dose, Randomized, Active Comparator-Controlled, Double-Masked, Three Parallel Groups, 36-week Study	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 20 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 20 weeks • 0.3 mg Ranibizumab Q4W: 0.3 mg ranibizumab intravitreal injections Q4W for 20 weeks • Followed by an observational period (up to 16 weeks); if eligible, patients received one injection of 0.3 mg ranibizumab then exited the study	**Total randomized** = 229 168 – treatment-naive 61 – previously treated with anti-VEGF	Patients with DME	20 weeks of treatment with primary analysis at Week 24	Completed / Full Report

DME–diabetic macular edema; ITT–intent to treat; N/A–not applicable; nAMD–neovascular age–related macular degeneration; PD–pharmacodynamic; PK–pharmacokinetic; PTI–personalized treatment interval (up to Q16W adjustable dosing in DME and DR); Q4W–every 4 weeks; Q8W–every 8 weeks; Q12W–every 12 weeks; Q16W–every 16 weeks; VEGF–vascular endothelial growth factor.

a Study JP39844, sponsored by Japanese co-development partner Chugai Pharmaceutical Co., Ltd., enrolled 4 patients with nAMD. and 8 patients with DME.

b Study drug dosing for patients on the PTI is extended, reduced or maintained at study drug dosing visits using 4-week increments to a maximum of every 16 weeks (Q16W) or a minimum of every 4 weeks (Q4W) based on the relative change of the central subfield thickness (CST) and best corrected visual acuity (BCVA) compared with the patient's reference CST and reference BCVA.

Age-related macular degeneration indication

Dose-response studies and main clinical studies

The applicant conducted two double blind randomised active controlled studies with ranibizumab 0.5mg intravitreally as the active control, AVENUE (BP29647) and STAIRWAY (CR39521) that could be construed as dose finding studies.

The primary objective of the phase II AVENUE study was to evaluate the efficacy of RO6867461 compared to ranibizumab monotherapy in treatment-naive and anti-vascular endothelial growth factor (VEGF) incomplete-responder patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). The study duration was up to 40 weeks with a treatment duration of 32 weeks and efficacy evaluation at 36 weeks.

The study was designed to allow the evaluation of RO6867461 in a treatment-naive patient population (comparison of Arms A, B, C, and D) and an anti-VEGF-incomplete-responder patient. The anti-VEGF-incomplete-responder population is defined as a subgroup of patients from Arms A and E (Population C) with a BCVA ≤68 letters at Week 12. Only one eye per patient was chosen as the study eye.

The study evaluated the following treatments: (A) 0.5 mg ranibizumab IVT every 4 weeks for 32 weeks; (B) 1.5mg faricimab administered 4- weekly for 32 weeks; (C) 6 mg faricimab IVT every 4 weeks for 32 weeks; (D) 6 mg faricimab IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg faricimab IVT every 8 weeks; (E) 0.5 mg ranibizumab IVT every 4 weeks up to Week 8 (3 injections), followed by 6 mg faricimab IVT every 4 weeks (6 injections).

The primary efficacy outcome measure in the treatment naive population (Population A; all patients randomized to Arms A, B, C and D) was the mean change in BCVA from baseline to Week 36 using the ETDRS-modified charts.

The primary efficacy outcome measure in the anti-VEGF-incomplete-responder population (Population C; all patients randomized to Arms A and E with a BCVA ≤68 at Week 12) was the mean change in BCVA from Week 12 baseline to Week 36.

Secondary efficacy endpoints included the proportion of patients gaining ≥ 15 letters from baseline in BCVA and mean change from baseline in foveal centre point thickness at Week 36 amongst others.

The primary endpoint of superiority of RO6867461 compared to 0.5 mg ranibizumab Q4W in the mean change of BCVA from baseline at Week 36 using ETDRS modified letter charts was not met. There was no statistically significant difference in BCVA outcomes in any faricimab treatment arm over 0.5 mg ranibizumab Q4W in the population of treatment-naïve patients with CNV secondary to AMD. The 6 mg faricimab Q8W (Arm D) provided numerically similar BCVA results to 6 mg faricimab Q4W (Arm C) dosing. Note the improvement from baseline in BCVA was numerically greater for the 1.5mg dose of faricimab.

Pre-defined incomplete-responder analysis: 0.5 mg ranibizumab Q4W/6 mg faricimab Q4W treatment arm (Arm E) did not demonstrate additional benefit compared to 0.5 mg ranibizumab Q4W arm in the protocol-defined incomplete-responder population (those not achieving 20/40 vision, or vision ≤68 letters, after 3 monthly loading doses of 0.5 mg ranibizumab Q4W), Population C in either BCVA or OCT (CST).

Table 10 BCVA Change from Baseline to Week 36 in the Treatment-naïve Population, Population A (Intent-to-Treat Population)

	0.5 mg Ranibizumab Q4W (N=68)	1.5 mg RO6867461 Q4W (N=46)	6 mg RO6867461 Q4W (N=39)	6 mg RO6867461 Q4W (Wk12)/ Q8W (Wk28) (N=46)
N	64	40	37	44
Observed values (SD)	8.5 (10.8)	10.9 (11.8)	5.9 (15.2)	6.3 (11.6)
LS Mean (80% CI for mean)	7.6 (5.4, 9.8)	9.2 (6.5, 11.8)	6.0 (3.2, 8.8)	6.1 (3.6, 8.6)
Difference vs. ranibizumab (80% CI)	–	1.6 (–1.6, 4.7)	–1.6 (–4.9, 1.7)	–1.5 (–4.6, 1.6)
p-value (vs. ranibizumab)	–	0.5244	0.5308	0.5309

Data sources: t_bcva_cb_mod_LSM_POPA; t_bcva_cb_mod_POPA; t_bcva_cb_POPA.

Least Squares Means from Linear Model Analysis.

BCVA=best corrected visual acuity; CI=confidence interval; LS=least squares; SD=standard deviation.

Table 11 BCVA Change from Week 12 Baseline to Week 36 in the Anti-VEGF-Incomplete-Responders, Population C (Intent-to-Treat Population)

	0.5 mg Ranibizumab Q4W (N=37)	0.5 mg Ranibizumab Q4W (Wk8)/6 mg RO6867461 Q4W (Wk32) (N=38)
N	35	37
Observed values (SD)	2.1 (7.0)	0.6 (6.5)
LS Mean (80% CI for mean)	1.7 (–0.7, 4.1)	0.04 (–2.3, 2.4)
Difference vs. ranibizumab (80% CI)	–	–1.7 (–3.8, 0.4)
p-value (vs. ranibizumab)	–	0.3034

Data sources: t_bcva_cb_mod_LSM_POPC; t_bcva_cb_mod_POPC; t_bcva_cb_POPC.

Least Squares Means from Linear Model Analysis.

BCVA=best corrected visual acuity; CI=confidence interval; LS=least squares; SD=standard deviation.

STAIRWAY

The study was a multicenter, randomized, active comparator-controlled (ranibizumab), subject and outcome-assessor masked, parallel group (three treatment arms), 52-week study in treatment-naïve patients with neovascular age-related macular degeneration (nAMD) conducted in the US.

The **primary efficacy** objective was to evaluate the efficacy of faricimab on visual acuity when administered at 12- and 16- week intervals.

Secondary efficacy objectives included evaluating the efficacy of faricimab on additional visual acuity outcomes, and anatomic outcome measures using spectral domain optical coherence tomography (SD-OCT) and fundus fluorescein angiography (FFA).

The study evaluated the following treatments: (A) 6 mg faricimab every 12 weeks (Q12W arm) (i.e. 6 mg faricimab IVT Q4W up to Week 12, followed by 6 mg faricimab IVT Q12W up to Week 48); (B) 6 mg faricimab every 16 weeks (Q16W arm) (i.e 6 mg faricimab IVT Q4W up to Week 12 (4 injections), followed by 6 mg faricimab IVT Q16W up to Week 48). A protocol-defined assessment of disease activity at Week 24 required Arm B patients with active disease to then receive a Q12W dosing interval of 6 mg faricimab for the remainder of the study. The comparator was ranibizumab 0.5mg IVT 4 weekly for 48 weeks.

The primary efficacy endpoint was mean change from baseline best corrected visual acuity (BCVA) at Week 40 using the Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts.

Secondary efficacy endpoints included the following: mean change from baseline BCVA over time using the ETDRS-like charts, proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters from baseline BCVA over time, Mean change from baseline in mean central subfield thickness CST over time amongst others.

At Week 40, the adjusted mean BCVA change from baseline in the study eye was 9.3, 12.5 and 11.4 letters (ETDRS) in the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, respectively. The difference in adjusted mean change from baseline in BCVA between the 6 mg faricimab Q12W and Q16W dosing arms when compared to the control 0.5 mg ranibizumab Q4W arm at Week 40 was -2.1 (CI -6.8, 2.6) and 1.1 (CI-3.4, 5.5) letters, respectively.

At Week 52, the adjusted mean BCVA change from baseline in the study eye was 10.1, 11.4, and 9.6 letters (ETDRS) for the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, respectively (Table 9). The difference between the 6 mg faricimab Q12W and Q16W dosing arms when compared to the control 0.5 mg ranibizumab Q4W arm, respectively, was 0.5 (CI -4.3, 5.3) and 1.8 (CI -2.7, 6.4) letters at Week 52, respectively.

Table 8 Mean Change from Baseline in BCVA at Week 40 (Randomized Patients)

	Faricimab Q12W (n=24)	Faricimab Q16W (n=31)	Ranibizumab Q4W (n=16)
Patients at Week 40 (n)N	21	28	15
Observed Mean (SD)	9.8 (10.8)	13.1 (11.7)	11.9 (12.8)
LS Mean (CI) [a]	9.3 (6.4, 12.3)	12.5 (9.9, 15.1)	11.4 (7.8, 15.0)
Difference (CI) vs. ranibizumab	−2.1 (−6.8, 2.6)	1.1 (−3.4, 5.5)	—

Data sources: t_ef_obsd_cb_RND_BCVA; t_ef_mm_rm_RND_BCVA_CHG

BCVA=best corrected visual acuity; CI=confidence interval; LS=least squares; SD=standard deviation.

Note: CI = 80% Confidence Interval.

[a] Mean BCVA change from baseline generated using mixed model for repeated measurement (MMRM) model. Model includes categorical covariates of treatment group, visit, and visit by treatment group interaction, and the continuous covariate of baseline BCVA.

At Week 52, 33.3%, 46.4%, and 37.5% of patients gained at least 15 letters in BCVA score from baseline in the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, respectively. The difference between the 6 mg faricimab Q12W and 6 mg faricimab Q16W arms when compared to 0.5 mg ranibizumab Q4W arms in the proportion of patients who gained at least 15 letters from baseline at Week 52 was -4.2% (CI -24.5, 16.2) and 8.9% (CI -10.7, 28.6), respectively.

Table 10 Proportion of Patients Gaining ≥15 letters from Baseline BCVA at Week 52 (Observed Data, Randomized Patients)

	Faricimab Q12W (n=24)	Faricimab Q16W (n=31)	Ranibizumab Q4W (n=16)
Patients at Week 52 (n)	21	28	16
% (CI) of patients	33.3 (20.2, 46.5)	46.4 (34.4, 58.5)	37.5 (22.0, 53.0)
% difference (CI) vs. ranibizumab	–4.2 (–24.5, 16.2)	8.9 (–10.7, 28.6)	—

Data source: t_ef_obsd_pp_RND_BCVA15G

Note: CI = 80% Confidence Interval. 80% CI for response rates and differences in response rates are calculated using the Wald method.

At baseline, the mean CFT assessed on SD-OCT was 290.8 µm, 280.8 µm, 375.6 µm for the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, respectively. On average, CFT values in the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, showed rapid decreases after the first treatment injection with final adjusted mean CFT changes from baseline at Week 52 of -141.0, -135.0, -136.1 µm in the 6 mg faricimab Q12W, 6 mg faricimab Q16W and 0.5 mg ranibizumab Q4W arms, respectively

Table 14 Mean Change from Baseline in Central Foveal Thickness at Week 52 (Linear Model [MMRM], Randomized Patients)

	Faricimab Q12W (n=24)	Faricimab Q16W (n=31)	Ranibizumab Q4W (n=16)
Patients at Week 52 (n)	21	28	16
LS Mean (CI) [a]	–141.0 (–157.1, –124.9)	–135.0 (–149.2, –120.8)	–136.1 (–156.0, –116.2)
Difference (CI) vs. ranibizumab	–4.9 (–30.6, 20.9)	1.1 (–23.6, 25.8)	—

Data sources: t_ef_mm_rm_RND_CFT_CHG

CFT=central foveal thickness; CI=confidence interval; LS=least squares; SD=standard deviation.

Note: CI = 80% Confidence Interval.

[a] Generated using mixed model for repeated measurement (MMRM) model. Model includes categorical covariates of treatment group, visit, and visit by treatment group interaction, and the continuous covariate of baseline CFT.

Table 9 Mean Change from Baseline in BCVA at Week 52 (Randomized Patients)

	Faricimab Q12W (n=24)	Faricimab Q16W (n=31)	Ranibizumab Q4W (n=16)
Patients at Week 52 (n)	21	28	16
Observed Mean (SD)	10.0 (10.0)	12.3 (12.1)	10.1 (12.8)
LS Mean (CI) [a]	10.1 (7.1, 13.1)	11.4 (8.8, 14.1)	9.6 (5.9, 13.3)
Difference (CI) vs. ranibizumab	0.5 (–4.3, 5.3)	1.8 (–2.7, 6.4)	—

Data sources: t_ef_obsd_cb_RND_BCVA; t_ef_mm_rm_RND_BCVA_CHG;

BCVA=best corrected visual acuity; CI=confidence interval; LS=least squares; SD=standard deviation.

Note: CI = 80% Confidence Interval.

[a] Mean BCVA change from baseline generated using mixed model for repeated measurement (MMRM) model. Model includes categorical covariates of treatment group, visit, and visit by treatment group interaction, and the continuous covariate of baseline BCVA.

Main study(ies)

For the neovascular age-related macular degeneration indication the applicant has submitted two phase III randomised, double-masked, active comparator (aflibercept) controlled studies that have the same design, inclusion and exclusion criteria and efficacy endpoints. Both studies are ongoing.

- Study GR40306 (TENAYA) enrolled its first patient on 19 February 2019. The last patient in the trial was randomised on 19 November 2019. The data cut off was 26 October 2020.
- Study GR40844 (LUCERNE) enrolled its first patient on 11 March 2019. The last patient was randomised on 1 November 2019 and the data cut off point was 5 October 2020.

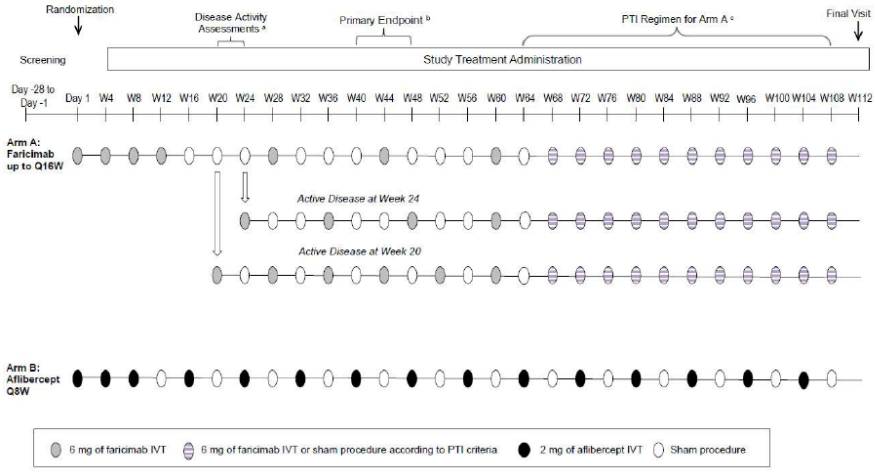
Study GR40306 (TENAYA) and Study GR40844 (LUCERNE)

Methods

TENAYA and LUCERNE are Phase III, multicenter, randomized, active comparator-controlled, double-masked, parallel-group, 112-week studies to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD. Figure 54 presents an overview of the study design.

Figure 54. Study Schema for TENAYA and LUCERNE.

Figure 1 Study Schema



Study Participants

The study population was made up of treatment naive patients with neovascular AMD. Patients had to have a functioning non-study eye. As part of the screening process, the central reading center (CRC) evaluated CFPs, FFA, and OCT images to provide an objective, masked assessment of patient eligibility.

The relevant inclusion criteria for TENAYA and LUCERNE were:

Age ≥50 years on Day 1

Patients had to meet the following ocular criteria for study entry:

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

There were a number of exclusion criteria related to general health including recent history of myocardial infarction, stroke and uncontrolled hypertension.

Ocular exclusion criteria for the study eye included the following: CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis; any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal fluid or subretinal fluid; presence at screening of central serous chorioretinopathy; RPE tear involving the macula on Day 1; subretinal haemorrhage of >50% of the total lesion area and/or that involved the fovea; fibrosis or atrophy of >50% of the total lesion area and/or that involved the fovea; any concurrent intraocular condition (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study; current vitreous haemorrhage on Day 1; uncontrolled glaucoma; spherical equivalent of refractive error demonstrating more than 8 diopters of myopia For patients who had undergone prior refractive or cataract surgery, the preoperative refractive error should not have exceeded -8 diopters of myopia; any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, intravitreal treatment (e.g., anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention.

Treatments

Patients randomized to Arm A received 6 mg of intravitreal faricimab Q4W up to Week 12. At Week 20, protocol-defined assessment of disease activity required patients in Arm A with active disease to be treated with a Q8W dosing regimen of 6 mg of faricimab (i.e., injections at Weeks 20, 28, 36, 44, 52, and 60).

A second protocol-defined assessment of disease activity at Week 24 required patients in Arm A with active disease (excluding those with active disease at Week 20 and therefore receiving a Q8W dosing regimen of 6 mg of intravitreal faricimab) to be treated with a Q12W dosing regimen of 6 mg of intravitreal faricimab (i.e., injections at Weeks 24, 36, 48, and 60).

Patients receiving faricimab who did not have active disease according to the protocol-defined criteria at Week 20 and Week 24 were treated with 6 mg of intravitreal faricimab Q16W (i.e., injections at Weeks 28, 44, and 60).

From Week 60 (when all patients in Arm A are scheduled to receive study drug) to Week 108, patients in Arm A will be treated according to a PTI dosing regimen (between Q8W and Q16W). At study drug dosing visits, treatment intervals can be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4 or 8 weeks), based on OCT, BCVA, and clinical assessment). This part of the study is not complete yet.

Patients randomized to the active comparator (Arm B), received a 2 mg dose of intravitreal aflibercept administered Q8W after 3 consecutive monthly doses during the 108-week treatment period (see Figure 54).

Both treatment arms (faricimab up to Q16W and aflibercept Q8W) maintained Q4W study visits for the duration of the study.

Dose modification was not allowed during the study.

Objectives

The primary efficacy objective was to evaluate the efficacy of intravitreal injections of the 6 mg dose of faricimab on BCVA outcomes compared with aflibercept There were a number of secondary objectives relating to other BCVA outcomes and anatomic measures.

The primary comparison was to test non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W), as measured by the primary endpoint - change from baseline in BCVA averaged over Weeks 40, 44, and 48, in the intent-to-treat (ITT) population. The non-inferiority test was conducted with a non-inferiority margin of 4 letters at the one-sided 0.02485 significance level.

The null hypothesis: H0: μfaricimab-μaflibercept ≤- 4 letters, and the alternative hypothesis: Ha: μfaricimab-μaflibercept >- 4 letters, were tested, where μfaricimab and μaflibercept are the expected change from baseline in BCVA averaged over Weeks 40, 44, and 48 for the faricimab and aflibercept arms respectively. If the lower bound of a two-sided 95.03% CI for the difference in adjusted means of the two treatments was greater than - 4 letters (the non-inferiority margin), then faricimab was considered non-inferior to aflibercept.

Outcomes/endpoints

The primary endpoint was the change from baseline BCVA (as assessed on the ETDRS chart at a starting distance of 4 meters based on the average at Weeks 40, 44 and 48). There were a number of secondary endpoints related to visual function, frequency of study drug administration and anatomical endpoints such as:

- Change from baseline in BCVA over time
- Proportion of patients gaining ≥15, ≥10, ≥5, or ≥0 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time
- Proportion of patients avoiding loss of ≥15, ≥10 or ≥5 letters in BCVA from baseline averaged over Weeks 40, 44, and 48 and over time
- Proportion of patients in the faricimab arm on a Q8W, Q12W, and Q16W treatment interval at Weeks 48, 60, and 112
- Number of study drug injections received through Weeks 48, 60, and 112
- Change from baseline in CST(ILM-RPE) based on an average at Weeks 40, 44, and 48 and over time

Randomisation and blinding (masking)

After written informed consent was obtained, all patients received a screening number assigned through the IxRS. A patient had to have satisfied all eligibility criteria prior to randomization through the IxRS. As part of the screening process, the central reading center (CRC) evaluated CFPs, FFA, and OCT images to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements were confirmed, site personnel contacted the IxRS at the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). Patients were randomized in a 1:1 ratio to one of two arms (faricimab up to Q16W or aflibercept Q8W).

After randomization and at each study treatment visit (i.e., including Day 1), the IxRS assigned the appropriate study treatment kit to be used. Patients were randomized on the same day study treatment was to be initiated (the Day 1 visit).

Randomization was stratified by the following baseline factors (Day 1):

- Baseline BCVA ETDRS letter score (≥ 74 letters, 73-55 letters, and ≤ 54 letters)

- Low luminance deficit (LLD) (< 33 letters, and ≥ 33 letters)
- Region (United States and Canada, Asia, and the rest of the world)

A stratified permuted-block randomization scheme was used to obtain approximately a 1:1 ratio among the treatment groups overall and within each of the above strata.

Screen fail patients were eligible for two additional re-screens during the enrolment period of the study. At re-screening, a new screening number was assigned to each patient through the IxRS and all screening visit assessments were performed. Only FFA images did not have to be repeated, provided that the same eye was selected for the study eye at re-screening and acceptable FFA images were received by the CRC within 4 weeks before the new Day 1 visit (randomization) date.

The studies were double-masked study. A minimum of two investigators per site were needed to fulfill the masking requirements of this study, and a masked and unmasked investigator are required to be present at each scheduled study visit. Patients received a sham injection at each 4 week visit where they were not due active treatment. The sham is a procedure that mimics an intravitreal injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

Sample Size

A sample size of approximately 320 patients in each arm provided greater than

90% power to show non-inferiority of faricimab to aflibercept in the change in BCVA

averaged over Weeks 40, 44, and 48 in the ITT population, using a non-inferiority margin

of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between two treatment arms;
- Standard deviation of 14 letters for the change from baseline in BCVA averaged over Weeks 40, 44, and 48;
- Two-sample t-test;
- 2.5% one-sided type I error rate;
- 10% dropout rate.

Estimand and Estimator

The primary Estimand was described as follows:

Population: Adult treatment-naive patients with nAMD, as defined by the inclusion/exclusion criteria (ITT Population);

Variable: Change in BCVA score from baseline averaged over Weeks 40, 44, and 48. BCVA score was based on the ETDRS VA chart assessed at a starting distance of 4 meters;

Population-level summary: Difference in adjusted mean between faricimab (up to Q16W) and aflibercept (Q8W) arms

Intercurrent events:

– Discontinuation of study treatment due to AEs or lack of efficacy not due to COVID-19: A treatment policy strategy was applied where all observed values were used regardless of the occurrence of the intercurrent event.

– Use of any prohibited systemic treatment or prohibited therapy in the study eye not due to COVID-19: A treatment policy strategy was applied where all observed values will be used regardless of the occurrence of the intercurrent event.

– Discontinuation of study treatment due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event.

– Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event.

– Missed dose(s) with potentially major impact on efficacy due to COVID-19: A hypothetical strategy was applied where all values were censored after the intercurrent event

– COVID-19 death: A hypothetical strategy was applied.

The primary analysis was performed using a MMRM. The model included the change from baseline at Weeks 4 to 48 as the response variable and included the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), as well as randomization stratification factors as fixed effects. Comparisons between the two treatment arms were made using a composite contrast over Weeks 40, 44, and 48. The MMRM model assumed an unstructured covariance structure, as pre-specified in the SAP. All MMRM analyses used an unstructured covariance structure. Missing data were implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism. Non-standard BCVA data (BCVA testing performed incorrectly) were excluded from the analyses.

Results

TENAYA participant flow

A total of 989 patients were screened, of which 318 patients failed screening, mainly due to not meeting the ocular inclusion criteria of subfoveal CNV or juxtafoveal/extrafoveal CNV with a subfoveal component (63 patients); CNV lesion of any type that exhibits all four characteristics listed in Section 3.5.1.2 (59 patients); BCVA of 78-24 letters, inclusive (n = 39); or meeting the exclusion criteria on FFA/CFP. A total of 671 treatment naive patients were randomized: 334 to the faricimab arm and 337 to the aflibercept arm (Figure 55) in 149 sites in 15 countries.

As specified in the protocol, three randomization stratification factors were used (baseline BCVA ETDRS letter score, LLD, and region) to balance these characteristics between the treatment arms

Two patients (1 patient in the faricimab arm and 1 patient in the aflibercept arm) were randomized but did not receive treatment, both due to physician decision.

Completion rates of study treatment at week 48 were high in both treatment groups 92.2% in the faricimab arm and 95.5% in the aflibercept arm.

LUCERNE

A total of 1012 patients were screened, of which 354 patients failed screening, most commonly due to not meeting inclusion criteria (227 patients). The main reasons for screen failure were not meeting the ocular inclusion criteria of subfoveal CNV or juxtafoveal/extrafoveal CNV with a subfoveal component

(65 patients); CNV lesion of any type that exhibits all the characteristics listed in Section 3.5.1.2 (70 patients); BCVA of 78 to 24 letters, inclusive (26 patients); or meeting the exclusion criteria on FFA/CFP (54 patients). A total of 658 treatment-naive patients with nAMD were randomized 1:1 into the study: 331 to the faricimab arm and 327 to the aflibercept arm (Figure 2) in 122 sites in 20 countries.

One patient in the aflibercept arm was randomized but did not receive treatment due to a reason of "other" (not eligible).

Treatment completion rates at Week 48 were high in both treatment arms 94.6% in the faricimab arm and 93.3% in the aflibercept arm.

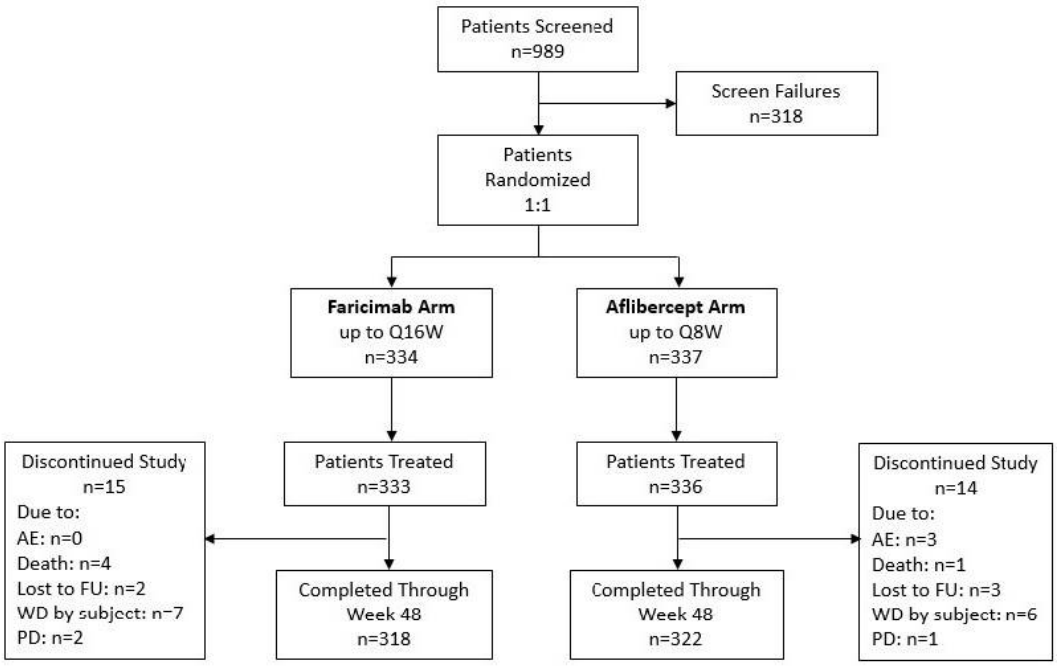
Reasons for discontinuation prior to Week 48 were broadly similar in both treatment arms in both studies.

Note both studies experienced mis-stratification of patients.

Figure 55. Patients' flow for TENAYA study.

TENAYA

Figure 2 Patient Disposition



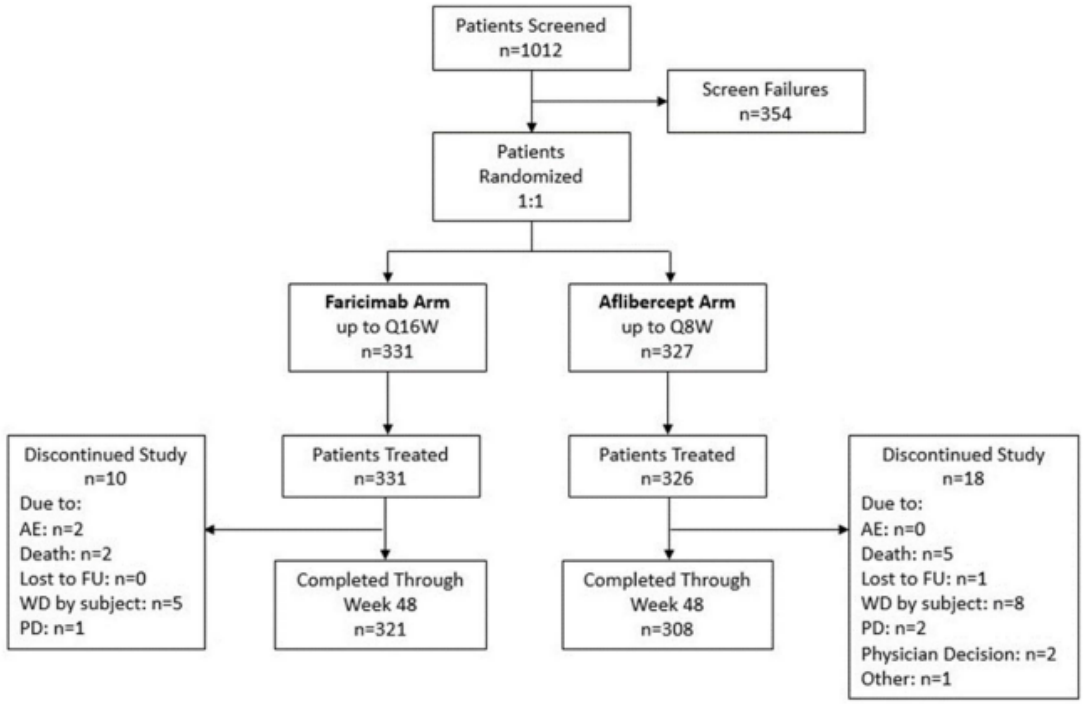
AE = adverse event; FU = follow-up; PD = physician decision; Q8W = every 8 weeks; Q16W = every 16 weeks; WD = withdrawal.

Note: Includes discontinuation occurring prior to Day 322 (first day of the Week 48 analysis visit window).

Source: t_ds_IT_26OCT2020_40306, t_pop_IT_26OCT2020_40306, Screen Failure list

LUCERNE

Figure 2 Patient Disposition



AE = adverse event; FU = follow-up; PD = physician decision; Q8W = every 8 weeks; Q16W = every 16 weeks; WD = withdrawal.

Note: Includes discontinuation occurring prior to Day 322 (first day of the Week 48 analysis visit window). Additional reasons for study discontinuation: 2 patients (1 patient in the faricimab up to Q16W arm and 1 patient in the aflibercept Q8W arm) discontinued the study due to protocol deviations, and 1 patient in the aflibercept Q8W arm discontinued due to other.

Baseline data

TENAYA

In the ITT population, baseline demographics were comparable between treatment arms. Overall, the mean age at randomization was 76.3 years (75.9 years in the faricimab arm and 76.7 years in the aflibercept arm).

The majority of patients were female (59.9%) and White (90.2%), from the United States and Canada (54.5%), and of Not Hispanic or Latino ethnicity (91.1%). Overall, 8.0% of patients were Asian, and predominantly Japanese (98.1%). This was comparable between treatment arms.

Baseline demographic characteristics in the PP population were comparable with the ITT population and generally comparable across arms

LUCERNE

In the ITT population, baseline demographics were comparable between treatment arms. The mean age at randomization was 75.5 years (74.8 years in the faricimab arm and 76.1 years in the aflibercept arm).

The majority of patients were female (59.4%) and White (83.3%). The majority of patients were from the regions rest of the world (49.1%) or United States and Canada (40.6%), and of Not Hispanic or Latino ethnicity (85.3%). Overall, 10.9% of patients were Asian, most commonly Korean (50.0%), Taiwanese (26.4%), and Chinese (19.4%). This was comparable between treatment arms.

Baseline demographic characteristics in the PP population were comparable with the ITT population and generally comparable across arms

Ocular baseline characteristics

TENAYA

In the ITT population, mean baseline BCVA and mean baseline CST in the study eye were comparable between the treatment arms (Table 20). Mean baseline BCVA values were 61.3 letters in the faricimab arm and 61.5 letters in the aflibercept arm. Mean baseline LLD values were 25.3 letters in the faricimab arm and 26.1 letters in the aflibercept arm. Overall, 56.2% of patients had a lens status of phakic and 43.8% had pseudophakic; this was comparable between treatment arms. Mean baseline CST (ILM-RPE, hereafter referred to as 'CST') was 360.5 µm in the faricimab arm and 356.1 µm in the aflibercept arm. Baseline, intraretinal fluid was absent in 53.4% of patients, subretinal fluid was absent in 32.8% of patients, and pigment epithelial detachment was absent in 8.2% of patients; this was comparable between treatment arms. Overall, the baseline absence of PED was comparable between the treatment arms (8.7% of patients in the faricimab arm and 7.7% in the aflibercept arm) but the mean (SD) baseline PED height was numerically greater in the faricimab arm (125.3 [161.0] µm vs. 116.9 [149.4] µm in the faricimab and aflibercept arms, respectively. At baseline, CNV lesion location (determined by FFA) was most commonly subfoveal (57.7%), followed by juxtafoveal (26.2%), and extrafoveal (14.3%). The most common CNV lesion types were occult (52.3%), classic (23.4%), and minimally classic (9.2%); this was comparable between treatment arms. Mean total area of CNV lesion (determined by FFA) was 4.7 mm^2 in the faricimab arm and 4.5 mm^2 in the aflibercept arm.

The mean time since nAMD diagnosis (as reported by the patient) was 1.5 months (median min-max]: 0.6 months [0-62]) in the faricimab arm, and 1.1 months (median [min-max]: 0.6 months [0-32]) in the aflibercept arm.

Baseline ocular characteristics in the PP population were comparable with the ITT population and generally comparable across arms

LUCERNE

In the ITT population, mean baseline BCVA and mean baseline CST in the study eye were comparable between the treatment arms (Table 20). Mean baseline BCVA values were 58.7 letters in the faricimab arm, and 58.9 letters in the aflibercept arm. Mean baseline LLD values were 25.0 letters in the faricimab arm and 25.8 letters in the aflibercept arm. Overall, 57.0% of patients had a lens status of phakic and 43.0% were pseudophakic; this was comparable between treatment arms. Mean baseline CST (ILM-RPE) was 353.1 µm in the faricimab arm, and 359.0 µm in the aflibercept arm. At baseline, intraretinal fluid was absent in 54% of patients, subretinal fluid was absent in 31.9% of patients, and pigment epithelial detachment was absent in 7.6% of patients; this was comparable between treatment arms. Overall, the baseline absence of PED was comparable between the treatment arms (6.9% of patients in the faricimab arm and 8.3% in the aflibercept arm), but the mean (SD) baseline PED height in the study eye was numerically greater in the faricimab arm (140.8 [170.9] µm vs. 108.2 [139.4] µm in the faricimab and aflibercept arms, respectively. At baseline, CNV lesion location (determined by FFA) was most commonly subfoveal (60.8%), followed by juxtafoveal (23.9%), and extrafoveal (13.1%). The most common CNV lesion types were occult (47.3%), classic (31.5%), and minimally classic (9.3%); this was comparable between treatment arms. Mean total area of CNV lesion (determined by FFA) was 4.7 mm^2 in the faricimab arm and 4.3 mm^2 in the aflibercept arm.

The mean time since AMD diagnosis was 3.2 months (median [min-max]: 0.6 months [0-187]) in the faricimab arm, and 1.7 months (median [min-max]: 0.7 months [0-51]) in the aflibercept arm. Baseline ocular characteristics in the PP population were comparable with the ITT population and generally comparable across arms.

Table 20. Ocular Baseline Characteristics in the Study Eye ITT Population				
	TTENAYA		LUCERNE	
	Faricimab 6mg (n=334)	Aflibercept 2mg (n=337)	Faricimab 6mg (n=331)	Aflibercept 2mg (n=327)
Study eye				
Right	166	178	168	170
left	168	159	163	157
Time since diagnosis				
0-10 days	62 (18.6%)	63 (18.7%)	77 (23.3%)	63 (19.3%)
10-31 days	186 (55.7%)	183 (54.3%)	144 (43.5%)	145 (44.3%)
1-3 months	45 (13.5%)	63 (18.7%)	56 (16.9%)	75 (22.9%)
4-6 months	13 (3.9%)	6(1.8%)	19 (5.7%)	17 (5.2%)
>6 months	8 (2.4%)	8 (2.4%)	21 (6.3%)	15 (4.6%)
unknown	20 (6%)	14 (4.2%)	14 (4.2%)	12 (3.7%)
BCVA (letters) Mean (SD)	61.3 (12.5)	61.5 (12.9)	58.7 (14)	58.9 (13.3)
BCVA (letters) categories				
≥ 74 (20/32 or better)	47 (14.1%)	52 (15.4%)	45 (13.6%)	39 (11.9%)
73-55 (20/40 to 20/80)	200 (59.9%)	201 (59.6%)	181 (54.7%)	183 (56%)
≤54 (20/80 or worse)	87 (26%)	84 (24.9%)	105 (31.7%)	105 (32.1%)
Low-Luminance Visual Acuity (letters) Mean (SD)	N = 331 36 (15.6)	N = 333 35.3 (16.4)	N = 327 33.6 (16.2)	N = 327 33.2 (16.8)
CST(ILM-BM) (microns) Mean (SD)	N =328 486.4 (178.6)	N =333 473.9 (166.8)	N = 327 490.3 (194.9)	N = 324 469.6 (176.4)
CST(ILM-RPE) (microns) Mean (SD)	N = 328 360.5 (124.1)	N = 332 356.1 (107)	N = 327 353.1 (120.1)	N = 323 359 (131.1)
Absence of IRF	N = 327	N = 334	N = 326	N = 325
Yes	181 (54.2%)	177 (52.5%)	184 (55.6%)	171 (52.3%)
No	146 (43.7%)	157 (46.6%)	142 (42.9%)	154 (47.1%)
Absence of SRF	N = 329	N = 332	N = 328	N = 325
Yes	113 (33.8%)	107 (31.8%)	107 (32.3%)	103 (31.5%)

N	216 (64.7%)	225 (66.8%)	221 (66.8%)	222 (67.9%)
Absence of PED	N = 329	N = 334	N = 327	N = 325
Yes	29 (8.7%)	26 (7.7%)	23 (6.9%)	27 (8.3%)
N	300 (89.8%)	308 (91.4%)	304 (91.8%)	298 (91.1%)
CNV Location by FFA	N = 334	N = 337	N = 331	N = 327
Subfoveal	201 (60.2%)	186 (55.2%)	209 (63.1%)	191 (58.4%)
Juxtafoveal	88 (26.3%)	88 (26.1%)	73 (22.1%)	84 (25.7%)
Extrafoveal	41 (12.3%)	55 (16.3%)	42 (12.7%)	44 (13.5%)
Missing/not done	4 (1.2%)	8 (2.4%)	7 (2.1%)	8 (2.4%)
CNV Lesion Type by FFA	N = 334	N = 337	N = 331	N = 327
Occult	177 (53%)	174 (51.6%)	171 (51.7%)	140 (42.8%)
Classic	84 (25.1%)	73 (21.7%)	98 (29.6%)	109 (33.3%)
Minimally classic	32 (9.6%)	30 (8.9%)	30 (9.1%)	31 (9.5%)
RAP	14 (4.2%)	27 (8%)	14 (4.2%)	15 (4.6%)
Predominantly classic	17 (5.1%)	19 (5.6%)	6 (1.8%)	16 (4.9%)
Missing/not done	4 (1.2%)	8 (2.4%)	7 (2.1%)	8 (2.4%)
PCV	6 (1.8%)	6 (1.8%)	5 (1.5%)	8 (2.4%)
Total Area of CNV lesion by FFA (mm2) Mean (SD)	N = 330 4.7 (4.8)	N = 330 4.5 (4.1)	N = 328 4.7 (4.7)	N =320 4.3 (4.3)

AMD = Age-related macular degeneration; BCVA = Best-corrected Visual Acuity; BM = Bruch's membrane; CRC = Central reading center;

CST = Central Subfield Thickness; CNV = Choroidal Neovascularization; FFA = Fundus fluorescein angiography; IRF = Intraretinal fluid; ILM = Internal limiting membrane; PCV = Polypoidal choroidal vasculopathy; PED = Pigment epithelial detachment; RAP = Retinal Angiomatous Proliferation; RPE = Retinal

pigment epithelium; SRF = Subretinal fluid.

Baseline is defined as the last available measurement obtained on or prior to randomization.

CST(ILM-BM) is defined as the distance between ILM and Bruch’s membrane (BM) as assessed by the CRC.

CST(ILM-RPE) is defined as the distance between ILM and Retinal Pigment Epithelium (RPE) as assessed by the CRC.

Numbers analysed

The primary efficacy analysis was conducted in the ITT population.

TENAYA

The ITT population included 671 patients (see Table 21).

Two patients were randomized but did not receive treatment and were not included in the safety population. Overall, 92 patients were excluded from the PP population due to protocol deviations (90 patients had major protocol deviations that impacted the efficacy evaluation or the treatment interval determination, and 2 patients were not dosed).

LUCERNE

The ITT population included 658 patients (Table 21). One patient was randomized but did not receive treatment and was not included in the safety population. Overall, 81 patients were excluded from the PP population due to protocol deviations (80 patients had major protocol deviations that impacted efficacy evaluation or the treatment interval determination, and 1 patient was not dosed.

Table 21. Overview of analysis populations TENAYA and LUCERNE

	TENEYA		LUCERNE	
	Faricimab 6mg	Aflibercept 2mg	Faricimab 6mg	Aflibercept 2mg
Intent-to-Treat Population (as Randomized)	334	337	331	327
Safety-Evaluable Population (as Treated)	333	336	331	326
Per-Protocol Population through Week 48 (as Treated)	284 (85%)	295 (87.5%)	286 (86.4%)	291 (89%)

Intent-to-Treat Population: All patients who are randomized in the study.

Safety-Evaluable Population: All patients who receive at least one injection of active study drug (faricimab or aflibercept) in the study eye.

Per-Protocol Population: All patients randomized in the study who receive at least one dose of study treatment and who do not have a major protocol deviation that impacts the efficacy evaluation or the treatment interval determination.

Outcomes and estimation

Confidence Intervals (CI): 95% CI is a rounding of 95.03% for the primary and secondary endpoints for the Individual studies. Pooled results CIs are 95%.

Primary endpoint

TENAYA

At Week 40/44/48, the adjusted mean change from baseline in BCVA was 5.8 and 5.1 letters in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from baseline in BCVA 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)

LUCERNE

At Week 40/44/48, the adjusted mean change from baseline in BCVA was 6.6 and 6.6 letters in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from baseline in BCVA 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) (Table 23).

For the primary efficacy analysis, a hypothetical strategy was applied for COVID-19 related intercurrent events where all values were censored after such intercurrent event. The primary analysis assessed in the ITT population excluded measurements after COVID-19 related intercurrent events (hypothetical strategy) and was performed based on all other observed data (treatment policy strategy for non-COVID-19 related intercurrent events), with the missing data imputed implicitly under the MAR assumption.

The following sensitivity/supplemental analyses were performed to assess the robustness of the results using the same MMRM method as the main analysis, but applying different handling strategies for the intercurrent events and missing data:

- LOCF: missing BCVA assessments due to any reason were imputed using the last available post-baseline observation prior to the occurrence of missing data (sensitivity analysis)
- Treatment policy strategy for all intercurrent events
- Hypothetical strategy for all intercurrent events.

In addition, the following analyses were also performed using the ANCOVA method and different handling strategies for the intercurrent events and missing data:

1. Trimmed means analysis performed using a truncated distribution, truncating patients with the worst outcome, with the assumption that patients have the worst outcome after non-COVID-19 related intercurrent events. Missing data and measurements after COVID-19 related intercurrent events, as well as missing data due to other reasons, were considered MAR and were censored
2. ANCOVA analysis with the average of non-missing values of Weeks 40, 44, and 48 assessments as the dependent variable. Measurements after COVID-19 related intercurrent events were censored and missing observations were not imputed
3. Multiple imputation, assuming a missing not at random (MNAR) mechanism for non-COVID-19 related missingness. Missing data and measurements after COVID-19 related intercurrent events, as well as missing data due to other reasons, were imputed using multiple imputation method assuming MAR.

Table 22. Change from Baseline in BCVA in the Study Eye averaged over Weeks 40, 44 and 48: MMRM Method (Primary Estimand), Intent-to-Treat Population

	TENAYA		LUCERNE	
	Faricimab 6 mg (N = 334)	**Afilbercept 2 mg** (N = 337)	**Faricimab 6 mg** (N = 331)	**Afilbercept 2 mg** (N = 327)

Average Wks 40, 44, 48 (n)	292 (87.4%)	300 (89%)	302 (91.2%)	291 (89%)
Adjusted mean (95% CI for adjusted means)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
Difference adjusted means (95% CI)	0.7 (-1.1, 2.5)		0.0 (-1.7, 1.8)	

"n" refers to the number of patients with at least one non-missing observation at Wks 40/44/48. Analyses included all patients randomized into the studies (the ITT population, denoted by N) regardless of missing assessments, as missing data were implicitly imputed by the MMRM method.

Table 23 Change from Baseline in BCVA in the Study Eye Averaged over Week 40/44/48

Method of analysis	TENAYA			LUCERNE		
	Faricimab 6 mg (N = 334) **Adjusted Mean (95% CI**	**Afilbercept 2 mg** (N = 337) **Adjusted Mean (95% CI)**	**Difference in Adjusted Means (95% CI)**	**Faricimab 6 mg** (N = 331) **Adjusted Mean (95% CI**	**Afilbercept 2 mg** (N = 327) **Adjusted Mean (95% CI)**	**Difference in Adjusted Means (95% CI)**
Primary analysis MMRM (ITT)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	0.7 (-1.1, 2.5) a	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)	0.0 (-1.7, 1.8) a
Sensitivity analysis LOCF MMRM (ITT)	5.9 (4.6, 7.1)	5.1 (3.9, 6.3)	0.7 (-1.1, 2.5)	6.8 (5.5, 8.0)	6.6 (5.4, 7.9)	0.1 (-1.6, 1.9)
PP MMRM	5.9 (4.5, 7.2) N = 284	5.6 (4.2, 6.9) N = 295	0.3 (-1.6, 2.2)	6.6 (5.2, 7.9) N = 286	6.7 (5.3, 8.0) N = 291	-0.1 (-2.0, 1.8)
Analysis Treatment Policy Strategy All Intercurrent	5.7 (4.4, 6.9)	5.0 (3.8, 6.3)	0.6 (-1.2, 2.4)	6.4 (5.2, 7.7)	6.6 (5.3, 7.8)	-0.1 (-1.9, 1.6)

Events – MMRM ITT						
Analysis of Hypothetical Strategy All Intercurrent *Events – MMRM* ITT	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	0.7 (-1.1, 2.5)	6.7 (5.4, 7.9)	6.5 (5.3, 7.7)	0.2 (-1.6, 1.9)
Trimmed Mean Analysis – ANCOVA ITT	7.9	7.5	0.4 (-1.2, 1.9)	9.2	9.4	-0.16 (-1.7, 1.4)
ANCOVA ITT	4.6 (2.8, 6.4)	4.3 (2.5, 6.1)	0.3 (-1.5, 2.2)	6.3 (4.6, 8.0)	6.5 (4.8, 8.3)	-0.2 (-2.1, 1.6)
Multiple Imputation Analysis – ANCOVA ITT	4.9 (3.2, 6.6)	3.9 (2.2, 5.6)	1 (-0.8, 2.8)	6.2 (4.6, 7.9)	6.5 (4.8, 8.2)	-0.2 (-2.0, 1.5)

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; COVID-19 = Coronavirus Disease 2019; ITT = intent-to-treat; LLD = low luminance deficit; MMRM = mixed-model repeated measurement; LOCF = last observation carried forward; PP = per-protocol. For the MMRM analysis, the model is adjusted for treatment arm, visit, visit-by-treatment arm interaction, baseline BCVA (continuous), baseline BCVA (≥ 74 letters, 73–55 letters, and ≤ 54 letters), baseline LLD (< 33 letters and ≥ 33 letters), and region (United States and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. The estimate of the difference between the two arms uses a composite contrast over Weeks 40, 44, and 48.

For the primary estimand and LOCF analyses, treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. For the treatment policy analysis, observed BCVA assessments were used regardless of the occurrence of intercurrent events. For the hypothetical strategy analysis, hypothetical strategy was applied to non-COVID-19 related and COVID-19 related intercurrent events. For the MMRM analyses, missing data were implicitly imputed by MMRM. For the LOCF analyses, missing data were imputed using the last post-baseline observation carried forward. Invalid BCVA values are excluded from analysis. 95% CI is a rounding of 95.03% CI.

a.Units: letters. For the primary analysis, if the lower bound of a two-sided 95% CI for the difference in adjusted means of the two treatments is greater than -4 letters (the non-inferiority margin), then faricimab is considered non-inferior to aflibercept.

Secondary efficacy endpoints

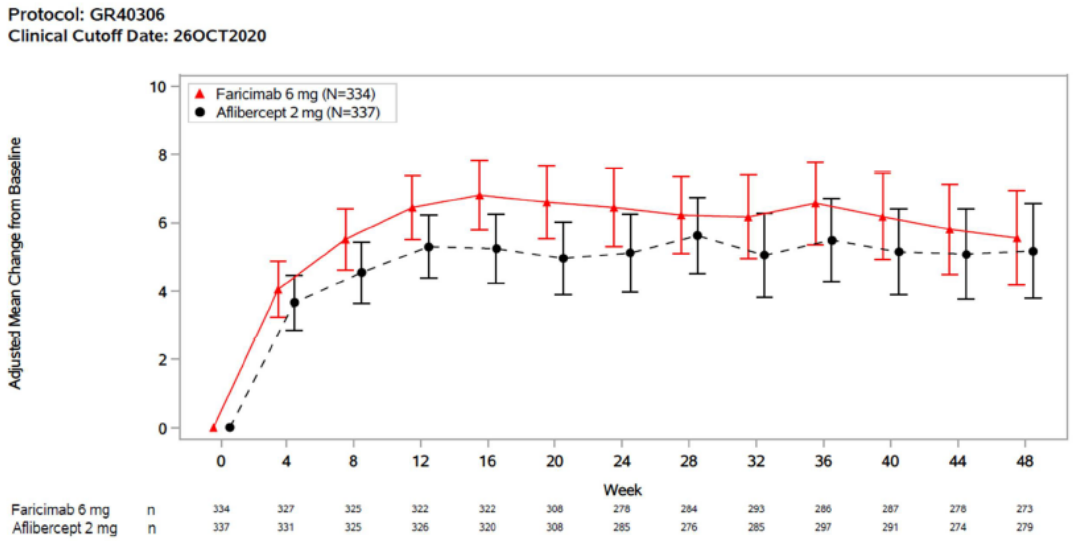
TENAYA

Change from Baseline in BCVA over Time

The change from baseline in BCVA through Week 48 was comparable between the faricimab and aflibercept arms. The results for change from baseline in BCVA through Week 48 for the sensitivity analysis and supplementary analyses were consistent with the main analysis. At all times in the TENAYA study BCVA gains from baseline was numerically greater for faricimab than aflibercept. This was also noted for the LUCERNE study but only up to week 36. Efficacy appeared similar in both treatment arms from Week 36 to Week 48.

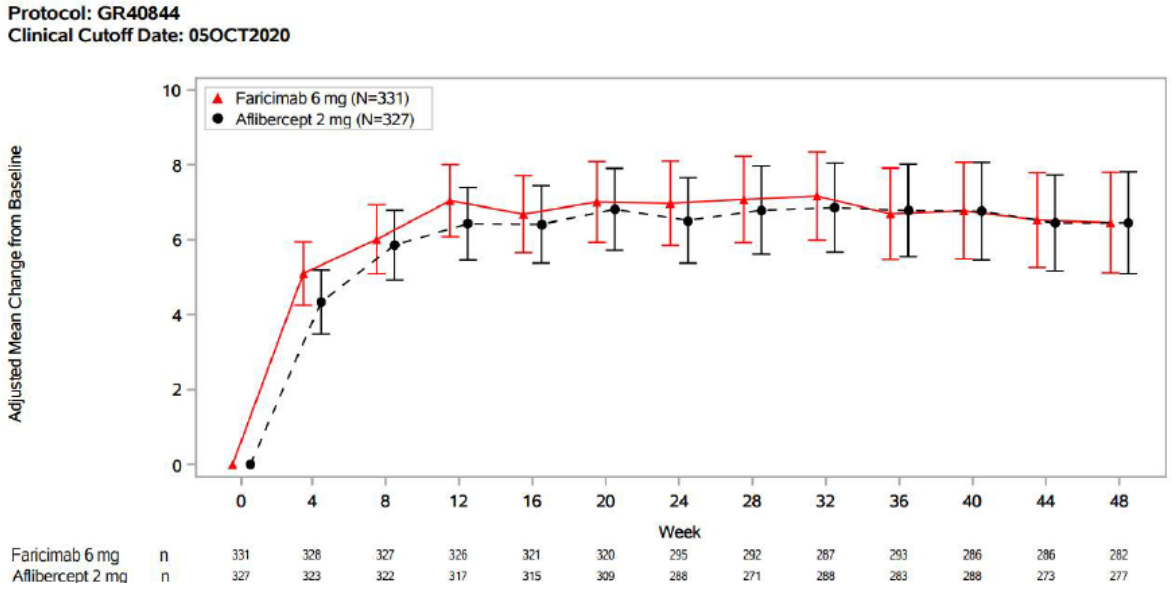
TENAYA

Figure 3 Change from Baseline in BCVA in the Study Eye through Week 48: MMRM Method (Primary Estimand), Intent-to-Treat Population



LUCERNE

Figure 3 Change from Baseline in BCVA in the Study Eye through Week 48: MMRM Method (Primary Estimand), Intent-to-Treat Population



Proportion of Patients Gaining ≥ 15, ≥ 10, ≥ 5 or ≥ 0 Letters from Baseline BCVA at Week 40/44/48

TENAYA

At Week 40/44/48, 20.0% and 15.7% of patients gained at least 15 letters in BCVA score from baseline in the faricimab and aflibercept arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline in the faricimab arm compared to the aflibercept arm at Week 40/44/48 was 4.3% (95% CI: - 1.6%, 10.1%). At Week 40/44/48 the proportion gaining ≥ 15 Letter or Achieving BCVA Snellen Equivalent of 20/20 or Better (BCVA ≥ 84 Letters) at Week 48 was 24.3% and 21.3% for faricimab and aflibercept respectively (Table 24). At Week 40/44/48, 56.4% and 57.0% of patients had a BCVA Snellen equivalent of 20/40 or better from baseline in the faricimab arm and the aflibercept arm, respectively.

LUCERNE

At Week 40/44/48, 20.2% and 22.2% of patients gained at least 15 letters in BCVA score from baseline in the faricimab and aflibercept arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline in the faricimab arm compared to the aflibercept arm at Week 40/44/48 was -2.0% (95% CI - 8.3%, 4.3%).

At Week 40/44/48, 24.5% and 26.2% of patients gained ≥ 15 letters or achieved BCVA Snellen equivalent of 20/20 or better from baseline in the faricimab arm and the aflibercept arm, respectively (Table 24).

At Week 40/44/48, 55.2% and 49.4% of patients had a BCVA Snellen equivalent of 20/40 or better from baseline in the faricimab arm and the aflibercept arm, respectively.

Table 24 Proportion of Patients (CMH estimate with 95% CI) Gaining Letters by Category in BCVA from Baseline in the Study Eye Averaged over Week 40/44/48: CMH Method (ITT Population)

	TENAYA			LUCERNE		
	Faricimab 6 mg (N = 334)	**Afilbercept 2 mg** (N = 337)	**Diff in CMH Weighted % Faricimab v Aflibercept**	**Faricimab 6 mg** (N = 331)	**Afilbercept 2 mg** (N = 327)	**Diff in CMH Weighted % Faricimab v Aflibercept**
Gaining ≥15 Letters in BCVA from Baseline	20% (15.6%, 24.4%)	15.7% (11.9%, 19.6%)	4.3% (-1.6%, 12.7%)	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)	-2.0% (-8.3%, 4.3%)
Gaining ≥ 15 Letter or Achieving BCVA Snellen Equivalent	24.3% (19.5%, 29.1%)	21.3% (16.8%, 25.7%)	3% (-3.6%, 9.5%)	24.5% (19.8%, 29.2%)	26.2% (21.2%, 31.1%)	-1.7% (-8.5%, 5.1%)

of 20/20 or Better (BCVA ≥ 84 Letters)						
Gaining ≥ 10 Letters in BCVA from Baseline	37.1% (31.7%, 42.4%)	31.7% (26.7%, 36.8%)	5.4% (-2.0%, 12.7%)	39.2% (34.1%, 44.4%)	35.8% (30.6%, 40.9%)	3.4% (-3.9%, 10.7%)
Gaining ≥5 Letters in BCVA from Baseline	59.2% (53.7%, 64.7%)	58% (52.6%, 63.5%)	1.2% (-6.6%, 8.9%)	60.5% (55.2%, 65.7%)	59.4% (53.9%, 64.9%)	1.0% (-6.6%, 8.6%)
Gaining ≥ 0 Letters in BCVA from Baseline	75.6% (70.8%, 80.3%)	76.8% (72.1%, 81.4%)	-1.2% (-7.9%, 5.4%)	82.2% (77.9%, 86.4%)	79.1% (74.5%, 83.6%)	3.1% (-3.1%, 9.3%)
Proportion with BCVA Snellen Equivalent of 20/40 or Better (BCVA ≥69 Letters)	56.4% (51.5%, 61.4%)	57% (51.9%, 62.1%)	-0.5% (-7.7%, 6.6%)	55.2% (50.1%, 60.2%)	49.4% (44.4%, 54.4%)	5.7% (-1.4%, 12.9%)
Proportion with BCVA Snellen Equivalent of 20/200 or worse (BCVA ≤38 Letters	6.4% (3.7%, 9.1%)	6.9% (4.2%, 9.5%)	-0.5% (-4.2%, 3.3%)	7.9% (5%, 10.8%)	7.5% (4.7%, 10.3%)	0.4% (-3.6%, 4.4%)
Avoiding a loss of ≥ 15 letters in BCVA from Baseline	95.4% (93%, 97.7%)	94.1% (91.5%, 96.7%)	1.3% (-2.2%, 4.8%)	95.8% (93.6%, 98%)	97.3% (95.5%, 99.1%)	-1.5% (-4.4%, 1.3%)

BCVA = best corrected visual acuity; CMH = Cochran-Mantel-Haenszel; COVID-19 = Coronavirus Disease 2019; ITT = intent-to-treat; LLD = low luminance deficit. The weighted estimate is based on CMH test stratified by baseline BCVA (≥ 74 letters, 73-55 letters, and ≤ 54 letters), baseline LLD (< 33 letters and ≥ 33 letters), and region (United States and Canada vs. the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

Missing data were not imputed. Invalid BCVA values are excluded from analysis. 95% CI is a rounding of 95.03% CI and estimates below 0% or above 100% are imputed as 0% or 100% respectively.

Change from Baseline in Central Subfield Thickness at Week 40/44/48

At Week 40/44/48, the adjusted mean change from baseline in CST was -136.8 µm and -129.4 µm for the faricimab and aflibercept arms, respectively in the TENAYA study (Table 25). The difference in adjusted mean change from baseline in CST between the faricimab arm when compared to the aflibercept arm at Week 40/44/48 was - 7.4 µm (95% CI: - 15.7, 0.8). Change from baseline over time to week 48 was similar in both treatment arms (Figure 56). Similar changes were seen in the LUCERNE study. At Week 40/44/48, the adjusted mean change from baseline in CST was -137.1 µm and -130.8 µm for the faricimab and aflibercept arms, respectively (Table 25). The difference in adjusted mean change from baseline in CST between the faricimab arm when compared to the aflibercept arm at Week 40/44/48 was -6.4 µm (95% CI -14.8, 2.1).

Table 25. Change from baseline in CST in LUCERNE (upper panel) and TENAYA (lower).

Table 17 Change from Baseline in Central Subfield Thickness in the Study Eye Averaged over Weeks 40/44/48: MMRM Method (ITT Population)

Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

Visit Statistics	Faricimab 6 mg (N=334)	Aflibercept 2 mg (N=337)
Average of Weeks 40, 44 and 48		
n	291	297
Adjusted Mean (SE)	-136.8 (2.97)	-129.4 (2.96)
95% CI for Adjusted Mean	(-142.6, -131.0)	(-135.2, -123.5)
Difference in Adjusted Means (SE)	-7.4 (4.19)	
95% CI for Difference in Adjusted Means	(-15.7, 0.8)	

Units: microns. BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; LLD = Low-luminance Deficit; MMRM = Mixed-Model Repeated-Measures. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (>=74 letters, 73 - 55 letters, and <= 54 letters), baseline LLD (<33 letters and >=33 letters), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks 40, 44 and 48. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. 95% CI is a rounding of 95.03% CI. CST is defined as the distance between ILM and retinal pigment epithelium (RPE), as assessed by CRC.

Table 17 Change from Baseline in Central Subfield Thickness in the Study Eye Averaged Over Weeks 40/44/48: MMRM Method (ITT Population)

Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

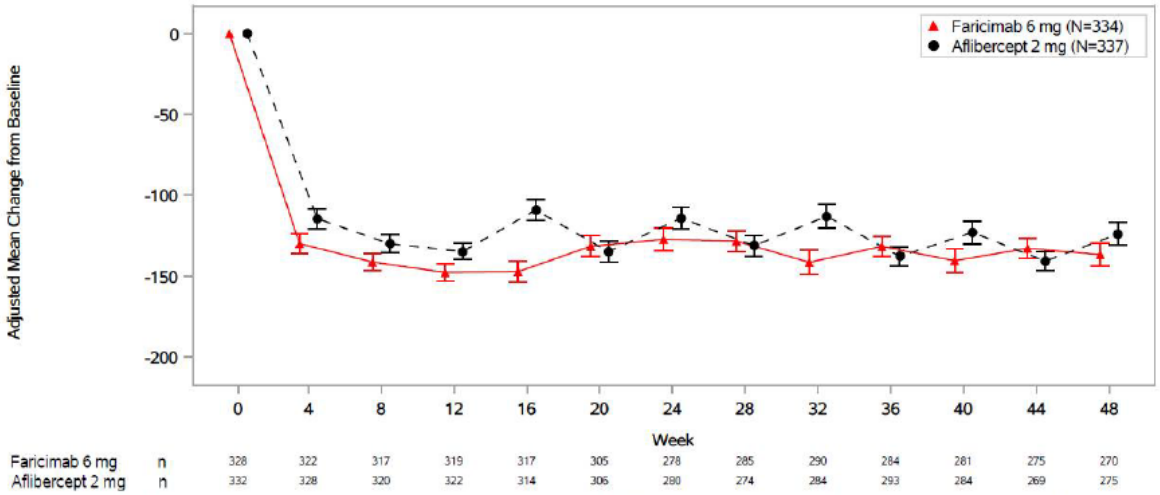
Visit Statistics	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=327)
Average of Weeks 40, 44 and 48		
n	299	287
Adjusted Mean (SE)	-137.1 (3.02)	-130.8 (3.05)
95% CI for Adjusted Mean	(-143.1, -131.2)	(-136.8, -124.8)
Difference in Adjusted Means (SE)	-6.4 (4.30)	
95% CI for Difference in Adjusted Means	(-14.8, 2.1)	

Figure 56. Change from baseline in CST over time.

TENAYA

Figure 9 Change from Baseline in Central Subfield Thickness in the Study Eye over Time through Week 48: MMRM Method (ITT Population)

Protocol: GR40306
Clinical Cutoff Date: 26OCT2020



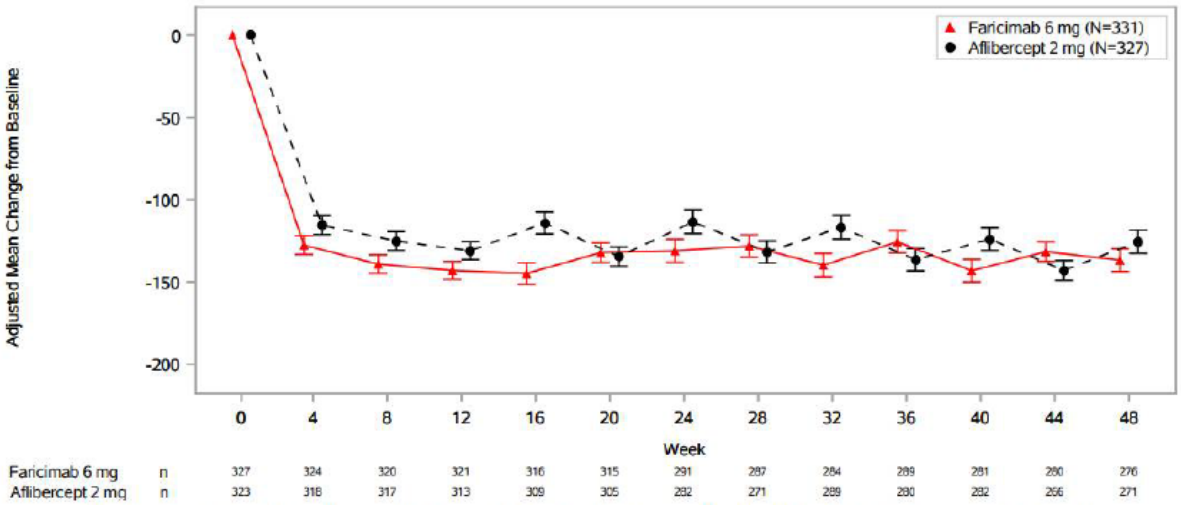
Faricimab 6 mg	n	328	322	317	319	317	305	278	285	290	284	281	275	270
Aflibercept 2 mg	n	332	328	320	322	314	306	280	274	284	293	284	269	275

Units: microns. BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; LLD = Low-luminance Deficit; MMRM = Mixed-Model Repeated-Measures. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (>=74 letters, 73 - 55 letters, and <= 54 letters), baseline LLD (<33 letters and >=33 letters), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. 95% CI is a rounding of 95.03% CI. CST is defined as the distance between ILM and retinal pigment epithelium (RPE), as assessed by CRC.

LUCERNE

Figure 9 Change from Baseline in Central Subfield Thickness in the Study Eye over Time Through Week 48: MMRM Method (ITT Population)

Protocol: GR40844
Clinical Cutoff Date: 05OCT2020



Faricimab 6 mg	n	327	324	320	321	316	315	291	287	284	289	281	280	276
Aflibercept 2 mg	n	323	318	317	313	309	305	282	271	289	280	282	266	271

Change from Baseline in NEI VFQ-25 Composite Score over Time

Patients treated with faricimab had a comparable mean change from baseline in the NEI VFQ-25 composite score at Week 24 and Week 48 compared with patients treated with aflibercept. At Week 48, the descriptive mean (SD) change from baseline in NEI VFQ-25 composite score was 4.82 (10.81) and 2.54 (10.93) in the faricimab and aflibercept arms, respectively. In the LUCERNE study, the descriptive mean (SD) change from baseline at Week 48 in NEI VFQ-25 composite score was 4.35 (10.65) and 5.55 (11.17) in the faricimbab and aflibercept arms respectively.

Ancillary analyses

The primary endpoint of the adjusted mean change from baseline in BCVA at Week 40/44/48 was analyzed across subgroups including:

- Baseline BCVA (≥ 74 letters, 73-55 letters, and ≤ 54 letters)
- Region (United States and Canada, Asia, and the rest of the world)
- LLD (< 33 letters and ≥ 33 letters)
- Choroidal neovascularization lesion subtype (classic, minimally classic, and occult)
- Total CNV lesion area (< 1 mm^2, 1-3 mm^2, and > 3 mm^2)
- CNV lesion size (< 1 mm^2, 1-3 mm^2, and > 3 mm^2)
- Age (< 75 years and ≥ 75 years)
- Gender
- Race (White, Asian, and other)

The differences in mean change in BCVA at Week 40/44/48 between the two treatment arms across subgroups were consistent with those of the overall population. In the ITT population, BCVA analyzed across subgroups was generally consistent with the overall population.

Table 26. Subgroup analysis change from baseline in BCVA Study eye at Week 40/44/48 MMRM method (ITT population)

	TENAYA					LUCERNE				
	Faricimab 6mg Q8W		Aflibercept 2mg		Diff adjusted mean 95% CI	Faricimab 6mg Q8W		Aflibercept 2mg		Diff adjusted mean 95% CI
	N	Adjusted mean	N	Adjusted mean		N	Adjusted mean	N	Adjusted mean	
All patients	292	5.8	300	5.1	0.7 (-1.1, 2.5)	302	6.6	291	6.6	0.0 (-1.7, 1.8)
Baseline BCVA ≥74 letters	42 177	1.9 5.3	48 174	3.2 4.6	-1.3 (-4.3, 1.6)	45 164	1.9 5.8	37 160	2.1 6.4	-0.2 (-4.0, 3.6)

73-55 ≤54	73	9.6	78	7.5	0.7 (-1.6, 2.9) 2.1 (-2.2, 6.5)	93	9.8	94	8.7	-0.5 (-2.9, 1.8) 1.1 (-2.4, 4.6)
Low lum def < 33 letters ≥ 33 letters	204 85	7.2 2.6	212 84	6.4 1.9	0.8 (-1.0, 2.6) 0.8 (-3.5, 5.1)	219 80	7.5 4.0	210 81	7.1 5.2	0.4 (-1.5, 2.3) -1.2 (-5.4, 3.1)
Age < 75 ≥75	117 175	8.1 4.4	108 192	6.8 4.2	1.3 (-1.4, 4.1) 0.2 (-2.2, 2.5)	150 152	6.6 6.6	124 167	7.3 9.1	-0.7 (-3.8, 2.4) 0.5 (-1.6, 2.6)
Gender Female Male	168 124	5.7 6.1	182 118	5.1 5.2	0.6 (-1.6, 2.8) 0.9 (-2.2, 4.0)	185 117	6.5 6.7	164 127	6.3 6.9	0.3 (-1.9, 2.4) -0.2 (-3.3, 2.8)
CNV lesion Occult Classic Min classic RAP	158 72 26 13	4.7 8.0 5.8 4.3	152 66 27 23	4.5 6.8 5.4 2.0	0.2 (-1.9, 2.3) 1.2 (-3.3, 5.7) 0.4 (-6.0, 6.8) 2.3 (-4.7, 9.4)	154 89 28	4.8 10.0 5.8	128 96 26	5.9 7.8 5.7	-1.1 (-3.4, 1.2) 2.2 (-1.6, 6.0) 0.1 (-5.2, 5.4)
CNV lesion size < 1mm^2 1-3 mm^2 >3mm^2	59 100 130	8.4 6.4 4.0	64 95 135	6.7 7.1 3.0	1.7 (-1.2, 4.6) -0.7 (-3.7, 2.3) 1.0 (-2.0, 4.0)	79 97 123	8.2 6.7 5.5	66 108 113	7.7 8.1 4.4	0.6 (-3.2, 4.3) -1.4 (-4.3, 1.5) 1.1 (-1.7, 3.9)
CNV les. Area	46	8.2	60	7.2		64	8.3	47	7.7	

< 1mm^2 1-3 mm^2 >3mm^2	92 150	6.8 4.7	81 153	6.6 3.6	1.0 (-2.1, 4.1) 0.3 (-2.7, 3.3) 1.1 (-1.7, 3.9)	88 147	6.9 5.8	104 135	7.2 5.4	0.6 (-3.1, 4.2) -0.2 (-3.4, 3.0) 0.4 (-2.3, 3.0)

For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (≥74 letters, 73-55 letters, ≤54 letters), baseline LLD (<33 letters, ≥33 letters) and region North America, Asia and rest of the world). The stratification factor is excluded if it is the subgroup. An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 40, 44 and 48. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related inter-current events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis.

In general the differences in mean change in BCVA at Week 40/44/48 between the two treatment arms across subgroups were consistent with those of the overall population. However within sub-groups there appears to be a pattern showing greater numerical improvement in BCVA from baseline in both treatment arms in specific groups within sub-groups e.g. those with a baseline BCVA of ≤ 54 letters, those with a low luminance deficiency of < 33 letters, those aged < 75 years, those with classic lesions and those with smaller lesion size.

Summary of main efficacy results

Table 27. Summary of efficacy for trial TENAYA (GR40306)

Title: 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)		
Study identifier	GR40306, TENAYA ClinicalTrials.gov Identifier: NCT03823287 EudraCT: 2018-002152-32	
Design	Multicenter, randomized, active comparator (aflibercept) controlled, double masked, parallel group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase (AVONELLE-X, Study GR42691):	112 weeks 28 days (screening visit to Day -1) 104 weeks
Hypothesis	Non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W) in the intent-to-treat (ITT) population.	

Treatments groups	Faricimab up to every 16 weeks (Q16W)		6 mg faricimab intravitreal injection on Day 1 then Q4W up to Week 12, followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by a personalized treatment interval (PTI; adjustable dosing administered in 8, 12 or 16-week intervals) regimen to Week 108; n=334 patients randomized.
	Aflibercept Q8W		2 mg aflibercept intravitreal injection on Day 1, then Q4W up to Week 8, followed by 2 mg of intravitreal aflibercept Q8W up to Week 108; n=337 patients randomized.
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 40/44/48	Change from baseline (CfBL) in BCVA averaged over Weeks 40, 44, and 48 (Week 40/44/48) measured using the Early Treatment Diabetic Retinopathy Scale (ETDRS) chart at a starting distance of 4 meters (NI margin of -4.0 letters)
	Secondary endpoint:	Prop. of pts gaining ≥ 15 letters in BCVA from BSL at Week 40/44/48	Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 40/44/48
	Secondary endpoint:	Prop. of pts avoiding loss of ≥ 15 letters in BCVA from BSL at Week 40/44/48	Proportion of patients avoiding loss of ≥ 15 letters in BCVA from baseline at Week 40/44/48
	Secondary endpoint:	Prop. of pts in the faricimab arm on a Q16W, Q12W, and Q8W interval at Week 48	Proportion of patients in the faricimab arm on a Q16W, Q12W, and Q8W treatment interval at Week 48
	Secondary endpoint:	CfBL in CST at Week 40/44/48	Change from baseline in central subfield thickness (CST) at Week40/44/48
Database lock	The summary is based on a datacut with a clinical cut-off date of 26 October 2020 for the primary analysis of efficacy data through Week 48.		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, with patients grouped according to the treatment assigned at randomization. The primary analysis was performed when all patients from the global enrollment phase had either completed the study through Week 48 or had discontinued from the study prior to Week 48, whichever was later.		
Descriptive statistics and estimate variability	Treatment group	Faricimab up to every 16 weeks (Q16W)	Aflibercept Q8W
	Number of subjects	N = 334	N = 337
	Primary Endpoint: CfBL in BCVA at Week 40/44/48 Adjusted Mean (95.03% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)
	Secondary endpoint: Prop. of pts gaining ≥ 15 letters in BCVA from BSL at Week 40/44/48 CMH Weighted Estimate (95.03% CI)	20.0% (15.6%, 24.4%)	15.7% (11.9%, 19.6%)
	Secondary endpoint: Prop. of pts avoiding loss of ≥ 15 letters in BCVA from BSL at Week 40/44/48 CMH Weighted	95.4% (93.0%, 97.7%)	94.1% (91.5%, 96.7 %)
	Secondary endpoint: Prop. of pts in the faricimab arm on a Q16W, Q12W, and Q8W interval at Week 48 Unadjusted proportion (95.03% CI)	Q16W: 45.7% (40.2%, 51.2%) Q12W: 34.0% (28.7%, 39.2%) Q8W: 20.3% (15.9%, 24.8%)	N/A

	Secondary endpoint: CfBL in CST at Week 40/44/48	-136.8 (-142.6, -131.0)	-129.4 (-135.2, -123.5)
Effect estimate per comparison	Primary Endpoint: CfBL in BCVA at Week 40/44/48	Comparison groups (MMRM)	Faricimab up to Q16W vs. Aflibercept Q8W
		Difference in Adjusted Means (95.03%) NI margin: -4 letters	0.7 (-1.1, 2.5)

Table 28. Summary of efficacy for trial LUCERNE (GR40844)

Title: 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)			
Study identifier	GR40844, LUCERNE ClinicalTrials.gov Identifier: NCT03823300 EudraCT: 2018-004042-42		
Design	Multicenter, randomized, active comparator (aflibercept) controlled, double masked, parallel group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase (AVONELLE-X, Study GR42691):		112 weeks 28 days (screening visit to Day -1) 104 weeks
Hypothesis	Non-inferiority of faricimab (up to Q16W) compared with aflibercept (Q8W) in the intent-to-treat (ITT) population.		
Treatments groups	Faricimab up to every 16 weeks (Q16W)		6 mg faricimab intravitreal injection on Day 1 then Q4W up to Week 12, followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by a personalized treatment interval (PTI; adjustable dosing administered in 8, 12 or 16-week intervals) to Week 108; n=331 patients randomized.
	Aflibercept Q8W		2 mg aflibercept intravitreal injection on Day 1, then Q4W up to Week 8, followed by 2 mg of intravitreal aflibercept Q8W up to Week 108; n=327 patients randomized.
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 40/44/48	Change from baseline in BCVA averaged over Weeks 40, 44, and 48 (Week 40/44/48) measured using the ETDRS chart at a starting distance of 4 meters (NI margin of -4.0 letters)
	Secondary endpoint:	Prop. of pts gaining ≥ 15 letters in BCVA from BSL at Week	Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 40/44/48

	Secondary endpoint:	Prop. of pts avoiding loss of ≥ 15 letters in BCVA from BSL at Week 40/44/48	Proportion of patients avoiding loss of ≥ 15 letters in BCVA from baseline at Week 40/44/48
	Secondary endpoint:	Prop. of pts in the faricimab arm on a Q16W, Q12W, and Q8W interval at Week 48	Proportion of patients in the faricimab arm on a Q16W, Q12W, and Q8W treatment interval at Week 48
	Secondary endpoint:	CfBL in CST at Week 40/44/48	Change from baseline in CST at Week40/44/48
Database lock	The summary is based on a datacut with a clinical cut-off date of 5 October 2020 for the primary analysis of efficacy data through Week 48.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, with patients grouped according to the treatment assigned at randomization. The primary analysis was performed when all patients from the global enrollment phase had either completed the study through Week 48 or had discontinued from the study prior to Week 48, whichever was later.		
Descriptive statistics and estimate variability	Treatment group	Faricimab up to every 16 weeks (Q16W)	Aflibercept Q8W
	Number of subjects	N = 331	N = 327
	Primary Endpoint: CfBL in BCVA at Week 40/44/48 Adjusted Mean	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
	Secondary endpoint: Prop. of pts gaining ≥ 15 letters in BCVA from BSL at Week 40/44/48 CMH Weighted Estimate (95.03% CI)	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)

	Secondary endpoint: Prop. of pts avoiding loss of ≥ 15 letters in BCVA from BSL at Week 40/44/48 CMH Weighted Estimate (95.03% CI)	95.8% (93.6%, 98.0%)	97.3% (95.5%, 99.1%)
	Secondary endpoint: Prop. of pts in the faricimab arm on a Q16W, Q12W, and Q8W interval at Week 48 Unadjusted proportion (95.03% CI)	Q16W: 44.9% (39.4%, 50.4%) Q12W: 32.9% (27.7%, 38.1%) Q8W: 22.2% (17.6%, 26.7%)	N/A
	Secondary endpoint: CfBL in CST at Week 40/44/48 Adjusted Mean	-137.1 (-143.1, -131.2)	-130.8 (-136.8, -124.8)
Effect estimate per comparison	Primary endpoint: CfBL in BCVA at Week 40/44/48	Comparison groups (MMRM)	Faricimab up to Q16W vs. Aflibercept Q8W
		Difference in Adjusted Means (95.03%) NI margin: -4 letters	0.0 (-1.7, 1.8)

Analysis performed across trials (pooled analyses and meta-analysis)

nAMD- persistence of efficacy and/or tolerance effects through week 60

Change from Baseline in BCVA at Week 52/56/60

In both TENAYA and LUCERNE, the adjusted mean change from baseline in BCVA averaged over Weeks 52, 56, and 60 in the faricimab arm was comparable to that in the aflibercept arm. Results were consistent with results observed at Week 40/44/48. At Week 52/56/60, the difference in adjusted mean change from baseline in BCVA between the faricimab and aflibercept arms was 0.7 (95% CI: -1.2, 2.7) in TENAYA and -0.6 (95% CI: -2.4, 1.3) in LUCERNE. In the pooled ITT population, the difference between treatment arms was 0.1 (95% CI: -1.2, 1.4) at Week 52/56/60.

Table 19 Change from Baseline in BCVA in the Study Eye from the Individual and Pooled Phase III nAMD Studies at Week 40/44/48 and at Week 52/56/60: MMRM Method (Primary Estimand) (ITT Population)

Visit Statistics	GR40306 (TENAYA) (N = 671) Faricimab 6 mg (N=334)	 Aflibercept 2 mg (N=337)	GR40844 (LUCERNE) (N = 658) Faricimab 6 mg (N=331)	 Aflibercept 2 mg (N=327)	Pooled (TENAYA and LUCERNE) (N = 1329) Faricimab 6 mg (N=665)	 Aflibercept 2 mg Q8W (N=664)
Average of Weeks 40, 44 and 48						
n [a]	292	300	302	291	594	591
Adjusted Mean (SE)	5.8 (0.64)	5.1 (0.64)	6.6 (0.64)	6.6 (0.64)	6.2 (0.45)	5.9 (0.45)
95% CI for Adjusted Mean	(4.6, 7.1)	(3.9, 6.4)	(5.3, 7.8)	(5.3, 7.8)	(5.3, 7.1)	(5.0, 6.7)
Difference in Adjusted Means (SE)	0.7 (0.91)		0.0 (0.91)		0.4 (0.64)	
95% CI for Difference in Adjusted Means	(−1.1, 2.5)		(−1.7, 1.8)		(−0.9, 1.6)	
Average of Weeks 52, 56 and 60						
n [a]	277	283	289	276	566	559
Adjusted Mean (SE)	5.4 (0.70)	4.6 (0.70)	6.6 (0.65)	7.1 (0.66)	6.0 (0.48)	5.9 (0.48)
95% CI for Adjusted Mean	(4.0, 6.8)	(3.3, 6.0)	(5.3, 7.9)	(5.8, 8.4)	(5.0, 6.9)	(4.9, 6.8)
Difference in Adjusted Means (SE)	0.7 (0.99)		−0.6 (0.93)		0.1 (0.68)	
95% CI for Difference in Adjusted Means	(−1.2, 2.7)		(−2.4, 1.3)		(−1.2, 1.4)	

Units: letters. BCVA=Best Corrected Visual Acuity; LLD = Low-luminance Deficit; MMRM = Mixed-Model Repeated-Measures.
For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA score (>=74 letters, 73-55 letters, and <=54 letters), low-luminance deficit (< 33 letters and >=33 letters), region (U.S. and Canada, Asia, and the rest of the world). The model for pooled also adjusted for study (GR40306 vs GR40844). An unstructured covariance structure is used. For the average over Weeks 40, 44, and 48, the estimate of the difference between the two groups uses a composite contrast over Weeks 40, 44 and 48. For the average over Weeks 52, 56, and 60, the estimate of the difference between the two groups uses a composite contrast over Weeks 52, 56 and 60. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.
Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. 95% CI is reported for pooled. 95.03% CI is reported for the individual studies.
[a] n is the number of patients with at least one evaluable assessment at these timepoints.
Source (Week 40/44/48): TENAYA: t_ef_mmrm_yr1_SBCVA_PREST_IT_26OCT2020_40306, LUCERNE: t_ef_mmrm_yr1_SBCVA_PREST_IT_05OCT2020_40844, Pooled (TENAYA and LUCERNE): t_ef_mmrm_yr1_SBCVA_PREST_IT_nAMD_HLS
Source (Week 52/56/60): t_ef_mmrm_yr1_SBCVA_PREST_W60_IT_nAMD_HLS

In both TENAYA and LUCERNE, the change from baseline in BCVA at Week 52/56/60 was consistent between the ITT and PP populations and was supported by multiple supplementary analyses.

Table 20 Summary of Change from Baseline in BCVA in the Study Eye from the Individual and Pooled Phase III nAMD Studies at Week 52/56/60: ITT Population and Select Supplementary Analyses

	GR40306 (TENAYA) (N = 671)			GR40844 (LUCERNE) (N = 658)			POOLED (TENAYA and LUCERNE) (N = 1329)		
	Faricimab 6 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)	Faricimab 6 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)	Faricimab 6 mg Adjusted Mean (SE) (95% CI)	Aflibercept 2 mg Adjusted Mean (SE) (95% CI)	Difference in Adjusted Means (SE) (95% CI)
Main Analysis – MMRM Method									
ITT Population	5.4 (0.70) (4.0, 6.8)	4.6 (0.70) (3.3 6.0)	0.7 (0.99) (−1.2, 2.7)	6.6 (0.65) (5.3, 7.9)	7.1 (0.66) (5.8, 8.4)	−0.6 (0.93) (−2.4, 1.3)	6.0 (0.48) (5.0, 6.9)	5.9 (0.48) (4.9, 6.8)	0.1 (0.68) (−1.2, 1.4)
Supplementary Analyses									
Per Protocol Analysis – MMRM Method									
PP Population	5.3 (0.75) (3.8, 6.8)	5.3 (0.75) (3.8, 6.7)	0.0 (1.06) (−2.0, 2.1)	7.0 (0.68) (5.7, 8.4)	7.4 (0.68) (6.0, 8.7)	−0.4 (0.97) (−2.3, 1.5)	6.2 (0.51) (5.2, 7.2)	6.3 (0.51) (5.3, 7.3)	−0.1 (0.72) (−1.6, 1.3)
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMRM Method									
ITT Population	5.1 (0.70) (3.7, 6.4)	4.4 (0.70) (3.1, 5.8)	0.6 (0.99) (−1.3, 2.6)	6.4 (0.65) (5.1, 7.7)	7.0 (0.66) (5.7, 8.3)	−0.6 (0.93) (−2.4, 1.2)	5.7 (0.48) (4.8, 6.7)	5.7 (0.48) (4.8, 6.6)	0.0 (0.68) (−1.3, 1.4)
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM Method									
ITT Population	5.4 (0.71) (4.0, 6.8)	4.6 (0.70) (3.2, 6.0)	0.7 (0.99) (−1.2, 2.7)	6.7 (0.64) (5.5, 8.0)	7.1 (0.65) (5.8, 8.4)	−0.4 (0.91) (−2.2, 1.4)	6.1 (0.48) (5.1, 7.0)	5.9 (0.48) (4.9, 6.8)	0.2 (0.67) (−1.1, 1.5)
Multiple Imputation Analysis – ANCOVA Method									
ITT Population	4.2 (0.94) (2.3, 6.0)	3.3 (0.94) (1.4, 5.1)	0.9 (0.97) (−1.0, 2.8)	6.5 (0.86) (4.8, 8.1)	7.3 (0.89) (5.6, 9.1)	−0.9 (0.93) (−2.7, 1.0)	5.2 (0.64) (3.9, 6.4)	5.2 (0.64) (3.9, 6.4)	0.0 (0.69) (1.4, 1.3)

Units: letters. ANCOVA = analysis of covariance; BCVA = Best-corrected Visual Acuity; ITT = Intent-to-Treat; LLD = Low-luminance Deficit; MMRM = Mixed-Model Repeated-Measures; PP = Per Protocol.

Change from Baseline in BCVA Over Time

The adjusted mean change from baseline in BCVA over time through Week 60 was comparable between the faricimab and aflibercept arms, and demonstrated consistency in BCVA response between Week 48 and Week 60 in both TENAYA and LUCERNE.

Figure 17 Study GR40306 (TENAYA): Plot of Change from Baseline in BCVA in the Study Eye through Week 60: MMRM Method (Primary Estimand) (ITT Population)

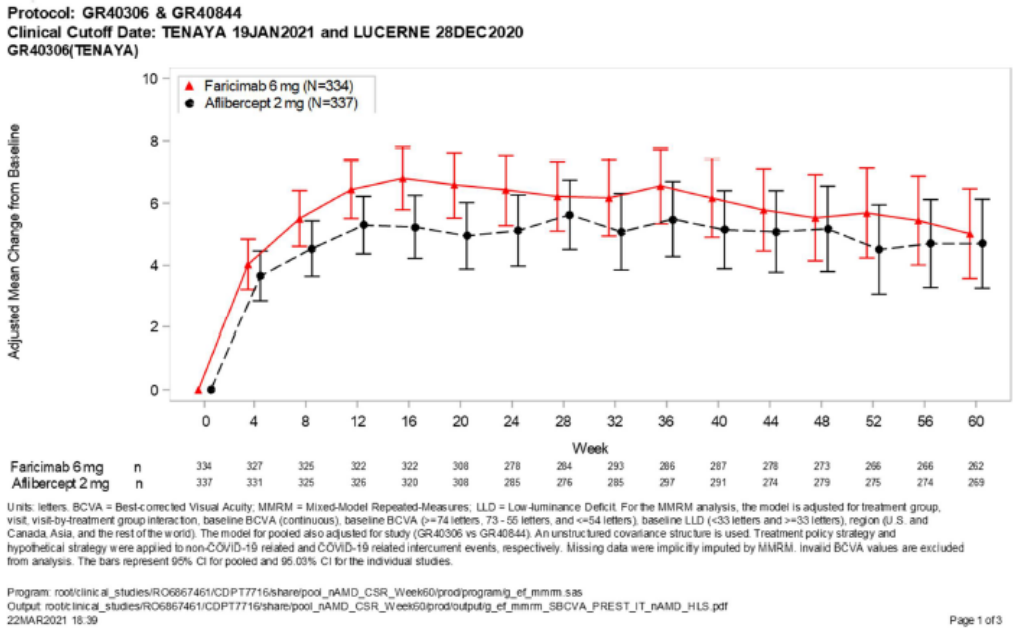
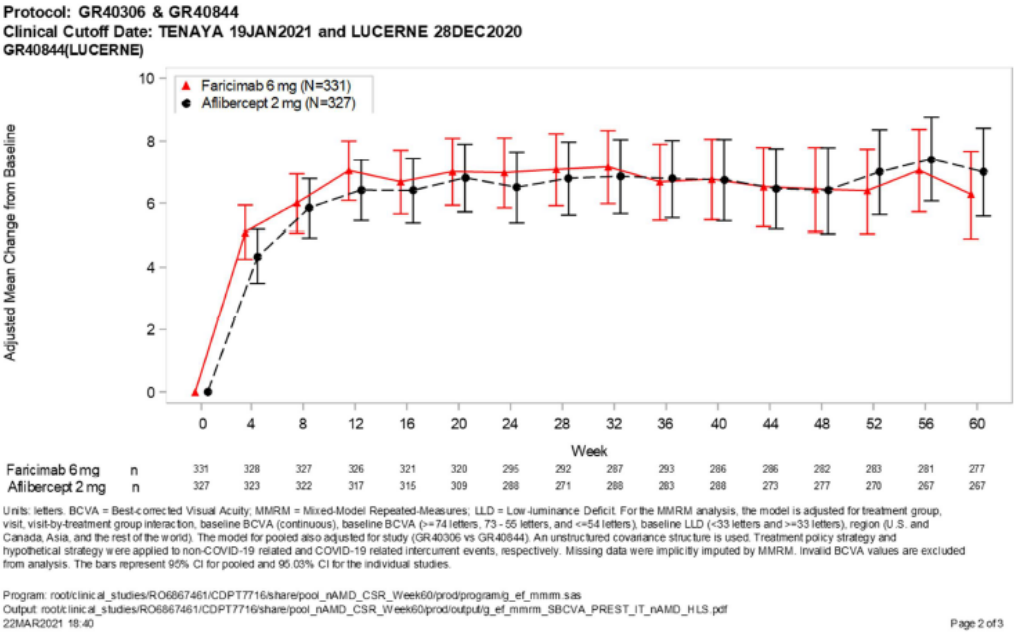


Figure 18 Study GR40844 (LUCERNE): Plot of Change from Baseline in BCVA in the Study Eye through Week 60: MMRM Method (Primary Estimand) (ITT Population)



<u>Proportion of Patients Gaining ≥ 15 Letters in BCVA from Baseline at Week 52/56/60 and Over Time through Week 60</u>

In both TENAYA and LUCERNE, the proportion of patients who gained ≥15 letters from baseline at Week 52/56/60 was comparable between the treatment arms, and was consistent with rates observed at Week 40/44/48. In the pooled ITT population, 20.9% and 20.2% of patients in the faricimab and aflibercept arms, respectively, gained ≥ 15 letters in BCVA score from baseline at Week 52/56/60; the difference between treatment arms was 0.7% (95% CI: -3.6%, 5.1%).

Table 22 Proportion of Patients Gaining ≥15 Letters in the Study Eye BCVA in the Individual and Pooled Phase III nAMD Studies at Week 40/44/48 and at Week 52/56/60: CMH Method (Primary Estimand) (ITT Population)

	GR40306 (TENAYA) (N = 671)		GR40644 (LUCERNE) (N = 658)		Pooled (TENAYA and LUCERNE) (N = 1329)	
Gaining >= 15 Letters in BCVA from Baseline	Faricimab 6 mg (N=334)	Aflibercept 2 mg (N=337)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=327)	Faricimab 6 mg (N=665)	Aflibercept 2 mg Q8W (N=664)
Average over Weeks 40, 44 and 48						
N [a]	292	300	302	291	594	591
CMH Weighted Estimate						
%	20.0%	15.7%	20.2%	22.2%	20.1%	19.0%
95% CI	(15.6%, 24.4%)	(11.9%, 19.6%)	(15.9%, 24.6%)	(17.7%, 26.8%)	(17.0%, 23.2%)	(16.0%, 22.0%)
Difference						
Difference in CMH Weighted %	4.3%		-2.0%		1.1%	
95% CI for Difference in CMH Weighted %	(-1.6%, 10.1%)		(-8.3%, 4.3%)		(-3.2%, 5.4%)	
Average over Weeks 52, 56 and 60						
N [a]	277	283	289	276	566	559
CMH Weighted Estimate						
%	19.2%	16.6%	22.6%	23.7%	20.9%	20.2%
95% CI	(15.0%, 23.5%)	(12.5%, 20.6%)	(18.1%, 27.1%)	(19.1%, 28.4%)	(17.8%, 24.0%)	(17.1%, 23.3%)
Difference						
Difference in CMH Weighted %	2.7%		-1.2%		0.7%	
95% CI for Difference in CMH Weighted %	(-3.2%, 8.5%)		(-7.7%, 5.3%)		(-3.6%, 5.1%)	

BCVA = Best-corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LLD = Low-luminance Deficit.
The weighted estimate is based on CMH test stratified by baseline BCVA (>=74 letters, 73 - 55 letters, and <=54 letters), baseline LLD (<33 letters and >=33 letters), region(U.S. and Canada, Asia, and the rest of the world). Pooled is also stratified by study (GR40306 vs GR40644). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were not imputed. Invalid BCVA values are excluded from analysis.95% CI is reported for pooled. 95.03% CI is reported for the individual studies. Estimates below 0% or above 100% are imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization.

[a] N is the number of patients with at least one evaluable assessment at these timepoints.

Source (Week 40/44/48): Table 13

Source (Week 52/56/60): t_ef_cmh_SBCVAG15_YR1_PREST_W60_IT_nAMD_HLS

Proportion of Patients avoiding a loss of ≥ 15 Letters in BCVA from Baseline at Week 52/56/60 and Over Time through Week 60

In both TENAYA and LUCERNE, the proportion of patients who avoided a loss of≥15 letters in BCVA score from baseline at Week 52/56/60 was comparable between the treatment arms, and was consistent with rates observed at Week 40/44/48. In the pooled ITT population, 95.2% and 95.1% of patients in the faricimab and aflibercept arms, respectively, avoided a loss of ≥ 15 letters in BCVA score from baseline at Week 52/56/60; the difference between arms was 0.1% (95% CI: -2.3%, 2.5%).

Table 23 Proportion of Patients Avoiding a Loss of ≥15 Letters in the Study Eye BCVA in the Individual and Pooled Phase III nAMD Studies at Week 40/44/48 and at Week 52/56/60: CMH Method (Primary Estimand) (ITT Population)

	GR40306 (TENAYA) (N = 671)		GR40844 (LUCERNE) (N = 658)		Pooled (TENAYA and LUCERNE) (N = 1329)	
Avoiding Loss of >= 15 Letters in BCVA from Baseline	Faricimab 6 mg (N=334)	Aflibercept 2 mg (N=337)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=327)	Faricimab 6 mg (N=665)	Aflibercept 2 mg Q8W (N=664)
Average over Weeks 40, 44 and 48						
N [a]	292	300	302	291	594	591
CMH Weighted Estimate						
%						
95% CI	95.4% (93.0%, 97.7%)	94.1% (91.5%, 96.7%)	95.8% (93.6%, 98.0%)	97.3% (95.5%, 99.1%)	95.6% (94.0%, 97.2%)	95.7% (94.1%, 97.3%)
Difference						
Difference in CMH Weighted %	1.3%		-1.5%		-0.1%	
95% CI for Difference in CMH Weighted %	(-2.2%, 4.8%)		(-4.4%, 1.3%)		(-2.4%, 2.1%)	
Average over Weeks 52, 56 and 60						
N [a]	277	283	289	276	566	559
CMH Weighted Estimate						
%	93.9%	94.1%	96.5%	96.1%	95.2%	95.1%
95% CI	(91.3%, 96.5%)	(91.4%, 96.8%)	(94.4%, 98.6%)	(94.0%, 98.3%)	(93.6%, 96.9%)	(93.4%, 96.8%)
Difference						
Difference in CMH Weighted %	-0.2%		0.4%		0.1%	
95% CI for Difference in CMH Weighted %	(-3.9%, 3.6%)		(-2.6%, 3.3%)		(-2.3%, 2.5%)	

BCVA = Best-corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LLD = Low-luminance Deficit.
The weighted estimate is based on CMH test stratified by baseline BCVA (>=74 letters, 73 - 55 letters, and <= 54 letters), baseline LLD (<33 letters and >=33 letters), region (U.S. and Canada, Asia, and the rest of the world). Pooled is also stratified by study (GR40306 vs GR40844). Asia and rest of the world regions are combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were not imputed. Invalid BCVA values are excluded from analysis. 95% CI is reported for pooled. 95.03% CI is reported for the individual studies. Estimates below 0% or above 100% are imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization.
[a] n is the number of patients with at least one evaluable assessment at these timepoints.

Source (Week 40/44/48): Table 14

Source (Week 52/56/60): t_ef_cmh_SBCVAL15_YR1_PREST_W60_IT_nAMD_HLS

Figure 20 Study GR40306 (TENAYA) : Proportion of Patients Avoiding a Loss of ≥15 Letters in BCVA from Baseline in the Study Eye over Time through Week 60: CMH Method (Primary Estimand) (ITT Population)

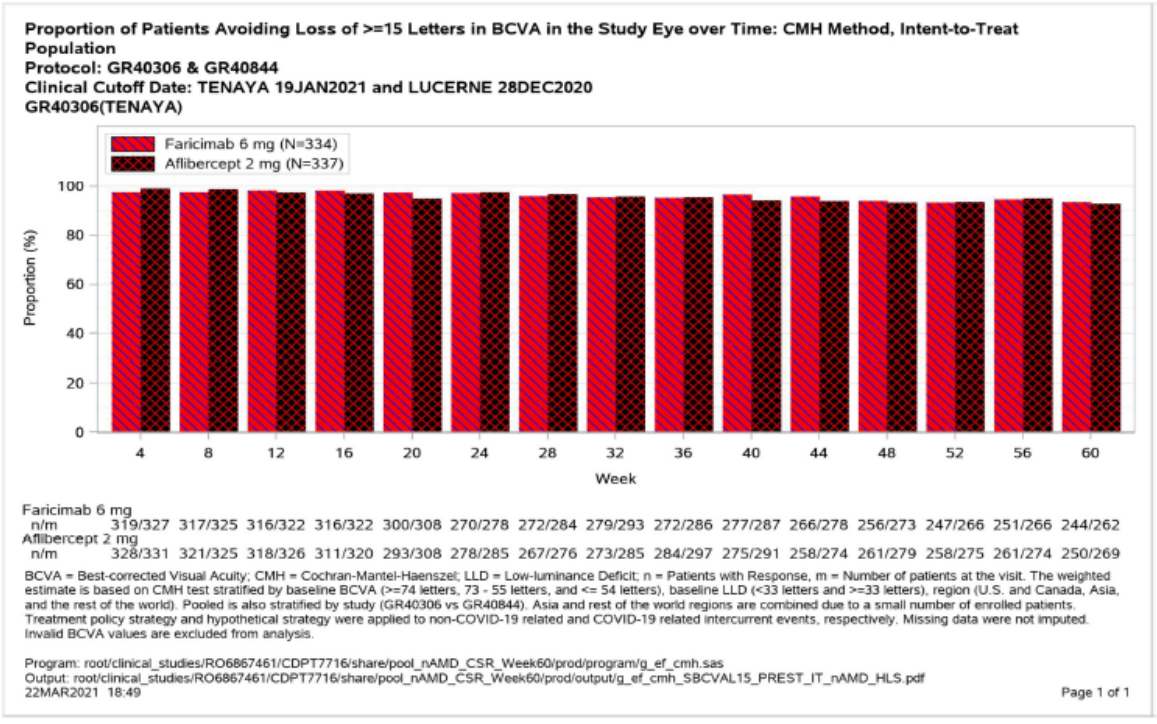
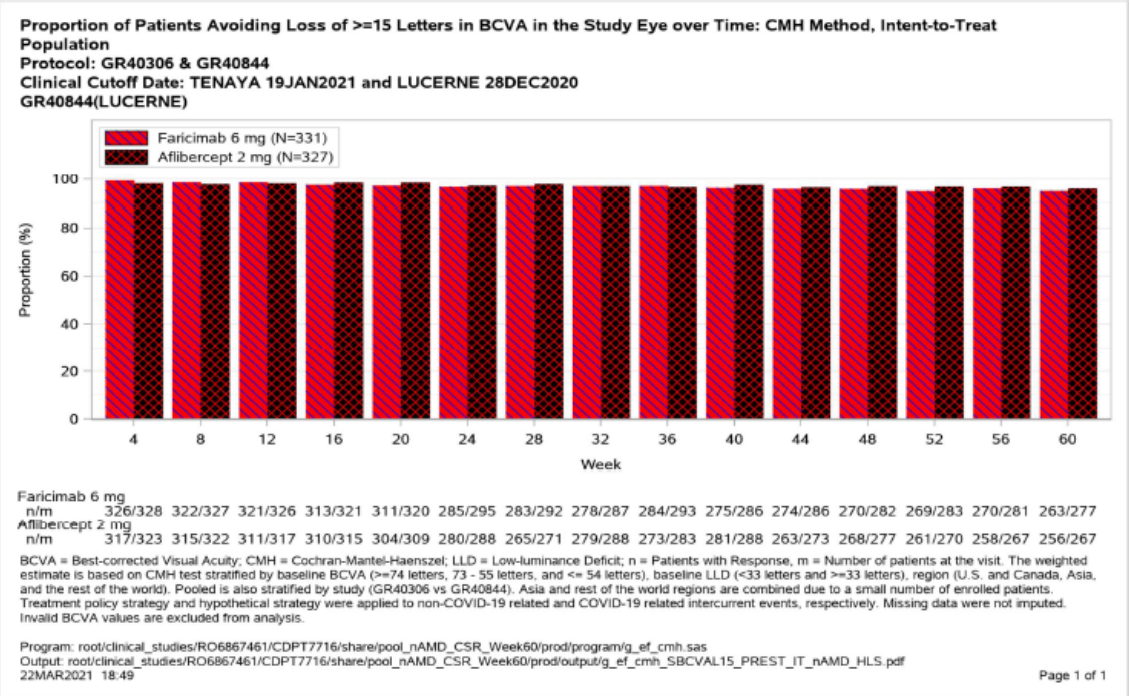


Figure 21 Study GR40844 (LUCERNE): Proportion of Patients Avoiding a Loss of ≥15 Letters in BCVA from Baseline in the Study Eye over Time through Week 60: CMH Method (Primary Estimand) (ITT Population)



<u>Proportion of patients in the faricimab arm on Q8W, Q12W, OR Q16W treatment interval at week 60</u>

In both TENAYA and LUCERNE, the proportions of faricimab-treated patients who were on a fixed dosing regimen of Q12W or Q16W at Week 60 were consistent with proportions observed at Week 48. In TENAYA and LUCERNE at Week 60, 79.8% and 78.4% of patients, respectively, in the faricimab dosing arm were on a fixed dosing regimen of Q12W or Q16W. In TENAYA, the proportions of faricimab-treated patients on a fixed Q8W, Q12W or Q16W treatment interval at Week 60 were 20.2%, 33.4% and 46.4%. In LUCERNE, the proportions of faricimab-treated patients on a fixed Q8W, Q12W, or Q16W treatment interval at Week 60 were 21.6%, 32.8%, and 45.6%. In the pooled ITT population at Week 60, 79.1% of patients in the faricimab dosing arm were on a fixed Q12W or Q16W dosing regimen. Overall, 20.9%, 33.1%, and 46.0% of patients were on a fixed Q8W, Q12W, and Q16W dosing regimen at Week 60. Percentages are based on the number of patients randomized to the

faricimab arm who had not discontinued the study at Week 60.

Table 24 Proportion of Patients in the Faricimab Arm from the Individual and Pooled Phase III nAMD Studies on a Q8W, Q12W, and Q16W Treatment Interval Among Those Completing Weeks 48 and 60

Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 and LUCERNE 28DEC2020

	GR40306 (TENAYA) (N=334)			GR40844 (LUCERNE) (N=331)			Pooled (TENAYA and LUCERNE) (N=665)		
	Faricimab 6 mg (N=334)			Faricimab 6 mg (N=331)			Faricimab 6 mg (N=665)		
Visit	Proportion n (%)	95% CI of Proportion		Proportion n (%)	95% CI of Proportion		Proportion n (%)	95% CI of Proportion	
Week 48									
N	315			316			631		
Q8W	64 (20.3%)	15.9%,	24.8%	70 (22.2%)	17.6%,	26.7%	134 (21.2%)	18.0%,	24.4%
Q12W	107 (34.0%)	28.7%,	39.2%	104 (32.9%)	27.7%,	38.1%	211 (33.4%)	29.8%,	37.1%
Q16W	144 (45.7%)	40.2%,	51.2%	142 (44.9%)	39.4%,	50.4%	286 (45.3%)	41.4%,	49.2%
Week 60									
N	302			305			607		
Q8W	61 (20.2%)	15.7%,	24.7%	66 (21.6%)	17.0%,	26.3%	127 (20.9%)	17.7%,	24.2%
Q12W	101 (33.4%)	28.1%,	38.8%	100 (32.8%)	27.5%,	38.1%	201 (33.1%)	29.4%,	36.9%
Q16W	140 (46.4%)	40.7%,	52.0%	139 (45.6%)	40.0%,	51.2%	279 (46.0%)	42.0%,	49.9%

Percentages are based on number of patients randomized to the faricimab arm who have not discontinued the study at specified visit.
Treatment interval at a given visit is defined as the treatment interval decision followed at that visit.
* Patients randomised to Faricimab receive 6 mg of intravitreal (IVT) faricimab Q4W up to Week 12 (4 injections) and undergo protocol-defined disease activity assessments at weeks 20 and 24. Patients with no evidence of active disease at weeks 20 and 24 received Q16W dosing through week 60; those with active disease at week 20 received Q8W dosing; patients with active disease only at week 24 received Q12W dosing.
95% CI is reported for pooled. 95.03% CI is reported for the individual studies.

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_CSR_Week60/prod/program/t_int_prop.sas
Adapted from Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_CSR_Week60/prod/output/t_int_prop_COMPW_IT_nAMD_HLS.out
22MAR2021 18:57 Page 1 of 1

Anatomic outcome measures using OCT

Change from Baseline in CST at Week 52/56/60

In both TENAYA and LUCERNE, patients in the faricimab and aflibercept arms had comparable reductions in CST from baseline at Week 52/56/60, with results comparable to the mean CST reductions achieved at Week 40/44/48. In the pooled ITT population, the adjusted mean change in CST from baseline at Week 52/56/60 was -135.1 and -136.1 µm in the faricimab and aflibercept arms, respectively; the difference between treatment arms was 1.0 µm (95% CI: -4.7, 6.8).

Table 25 Change from Baseline in CST in the Study Eye at Week 40/44/48 and at Week 52/56/60 in Individual and Pooled Phase III nAMD Studies: MMRM Method (Primary Estimand) (ITT Population)

	GR40306 (TENAYA) (N = 671)		GR40844 (LUCERNE) (N = 658)		Pooled (TENAYA and LUCERNE) (N = 1329)	
Visit Statistics	Faricimab 6 mg (N=334)	Aflibercept 2 mg (N=337)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=327)	Faricimab 6 mg (N=665)	Aflibercept 2 mg Q8W (N=664)
Average of Weeks 40, 44 and 48						
n a	291	297	299	287	590	584
Adjusted Mean (SE)	-136.8 (2.97)	-129.4 (2.96)	-137.1 (3.02)	-130.8 (3.05)	-137.0 (2.11)	-130.1 (2.12)
95% CI for Adjusted Mean	(-142.6, -131.0)	(-135.2, -123.5)	(-143.1, -131.2)	(-136.8, -124.8)	(-141.2, -132.9)	(-134.2, -125.9)
Difference in Adjusted Means (SE)	-7.4 (4.19)		-6.4 (4.30)		-7.0 (2.99)	
95% CI for Difference in Adjusted Means	(-15.7, 0.8)		(-14.8, 2.1)		(-12.8, -1.1)	
Average of Weeks 52, 56 and 60						
n *	277	280	287	273	564	553
Adjusted Mean (SE)	-134.5 (3.02)	-135.5 (3.01)	-135.7 (2.84)	-137.0 (2.88)	-135.1 (2.07)	-136.1 (2.08)
95% CI for Adjusted Mean	(-140.5, -128.6)	(-141.5, -129.6)	(-141.2, -130.1)	(-142.7, -131.3)	(-139.2, -131.1)	(-140.2, -132.1)
Difference in Adjusted Means (SE)	1.0 (4.26)		1.4 (4.05)		1.0 (2.94)	
95% CI for Difference in Adjusted Means	(-7.4, 9.4)		(-6.6, 9.3)		(-4.7, 6.8)	

Units: microns. BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; LLD = Low-luminance Deficit; MMRM = Mixed-Model Repeated-Measures.
For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (>=74 letters, 73 - 55 letters, and <= 54 letters), baseline LLD (<33 letters and >=33 letters), region (U.S. and Canada, Asia, and the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. The model for pooled also adjusted for study (GR40306 vs GR40844). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks 52, 56 and 60. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM.95% CI is reported for pooled. 95.03% CI is reported for the individual studies. CST is defined as the distance between ILM and retinal pigment epithelium (RPE), as assessed by CRC.
* n is the number of patients with at least one evaluable assessment at these timepoints.
Source (Week 40/44/48): Table 16
Source (Week 52/56/60): t_ef_mmrm_yr1_SSRCST_PREST_W60_IT_nAMD_HLS

Change from Baseline in CST Over Time through Week 60

In both TENAYA and LUCERNE, patients in the faricimab and aflibercept arms had comparable reductions in CST from baseline over time through Week 60.

Figure 22 Study GR40306 (TENAYA): Change from Baseline in CST in the Study Eye over Time through Week 60: MMRM Method (Primary Estimand) (ITT Population)

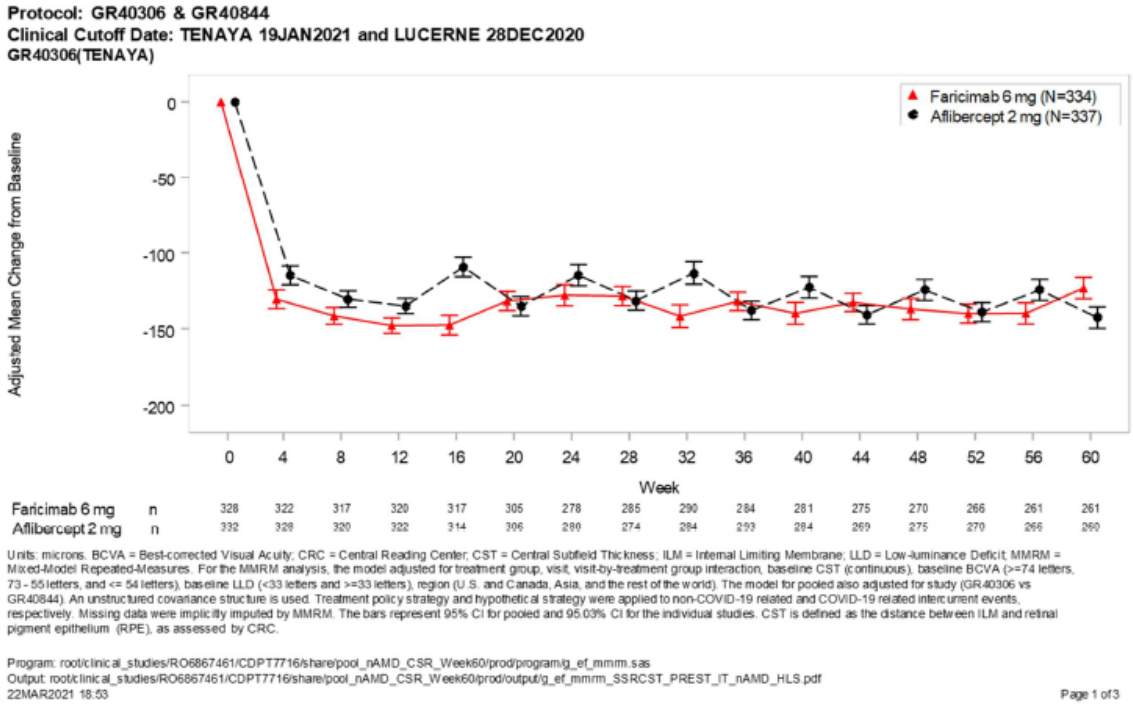
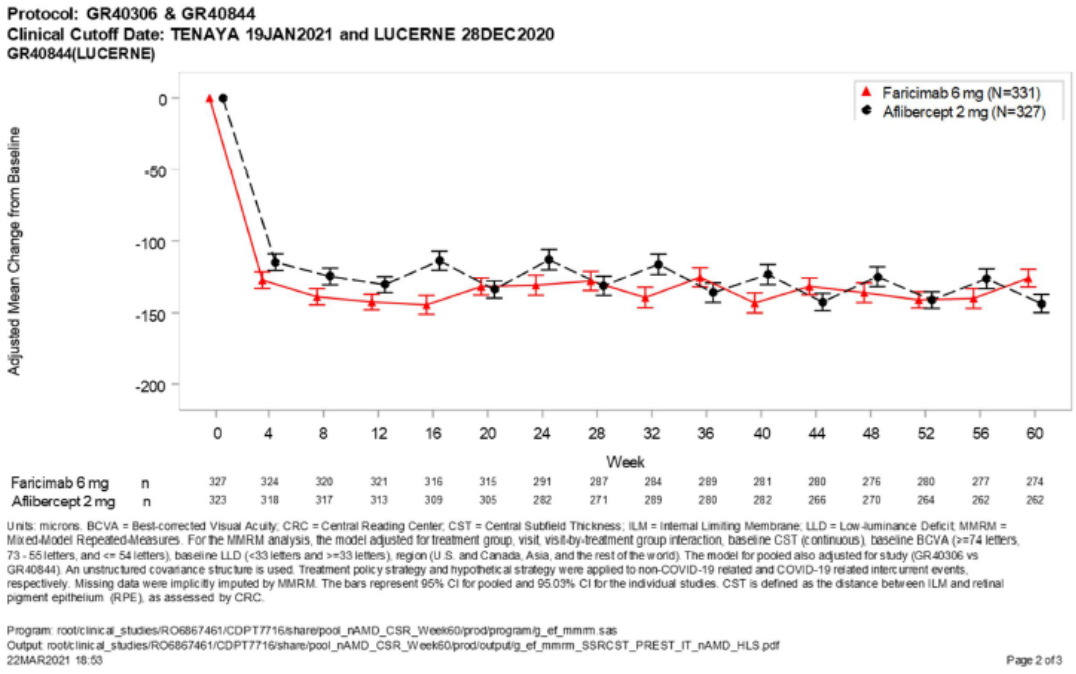


Figure 23 Study GR40844 (LUCERNE): Change from Baseline in CST in the Study Eye over Time through Week 60: MMRM Method (Primary Estimand) (ITT Population)



Clinical studies in special populations

No studies were conducted in special populations.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled trials			

Diabetic macular oedema

In support of the indication the applicant submitted one phase II study (BOULEVARD BP30099) that could be construed as a dose finding study and two phase III (RHINE and YOSEMITE) main studies.

Dose-response studies and main clinical studies

BOULEVARD was a multiple-center, multiple dose, randomized, active comparator controlled (ranibizumab 0.3mg), double-masked, three parallel group study in patients with diabetic macular oedema.

The primary objective of this study was to evaluate the efficacy of faricimab compared with the active comparator ranibizumab in treatment naive patients with center-involving diabetic macular edema (CIDME).

Secondary efficacy objectives included exploring the duration of effect of RO6867461

The three treatments arms of this study were as follows (see Figure 57):

- Arm A: 0.3 mg ranibizumab IVT
- Arm B: 1.5 mg RO6867461 IVT
- Arm C: 6 mg RO6867461 IVT

The total duration of the study for each patient was up to 40 weeks, with screening up to 4 weeks, study treatment period from Day 1(baseline) to Week 20, an observational period from week 20 to week 36 or earlier and a safety follow-up call during the observation period and 7 days after ranibizumab administration. All treatments were administered every 4 weeks.

Up to 210 patients were planned to be randomized, including approximately 150 treatment-naive patients and approximately 60 patients who had been previously treated with IVT anti-VEGF. Approximately 50 treatment-naive patients were planned to be randomized into each arm (1:1:1 randomization scheme) and approximately 30 patients previously treated with IVT anti-VEGF were to be randomized into arms A and C.

Patients had to meet the following criteria for inclusion:

- Macular oedema associated with diabetic retinopathy defined as macular thickening by spectral domain optical coherence tomography (SD-OCT) involving the center of the macula: central subfield thickness (CST) of ≥325 µm with Spectralis® (Heidelberg) at screening (where Spectralis was not available, the following devices and CST thresholds were acceptable: CST ≥315 µm for Cirrus™, CST ≥315 µm for Topcon™, CST ≥295 µm for Optovue™)

- Decreased visual acuity attributable primarily to DME, with BCVA letter score of 73-24 letters (inclusive) on ETDRS-like charts (20/40-20/320 Snellen equivalent) on Day 1
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

The primary efficacy endpoint was mean change in BCVA (ETDRS letters) from baseline at Week 24 in treatment-naive patients. Secondary efficacy endpoints included: proportion of patients gaining ≥15 letters from baseline BCVA at Week 24; mean change from baseline in foveal center point thickness (FCPT, also referred to as Central Retinal Thickness [CRT]) at Week 24. Analysis of the primary endpoint and secondary endpoints was also carried out in the previously treated population.

In total, 168 treatment-naive patients were randomized into Study BP30099, 59 to the 0.3 mg ranibizumab arm, 54 to the 1.5 mg RO6867461 arm, and 55 to the 6 mg RO6867461 arm (Table 29). Two patients in the 6 mg RO6867461 arm were excluded from the analysis populations due to GCP non-compliance at a single site.

A total of 61 patients who had received prior anti-VEGF treatment were randomized: 31 to the 0.3 mg ranibizumab arm and 29 to the 6 mg RO6867461 arm. One previously treated patient was incorrectly randomized to the 1.5 mg RO6867461 arm; this patient was excluded from the efficacy analyses.

Table 29 Summary of analysis populations

	Treatment-naïve			Previously treated		
	0.3mg ranibizumab N = 59	1.5mg RO6867461 N = 54	6mg RO6867461 N = 55	0.3mg ranibizumab N = 31	1.5mg RO6867461 N = 1	6mg RO6867461 n = 29
Randomised	59	54	55	31	1	29
All patients population Total exclusions	59 0	54 0	53 2	31	1	29
Intent to treat population	59	54	53	31	1	29

In the treatment-naive patient population, the mean change from baseline in BCVA at Week 24 resulted in a statistically significant +3.6 ETDRS-letter difference in the 6 mg RO6867461 arm compared with the 0.3 mg ranibizumab arm (p=0.03, 80% CI: 1.5, 5.6; Table 30); the difference for the 1.5 mg RO6867461 arm compared with the 0.3 mg ranibizumab arm was not statistically significant (+1.4 letters, p=0.37, 80% CI:-0.6, 3.4).

The adjusted (by MMRM model) absolute mean change from baseline at Week 24 was 10.3, 11.7, and 13.9 ETDRS-letters for the 0.3 mg ranibizumab, 1.5 mg RO6867461, and 6 mg RO6867461 arms respectively.

Table 30. Summary of mean change from baseline in BCVA

Table 17 Summary of Mean Change from Baseline in BCVA at Week 24 (Treatment-Naive Patients)

	0.3 mg Ranibizumab N=59	1.5 mg RO6867461 N=54	6 mg RO6867461 N=53
n	49	49	44
Observed values (SD)	10.1 (8.6)	12.3 (8.1)	14.8 (10.6)
LS mean (CI)	10.3 (8.8, 11.9)	11.7 (10.1, 13.3)	13.9 (12.2, 15.6)
Difference (CI) vs. ranibizumab	–	1.4 (-0.6, 3.4)	3.6 (1.5, 5.6)
p-value	–	0.37	0.03

BCVA=best corrected visual acuity
Data source: t_bcva_cb_mod_ITT_TN, t_bcva_cb_mod_LSM_ITT_TN, t_bcva_ITT_TN

Results of the linear model analysis in treatment-naive patients are presented in Figure 3 and Table 17.

Secondary endpoints

For previously treated patients, the model-based changes from baseline were 8.3 and 9.6 letters for 0.3 mg ranibizumab and 6 mg RO6867461 arms, respectively. The difference of +1.3 letters was not statistically significant (p=0.63, 80% CI:-2.3, 5.0). The unadjusted mean change from baseline at Week 24 was 9.3, and 11.1 letters for the 0.3 mg ranibizumab, and 6 mg RO6867461 arms, respectively (Table 31).

In the total All Patients (ITT) population (both treatment-naive and previously treated patients), the effect was smaller than for the treatment-naive population, but still statistically significant (p=0.04, 80% CI: 1.1, 4.8) with +2.9 letter difference in the 6 mg RO6867461 arm compared with the 0.3 mg ranibizumab arm. In the 1.5 mg RO6867461 arm the difference at Week 24 to 0.3 mg ranibizumab was not statistically significant with a change of +2.3 letters from baseline (p=0.15, CI: -0.2, 4.3). The absolute change from baseline at Week 24 was 9.4, 11.7, and 12.3 letters for the 0.3 mg ranibizumab, 1.5 mg RO6867461, and 6 mg RO6867461 treatment arm, respectively.

Table 31. BCVA change from baseline at Week 24

Table 18 Summary of Mean Change from Baseline in BCVA at Week 24 for Previously-Treated and All Patients (All Patients)

	0.3 mg Ranibizumab	1.5 mg RO6867461	6 mg RO6867461
Previously Treated Patients	n=28	n=1	n=23
Observed values (SD)	9.3 (7.7)	–	11.1 (12.2)
LS mean (CI)	8.3 (5.7, 10.8)	–	9.6 (7.0, 12.3)
Difference (CI) vs. ranibizumab	–	–	1.3 (-2.3, 5.0)
p-value	–	–	0.63
All Patients	n=77	n=50	n=67
Observed values (SD)	9.8 (8.2)	12.2 (8.1)	13.5 (11.2)
LS mean (CI)	9.4 (8.1, 10.7)	11.7 (10.0, 13.4)	12.3 (10.9, 13.7)
Difference (CI) vs. ranibizumab	–	2.3 (0.2, 4.3)	2.9 (1.1, 4.7)
p-value	–	0.15	0.04

BCVA=best corrected visual acuity

Data source: t_bcva_cb_mod_ITT_PT, t_bcva_cb_mod_LSM_ITT_PT, t_bcva_ITT_PT, t_bcva_cb_mod_ITT, t_bcva_cb_mod_LSM_ITT, t_bcva_ITT

Note: Nominal p-value was reported without correction for multiple comparisons.

. Starting from Week 8 up to Week 24, patients in both 1.5 mg RO6867461 and 6 mg RO6867461 arms had a numerically higher proportion of patients gaining ≥15 letters BCVA than patients in the 0.3 mg ranibizumab arm.

At Week 24, 36.7% and 43.2% of observed treatment-naive patients in the 1.5 mg RO6867461and 6 mg RO6867461 arms, respectively, gained ≥15 letters from baseline compared with 32.7% of patients in the 0.3 mg ranibizumab arm (Table 32).

The proportions of previously-treated patients gaining ≥15 letters at Week 24 were 17.9% and 26.1% for the 0.3 mg ranibizumab and 6 mg RO6867461 treatment arms respectively (Table 32).

Table 32. Proportions of patients gaining at least 15 letters at Week 24

Table 19 Proportion of Patients Gaining ≥15 Letters BCVA at Week 24 (All Patients)

	0.3 mg Ranibizumab	1.5 mg RO6867461	6 mg RO6867461
Treatment-Naive Patients	n=59	n=54	n=53
Observed % of patients	32.7	36.7	43.2
LS mean % (CI)	35.3 (27.3, 44.1)	36.0 (27.9, 45.0)	42.5 (33.5, 52.1)
% difference (CI) vs. ranibizumab	-	0.8 (-11.3, 12.8)	7.3 (-5.4, 19.9)
p-value	-	0.94	0.46
Previously Treated Patients	n=31	n=1	n=29
Observed % of patients	17.9	-	26.1
LS mean % (CI)	16.8 (9.6, 27.8)	-	23.2 (14.1, 35.7)
% difference (CI) vs. ranibizumab	-	-	6.4 (-7.7, 20.5)
p-value	-		0.56
All Patients	n=90	n=55	n=82
Observed % of patients	27.3	36.0	37.3
LS mean % (CI)	28.7 (22.7, 35.5)	35.3 (27.4, 44.2)	35.9 (28.9, 43.6)
% difference (CI) vs. ranibizumab	-	6.6 (-4.0, 17.2)	7.2 (-2.6, 17.0)
p-value	-	0.43	0.34

BCVA=best corrected visual acuity

Data source: t_bcva_cat_ITT_TN; t_bcva_cat_ITT_PT; t_bcva_cat_ITT_WK24; t_bcva_mod_gain15_ITT_TN, t_bcva_mod_gain15_ITT_PT, t_bcva_mod_gain15_ITT, t_bcva_mod_gain15_LSM_ITT_TN, t_bcva_mod_gain15_LSM_ITT_PT, t_bcva_mod_gain15_LSM_ITT

Note: Nominal p-value was reported without correction for multiple comparisons.

Mean change from baseline in foveal centre point thickness at Week 24

The adjusted mean difference in FCPT change from baseline at Week 24 was -6.5 µm and -22.8 µm between 0.3 mg ranibizumab and the 1.5 mg RO6867461 and 6 mg RO6867461 arms, respectively in the treatment naïve population.

For the previously treated patient population, the adjusted mean difference in FCPT change from baseline at Week 24 was also not statistically significant (-49.2 µm, p=0.07) for the 6 mg RO6867461 treatment arm compared with the 0.3 mg ranibizumab arm. The difference in mean change from baseline at Week 24 in the reduction of FCPT for the All Patients population was statistically significant for the 6 mg RO6867461 arm compared with the 0.3 mg ranibizumab arm (-29.2 µm, p=0.05, 80% CI: -47.8,-10.6).

The absolute mean change from baseline at Week 24 was -212.1 µm, -260.2 µm, and -227.8 µm for 0.3 mg ranibizumab, 1.5 mg RO6867461, and 6 mg RO6867461, respectively (Table 33).

Table 33 Mean Change from Baseline in Foveal Center Point Thickness at Week 24 (All Patients)

	0.3 mg Ranibizumab	**1.5 mg RO6867461**	**6 mg RO6867461**
Treatment naïve	N =59	N = 54	N = 53
Change from baseline (µm) (SD)	-225.4 (185.8)	-263.4 (199.9)	-233.2 (138.4)
LS mean % (80% CI)	-243.4 (-261.6, -225.2)	-249.9 (-269.5, -230.4)	-266.2 (-286.6, -245.8)
Diff in LS means vs ranibizumab (80% CI)		-6.5 (-27.8, 14.7)	-22.8 (-44.5, -1.2)
p-value		0.69	0.18
Previously treated	N = 31	N =1	N = 29
Change from baseline (µm) (SD)	-188.8 (158.3)		-217.5 (160.3)
LS mean % (80% CI)	-162.1		-211.3 (-237.1, -185.5)
Diff in LS means vs ranibizumab (80% CI)	(-186.9, -137.3)		-49.2 (-84.2, -14.2)
p-value			0.07
All patients	N = 90	N =55	N = 82
Change from baseline (µm) (SD)	-212.1 (176.2)	-260.2 (199.1)	-227.8 (145.3)
LS mean % (80% CI)	-210.7	-228.0 (-246.4, -209.7)	-239.9 (-255.2, -224.6)
Diff in LS means vs ranibizumab (80% CI)	(-225.0, -196.4)	-17.3 (-38.0, 3.4)	-29.2 (-47.8, -10.6)
p-value		0.28	0.05

Note: Nominal p-value was reported without correction for multiple comparisons

2.4.5.1. Main studies

Study GR40398 (RHINE): A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients with Diabetic Macular Edema. Report No. 1102957

Study GR40349 (YOSEMITE): A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients with Diabetic Macular Edema. Report No. 1102956

Methods

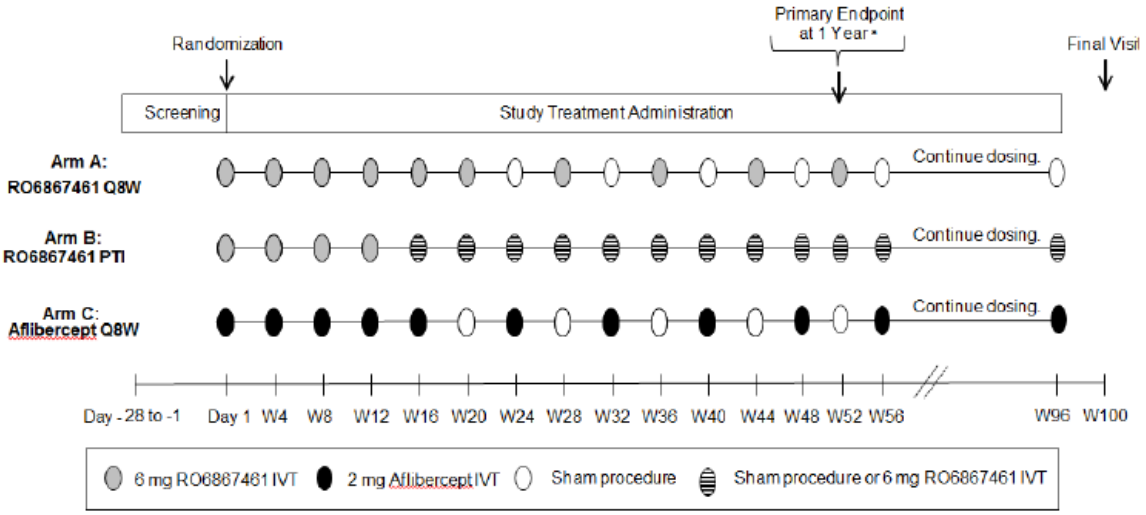
RHINE and YOSEMITE are Phase III, double-masked, multicenter, randomized, active comparator-controlled, parallel-group studies, evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab administered by intravitreal injection at 8-week intervals or PTI of approximately 100 weeks' duration (excluding the screening period) to patients with DME. Aflibercept

2mg administered 4-weekly to Week 16, followed thereafter by 8 weekly dosing was the control arm. An overview of the study design is presented in Figure 57.

Only one eye was assigned as the study eye. If both eyes were considered eligible, the eye with the worse best-corrected visual acuity (BCVA), as assessed at screening, was selected as the study eye unless the investigator deemed the other eye to be more appropriate for treatment in the study.

Figure 57. Study Schematic for RHINE and YOSEMITE

Figure 1 Study Treatment Schema



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

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

Study Participants

These studies were conducted in patients with decreased vision due to DME who met all of the eligibility criteria. Patients who were both naive to anti-VEGF therapy in the study eye and those who had previously been treated with anti-VEGF therapy in the study eye were included. The target for participation of previously anti-VEGF-treated patients was capped at a minimum of 10% and a maximum 25% of enrolment.

Patients had to be adults with a documented diagnosis of Type 1 or Type 2 diabetes mellitus as defined by the American Diabetes Association or by WHO criteria. Patients should be current regular users of insulin or other anti-diabetic injectable drugs (e.g., dulaglutide and liraglutide) and/or Current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes. HbA1c of ≤ 10% within 2 months prior to the Day 1 visit date.

Ocular inclusion criteria included the following:

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

Exclusion criteria

There were a large number of non-ocular exclusion criteria including: those relating to poor management of diabetes mellitus, history of allergy to biological agents, history of cancer in the previous 12 months, renal failure likely to require dialysis in the course of the trial, history of myocardial infarction or stroke in the prior 12 months, uncontrolled blood pressure and systemic treatment for suspected or active systemic infection.

Main ocular exclusion criteria

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

Treatments

There were three treatment arms

- Arm A 6 mg intravitreal faricimab injections Q4W to Week 20, followed by 6 mg intravitreal faricimab injections Q8W to Week 96, followed by the final study visit at Week 100.
- Arm B 6 mg intravitreal faricimab injections Q4W to at least Week 12, followed by PTI dosing of 6 mg intravitreal faricimab injections to Week 96, followed by the final study visit at Week 100.

Patients randomized to the PTI arm (Arm B) were treated with faricimab on a Q4W dosing interval until at least the patient's Week 12 visit, or a later visit when CST met the predefined reference CST threshold (CST < 325 µm for Spectralis SD-OCT, or < 315 µm for Cirrus SD-OCT or Topcon SD-OCT), as determined by the central reading center (CRC). The reference CST is used at study drug dosing visits by the IxRS for the drug dosing interval decision-making.

After a patient's initial reference CST was established, their study drug dosing interval was increased by 4 weeks to an initial Q8W dosing interval by the IxRS. From this point forward, the study drug dosing interval was extended, reduced, or maintained based on assessments made at study drug dosing visits.

Interval extended by 4 weeks:

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

Interval maintained:

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

Interval reduced by 4 weeks:

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

Interval reduced by 8 weeks:

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

Arm C 2 mg intravitreal aflibercept injections Q4W to Week 16, followed by 2 mg intravitreal aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

Objectives

The primary efficacy objective was to evaluate the efficacy of intravitreal injections of the 6-mg dose of faricimab on BCVA outcomes.

The key secondary efficacy objective was to evaluate the efficacy of faricimab on DR severity outcomes

Other secondary efficacy objectives included the following: evaluate efficacy of faricimab on additional BCVA outcomes; evaluate efficacy of faricimab on additional DR outcomes; evaluate faricimab treatment intervals in the PTI arm; evaluate the efficacy of faricimab on anatomical outcome measures using SD-OCT; evaluate the efficacy of faricimab on patient-reported vision-related functioning and quality of life using the NEI VFQ-25

For each of the two faricimab arms (Q8W and PTI), the following three hypotheses were tested separately against the active comparator (aflibercept Q8W) at an overall significance level of $\alpha = 0.0496$ using a graph-based testing procedure (Bretz et al. 2009, Bretz et al. 2011) to control for the overall type I error rate:

- Non-inferiority of faricimab compared with aflibercept Q8W in the intent-to-treat (ITT) population with a non-inferiority margin of 4 letters
- Superiority of faricimab compared with aflibercept Q8W in the treatment naive (TN) population
- Superiority of faricimab compared with aflibercept Q8W in the ITT population.

For each faricimab group (Q8W or PTI) the null hypothesis for the non-inferiority comparison:

H0: $\mu^{faricimab}$-$\mu^{aflibercept} \leq -4$ letters, and the alternative hypothesis:

Ha: $\mu^{faricimab}$-$\mu^{aflibercept} > -4$ letters, will be tested, for which $\mu^{faricimab}$ and $\mu^{aflibercep}$ are the expected change from baseline in BCVA averaged over Weeks 48, 52, and 56 for the treatment group in question (faricimab Q8W or PTI) and the active comparator (aflibercept Q8W), respectively.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure was based on the ETDRS VA chart assessed at a starting distance of four meters

Secondary endpoints

Key secondary endpoint

- Proportion of patients with a ≥ 2-step DRS improvement from baseline on the ETDRS DRSS at Week 52

Other secondary endpoints

- Change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) over Time
- Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time and at 1 year
- Proportion of patients with a ≥ 2-step DRS improvement from baseline on the ETDRS DRSS over time
- Proportion of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 52, Week 96, and over time
- Proportion of patients in the PTI arm at Week 52 who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W
- Change from baseline in CST at 1 year
- Change from baseline in NEI VFQ-25 composite score over time and at Week 52

Randomisation and blinding (masking)

After written informed consent had been obtained, all patients received a screening number assigned through the IxRS. A patient had to satisfy all eligibility criteria prior to randomization through the IxRS. As part of the screening process, the CRC evaluated CFPs and SD-OCT images to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements were confirmed, site personnel contacted the IxRS at the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). Patients were randomized in a 1:1:1 ratio to either faricimab Q8W, faricimab PTI, or aflibercept Q8W. After randomization and at each study treatment visit (i.e., including Day 1), the IxRS assigned the appropriate study treatment kit to be used. Patients were randomized on the same day study treatment was to be initiated (the Day 1 visit).

Randomization was stratified by the following baseline factors (Day 1):

- Baseline BCVA ETDRS letter score (≥ 64 letters vs. < 64 letters)
- Prior intravitreal anti-VEGF treatment (yes vs. no)
- Region (United States and Canada, Asia, and the rest of the world).

Patients who were not eligible for enrolment (screen failures) may have been eligible for re-screening for up to an additional two times during the enrolment period of the study.

These are double-masked studies. A minimum of two investigators per site are needed to fulfill the masking requirements, and both are required to be present at each scheduled study visit.

All patients received a sham procedure (the blunt end of an empty syringe was pressed against the anaesthetised eye) at the 4-weekly visits at which they did not receive faricimab or aflibercept.

Sample Size

A sample size of approximately 300 patients in each arm will provide greater than 90% power to show non-inferiority of faricimab to aflibercept (pairwise comparisons between the active comparator and each of the faricimab arms) in the ITT population, using a non-inferiority margin of 4 letters and under the following assumptions:

- True mean difference between faricimab and aflibercept of 0 letters
- Standard deviation (SD) of 11 letters for the change from baseline in BCVA averaged over Week 48, Week 52, and Week 56
- Two-sample *t*-test
- 1.25% one-sided type I error rate
- 10% dropout rate

Statistical methods

Unless otherwise noted, analyses of efficacy outcome measures were stratified by baseline BCVA ETDRS letter score, as assessed on Day 1 (64 letters or better vs. 63 letters or worse), prior intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). The stratification factors as recorded in IxRS were used. The primary comparisons were the pairwise comparisons between the active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI). Continuous outcomes were analyzed using a mixed model for repeated measures (MMRM). Binary endpoints were analyzed using stratified estimation for binomial proportions. The estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each of the three treatment arms and for the difference in means or proportions between pairwise comparisons of active comparator (aflibercept Q8W) and each of the faricimab arms (Q8W and PTI).

Results

RHINE

A total of 1715 patients were screened, and 764 patients failed screening due to not meeting the inclusion criteria. The main reasons for screen failure were: not having a BCVA of 73 to 25 letters inclusive (20/40 to 20/320) range; having concurrent exclusionary ocular diagnoses such as tractional retinal detachment, pre-retinal fibrosis, or epiretinal membrane involving the fovea or disrupting the

macular architecture in the study eye; and failing to meet the criterion for macular thickening secondary to DME involving the center of the fovea.

As specified in the protocol, three randomization stratification factors were used (baseline BCVA ETDRS letter score, prior IVT anti-VEGF treatment, and region) to balance these characteristics across the treatment arms. Overall, 35 patients were mis-stratified by the incorrect BCVA letter score category (63 letters or worse, or 64 letters or better) and 33 patients were mis-stratified by the incorrect prior intravitreal anti-VEGF therapy category. Taking both types of mis-stratification 9.8% were mis-stratified in the faricimab Q8W arm, 6% in the faricimab PTI arm and 5.7% in the aflibercept arm.

One patient in the aflibercept Q8W arm was randomized but did not receive any treatment. This patient did not receive treatment because they were registered in IxRS in error.

Overall, in the ITT population, 7.6%, 3.4%, and 6.1% of patients discontinued treatment prior to Week 56 in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most frequent reasons for treatment discontinuation were withdrawal by subject (2.2%, 1.3%, 1.6% in the three treatment arms, respectively), lost to follow-up (1.9%, 1.3%, 1.0% in the three treatment arms, respectively), and AEs (1.3%, 0.9%, 1.3% in the three treatment arms, respectively.

YOSEMITE

A total of 1532 patients were screened, and 592 patients failed screening due to not meeting the inclusion criteria. The reasons for screen failure were similar to those for the RHINE study.

Stratification was similar in both trials, 39 patients were mis-stratified by the incorrect BCVA letter score category (63 letters or worse, or 64 letters or better;) and 24 patients were mis-stratified by the incorrect prior intravitreal anti-VEGF therapy category. In total 21 (6.7%) were mis-stratified in Faricimab Q8W arm, 25 (8%) in the Faricimab PTI arm and 13 (4.2%) in the aflibercept arm.

Three patients (2 patients in the faricimab Q8W arm and 1 patient in the aflibercept Q8W arm) were randomized but did not receive any treatment. The reasons for these patients not receiving treatment were withdrawal by subject and a protocol deviation of exclusion criteria (study eye: tractional retinal detachment, pre-retinal fibrosis, or epiretinal membrane) for the 2 patients in the faricimab Q8W arm, and a protocol deviation of exclusion criteria (any use of medicated intraocular implants within 6 months of Day 1) for the patient in the aflibercept Q8W arm.

Overall, in the ITT population, 9.9%, 9.6%, and 8.4% of patients discontinued treatment prior to Week 56 in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most frequent reasons for treatment discontinuation were withdrawal by subject (1.9%, 1.6%, 3.5% in the three treatment arms, respectively), death (2.2%, 2.9%, 1.3% in the three treatment arms, respectively) and lost to follow-up (2.2%, 2.2%, 1.3% in the three treatment arms, respectively; Table 34).
Two patients withdrew from treatment for reasons categorized as other; 1 patient in the faricimab PTI arm left the country to visit family with no set return date, and for 1 patient in the aflibercept Q8W arm it was mutually agreed (between the Sponsor and investigator) that treatment with the current standard of care was more appropriate due to the patient's existing comorbidities

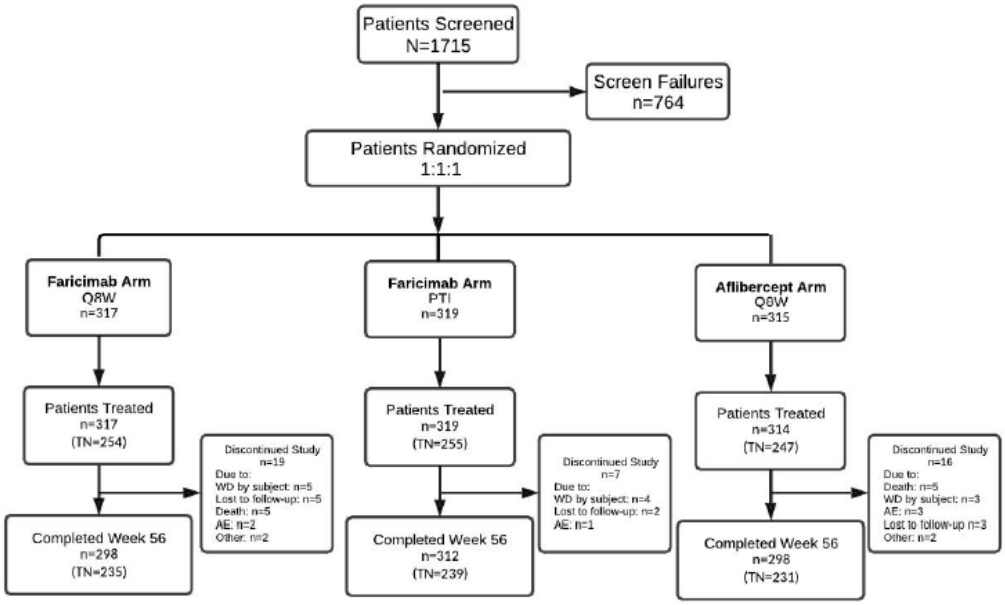
Table 34 Summary of Patient Disposition and Reason for Discontinuation from treatment prior to Week 56 (ITT Population)

	Yosemite			RHINE		
	Faricimab 6mg Q8W n = 315	Faricimab 6mg PTI n =313	Aflibercept 2mg Q8W n = 312	Faricimab 6mg Q8W n = 317	Faricimab 6mg PTI n =319	Aflibercept 2mg Q8W n =315

Number randomised	315	313	312	317	319	315
Number treated	313 (99.4%)	313 (100%)	311 (99.7%)	317 (100%)	319 (100%)	314 (99.7%)
DC treatment prior to week 56 (total)	31 (9.9%)	30 (9.6%)	26 (8.4%)	24 (7.6%)	11 (3.4%)	19 (6.1%)
Adverse event	6 (1.9%)	7 (2.2%)	3 (1%)	4 (1.3%)	3 (0.9%)	4 (1.3%)
Pregnancy	0	1 (0.3%)	0	0	0	0
Death	7 (2.2%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	0	5 (1.6%)
Lack of efficacy	1 (0.3%)	0	1 (0.3%)	0	0	0
Loss to follow up	7 (2.2%)	7 (2.2%)	4 (1.3%)	6 (1.9%)	4 (1.3%)	3 (1%)
Protocol deviation	0	0	1 (0.3%)	0	0	0
Patient withdrawal	6 (1.9%)	5 (1.6%)	11 (3.5%)	7 (2.2%)	4 (1.3%)	5 (1.6%)
Physician decision	3 (1%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Other	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)

RHINE

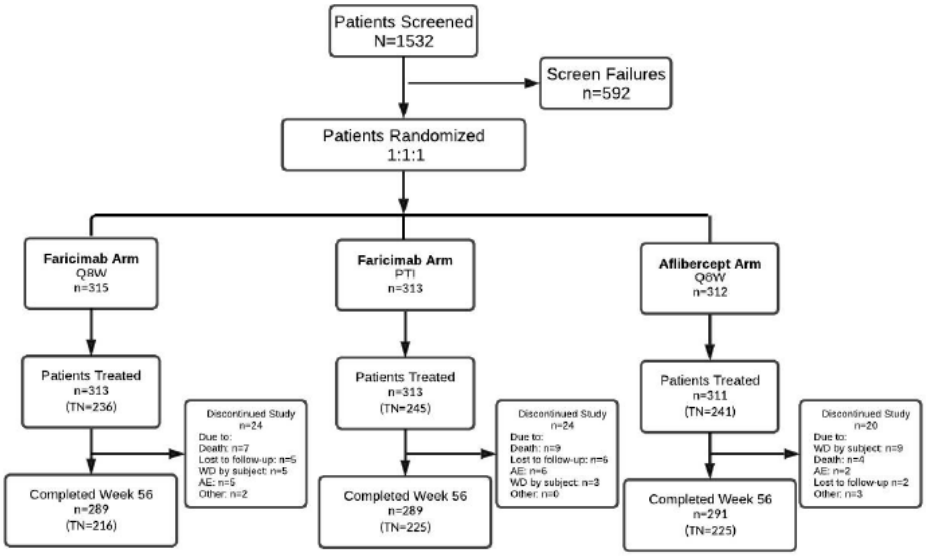
Figure 4 Patient Disposition



AE=adverse event; PTI=personalized treatment interval; TN=treatment-naive; Q8W=every 8 weeks; WD=withdrawal.
Note: Includes discontinuation occurring prior to Day 378 (first day of Week 56 analysis visit window). For the purpose of the figure the category 'Other' comprises all categories not individually described. Sources: t_ds_IT_19OCT2020_40398, t_pop_IT_19OCT2020_40398, Screen Failure list

YOSEMITE

Figure 4 Patient Disposition



AE=adverse event; PTI=personalized treatment interval; TN=treatment-naive; Q8W=every 8 weeks; WD=withdrawal.
Note: Includes discontinuation occurring prior to Day 378 (first day of Week 56 analysis visit window). For the purpose of the figure the category 'Other' comprises all categories not individually described. Sources: t_ds_IT_20OCT2020_40349, t_pop_IT_20OCT2020_40349, Screen Failure list

Baseline data

RHINE

In the ITT population, baseline demographics were comparable across all treatment arms (Table 35). The overall mean age at randomization was 62.2 years (62.5 years in the faricimab Q8W arm, 61.6 years in the faricimab PTI arm, and 62.3 years in the aflibercept Q8W arm) with the majority of patients (57.0%) in the < 65 years of age category.

The majority (60.9%) of patients were male, white (79.1%), from the 'Rest of the world countries' (i.e. not USA/Canada or Asia, 56.5%), and of Not Hispanic or Latino ethnicity (76.1%).

Baseline demographic characteristics in the TN population were similar to the ITT population and generally comparable across arms

In the ITT population, baseline non-ocular characteristics were comparable across treatment arms. The majority of patients had Type 2 diabetes (94.1%) and the mean (SD) HbA1c was 7.7% (1.2), as expected based on the inclusion criterion of HbA1c of ≤ 10% within 2 months prior to the Day 1 visit date. Baseline non-ocular characteristics in the TN population were similar and comparable across treatment arms

YOSEMITE

In the ITT population, baseline demographics were comparable across all treatment arms (Table 35). The overall mean age at randomization was 62.2 years (61.6 years in the faricimab Q8W arm, 62.8 years in the faricimab PTI arm, and 62.2 years in the aflibercept Q8W arm) with the majority of patients (57.1%) in the < 65 years of age category.

The majority (59.8%) of patients were male, white (78.1%), from the U.S. and Canada (53.5%), and of Not Hispanic or Latino ethnicity (86.5%).

Baseline demographic characteristics in the TN population were similar to the ITT population and generally comparable across arms

In the ITT population, baseline non-ocular characteristics were comparable across treatment arms. The majority of patients had Type 2 diabetes (94.6%) and the mean (SD) HbA1c was 7.6% (1.1), as expected based on the inclusion criterion of HbA1c of ≤ 10% within 2 months prior to the Day 1 visit date.

Baseline non-ocular characteristics in the TN population were similar and comparable across treatment arms

Table 35. Baseline Demographics (ITT Population)

	RHINE			YOSEMITE		
	Faricimab 6mg Q8W N =317	Faricimab 6mg PTI N = 319	Aflibercept 2mg Q8W n = 315	Faricimab 6mg Q8W N = 315	Faricimab 6mg PTI N = 313	Aflibercept 2mg Q8W n = 312
Region Rest of the World US and Canada Asia	 178 (56.2%) 110 (34.7%) 29 (9.1%)	 179 (56.1%) 111 (34.8%) 29 (9.1%)	 180 (57.1%) 109 (34.6%) 26 (8.3%)	 127 (40.3%) 167 (53%) 21 (6.7%)	 126 (40.3%) 168 (53.7%) 19 (6.1%)	 124 (39.7%) 168 (53.8%) 20 (6.4%)
Age Mean (SD)	 62.5 (10.1)	 61.6 (10.1)	 62.3 (10.1)	 61.6 (9.5)	 62.8 (10)	 62.2 (9.6)
Age-group < 65 ≥ 65 - < 75 ≥ 75 - < 84 ≥ 85	 176 (55.5%) 111 (35%) 29 (9.1%) 1 (0.3%)	 183 (57.4%) 110 (34.5%) 25 (7.8%) 1 (0.3%)	 183 (58.1%) 104 (33%) 27 (8.6%) 1 (0.3%)	 188 (59.7%) 105 (33.3% 21 (6.7%) 1 (0.3%)	 169 (54%) 115 (36.7%) 28 (8.9%) 1 (0.3%)	 180 (57.7%) 105 (33.7%) 27 (8.7%) 0
Sex Male Female	 194 (61.2%) 123 (38.8%)	 199 (62.4%) 120 (37.6%)	 186 (59%) 129 (41%)	 187 (59.4%) 128 (40.6%)	 197 (62.9%) 116 (37.1%)	 178 (57.1%) 134 (42.9%)

Race						
Black or African American	18 (5.7%)	23 (7.2%)	24 (7.6%)	22 (7%)	25 (8%)	12 (3.8%)
White	250 (78.9%)	249 (78.1%)	253 (80.3%)	241 (76.5%)	240 (76.7%)	253 (81.1%)
Asian*	34 (10.7%)	36 (11.3%)	32 (10.2%)	31 (9.8%)	26 (8.3%)	27 (8.7%)
Other	4 (1.2%)	1 (0.3%)	1 (0.3%)	8 (2.5%)	6 (1.9%)	10 (3.2%)
Unknown	11 (3.5%)	10 (3.1%)	5 (1.6%)	13 (4.1%)	16 (5.1%)	10 (3.2%)

Asian* = Chinese, Taiwanese, Asian Indian, Korean, Malaysian, Vietnamese, Japanese, Asian other

Baseline ocular characteristics

RHINE

In the ITT population, mean baseline BCVA and mean baseline CST in the study eye was comparable across the treatment arms (Table 36). Mean baseline BCVA values were 61.9 letters in the faricimab Q8W arm; 62.5 letters in the faricimab PTI arm; and 62.1 letters in the aflibercept Q8W arm. Mean baseline CST values were 466.2 µm in the faricimab Q8W arm; 471.3 µm in the faricimab PTI arm; and 477.3 µm in the aflibercept Q8W arm.

Patient-reported mean (SD) time since DME diagnosis was 20.0 (34.2) months, while the median (min-max) was 6.6 months (0-380). The categorical data for diagnosis ≤ 3 months or > 3 months is shown in Table 36. The mean (SD) time since last anti-VEGF treatment in previously-treated patients was 18.7 (19.2) months. Baseline DR status was generally comparable across the treatment arms. The majority of patients (approximately 60%) had moderate-to-severe (DRSS 43/47/53) NPDR, followed by mild (DRSS < 43) NPDR (approximately 30%), and PDR (DRSS > 53) (approximately 8%).

As per study design, the majority of patients were naive to anti-VEGF therapy in the study eye (79.6%) with a comparable proportion of TN patients across all treatment arms; the remaining patients were previously treated with anti-VEGF therapy in the study eye.

Because approximately 80% of the ITT population consisted of TN patients, there were expected differences between the populations in the time since diagnosis data. Patient reported mean (SD) time since DME diagnosis was 15.9 (34.1) months in the TN population, while the median (min-max) was 3.5 (0-380) months.

YOSEMITE

In the ITT population, mean baseline BCVA and mean baseline CST in the study eye were comparable across the treatment arms. Mean baseline BCVA values were 62.0 letters in the faricimab Q8W arm; 61.9 letters in the faricimab PTI arm; and 62.2 letters in the aflibercept Q8W arm. Mean baseline CST values were 492.3 µm in the faricimab Q8W arm; 485.8 µm in the faricimab PTI arm; and 484.5 µm in the aflibercept Q8W arm.

Patient-reported mean (SD) time since DME diagnosis was 16.4 (29.1) months, while the median (min-max) was 3.1 months (0-304). The categorical data for time since diagnosis (≤ 3 months or > 3 months) are shown in Table 36. The mean (SD) time since last anti-VEGF treatment in previously-treated patients was 18.3 (17.3) months. Baseline DR status was generally comparable across the treatment arms. The majority of patients (approximately 60%) had moderate-to-severe (DRSS 43/47/53) NPDR, followed by mild (DRSS < 43) NPDR (approximately 30%), and PDR (DRSS > 53) (approximately 8%).

As per study design, the majority of patients were naive to anti-VEGF therapy in the study eye (77.1%) with a comparable proportion of TN patients across all treatment arms; the remaining patients were previously treated with anti-VEGF therapy in the study eye.

Because approximately 77% of the ITT population consisted of TN patients, there were expected differences between the populations in the time since diagnosis data. The mean and median patient-reported mean (SD) time since DME diagnosis was 9.7 (23.4) months in the TN population, while the median (min-max) was 1.6 (0-304) months.

Table 36. Ocular Baseline Characteristics in the Study Eye (ITT Population)

	RHINE			YOSEMITE		
	Faricimab 6mg Q8W N =317	Faricimab 6mg PTI N = 319	Aflibercept 2mg Q8W N = 315	Faricimab 6mg Q8W N = 315	Faricimab 6mg PTI N = 313	Aflibercept 2mg Q8W n = 312
Months since DME diagnosis (n) Mean (SD)	275 18.9 (32.2)	277 20.7 (33)	273 20.3 (37.1)	297 14 (21.7)	292 17.6 (36.2)	296 17.5 (27.6)
Months since DME diagnosis (n) ≤ 3 months > 3 months Unknown	317 104 (32.8%) 171 (53.9%) 42 (13.2%)	319 104 (32.6%) 173 (54.2%) 42 (13.2%)	315 111 (35.2%) 162 (51.4%) 42 (13.3%)	315 143 (45.4%) 154 (48.9%) 18 (5.7%)	313 153 (48.9%) 139 (44.4%) 21 (6.7%)	312 145 (46.5%) 151 (48.4%) 16 (5.1%)

BCVA letters (n) Mean (SD)	316 61.9 (10.1)	317 62.5 (9.3)	315 62.1 (9.4)	315 62 (9.9)	313 61.9 (10.2)	312 62.2 (9.5)
BCVA letters categories (n) ≤ 38 (20/200 or worse) 39 – 63 (worse than 20/50) ≥ 64 (20/50 or better) Missing/invalid	317 14 (4.4%) 128 (40.4%) 174 (54.9%) 1 (0.3%)	319 11 (3.4%) 132(41.4 %) 174 (54.5%) 2 (0.6%)	315 9 (2.9%) 132 (41.9%) 174 (55.2%) 0	315 15 (4.8%) 132 (41.9%) 168 (53.3%) 0	313 12 (3.8%) 126 (40.3%) 175 (55.9%) 0	312 12 (3.8%) 132 (42.3%) 168 (53.8%) 0
CST (ILM-BM) (microns) (n) Mean (SD) Median Missing/ungradable	314 466.2 (119.4) 445.0 3	316 471.3 (127) 442 3	312 477.3 (129.4) 448 3	312 492.3 (135.8) 476.5 3	312 485.8 (130.8) 461.5 1	308 484.5 (131.1) 458 4
Macular Ischaemic Non-Perfusion Yes	317 126 (39.7%)	319 138 (43.3%)	315 132 (41.9%)	315 127 (40.3%)	313 117 (37.4%)	312 122 (39.1%)
Macular leakage Yes	317 300 (94.6%)	319 309 (96.9%)	315 299 (94.9%)	315 305 (96.8%)	313 301 (96.2%)	312 293 (93.9%)
Previously treated with anti-VEGF Yes No (treatment naïve)	317 63 (19.9%) 254 (80.1%)	319 64 (20.1%) 225 (79.9%)	315 67 (21.3%) 248 (78.7%)	315 77 (24.4%) 238 (75.6%)	313 68 (21.7%) 245 (78.3%)	312 70 (22.4%) 242 (77.6%)
Time since last anti-VEGF –months Mean (SD) Median	58 20.7 (20.8) 12.2	58 15.5 (19.5) 8.4	67 19.9 (17.4) 11.9	75 20.5 (20.5) 12.2	67 17.6 (17.2) 13.3	65 16.6 (12.6) 12.9
Diabetic retinopathy status 1 – DRS Level 10, 12	317 2 (0.6%)	319 4 (1.3%)	315 1 (0.3%)	315 2 (0.6%)	313 3 (1%)	312 4 (1.3%)

2 DRS level 14A, 14B, 14C, 14Z, 15, 20 3 DRS 35A, 35B, 35C, 35D, 35E, 35F 4 DRS level 43A, 43B 5 DRS level 47A, 47B, 47C, 47D 6 DRS 53A, 53B, 53C, 53D, 53E 7 DRS 61A, 61B 8 DRS 65A, 65B, 65C 9 DRS 71A, 71B, 71C, &71D 10 DRS 75 11 DRS 81 12 DRS 85A, 85B 90 DRS level 90 Missing	3 (0.9% 90 (28.4%) 88 (27.8%) 59 (18.6%) 50 (15.8%) 12 (3.8%) 6 (1.9%) 2 (0.6%) 0 0 0 2 (0.6%) 3 (0.9%)	10 (3.1%) 92 (28.8%) 72 (22.6%) 63 (19.7%) 36 (11.3%) 26 (8.2%) 10 (3.1%) 1 (0.3%) 0 0 0 5 (1.6%) 0	6 (1.9%) 94 (29.8%) 79 (25.1%) 54 (17.1%) 51 (16.2%) 11 (3.5%) 6 (1.9%) 3 (1%) 0 0 0 5 (1.6%) 5 (1.6%)	4 (1.3%) 84 (26.7%) 84 (26.7%) 67 (21.3%) 46 (14.6%) 16 (5.1%) 6 (1.9%) 0 0 0 0 4 (1.3%) 2 (0.6%)	6 (1.9%) 92 (29.4%) 86 (27.5%) 59 (18.8%) 40 (12.8%) 11 (3.5%) 9 (2.9%) 1 (0.3%) 0 0 0 5 (1.6%) 1 (0.3%)	10 (3.2%) 83 (26.6%) 85 (27.2%) 54 (17.3%) 49 (15.7%) 9 (2.9%) 7 (2.2%) 2 (0.6%) 0 0 0 7 (2.2%) 2 (0.6%)

BCVA=Best Corrected Visual Acuity; CRC = Central Reading Center; CST=Central Subfield Thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; ILM = Internal Limiting Membrane; NPDR = non-proliferative diabetic retinopathy; PTI = Personalized Treatment Interval (from Q4W up to Q16W); PDR = proliferative diabetic retinopathy; VEGF = Vascular Endothelial Growth Factor.

Baseline is the last available value taken on or prior to randomization.

Diabetic retinopathy status: 1 = DR absent; 2 = DR questionable/ microaneurysm only; 3 = mild non-proliferative retinopathy; 4 = moderate non-proliferative retinopathy; 5 = moderately-severe non-proliferative retinopathy; 6 = severe non-proliferative retinopathy; 7 = mild proliferative diabetic retinopathy; 8 = moderate proliferative diabetic retinopathy; 9 = high risk proliferative diabetic retinopathy; 10 = high risk proliferative diabetic retinopathy; 11 = advanced proliferative diabetic retinopathy; 12 = advanced proliferative diabetic retinopathy; 90 = cannot grade

Numbers analysed

The primary endpoint was analysed in the ITT population. A supplementary analysis was carried out in the per protocol population (Table 3)

Table 3. Overview of analysis populations, YOSEMITE and RHINE trials

	YOSEMITE			RHINE		
	Faricimab 6mg Q8W n = 315	Faricimab 6mg PTI n =313	Aflibercept 2mg Q8W n = 312	Faricimab 6mg Q8W n = 317	Faricimab 6mg PTI n =319	Aflibercept 2mg Q8W n =315

Intent to treat as randomised	315	313	312	317	319	315
Per protocol thru' week 56 as treated	251 (79.7%)	275 (87.9%)	274 (87.8%)	258 (81.4%)	271 (85%)	273 (86.7%)
Treatment naive as randomised	238 (75.6%)	245 (78.3%)	242 (77.6%)	254 (80.1%)	255 (80%)	248 (78.7%)

Per protocol population defined as the subset of patients who did not have a major protocol deviation that may have impacted the efficacy evaluation or the treatment interval determination.

Outcomes and estimation

Confidence Intervals (CI): 97.5% CI is a rounding of 97.52% CI for the primary and key secondary endpoints, and 95% CI is a rounding of 95.04% CI for other secondary endpoints. Pooled results are presented with 95% CIs.

RHINE

In the ITT population, patients treated with faricimab Q8W or PTI had a non-inferior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W, as the lower bound of the 97.5% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than -4 letters. 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, PTI, and aflibercept Q8W arms, respectively. The difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared to 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 (Table 37).

In the TN population, patients treated with faricimab Q8W or PTI did not have a superior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W. The results of the TN population were similar to the results of the ITT population where the difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 48/52/56 was 1.1 letters (97.5% CI: -0.7, 3.0; p = 0.1718) and 0.6 letters (97.5% CI:-1.2, 2.4; p = 0.4602), respectively (Table 37).

Table 37.

Change from Baseline in BCVA in the Study Eye averaged over Weeks 48, 52 and 56: MMRM Method with 97.5% CI (Primary Estimand), Intent-to-Treat Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

Visit Statistics	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=315)
Average of Week 48, 52 and 56			
n	268	293	279
Adjusted Mean (SE)	11.8 (0.52)	10.8 (0.51)	10.3 (0.52)
97.5% CI for Adjusted Mean	(10.6, 13.0)	(9.6, 11.9)	(9.1, 11.4)
Difference (vs. Aflibercept) in Adjusted Means (SE)	1.5 (0.73)	0.5 (0.73)	
97.5% CI for Difference in Adjusted Means	(-0.1, 3.2)	(-1.1, 2.1)	
P-value (for superiority test)	0.0361	0.4930	

Units: letters. BCVA=Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; PTI = Personalized Treatment Interval (from Q4W up to Q16W). For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. 97.5% CI is a rounding of 97.52% CI.

Table 38 Summary of Change from Baseline in BCVA in the Study Eye at Week 48/52/56 RHINE					
	Faricimab 6 mg Q8W Adjusted Mean (97.5% CI)	**Faricimab 6 mg PTI Adjusted Mean(97.5% CI)**	**Aflibercept 2 mg Q8W Adjusted Mean (97.5% CI)**	**Diff. in Adjusted Means (97.5% CI) (Faricimab Q8W vs. Aflibercept)**	**Diff in Adjusted Means (97.5% CI) (Faricimab PTI vs. Aflibercept)**
Primary Analysis-MMRM					
ITT	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)	1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)
TN	11.7 (10.4, 13.0)	11.2 (9.9, 12.4)	10.5 (9.2, 11.9)	1.1 (-0.7, 3.0)	0.6 (-1.2, 2.4)
Sensitivity analysis					
LOCF MMRM ITT	11.7 (10.6, 12.9)	10.7 (9.6, 11.9)	10.1 (9.0, 11.2)	1.6 (0.0, 3.2)	0.6 (-1.0, 2.2)

Supplementary Analyses PP MMRM PP popn.	11.9 (10.6, 13.2)	10.7 (9.5, 12.0)	10.4 (9.1, 11.6)	1.5 (-0.3, 3.3)	0.3 (-1.4, 2.1)
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMMRM ITT popn.	11.7 (10.5, 12.9)	10.7 (9.5, 11.8)	10.2 (9.1, 11.4)	1.5 (-0.2, 3.1)	0.5 (-1.2, 2.1)
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM method ITT popn.	11.9 (10.7, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)	1.6 (0.0, 3.2)	0.5 (-1.1, 2.1)
Trimmed Mean Analysis – ANCOVA ITT popn.	12.6	11.7	11.6	1.0 (-0.5, 2.5)	0.1 (-1.4, 1.6)
Multiple Imputation Analysis – ANCOVA ITT popn	11.0 (9.8, 12.2)	10.1 (8.9, 11.2)	9.5 (8.3, 10.7)	1.5 (0.1, 3.0)	0.6 (-0.8, 2.0)
ANCOVA Analysis – ANCOVA ITT popn	11.1 (9.7, 12.4)	10.1 (8.8, 11.5)	10.0 (8.6, 11.3)	1.1 (-0.6, 2.8)	0.2 (-1.5, 1.8)

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks; TN = treatment naive.
Note: ITT population: faricimab Q8W = 315, faricimab PTI = 313, aflibercept = 312; TN population: faricimab Q8W = 238, faricimab PTI = 245, aflibercept = 242; PP population: faricimab Q8W = 251, faricimab PTI = 275, aflibercept = 274.
Note: For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs >= 64 letters), region (U.S. and Canada, Asia, and the rest of the world), and for the ITT and PP population prior intravitreal anti-VEGF therapy (yes vs. no). An unstructured covariance structure was used. The estimate of the difference between the two groups used a composite contrast over Weeks 48, 52 and 56. For the primary estimand and LOCF analyses, treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. For the treatment policy analysis, observed BCVA assessments were used regardless of the occurrence of intercurrent events. For the hypothetical strategy analysis, hypothetical strategy was applied to non-COVID-19 related and COVID-19 related intercurrent events. For the MMRM analyses, missing data were implicitly imputed by MMRM. For the LOCF analysis, missing data were implicitly imputed by using the last post-baseline observation carried forward. Invalid BCVA values were excluded from analysis.
Note: For trimmed mean analysis, distribution of the test statistics was estimated by permutation test with 30,000 samples. Patients were considered to have the worst outcomes and were trimmed if any of the following occurred: 1.Patient had intercurrent events not related to COVID-19 prior to Week 48; 2.Patient had a missing BCVA
assessment at Week 48 and had intercurrent events not related to COVID-19 at Week 48; 3.Patient had missing BCVA assessments at Weeks 48 and 52, and had intercurrent events that were not related to COVID-19 in either one of these two visits; 4.Patient had missing BCVA assessments at Weeks 48, 52 and 56, and had intercurrent events not related to COVID-19 in either one of these three visits.
Note: For multiple imputation, the analysis is the same as described for ANCOVA below except missing post-baseline BCVA assessments after the occurrence of intercurrent events that were not due to COVID-19 were imputed using MI assuming not MAR. BCVA assessments after censoring due to COVID-19 related intercurrent events were imputed using MI assuming MAR. Other missing post-baseline BCVA assessments were imputed assuming MAR.
Note: For the ANCOVA analysis, the model used the average of non-missing change from baseline in BCVA at Weeks 48, 52 and 56 as the response variables adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior intravitreal anti-VEGF

therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were not imputed. Invalid BCVA values were excluded from analysis.

97.5% CI is a rounding of 97.52% CI.

YOSEMITE

In the ITT population, patients treated with faricimab Q8W or PTI had a non-inferior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W, as the lower bound of the 97.5% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than -4 letters. 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, PTI, and aflibercept Q8W arms, respectively. The difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared to 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 (Table 39).

In the TN population, patients treated with faricimab Q8W or PTI did not have a superior mean change from baseline in BCVA at Week 48/52/56 compared with patients treated with aflibercept Q8W. The results of the TN population were similar to the results of the ITT population where the difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 48/52/56 was -0.7 letters (97.5% CI: -2.8, 1.4; p = 0.4699) and 0 letters (97.5% CI:-2.1, 2.2; p =0.9650), respectively (Table 40).

Table 39.

Change from Baseline in BCVA in the Study Eye averaged over Weeks 48, 52 and 56: MMRM Method with 97.5% CI (Primary Estimand), Intent-to-Treat Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

Visit Statistics	Faricimab 6 mg Q8W (N=315)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=312)
Average of Week 48, 52 and 56			
n	271	276	276
Adjusted Mean (SE)	10.7 (0.56)	11.6 (0.56)	10.9 (0.56)
97.5% CI for Adjusted Mean	(9.4, 12.0)	(10.3, 12.9)	(9.6, 12.2)
Difference (vs. Aflibercept) in Adjusted Means (SE)	-0.2 (0.79)	0.7 (0.79)	
97.5% CI for Difference in Adjusted Means	(-2.0, 1.6)	(-1.1, 2.5)	
P-value (for superiority test)	0.7967	0.3772	

Units: letters. BCVA=Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; PTI = Personalized Treatment Interval (from Q4W up to Q16W). For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. 97.5% CI is a rounding of 97.52% CI.

Table 40 Summary of Change from Baseline in BCVA in the Study Eye at Week 48/52/56 YOSEMITE

	Faricimab 6 mg Q8W	**Faricimab 6 mg**	**Aflibercept 2 mg Q8W**	**Diff. in Adjusted**	**Diff in Adjusted**

	Adjusted Mean (97.5% CI)	**PTI** **Adjusted Mean(97.5% CI)**	**Adjusted Mean (97.5% CI)**	**Means (97.5% CI) (Faricimab Q8W vs.** **Aflibercept)**	**Means (97.5% CI) (Faricimab PTI vs.** **Aflibercept)**
Primary Analysis- MMRM ITT TN	10.7 (9.4, 12.0) 10.6 (9.1, 12.1)	11.6 (10.3, 12.9) 11.4 (9.9, 12.8)	10.9 (9.6, 12.2) 11.3 (9.8, 12.8)	-0.2 (-2.0, 1.6) -0.7 (-2.8, 1.4)	0.7 (-1.1, 2.5) 0.0 (-2.1, 2.2)
Sensitivity analysis LOCF MMRM ITT	10.6 (9.4, 11.8)	11.3 (10.1, 12.6)	10.7 (9.5, 12.0)	-0.1 (-1.9, 1.6)	0.6 (–1.1, 2.4)
Supplementary Analyses PP MMRM PP	10.8 (9.4, 12.1)	11.8 (10.5, 13.2)	11.2 (9.9, 12.5)	-0.4 (-2.3, 1.5)	0.7 (-1.2, 2.5)
Analysis using Treatment Policy Strategy for All Intercurrent Events – MMMRM ITT popn.	10.6 (9.3, 11.8)	11.5 (10.2, 12.7)	10.8 (9.6, 12.1)	-0.3 (-2.0, 1.5)	0.6 (-1.1, 2.4)
Analysis using Hypothetical Strategy for All Intercurrent Events – MMRM method ITT popn.	10.8 (9.5, 12.0)	11.6 (10.4, 12.9)	10.9 (9.7, 12.2)	-0.1 (-1.9, 1.6)	0.7 (-1.1, 2.5)
Trimmed Mean Analysis – ANCOVA ITT popn.	11.1	11.9	11.4	-0.3 (-1.8, 1.2)	0.5 (-1.0, 2.0)
Multiple Imputation					

Analysis – ANCOVA ITT popn	9.8 (8.5, 11.2)	10.8 (9.4, 12.1)	10.1 (8.8, 11.5)	-0.3 (-1.9, 1.2)	0.6 (-0.9, 2.2)
ANCOVA Analysis – ANCOVA ITT popn	9.7 (8.1, 11.3)	10.8 (9.3, 12.4)	10.2 (8.6, 11.7)	-0.5 (-2.3, 1.4)	0.7 (-1.2, 2.5)

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; MMRM = mixed model for repeated measures; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks; TN = treatment naive.
Note: ITT population: faricimab Q8W = 315, faricimab PTI = 313, aflibercept = 312; TN population: faricimab Q8W = 238, faricimab PTI = 245, aflibercept = 242; PP population: faricimab Q8W = 251, faricimab PTI = 275, aflibercept = 274.
Note: For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs >= 64 letters), region (U.S. and Canada, Asia, and the rest of the world), and for the ITT and PP population prior intravitreal anti-VEGF therapy (yes vs. no). An unstructured covariance structure was used. The estimate of the difference between the two groups used a composite contrast over Weeks 48, 52 and 56. For the primary estimand and LOCF analyses, treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. For the treatment policy analysis, observed BCVA assessments were used regardless of the occurrence of intercurrent events. For the hypothetical strategy analysis, hypothetical strategy was applied to non-COVID-19 related and COVID-19 related intercurrent events. For the MMRM analyses, missing data were implicitly imputed by MMRM. For the
LOCF analysis, missing data were implicitly imputed by using the last post-baseline observation carried forward. Invalid BCVA values were excluded from analysis.
Note: For trimmed mean analysis, distribution of the test statistics was estimated by permutation test with 30,000 samples. Patients were considered to have the worst outcomes and were trimmed if any of the following occurred: 1.Patient had intercurrent events not related to COVID-19 prior to Week 48; 2.Patient had a missing BCVA
assessment at Week 48 and had intercurrent events not related to COVID-19 at Week 48; 3.Patient had missing BCVA assessments at Weeks 48 and 52, and had intercurrent events that were not related to COVID-19 in either one of these two visits; 4.Patient had missing BCVA assessments at Weeks 48, 52 and 56, and had intercurrent events not related to COVID-19 in either one of these three visits.
Note: For multiple imputation, the analysis is the same as described for ANCOVA below except missing post-baseline BCVA assessments after the occurrence of intercurrent events that were not due to COVID-19 were imputed using MI assuming not MAR. BCVA assessments after censoring due to COVID-19 related intercurrent events were imputed using MI assuming MAR. Other missing post-baseline BCVA assessments were imputed assuming MAR.
Note: For the ANCOVA analysis, the model used the average of non-missing change from baseline in BCVA at Weeks 48, 52 and 56 as the response variables adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were not imputed. Invalid BCVA values were excluded from analysis.

97.5% CI is a rounding of 97.52% CI.

The proportion of patients achieving a ≥ 2-step improvement in DRS from baseline as measured on the ETDRS DRSS at Week 52 was a key secondary endpoint. In the RHINE study the proportion of patients achieving a ≥ 2-step improvement in DRS from baseline as measured on the ETDRS DRSS at Week 52 was 44.2%, 43.7%, and 46.8% in the faricimab Q8W, faricimab PTI and aflibercept arms respectively

In the ITT population, the pre-specified DRSS non-inferiority (margin of 10%) was not met as the lower bound of the 97.5% confidence interval for the difference in the adjusted proportion between the faricimab and aflibercept arms was below -10% for both the faricimab Q8W and PTI arms at Week 52: -2.6% (97.5% CI: -12.6%, 7.4%) and -3.5% (97.5% CI: -13.4%, 6.3%), respectively (Table 41).

In the TN population, the difference in the adjusted proportion of patients who had a ≥ 2-step improvement in DRS from baseline on ETDRS DRSS between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 52 was -5.4% (97.5% CI: -16.9%, 6.1%; p = 0.3009) and -6.9% (97.5% CI: -18.3%, 4.4%; p = 0.1735), respectively (Table 41).

Table 41 Proportion of Patients with ≥ 2-Step DRS Improvement in the Study Eye from Baseline on the ETDRS DRSS at Week 52 RHINE GR40398

	Faricimab 6 mg Q8W CMH Weighted %	**Faricimab 6 mg PTI CMH Weighted %**	**Aflibercept 2 mg Q8W CMH Weighted %**	**Difference in CMH Weighted % (97.5% CI) (Faricimab Q8W vs. Aflibercept)**	**Difference in CMH Weighted % (97.5% CI) (Faricimab PTI vs. Aflibercept)**
Key secondary endpoint ITT popn	44.2% (37.1%, 51.4%)	43.7% (36.8%, 50.7%)	46.8% (39.8%, 53.8%)	−2.6% (−12.6%, 7.4%)	−3.5% (−13.4%, 6.3%)
TN popn.	46.9% (38.7%, 55.1%)	45.7% (37.8%, 53.7%)	52.3% (44.2%, 60.4%)	−5.4% (−16.9%, 6.1%)	−6.9% (−18.3%, 4.4%)
Per Protocol Analysis PP popn	45.8% (38.4%, 53.2%)	45.6% (38.4%, 52.7%)	46.8% (39.5%, 54.1%)	−1.0% (−11.4%, 9.4%)	−1.6% (−11.8%, 8.6%)

CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ETDRS DRS = Early Treatment Diabetic Retinopathy Study diabetic retinopathy severity; ITT = intent-to-treat; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks; TN = treatment naive.

Note: ITT population: faricimab Q8W = 315, faricimab PTI = 313, aflibercept = 312; TN population: faricimab Q8W = 238, faricimab PTI = 245, aflibercept = 242; PP population: faricimab Q8W = 251, faricimab PTI = 275, aflibercept = 274.

Note: The sample size for each analysis is based on the intercurrent event handling.

Note: CMH weighted % for aflibercept arm presented for faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for for faricimab PTI vs. aflibercept comparison is similar to the one shown above; the weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. >= 64 letters), region (U.S. and Canada vs. the rest of the world), and for ITT and PP population prior intravitreal anti-VEGF therapy (yes vs. no). Asia and rest of the world regions are combined due to a small number of enrolled patients. For the primary estimand, treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

In the YOSEMITE study the proportion of patients achieving a ≥ 2-step improvement in DRS from baseline as measured on the ETDRS DRSS at Week 52 was 46.0%, 42.5%, and 35.8% in the faricimab Q8W, faricimab PTI and aflibercept arms respectively.

In the ITT population, the pre-specified DRSS non-inferiority (margin of 10%) was met as the lower bound of the 97.5% confidence interval for the difference in the adjusted proportion between the faricimab and aflibercept arms was above -10% for both the faricimab Q8W and PTI arms at Week 52: 10.2% (97.5% CI: 0.3%, 20.0%) and 6.1% (97.5% CI: -3.6%, 15.8%), respectively (Table 42).

In the TN population, superiority was not met. The results of the TN population were similar to the results of the ITT population where the difference in the adjusted proportion of patients who had a ≥ 2-step improvement in DRS from baseline on ETDRS DRSS between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 52 was 7.2% (97.5% CI: -4.6%, 18.9%; p = 0.1761) and 4.8% (97.5% CI: -6.7%, 16.3%; p = 0.3539), respectively (Table 42).

Table 42 Proportion of Patients with ≥ 2-Step DRS Improvement in the Study Eye from Baseline on the ETDRS DRSS at Week 52 YOSEMITE GR40349

	Faricimab 6 mg Q8W CMH Weighted %	**Faricimab 6 mg PTI CMH Weighted %**	**Aflibercept 2 mg Q8W CMH Weighted %**	**Difference in CMH Weighted % (97.5% CI) (Faricimab Q8W vs. Aflibercept)**	**Difference in CMH Weighted % (97.5% CI) (Faricimab PTI vs. Aflibercept)**
Key secondary endpoint ITT popn	46.0% (38.8%, 53.1%)	42.5% (35.5%, 49.5%)	35.8% (29.1%, 42.5%)	10.2% (0.3%, 20.0%)	6.1% (-3.6%, 15.8%)
TN popn.	49.7% (41.2%, 58.2%)	47.6% (39.5%, 55.8%)	42.5% (34.4%, 50.6%)	7.2% (-4.6%, 18.9%)	4.8% (-6.7%, 16.3%)
Per Protocol Analysis PP popn	46.4% (38.9%, 53.9%)	43.1% (35.9%, 50.4%)	37.3% (30.3%, 44.3%)	9.1% (-1.2%, 19.3%)	4.9% (-5.2%, 15.0%)

CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ETDRS DRS = Early Treatment Diabetic Retinopathy Study diabetic retinopathy severity; ITT = intent-to-treat; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks; TN = treatment naive.

Note: ITT population: faricimab Q8W = 315, faricimab PTI = 313, aflibercept = 312; TN population: faricimab Q8W = 238, faricimab PTI = 245, aflibercept = 242; PP population: faricimab Q8W = 251, faricimab PTI = 275, aflibercept = 274.

Note: The sample size for each analysis is based on the intercurrent event handling.

Note: CMH weighted % for aflibercept arm presented for faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for for faricimab PTI vs. aflibercept comparison is similar to the one shown above; the weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 letters vs. >= 64 letters), region (U.S. and Canada vs. the rest of the world), and for ITT and PP population prior intravitreal anti-VEGF therapy (yes vs. no). Asia and rest of the world regions are combined due to a small number of enrolled patients. For the primary estimand, treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

In the ITT population in the RHINE study at Week 48/52/56, 33.8%, 28.5%, and 30.3% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively (Table 43a). The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q8W and faricimab PTI arms when compared with the aflibercept Q8W arm at Week 48/52/56 was 3.5% and -2.0%, respectively. Comparable results were also seen across all three treatment arms for patients gaining ≥10, ≥5, or ≥0 letters in BCVA from baseline at Week 48/52/56

In the ITT population in the YOSEMITE study at Week 48/52/56, 29.2%, 35.5%, and 31.8% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively (Table 43b). The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q8W and faricimab PTI arms when compared with the aflibercept Q8W arm at Week 48/52/56 was -2.6% and 3.5%, respectively.

Table 43a Proportion of Patients Gaining Letters by Category in BCVA from Baseline in the Study Eye from baseline averaged over Weeks 48, 52 and 56: CMH Method (ITT Population) RHINE

	Faricimab 6 mg Q8W (ITT N=317) CMH Weighted Estimate (95% CI)	**Faricimab 6 mg PTI (ITT N=319)** CMH Weighted Estimate (95% CI)	**Aflibercept 2 mg Q8W (ITT N=315)** CMH Weighted Estimate (95% CI)	**Diff between Faricimab Q8W and Aflibercept** CMH Weighted Estimate (95% CI)	**Diff between Faricimab PTI and Aflibercept** CMH Weighted Estimate (95% CI)
Gaining ≥ 15 letters	33.8% (28.4%, 39.2%)	28.5% (23.6%, 33.3%)	30.3% (25.0%, 35.5%)	3.5% (-4.0%, 11.1%)	-2.0% (-9.1%, 5.2%)

BCVA = best corrected visual acuity; CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks.
Note: CMH weighted % for aflibercept arm presented for faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for faricimab PTI vs. aflibercept comparison are similar to those shown above; the weighted estimate was based on CMH test stratified by baseline BCVA score (< 64 letters vs. >= 64 letters), prior IVT anti-VEGF therapy (yes vs. no), and region (U.S. and Canada vs. the rest of the world). Asia and rest of the world regions were combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing assessments were not imputed. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.04% CI and estimates below 0% or above 100% were imputed as 0% or 100% respectively. Baseline was defined as the last available measurement obtained on or prior to randomization

Table 43b Proportion of Patients Gaining Letters by Category in BCVA from Baseline in the Study Eye averaged

over Weeks 48, 52 and 56: CMH Method (ITT Population) YOSEMITE

	Faricimab 6 mg Q8W	**Faricimab 6 mg PTI (ITT N=313)**	**Aflibercept 2 mg Q8W (ITT N=312)**	**Diff between Faricimab Q8W and Aflibercept**	**Diff between Faricimab PTI and Aflibercept**

	(ITT N=315) CMH Weighted Estimate (95% CI)	CMH Weighted Estimate (95% CI)	CMH Weighted Estimate (95% CI)	CMH Weighted Estimate (95% CI)	CMH Weighted Estimate (95% CI)
Gaining ≥ 15 letters	29.2% (23.9%, 34.5%)	35.5% (30.1%, 40.9%)	31.8% (26.6%, 37.0%)	-2.6% (-10.0%, 4.9%)	3.5% (-4.0%, 11.1%)

BCVA = best corrected visual acuity; CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PTI = personalized treatment interval (from Q4W up to Q16W); Q8W = every 8 weeks.
Note: CMH weighted % for aflibercept arm presented for faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for faricimab PTI vs. aflibercept comparison are similar to those shown above; the weighted estimate was based on CMH test stratified by baseline BCVA score (< 64 letters vs. >= 64 letters), prior IVT anti-VEGF therapy (yes vs. no), and region (U.S. and Canada vs. the rest of the world). Asia and rest of the world regions were combined due to a small number of enrolled patients. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing assessments were not imputed. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.04% CI and estimates below 0% or above 100% were imputed as 0% or 100% respectively. Baseline was defined as the last available measurement obtained on or prior to randomization

In the RHINE study at Week 52, 13.3%, 15.6%, 20.1%, and 51.0% of patients in the PTI arm were on a Q4W, Q8W, Q12W or Q16W treatment interval, respectively. The proportion of patients achieving a faricimab dosing interval of Q12W or Q16W and maintaining it without an injection interval decrease below Q12W through Week 52 was 64.3%.

In the YOSEMITE study at Week 52, 10.8%, 15.4%, 21.0% and 52.8% of patients in the PTI arm were on a Q4W, Q8W, Q12W or Q16W treatment interval, respectively. The proportion of patients achieving a faricimab dosing interval of Q12W or Q16W and maintaining it without an injection interval decrease below Q12W through Week 52 was 67.8%.

In the RHINE study in the ITT population patients treated with faricimab Q8W or PTI had numerically greater reductions in CST from baseline at Week 48/52/56 compared with patients treated with aflibercept Q8W. At Week 48/52/56 the adjusted mean change from baseline in CST was -195.8 µm, -187.6 µm, and -170.1 µm in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 48/52/56 was -25.7 µm and -17.6 µm respectively

In the YOSEMITE study in the ITT population patients treated with faricimab Q8W or PTI also had numerically greater reductions in CST from baseline at Week 48/52/56 compared with patients treated with aflibercept Q8W. At Week 48/52/56, the adjusted mean change from baseline in CST was -206.6 µm, -196.5 µm, and -170.3 µm in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 48/52/56 was -36.2 µm and -26.2 µm, respectively (Table 44).

For both studies patients treated with faricimab Q8W or PTI consistently had numerically greater reductions in mean change from baseline in CST through Week 56 compared with the aflibercept arm

Table 44 Change from Baseline in CST (ILM-BM) in the Study Eye averaged over Weeks 48, 52 and 56: MMRM Method (ITT Population) RHINE and YOSEMITE

	RHINE			YOSEMITE		
	Faricimab 6mg Q8W n = 317	Faricimab 6mg PTI n= 319	Aflibercept 2mg Q8W n = 315	Faricimab 6mg Q8W n = 315	Faricimab 6mg PTI n= 313	Aflibercept 2mg Q8W n = 312
Average Wk 48/52/56						
N	265	291	276	271	275	272
Adjusted mean (95% CI)	-195.8 (-204.1, -187.5)	-187.6 (-195.8, -179.5)	-170.1 (-178.3, -161.8)	-206.6 (-214.7, -198.4)	-196.5 (-204.7, -188.4)	-170.3 (-178.5, 162.2)
Diff v aflibercept adj mean (95% CI)	-25.7 (-37.4, -14.0)	-17.6, (-29.2, -6.0)		-36.2 (-47.8, -24.7)	-26.2 (-37.7, -14.7)	

Units: microns. BCVA = Best-corrected Visual Acuity; CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; MMRM = Mixed-Model Repeated- Measures; PTI = Personalized Treatment Interval (from Q4W up to Q16W). For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. The estimate of the difference between the two groups is using a composite contrast over Weeks48, 52 and 56. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. 95% CI is a rounding of 95.04% CI. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by CRC.

Ancillary analyses

The following subgroups were analyzed with respect to the primary efficacy endpoint and key secondary endpoint using the same method as specified above for each respective endpoint. Forest plots were created to summarize the results. The subgroup categories defined in the SAP were combined when there was not enough representation of a specific subpopulation.

- Baseline BCVA (≥ 64 letters and ≤ 63 letters)
- Region (U.S. and Canada, Asia, and the rest of the world)

- Prior intravitreal anti-VEGF therapy (yes and no)
- Baseline DRS (< 47, 47-53 and > 53 ETDRS DRSS)
- Baseline HbA1c (≤ 8% and > 8%)
- Age (< 65 years and ≥ 65 years)
- Gender (female and male)
- Race (White, Asian, and other)

Results are shown in Tables 45 and 46.

Table 45 Subgroup analysis change from baseline in BCVA in the study eye averaged over weeks 48, 52 and 56 for Faricimab Q8W v Aflibercept Q8W: MMRM method (ITT population)

	RHINE					YOSEMITE				
	Faricimab 6mg		Aflibercept 2mg		Diff adjusted mean 95% CI	Faricimab 6mg		Aflibercept 2mg		Diff adjusted mean 95% CI
	n	Adj. mean	n	Adj. mean		n	Adj mean	n	Adj. mean	
All patients	268	11.8	279	10.3	1.5 (0.1, 3.0)	271	10.7	276	10.9	-0.2 (-1.8, 1.4)
Baseline BCVA										
≥64 letters	145	8.9	151	8.4	0.5 (-1.2, 2.2)	150	9.5	147	8.9	0.6 (-1.2, 2.5)
< 63 letters	123	15.4	128	12.5	2.9 (0.5, 5.3)	121	12.2	129	13.3	-1.1 (-3.6, 1.5)
Region										
US Canada	89	11.9	96	11.1	0.7 (-1.8, 3.3)	151	10.6	147	12.4	-1.7 (-3.8, 0.3)
Asia	28	10.9	25	10.3	0.7 (-3.7, 5.0)	20	11.1	19	6.9	4.2 (-0.8, 9.2)
Rest of World	151	11.9	158	9.7	2.2 (0.3, 4.0)	100	10.9	110	9.6	1.3 (-1.2, 3.9)
Prior IVT anti-VEGF										
Yes	60	12.2	66	9.1	3.0 (-0.1, 6.2)	71	10.9	64	9.5	1.4 (-1.2, 4.1)
No	208	11.7	213	10.5	1.1 (-0.5, 2.8)	200	10.6	212	11.3	-0.7 (-2.6, 1.2)
Baseline DRSS										
< 47	153	10.8	154	9.7	1.1 (-0.8, 3.0)	147	10.1	157	10.5	-0.4 (-2.3, 1.5)
47-53	94	13.0	97	11.6	1.4 (-1.0, 3.9)	101	11.0	93	12.2	-1.1 (-3.9, 1.6)
>53	17	13.3	20	8.2	5.1 (-1.4, 11.6)	19	15.1	17	6.8	8.3 (-1.2, 17.9)
Baseline HbA1c										

≤ 8% >8%	168 99	12.5 10.5	171 104	9.8 10.5	2.7 (0.9, 4.4) 0.0 (-2.6, 2.6)	189 82	11.4 9.2	186 90	11.0 10.9	0.4 (-1.3, 2.1) -1.7 (-5.0, 1.5)
Baseline age < 65 ≥ 65	 151 117	 12.0 11.6	 167 112	 11.0 9.0	 1.0 (-0.9, 2.9) 2.6 (0.4, 4.8)	 163 108	 12.2 8.3	 163 113	 12.4 8.8	 -0.2 (-2.2, 1.9) -0.5 (-2.8, 1.8)
Sex Male Female	 158 110	 11.9 11.6	 165 114	 10.1 10.4	 1.7 (-0.1, 3.6) 1.2 (-1.1, 3.5)	 162 109	 11.0 10.2	 155 121	 10.7 11.3	 0.4 (-1.7, 2.4) -1.1 (-3.5, 1.3)
Race White Asian Other	 210 33 25	 11.8 11.0 12.4	 221 31 27	 9.9 10.3 12.7	 1.9 (0.3, 3.6) 0.7 (-3.2, 4.7) -0.3 (-5.9, 5.4)	 207 29 35	 11.0 10.2 9.2	 228 23 25	 11.6 7.8 8.2	 -0.6 (-2.2, 1.1) 2.4 (-2.3, 7.0) 1.0 (-5.6, 7.6)

BCVA = best corrected visual acuity; MMRM = Mixed-Model Repeated- Measures. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). The stratification factor is excluded if it is the subgroup. An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.04% CI.

Table 46. Subgroup analysis change from baseline in BCVA in the study eye averaged over weeks 48, 52 and 56 for Faricimab PTI v Aflibercept Q8W: MMRM method (ITT population)

	RHINE					YOSEMITE				
	Faricimab 6mg PTI		Aflibercept 2mg		Diff adjusted mean 95% CI	Faricimab 6mg PTI		Aflibercept 2mg	Diff adjusted mean 95% CI	
	n	Adj. mean	n	Adj. mean		n	Adj mean	n	Adj. mean	
All patients	293	10.8	279	10.3	0.5 (-0.9, 1.9)	276	11.6	276	10.9	-0.7 (-0.9, 2.3)
Baseline BCVA n ≥64 letters < 63 letters	 161 132	 7.9 14.2	 151 128	 8.4 12.5	 -0.4 (-2.1, 1.3) 1.7 (-0.6, 4.1)	 157 119	 9.1 14.7	 147 129	 8.9 13.3	 0.3 (-1.6, 2.1) 1.4 (-1.2, 4.0)
Region US Canada Asia	 101 27 165	 11.9 11.4 9.9	 96 25 158	 11.1 10.3 9.7	 0.8 (-1.7, 3.3) 1.1 (-3.3, 5.6) 0.2 (-1.7, 2.0)	 151 19 106	 13.3 8.1 9.8	 147 19 110	 12.4 6.9 9.6	 0.9 (-1.2, 3.0) 1.2 (-3.9, 6.3) 0.2 (-2.3, 2.7)

Rest of World										
Prior IVT anti-VEGF Yes No	62 231	9.1 11.2	66 213	9.1 10.5	-0.1 (-3.2, 3.1) 0.6 (-1.0, 2.2)	61 215	12.5 11.4	64 212	9.5 11.3	3.0 (0.3, 5.7) 0.0 (-1.8,1.9)
Baseline DRSS < 47 47-53 >53	165 89 34	9.7 12.0 13.2	154 97 20	9.7 11.6 8.2	-0.0 (-1.9, 1.9) 0.4 (-2.1, 2.9) 5.0 (-0.6, 10.6)	165 88 18	10.6 13.6 13.2	157 93 17	10.5 12.2 6.8	0.0 (-1.9, 1.9) 1.5 (-1.4, 4.3) 6.4 (-3.1, 15.9)
Baseline HbA1c ≤ 8% >8%	186 102	10.5 11.2	171 104	9.8 10.5	0.7 (-1.0, 2.4) 0.7 (-1.9, 3.3)	172 101	11.8 11.4	186 90	11.0 10.9	0.8 (-0.9, 2.6) 0.5 (-2.6, 3.6)
Baseline age < 65 ≥ 65	164 129	11.6 9.6	167 112	11.0 9.0	0.6 (-1.3, 2.5) 0.5 (-1.7, 2.7)	153 123	13.2 9.7	163 113	12.4 8.8	0.8 (-1.3, 2.9) 0.9 (-1.3, 3.1)
Sex Male Female	182 111	11.4 9.7	165 114	10.1 10.4	1.2 (-0.6, 3.1) -0.7 (-3.0, 1.6)	174 102	12.0 10.8	155 121	10.7 11.3	1.4 (-0.7, 3.4) -0.5 (-2.9, 2.0)
Race White Asian Other	232 33 28	10.8 11.1 9.6	221 31 27	9.9 10.3 12.7	0.9 (-0.7, 2.5) 0.8 (-3.2, 4.7) -3.1 (-8.6, 2.4)	213 26 37	12.3 9.7 9.0	228 23 25	11.6 7.8 8.2	0.7 (-0.9, 2.4) 1.8 (-3.0, 6.6) 0.8 (-5.8, 7.3)

BCVA = best corrected visual acuity; MMRM = Mixed-Model Repeated- Measures. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). The stratification factor is excluded if it is the subgroup. An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.04% CI.

Long-term data to Week 100 YOSEMITE and RHINE studies

The global enrolment cohorts completed Week 100 of the DME Phase III studies (YOSEMITE and RHINE) on September and August 2021, respectively, with the last patient rolling over to the extension study RHONE-X on 15 September 2021. The efficacy and safety of the PTI dosing regimen was assessed for both studies for the entire 2-year study period up to Week 100.

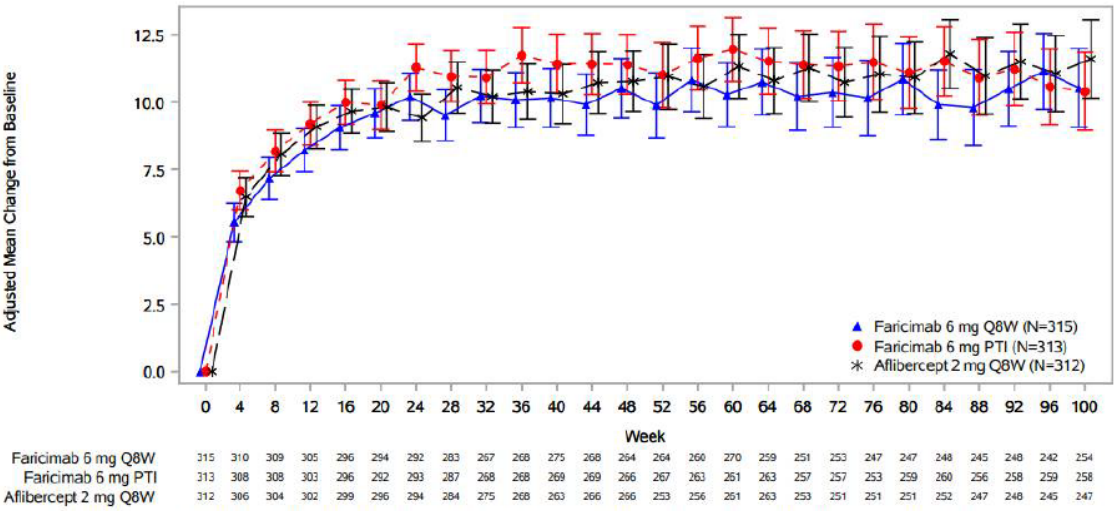
- In both YOSEMITE and RHINE, the mean change from baseline in BCVA averaged over Weeks 92, 96, and 100 (Week 92/96/100) was comparable across the faricimab Q8W, faricimab PTI

and aflibercept Q8W arms (Figure 58 and Figure 59, respectively). At Week 92/96/100 the adjusted mean change from baseline in BCVA was 10.7, 10.7, and 11.4 letters in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms in YOSEMITE and 10.9, 10.1, and 9.4 letters, respectively, in RHINE. The difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI dosing arms when compared to the aflibercept Q8W arm at Week 92/96/100 was -0.7 letters (95% CI: -2.6, 1.2) and -0.7 letters (95% CI: -2.5, 1.2), respectively, in YOSEMITE, and 1.5 letters (95% CI: -0.5, 3.6) and 0.7 letters (95% CI: -1.3, 2.7), respectively, in RHINE. The final BCVA efficacy results (Week 92/96/100) are consistent with the efficacy results at the time point of the primary analysis (averaged over Weeks 48, 52, and 56)

Figure 57. Yosemite: Change from baseline in BCVA

Figure 1 YOSEMITE: Change from Baseline in BCVA in the Study Eye through Week 100: MMRM Method (Primary Estimand), ITT Population

Protocol: GR40349



Faricimab 6 mg Q8W	315	310	309	305	296	294	292	283	267	268	275	268	264	264	260	270	259	251	253	247	247	248	245	248	242	254
Faricimab 6 mg PTI	313	308	308	303	296	292	293	287	268	268	269	269	266	267	263	261	263	257	257	253	259	260	256	258	259	258
Aflibercept 2 mg Q8W	312	306	304	302	299	296	294	284	275	268	263	266	266	253	256	261	263	253	251	251	251	252	247	248	245	247

Units: letters. BCVA=Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; PTI = Personalized Treatment Interval (from Q4W up to Q16W). For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.04% CI.

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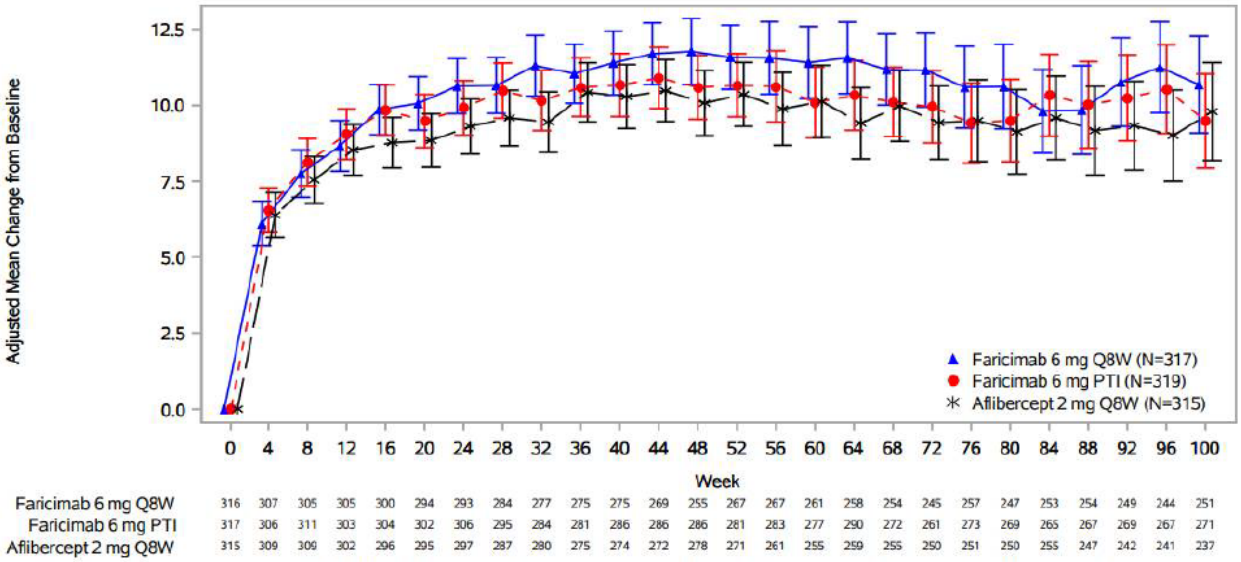
24NOV2021 2:15

Figure 58. RHINE: Change from baseline in BCVA

Figure 2 RHINE: Change from Baseline in BCVA in the Study Eye through Week 100: MMRM Method (Primary Estimand), ITT Population

Protocol: GR40398



Faricimab 6 mg Q8W	316	307	305	305	300	294	293	284	277	275	275	269	255	267	267	261	258	254	245	257	247	253	254	249	244	251
Faricimab 6 mg PTI	317	306	311	303	304	302	306	295	284	281	286	286	286	281	283	277	290	272	261	273	269	265	267	269	267	271
Aflibercept 2 mg Q8W	315	309	309	302	296	295	297	287	280	275	274	272	278	271	261	255	259	255	250	251	250	255	247	242	241	237

Units: letters. BCVA=Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; PTI = Personalized Treatment Interval (from Q4W up to Q16W). For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.04% CI.

Program: root/clinical_studies/RO6867461/CDT70122/share/CSR_Final/prod/program/g_ef_mmrm.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40398/data_analysis/CSR_Final/prod/output/g_ef_mmrm_SBCVA_PREST_IT_28OCT2021_40398.pdf
24NOV2021 3:36

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Table 47. YOSEMITE and RHINE: Change from baseline in BCVA

Table 2 YOSEMITE and RHINE: Change from Baseline in BCVA in the Study Eye Averaged Over Weeks 48, 52 and 56: MMRM Method with 97.5% CI (Primary Estimand) (ITT Population)

	GR40349 (YOSEMITE) (N=940)			GR40398 (RHINE) (N=951)		
Visit Statistics	Faricimab 6 mg Q8W (N=315)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=312)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=315)
Average of Week 48, 52 and 56						
n	271	276	276	268	293	279
Adjusted Mean (SE)	10.7 (0.56)	11.6 (0.56)	10.9 (0.56)	11.8 (0.52)	10.8 (0.51)	10.3 (0.52)
97.5% CI for Adjusted Mean	(9.4, 12.0)	(10.3, 12.9)	(9.6, 12.2)	(10.6, 13.0)	(9.6, 11.9)	(9.1, 11.4)
Difference (vs. Aflibercept) in Adjusted Means (SE)	-0.2 (0.79)	0.7 (0.79)		1.5 (0.73)	0.5 (0.73)	
97.5% CI for Difference in Adjusted Means	(-2.0, 1.6)	(-1.1, 2.5)		(-0.1, 3.2)	(-1.1, 2.1)	
P-value (for superiority test)	0.7967	0.3772		0.0361	0.4930	

Units: letters. BCVA=Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures;
PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 letters vs. >= 64 letters), prior Intravitreal anti-VEGF therapy (yes vs. no), and region (U.S. and Canada, Asia, and the rest of the world).
An unstructured covariance structure is used. The estimate of the difference between the two groups uses a composite contrast over Weeks 48, 52 and 56. Treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis.
97.5% CI is a rounding of 97.52% CI.

Sources:
YOSEMITE Primary CSR, Report 1102956, t_ef_mmrm_yr1_97_SBCVA_PREST_IT_20OCT2020_40349;
RHINE Primary CSR, Report 1102957, t_ef_mmrm_yr1_97_SBCVA_PREST_IT_19OCT2020_40398.

- During the 2-year period of YOSEMITE and RHINE, patients in the PTI dosing arm were able to follow an individualized dosing regimen based on a treat-and-extend concept, which allowed dosing interval extension, maintenance or reduction based on the CST and BCVA

change at study dosing visits after completion of the initial four Q4W doses. Therefore, during a 2-year period of the studies, patients could have up to a maximum of four full Q16W dosing cycles and up to a maximum of six full cycles of Q12W dosing (study schematic below, Figure 59).

- The proportions of patients in the PTI arm on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 96 (last study visit where a treatment decision was made) were 7.0%, 14.8%, 18.1%, 60.0% in YOSEMITE, and 10.1%, 11.8%, 13.6%, 64.5% in RHINE (Table 3).
- Therefore, at Week 96, the total of patients in the faricimab PTI arm who achieved a Q16W or Q12W dosing interval was 78% in each of the two studies (60% on Q16W + 18.1% on Q12W in YOSEMITE and 64.5% on Q16W + 13.6% on Q12W in RHINE; Table 48).

Table 48.

Table 3 YOSEMITE and RHINE: Proportion of Patients in the PTI Arm on a Q4W, Q8W, Q12W, or Q16W Treatment Interval at Week 96, Intent-to-Treat Population

	YOSEMITE Faricimab PTI (N=313)	RHINE Faricimab PTI (N=319)
N	270	287
Q4W	19 (7.0%)	29 (10.1%)
Q8W	40 (14.8%)	34 (11.8%)
Q12W	49 (18.1%)	39 (13.6%)
Q16W	162 (60.0%)	185 (64.5%)

PTI=Personalized Treatment Interval (from Q4W up to Q16W); Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.
Source: t_int_prop_IT_DME_HLSY2.

- Through Week 96, the proportion of patients in the faricimab PTI arm who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W was 60.4% in YOSEMITE and 63.1% in RHINE.
- The proportion of patients at Week 96 who achieved a Q16W treatment interval without an injection interval decrease below Q16W was 52.6% in YOSEMITE and 58.2% in RHINE.
- Among patients who were on a Q12W or Q16W interval at Week 52, the proportion of patients who remained on Q12W or Q16W dosing without an interval decrease below Q12W through Week 96 was 75.0% in YOSEMITE and 83.5% in RHINE
- Among patients who were on a Q16W interval at Week 52, the proportion of patients who remained on Q16W dosing without an interval decrease below Q16W through Week 96 was 69.9% in YOSEMITE and 81.8% in RHINE.
- The maintenance of vision gains achieved at Year 1 through Year 2 across all three treatment arms was supported by anatomical results as measured on SD-OCT. The benefit of faricimab Q8W and faricimab PTI treatment as compared to aflibercept Q8W was observed on the endpoints of CST change from baseline over time, proportions of patients with absence of DME over time, and proportions of patients with absence of IRF over time
- Additionally, the proportions of patients with a ≥2-step DRS improvement across both faricimab treatment arms in the YOSEMITE and RHINE studies at Week 52 (46.0% and 44.2% in faricimab Q8W arms, 42.5% and 43.7% faricimab PTI arms, respectively) were maintained

at Week 96 (51.4% and 53.5% in faricimab Q8W arms, 42.8% and 44.3% faricimab PTI arms, respectively); The 11 percentage point difference between the aflibercept arms of YOSEMITE and RHINE studies in the proportions of patients with ≥2-step DRS improvement at Week 52 (35.8% in YOSEMITE versus 46.8% in RHINE; was no longer apparent at Week 96. At Week 96, aflibercept-treated patients in both studies achieved comparable ≥ 2-step DRSS improvements (42.2% in YOSEMITE and 43.8% in RHINE;

- In summary, the BCVA gains achieved by patients on PTI dosing at Year 1, which were non-inferior compared to standard of care aflibercept Q8W dosing, were maintained along with the anatomical benefits over time up to Year 2. Through Week 100, patients in the PTI arm were able to complete up to a maximum of four Q16W cycles or up to six Q12W cycles in the Phase III DME program. At Week 96, there were 78% of patients in the faricimab PTI arm who achieved a Q16W or Q12W dosing interval in each study.

Among the patients on a Q16W interval at Week 52, 70% or more maintained Q16W dosing without an interval decrease through Week 96 reproducibly in both studies.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 49. Summary of efficacy for trial RHINE (GR40398)

Title: A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab (RO6867461) in patients with diabetic macular edema (RHINE)		
Study identifier	GR40398, RHINE ClinicalTrials.gov Identifier: NCT03622593 EudraCT: 2017-005105-12	
Design	Multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy, safety, durability, and pharmacokinetics of faricimab in patients with diabetic macular edema	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase (RHONE-X; Study GR41987):	100 weeks 28 days (screening visit to Day -1) 104 weeks
Hypothesis	For each of the two faricimab arms (Q8W and PTI): • non-inferiority of faricimab compared with aflibercept Q8W in the intent to treat (ITT) population, • superiority of faricimab compared with aflibercept Q8W in the treatment naive (TN) population, • superiority of faricimab compared with aflibercept Q8W in the ITT population	

Treatments groups	Faricimab 6 mg Q8W		6 mg faricimab intravitreal injection on Day 1 then Q4W to Week 20, followed by Q8W to Week 96; n=317 patients randomized
	Faricimab 6 mg PTI (personalized treatment interval)		6 mg faricimab intravitreal injection on Day 1 then Q4W to at least Week 12, followed by PTI (adjustable dosing administered in 4, 8, 12 or 16-week intervals) to Week 96; n=319 patients randomized
	Aflibercept 2 mg Q8W		2 mg aflibercept intravitreal injection on Day 1 then Q4W to Week 16, followed by Q8W to Week 96; n=315 patients randomized
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 48/52/56	Change from baseline in BCVA averaged over Weeks 48, 52, and 56 (Week 48/52/56) measured using the ETDRS visual acuity chart at a starting distance of 4 meters (NI margin of -4.0 letters).
	Secondary endpoint	CfBL in BCVA at Week 92/96/100	Change from baseline (CfBL) in BCVA averaged over Weeks 92, 96, and 100 (Week 92/96/100) measured using the ETDRS visual acuity chart at a starting distance of 4 meters
	Secondary endpoint:	Prop. of pts gaining ≥15 letters in BCVA from BL at Week 48/52/56	Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 48/52/56
	Secondary endpoint	Prop. of pts gaining ⩾15 letters in BCVA from BL at Week 92/96/100	Proportion of patients gaining ⩾15 letters in BCVA from baseline at Week 92/96/100
	Secondary endpoint:	Prop. of pts avoiding a loss of ≥ 15 letters in BCVA from BL at Week 48/52/56	Proportion of patients avoiding a loss of ≥ 15 letters in BCVA from baseline at Week 48/52/56
	Secondary endpoint	Prop. of pts avoiding a loss of ⩾15 letters in BCVA from BL at Week 92/96/100	Proportion of patients avoiding a loss of ⩾15 letters in BCVA from baseline at Week 92/96/100

	Secondary endpoint:	Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 52	Proportion of patients in the PTI arm on a Q16W, Q12W, Q8W, or Q4W treatment interval at Week 52
	Secondary endpoint	Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 96	Proportion of patients in the PTI arm on a Q16W, Q12W, Q8W, or Q4W treatment interval at Week 96
	Secondary endpoint:	Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 52	Proportion of patients with a ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52
	Secondary endpoint	Prop. of pts with a 2-step DRS improv. from BL on the ETDRS DRSS at Week 96	Proportion of patients with a ⩾2-step DRS improvement from baseline on the ETDRS DRSS at Week 96
	Secondary endpoint:	CfBL in CST at Week 48/52/56	Change from baseline in CST at Week 48/52/56
	Secondary endpoint	CfBL in CST at Week 92/96/100	Change from baseline in CST at Week 92/96/100
Database lock	The summary is based on a datacut with clinical cut-off date of 19 October 2020 for the primary analysis of efficacy data through Week 56 and a data snapshot date of 28 October 2021 for the updated analysis of efficacy data through Week 100.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, with patients grouped according to treatment assigned at randomization. The primary analysis was performed when all patients from the global enrollment phase had either completed the study through Week 56 or had discontinued from the study prior to Week 56, whichever was later.		

Descriptive statistics and estimate variability	Treatment group	Faricimab 6 mg Q8W	Faricimab 6 mg PTI	Aflibercept 2 mg Q8W
	Number of subject	N=317	N=319	N=315
	Primary Endpoint: CfBL in BCVA at Week 48/52/56 Adjusted Mean (97.52% CI)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
	Secondary Endpoint: Prop. of pts gaining ≥15 letters in BCVA from BL at Week 48/52/56 CMH Weighted Estimate (95.04% CI)	33.8% (28.4%, 39.2%)	28.5% (23.6%, 33.3%)	30.3% (25.0%, 35.5%)
	Secondary Endpoint: Prop. of pts avoiding a loss of ≥15 letters in BCVA from BL at Week 48/52/56 CMH Weighted Estimate (95.04% CI)	98.9% (97.6%, 100.0%)	98.7% (97.4%, 100.0%)	98.6% (97.2%, 99.9%)
	Secondary Endpoint: Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 52 Unadjusted proportion (95% CI)	N/A	Q16W: 51.0% (45.4%, 56.6%) Q12W: 20.1% (15.6%, 24.6%) Q8W: 15.6% (11.5%, 19.6%) Q4W: 13.3% (9.5%, 17.1%)	N/A
	Secondary Endpoint: Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 52 CMH Weighted % (97.52% CI)	44.2% (37.1%, 51.4%)	43.7% (36.8%, 50.7%)	46.8% (39.8%, 53.8%)
	Secondary Endpoint: CfBL in CST at Week 48/52/56 Adjusted Mean (95.04% CI)	-195.8 (-204.1, -187.5)	-187.6 (-195.8, -179.5)	-170.1 (-178.3, -161.8)

Effect estimate per comparison	Primary endpoint: CfBL in BCVA at Week 48/52/56	Comparison groups (MMRM)	Faricimab vs. Aflibercept Q8W	
		Difference in Adjusted Means (97.52% CI) NI margin: -4 letters	Faricimab Q8W vs. Aflibercept: 1.5 (-0.1, 3.2)	
			Faricimab PTI vs. Aflibercept: 0.5 (-1.1, 2.1)	
Analysis description	**Updated Analysis through Week 100**			
Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, with patients grouped according to treatment assigned at randomization. The Week 100 was performed when all patients from the global enrollment phase had either completed the study through Week 100 or had discontinued early from the study, all data from the global enrollment phase were in the database and had been cleaned and verified.			
Descriptive statistics and estimate variability	Treatment group	Faricimab 6 mg Q8W *{as per above terminology}*	Faricimab 6 mg PTI *{as per above terminology}*	Aflibercept 2 mg Q8W *{as per above terminology}*
	Number of subject	N=317	N=319	N=315
	Secondary Endpoint: CfBL in BCVA at Week 92/96/100 Adjusted Mean (95.04% CI)	10.9 (9.5, 12.3)	10.1 (8.7, 11.5)	9.4 (7.9, 10.8)
	Secondary Endpoint: Prop. of pts gaining ≥15 letters in BCVA from BL at Week 92/96/100 CMH Weighted Estimate (95.04% CI)	39.8% (34.0%, 45.6%)	31.1% (26.1%, 36.1%)	39.0% (33.2%, 44.8%)
	Secondary Endpoint: Prop. of pts avoiding a loss of ≥15 letters in BCVA from BL at Week 92/96/100 CMH Weighted Estimate (95.04% CI)	96.6% (94.4%, 98.8%)	96.8% (94.8%, 98.9%)	97.6% (95.7%, 99.5%)

	Secondary Endpoint: Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 96 Unadjusted proportion (95% CI)	N/A	Q16W: 64.5% (58.9%, 70.0%) Q12W: 13.6% (9.6%, 17.6%) Q8W: 11.8% (8.1%, 15.6%) Q4W: 10.1% (6.6%, 13.6%)	N/A
	Secondary Endpoint: Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 96 CMH Weighted % (95.04% CI)	53.5% (46.9%, 60.1%)	44.3% (37.9%, 50.7%)	43.8% (37.2%, 50.4%)
	Secondary Endpoint: CfBL in CST at Week 92/96/100 Adjusted Mean (95.04% CI)	-202.6 (-211.1, -194.2)	-197.1 (-205.3, -188.9)	-185.6 (-194.1, -177.1)
Effect estimate per comparison	Secondary endpoint: CfBL in BCVA at Week 92/96/100	Comparison groups (MMRM)	Faricimab vs. Aflibercept Q8W	
		Difference in Adjusted Means (95.04% CI)	Faricimab Q8W vs. Aflibercept: 1.5 (-0.5, 3.6)	
			Faricimab PTI vs. Aflibercept: 0.7 (-1.3, 2.7)	

Table 50. Summary of efficacy for trial YOSEMITE (GR40349)

Title: A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab (RO6867461) in patients with diabetic macular edema (YOSEMITE)			
Study identifier	GR40349, YOSEMITE ClinicalTrials.gov Identifier: NCT03622580 EudraCT: 2017-005104-10		
Design	Multicenter, randomized, double-masked, active comparator-controlled (aflibercept) study to evaluate the efficacy, safety, durability, and pharmacokinetics of faricimab in patients with diabetic macular edema		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase (RHONE-X; Study GR41987):		100 weeks 28 days (screening visit to Day -1) 104 weeks
Hypothesis	For each of the two faricimab arms (Q8W and PTI): • non-inferiority of faricimab compared with aflibercept Q8W in the intent to treat (ITT) population, • superiority of faricimab compared with aflibercept Q8W in the treatment naive (TN) population, • superiority of faricimab compared with aflibercept Q8W in the ITT population		
Treatments groups	Faricimab 6 mg Q8W		6 mg faricimab intravitreal injection on Day 1 then Q4W to Week 20, followed by Q8W to Week 96; n=315 patients randomized
	Faricimab 6 mg PTI (personalized treatment interval)		6 mg faricimab intravitreal injection on Day 1 then Q4W to a least Week 12, followed by PTI (adjustable dosing administe in 4, 8, 12 or 16-week intervals) to Week 96; n=313 patient randomized.
	Aflibercept 2 mg Q8W		2 mg aflibercept intravitreal injection on Day 1 then Q4W to Week 16, followed by Q8W to Week 96; n=312 patients randomized.
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 48/52/56	Change from baseline (CfBL) in BCVA averaged over Weeks 52, and 56 (Week 48/52/56) measured using the ETDRS vis acuity chart at a starting distance of 4 meters (NI margin of 4.0 letters).
	Secondary endpoint:	CfBL in BCVA at Week 92/96/100	Change from baseline (CfBL) in BCVA averaged over Weeks 96, and 100 (Week 92/96/100) measured using the ETDRS visual acuity chart at a starting distance of 4 meters

	Secondary endpoint:	Prop. of pts gaining ≥ 15 letters in BCVA from BL at Week 48/52/56	Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 48/52/56
	Secondary endpoint:	Prop. of pts gaining ≥15 letters in BCVA from BL at Week 92/96/100	Proportion of patients gaining ≥15 letters in BCVA from base at Week 92/96/100
	Secondary endpoint:	Prop. of pts avoiding a loss of ≥ 15 letters in BCVA from BL at Week 48/52/56	Proportion of patients avoiding a loss of ≥ 15 letters in BCVA from baseline at Week 48/52/56
	Secondary endpoint:	Prop. of pts avoiding a loss of ≥15 letters in BCVA from BL at Week 92/96/100	Proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline at Week 92/96/100
	Secondary endpoint:	Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 52	Proportion of patients in the PTI arm on a Q16W, Q12W, Q8 or Q4W treatment interval at Week 52
	Secondary endpoint:	Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 96	Proportion of patients in the PTI arm on a Q16W, Q12W, Q8 or Q4W treatment interval at Week 96
	Secondary endpoint:	Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 52	Proportion of patients with a ≥2-step DRS improvement fron baseline on the ETDRS DRSS at Week 52

	Secondary endpoint:	Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 96	Proportion of patients with a ≥2-step DRS improvement fron baseline on the ETDRS DRSS at Week 96
	Secondary endpoint:	CfBL in CST at Week 48/52/56	Change from baseline in CST at Week 48/52/56
	Secondary endpoint:	CfBL in CST at Week 92/96/100	Change from baseline in CST at Week 92/96/100
Database lock	The summary is based on a datacut with clinical cut-off date of 20 October 2020 for the primary analysis of efficacy data through Week 56 and the final analyses of efficacy data through Week 100.		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, w patients grouped according to treatment assigned at randomization. The primary analysis was performed when all patients from the global enrollment phase had either completed the study through Week 56 or had discontinued from the study prior to We 56, whichever was later.			
Descriptive statistics and estimate variability	Treatment group	Faricimab Q8 6 mg Q8W *{as per above terminology}*	Faricimab PTI 6 mg PTI *{as per above terminology}*	Aflibercept 2 mg Q8W *{as per above terminolo*
	Number of subjects	N=315	N=313	N=312
	Primary Endpoint: CfBL in BCVA at Week 48/52/56 Adjusted Mean (97.52% CI)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)
	Secondary Endpoint: Prop. of pts gaining ≥15 letters in BCVA from BL at Week 48/52/56	29.2% (23.9%, 34.5%)	35.5% (30.1%, 40.9%)	31.8% (26.6%, 37.0%)

	CMH Weighted Estimate (95.04% CI)			
	Secondary Endpoint: Prop. of pts avoiding a loss of ≥15 letters in BCVA from BL at Week 48/52/56 CMH Weighted Estimate (95.04% CI)	98.1% (96.5%, 99.7%)	98.6% (97.2%, 100.0%)	98.9% (97.6%, 100.0%)
	Secondary Endpoint: Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 52 Unadjusted proportion (95% CI)	N/A	Q16W: 52.8% (47.0%, 58.6%) Q12W: 21.0% (16.3%, 25.7%) Q8W: 15.4% (11.2%, 19.6%) Q4W: 10.8% (7.2%, 14.4%)	N/A
	Secondary Endpoint: Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 52 CMH Weighted % (97.52% CI)	46.0% (38.8%, 53.1%)	42.5% (35.5%, 49.5%)	35.8% (29.1%, 42.5%)
	Secondary Endpoint: CfBL in CST at Week 48/52/56 Adjusted Mean (95.04% CI)	-206.6 (-214.7, -198.4)	-196.5 (-204.7, -188.4)	-170.3 (-178.5, -162.2)
Effect estimate per comparison	Primary endpoint: CfBL in BCVA at Week 48/52/56	Comparison groups (MMRM)		Faricimab vs. Aflibercept Q8W

		Difference in Adjusted Means (97.52% CI) NI margin: -4 letters		Faricimab Q8W vs. Aflibercept -0.2 (-2.0, 1.6)
				Faricimab PTI vs. Aflibercept: 0.7 (-1.1, 2.5)
Analysis description	**Final Analysis through Week 100**			
Analysis population and time point description	Intent to treat (ITT) population: comprised all patients who were randomized in the study, w patients grouped according to treatment assigned at randomization. The final analysis was performed when all patients from the global enrollment phase had eith completed the study through Week 100 or had discontinued early from the study, all data fro the global enrollment phase were in the database and had been cleaned and verified.			
Descriptive statistics and estimate variability	Treatment group	Faricimab Q8 6 mg Q8W *{as per above terminology}*	Faricimab PTI 6 mg PTI *{as per above terminology}*	Aflibercept 2 mg Q8W *{as per above terminolo*
	Number of subjects	N=315	N=313	N=312
	Secondary Endpoint: CfBL in BCVA at Week 92/96/100 Adjusted Mean (95.04% CI)	10.7 (9.4, 12.1)	10.7 (9.4, 12.1)	11.4 (10.0, 12.7)
	Secondary Endpoint: Prop. of pts gaining ≥15 letters in BCVA from BL at Week 92/96/100 CMH Weighted Estimate (95.04% CI)	37.2% (31.4%, 42.9%)	38.2% (32.8%, 43.7%)	37.4% (31.7%, 43.0%)

	Secondary Endpoint: Prop. of pts avoiding a loss of ≥15 letters in BCVA from BL at Week 92/96/100 CMH Weighted Estimate (95.04% CI)	97.6% (95.7%, 99.5%)	97.8% (96.1%, 99.5%)	98.0% (96.2%, 99.7%)
	Secondary Endpoint: Prop. of pts in the PTI arm on a Q16W, Q12W, Q8W, or Q4W interval at Week 96 Unadjusted proportion (95% CI)	N/A	Q16W: 60% (54.1%,65.9%) Q12W: 18.1% (13.5%, 22.8%) Q8W: 14.8% (10.6%, 19.1%) Q4W: 7.0% (4.0%, 10.1%)	N/A
	Secondary Endpoint: Prop. of pts with a ≥2-step DRS improv. from BL on the ETDRS DRSS at Week 96 CMH Weighted % (95.04% CI)	51.4% (44.8%, 57.9%)	42.8% (36.6%, 49.0%)	42.2% (35.9%, 48.5%)
	Secondary Endpoint: CfBL in CST at Week 92/96/100 Adjusted Mean (95.04% CI)	-216.0 (-224.0, -208.0)	-204.5 (-212.4, -196.5)	-196.3 (-204.3, -188.2)
Effect estimate per comparison	Secondary endpoint: CfBL in BCVA at Week 92/96/100	Comparison groups (MMRM)		Faricimab vs. Aflibercept Q8W
		Difference in Adjusted Means (95.04% CI)		Faricimab Q8W vs. Aflibercept -0.7 (-2.6, 1.2)
				Faricimab PTI vs. Aflibercept: -0.7 (-2.5, 1.2)

2.4.5.2. Analysis performed across trials (pooled analyses and meta-analysis)

The Applicant provided pooled analyses of data across the two pivotal Phase III studies Yosemite and Rhine. Due to the identical design of the two studies and the comparable baseline characteristics of the recruited population, this is considered acceptable. The analyses were in line with the results achieved in the individual studies. Differences in efficacy results across the Phase III studies were already discussed in the results section above.

The key secondary EP "Proportion of patients with ≥ 2-step DRS improvement from baseline at week 52", which was met in Yosemite but not met in Rhine, revealed comparable results across the three treatment arms in the pooled analysis.

2.4.6. Discussion on clinical efficacy

Design and conduct of studies to support both indications (neovascular age-related macular degeneration and diabetic macular oedema.

A number of GCP irregularities were reported in the studies which led to a triggered GCP inspection at the request of the CHMP.

The Sponsor identified two breaches of GCP in the Phase III studies: 1) potential unmasking of 2 patients due to an internal software, and 2) unconsented optional plasma samples or optional aqueous humor samples were collected from a total of 235 patients across all 4 phase III studies.

A GCP inspection was conducted remotely at the sponsor (Roche/Genentech) site in the USA, all participants, including the inspectors conducted the inspection using video conferencing; and at one investigational site in Slovakia. The site inspection was conducted on site. At the inspection of the sponsor site Genentech/Roche there were 1 critical, 15 major and 8 minor findings. At the inspection of the investigator site in Slovakia there were 0 critical, 5 major and 8 minor findings. The inspectors recommended acceptance of all data of all four inspected trials for the assessment of the Vabysmo MAA.

Neovascular age-related macular degeneration indication (nAMD)

Design and conduct of clinical studies

In support of this indication the Applicant submitted two phase II studies which can be considered as dose-finding studies and two ongoing duplicate phase III studies that can be considered pivotal. All four studies were in treatment naïve nAMD populations.

All studies were randomised active controlled double-blind trials. The randomisation of the phase III studies was stratified according to BCVA (≥ 74 letters, 73-55 letters, and ≤ 54 letters); low luminance deficit (< 33 letters, and ≥ 33 letters) and region (North America, Asia and rest of the world). Both studies had patients mis-stratified in the BCVA and low luminance strata.

The active comparator in the phase II trials was ranizibumab 0.5mg IVT, whilst the comparator in the phase III trials is aflibercept 2mg IVT. The Applicant justified the change to use of aflibercept as an active control in the phase III trials on the basis that the product is a globally approved anti-VEGF treatment for nAMD with an eight weekly maintenance regimen. It is noted that aflibercept has been

accepted as the active control arm in the MA for brolucizumab (Beovu). The study design allowed for three different treatment intervals (8 weekly, 12 weekly or 16 weekly) for faricimab dependent on disease stability at weeks 20 and 24 following four weekly dosing up to and including week 12. From week 60 patients in the faricimab arm will be treated on a personal treatment interval (PTI) schedule. Study drug dosing intervals in the PTI regimen will be determined by calculations made automatically by the IxRS based on an algorithm that includes data on change in CST, change in BCVA, and presence of new macular hemorrhage.

The treatment regimen for aflibercept was fixed after an initial treatment phase with 3 monthly injections up to week 8, with following injections every 2 months. No personalised treatment was allowed, even though the EU Summary of Product Characteristic would allow longer treatment intervals of up to 16 weeks, this regimen was not approved in other countries participating in these global trials. The total number of injections was thus maintained in the control groups regardless of the disease activity of the patients, contrary to the faricimab groups. Although a reduced need for injections while maintaining visual acuity would pose a significant benefit, due to the fixed comparator regimen, the clinical development does not allow to demonstrate strong conclusion on the reduction of the treatment burden of faricimab 6 mg compared to a standard of care.

Both phase III studies and the STAIRWAY phase II study were non-inferiority studies with a non-inferiority margin of – 4 letters. This is considered acceptable from both a statistical and clinical point of view.

Regarding the study population only treatment naïve patients were recruited. The Applicant has justified the non-inclusion of treatment experienced patients on the basis of challenges in determining an appropriate non-inferiority margin for change in visual function in a mixed treatment naive and pre-treated population given that pre-treated patients have a lower capacity to benefit from treatment than treatment naïve patients (supported by data from the literature). In addition, the registration studies for ranibizumab, aflibercept and brolucizumab only included treatment naïve patients. The non-inferiority margin of the Phase III faricimab studies for nAMD is based on data from the MARINA and ANCHOR ranibizumab pivotal nAMD studies and is also supported by data from the VIEW1 and VIEW2 aflibercept pivotal nAMD studies, all of which included only treatment naive patients.

The Applicant has also presented data on the maintenance of visual function following a switch in anti-VEGF therapy. In the phase II Avenue study, patients maintained visual gains after switching from ranibizumab to faricimab. Although this study included only a limited number of patients and had a shorter study duration, results support the maintenance of a treatment effect in previously treated patients. Real world data from other anti-VEGF therapies also indicate that vision can be maintained after a therapy switch. The responses are considered acceptable and it is not proposed to restrict the indication to treatment naïve patients.

The inclusion criterion threshold for the focal lesion size of ≤ 9 disc areas (DA) on FFA was considered likely to exclude a more advanced nAMD population. The VIEW study for aflibercept included patients with a DA of ≤ 12 disc areas. This raised questions regarding the generalisability of the results to a more advanced population. In their response the applicant justified the exclusion of patients with larger lesion sizes i.e. > 9 and < 12 disc areas on the basis that nowadays treatment is initiated earlier because of better outcomes and consequently lesion sizes are not as large as those treated in earlier registration studies e.g. ranibizumab and aflibercept. Consequently, the proportion of study subjects with a lesion size between 9 and 12 disc areas is likely to be small. The average CNV lesion size in the HAWK study brolucizumab is similar to the lesion size in the TENAYA and LUCERNE studies, whilst the lesion size in the HARRIER study is smaller. The Applicant’s argumentation is accepted. In addition,

only unilateral treatment was allowed in the phase III studies. With regard to establishing efficacy and safety profiles of faricimab, this strategy was considered acceptable.

During previous advice, the Applicant was further recommended to select the study eye at random. According to the protocol synopsis if both eyes were considered eligible, the eye with the worse BCVA, as assessed at screening, was selected as the study eye.

For all four studies, the primary endpoint was the change from baseline in BCVA (as measured on the ETDRS chart at a starting distance of 4 meters). For the AVENUE phase II study this was evaluated at 20 weeks and at Week 40 for the phase II STAIRWAY study. For the phase III studies the primary endpoint was evaluated by averaging the change from baseline over Weeks 40, 44 and 48. There were a number of other supportive visual endpoints including: a responder analysis for gain in ≥ 15, ≥10, ≥ 5 letters BCVA from baseline as well as a responder analysis for avoidance of a loss of letters; change from baseline BCVA over time. Anatomical secondary endpoints included change from baseline in central subfield thickness (CST), absence of sub-retinal and intra-retinal fluid and change in lesion size. Descriptive data was provided on frequency of faricimab administration. Change from baseline in NEI VFQ-25 composite score over time was an exploratory endpoint. The primary and supporting secondary endpoints in particular those related to vision are considered appropriate given that the objective of treatment is to improve vision and/or prevent any further deterioration. Change in CST is an accepted biomarker.

The primary endpoint was evaluated in the ITT population in both pivotal studies using an MMRM model. A sensitivity analysis was conducted in the ITT population using last observation carried forward. Supplementary analyses included a per-protocol analysis; a treatment policy strategy analysis for all intercurrent events and a hypothetical strategy for all intercurrent events. All were conducted using an MMRM model and all except the per protocol analysis were conducted in the ITT population.

Both phase III studies are conducted in tandem and have both been affected by the COVID-19 pandemic, with some patients being unable to attend treatment visits including those at weeks 40, 44 and 48. Prior to finalisation, the analysis plan was updated to address intercurrent events due to COVID-19. Uncertainties with respect to conclusions about the treatment schedule remain, as there likely have been substantial deviations from the prescribed dosing schedule (across all arms) due to the pandemic situation. In TENAYA 27 patients [8.1%] and 31 patients [9.2%], and in LUCERNE 25 patients [7.6%] and 21 patients [6.4%] in the faricimab and aflibercept arms, respectively, missed an active dose due to COVID-19. With regard to these intercurrent events, the Applicant has provided additional analysis on how many patients in each of the different treatment intervals were affected and when the actual dose was received and discussed any potential impact on efficacy analysis. These intercurrent events are not believed to have impacted on treatment outcomes.

In conclusion, the design of the studies is considered adequate.

Efficacy data and additional analyses

Both pivotal studies showed an improvement from baseline in BCVA averaged over weeks 40, 44 and 48. The adjusted mean change from baseline in BCVA at week 40/44/48 in the TENAYA study was 5.8 and 5.1 letters in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from baseline in BCVA at week 40/44/48 between the faricimab arm and aflibercept arm was 0.7 letters (95% CI: - 1.1, 2.5). The adjusted mean change from baseline in BCVA was 6.6 letters in both the faricimab and aflibercept arms of the LUCERNE study with the difference in adjusted mean change from baseline between the faricimab arm and aflibercept arm of 0.0 letters (95% CI - 1.7, 1.8). In both studies, the lower bound of the 95% CI were above -2 and clearly above the non-inferiority margin of -4. A sensitivity analysis using LOCF and supplementary analyses including per

protocol, a treatment policy strategy analysis for all intercurrent events and a hypothetical strategy for all intercurrent events all produced similar results. Similar results between treatment arms in both studies for the responder analysis of patients gaining ≥ 15 letters from baseline BCVA (TENAYA: faricimab 20%, aflibercept 15.7%; LUCERNE faricimab 20.2%, aflibercept 22.2%) and reduction from baseline in CST of the order of 130µm are all supportive of non-inferiority. The results are considered clinically relevant.

The Applicant has provided further data to address the potential impact of intercurrent events due to COVID-19. Overall, it is not considered that these events have impacted the overall study outcomes.

During the initial assessment, there were uncertainties regarding the durability of effect particularly in the longer faricimab treatment intervals, which were resolved following provision of week 52/56/60 data. Patients randomised to faricimab could have been assigned from the Week 20/24 treatment visits to one of three treatment intervals (dependent on specific criteria relating to CST and BCVA), namely an 8, 12 or 16 week interval. The study design did not allow for modification of the faricimab dose in the case of an inadequate response. The period of follow up from Week 20/24 to Week 48 was considered to be inadequate to make any judgement on durability of response particularly in those treated at a 16 week interval. However further data confirmed that BCVA gains at 12 weeks in those treated with faricimab 6mg Q16W were preserved when averaged over Weeks 52/56/60.

The proportions of faricimab-treated patients on a fixed Q8W, Q12W, or Q16W treatment interval at Week 48 were 20.3%, 34.0%, and 45.7% in TENAYA and 22.2%, 32.9%, and 44.9% in LUCERNE. The Applicant provided efficacy results for the individual treatment intervals (Q8W, Q12W and Q16W, respectively) which showed that in the TENAYA study change from baseline BCVA averaged over weeks 52, 56 and 60 was greater for those treated with faricimab 6mg at Q16W intervals compared to faricimab at Q8W, Q12W or aflibercept at Q8W intervals. This difference was less marked in the LUCERNE study.

Efficacy assessments at week 60 included three cycles of Q16W and four cycles of Q12W and results were provided as average from weeks 52, 56 and 60. The difference in change in BCVA at week 52/56/60 was 0.7 (95% CI: -1.2, 2.7) in TENAYA and -0.6 (95% CI: -2.4, 1.3) in LUCERNE. In the pooled ITT population, the difference between treatment arms was 0.1 (95% CI: -1.2, 1.4) at Week 52/56/60. Also week 60 data for secondary endpoints are comparable between faricimab and aflibercept. In the pooled ITT population, 20.9% and 20.2% of patients in the faricimab and aflibercept arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 52/56/60 with a difference of 0.7% (95% CI: -3.6%, 5.1%) between the treatment arms. Overall, additional data up to week 60 support the results observed for primary and secondary efficacy endpoints seen at earlier timepoints.

Regarding section 4.2 of the SmPC the amended posology proposed by the Applicant is in the main accepted

Diabetic macular oedema indication

Design and conduct of clinical studies

The Applicant submitted one Phase II (BOULEVARD) that could be considered dose finding and two phase III (RHINE and YOSEMITE) studies that can be considered pivotal in support of this indication. The phase III studies are duplicate studies.

All studies were randomised active controlled double-blind trials. The phase III studies were stratified by baseline BCVA ETDRS score (≥ 64 letters v < 64 letters), prior intravitreal anti-VEGF treatment and

region (North America, Asia and rest of the world). A number of patients in each of the phase III studies were mis-stratified.

The BOULEVARD study was a superiority study. Overall, the design of the study is considered acceptable. Regarding the selected dose of the comparator (0.3 mg ranibizumab), there is a discrepancy with what is approved in the European Union and this is regarded suboptimal. In the European Union, the approved dose of Ranibizumab is 0.5 mg. However, the selection of the 0.3 mg dose might rely on the fact that the study was only conducted in the US, where Ranibizumab is approved for the 0.3 mg dose. In the EPAR of Ranibizumab, it is stated that no statistically significant differences between the 0.3 mg and 0.5 mg doses are obtained. However, due to the consistency of the trends and an increased benefit from the higher dose across all the pivotal trials, the higher dose was approved. Thus, it would have been preferred that the Applicant would have chosen the approved 0.5 mg dose over the non-approved 0.3 mg dose for the comparator. However, in light of the fact that the results of this study are only regarded as supportive, the selection of the lower dose for the active comparator Ranibizumab is accepted.

The RHINE and YOSEMITE studies are non-inferiority studies with a non-inferiority margin of - 4 letters on the BCVA EDTRS chart. Superiority of faricimab compared to aflibercept was also planned to be tested in the treatment naïve population and then in the ITT population. The chosen non-inferiority margin is considered acceptable from a clinical and a statistical point of view.

All studies included patients with diabetic macular oedema who were either treatment naïve or had previously been treated with IVT anti-VEGF products. Pre-treated patients were capped at 25% of the total study population in the phase III studies. Patients with HbA1C > 10% were excluded from the study unlike the VIVID and VISTA studies which included diabetic patients with HbA1C ≤ 12%.

For the phase II study, which was conducted in the US, the active control arm was ranibizumab 0.3mg in line with the approved FDA posology for diabetic macular oedema but lower than the 0.5mg posology authorised in the EU. The control arm for the phase III studies was aflibercept 2mg administered 4 weekly until week 16 and then 8-weekly. This is in line with the EU approved posology for diabetic macular oedema of one injection per month for five consecutive doses, followed by one injection every two months in the first year of treatment. Similar or better efficacy versus ranibizumab up to 1 year in diabetic macular oedema has been shown in a systematic review (Virgili 2018). Two dose schedules of faricimab 6mg an eight weekly and a personal treatment interval (PTI) schedule were compared to aflibercept. Those in the faricimab Q8W arm received a Q4W dose up to Week 20 and those in the PTI arm received a Q4W dose up to at least Week 12.

In the PTI arm, the dosing interval could be maintained or increased by 4 weeks/ decreased by 4 or 8 weeks increments, based on the relative change of the CST and BCVA compared with reference CST and reference BCVA. It seems as if this algorithm was based on the anatomical outcome rather than on the BCVA, as e.g. the interval was reduced if the CST increased by 20% compared to the reference CST (independent of BCVA change). However, the interval was only maintained and not reduced if the patients lost more than 10 letters on the BCVA compared to reference BCVA and the CST increased by less than 10%. The Applicant was asked to explain the rationale of this algorithm in detail as it was questioned how far an improvement in an anatomical outcome with a concomitant decrease in the BCVA score could have justified the maintenance of the treatment interval. In their response, the Applicant explained the algorithm on which the treatment interval extension/maintenance/reduction was based in detail. The Applicant justified the focus on CST measurement rather than BCVA on the basis that this was an objective measure and unlike BCVA unlikely to be affected by other factors unrelated to DME. Given the study results of RHINE and YOSEMITE (similar gains in BCVA across study groups, similar proportion of patients avoiding a loss of letters in BCVA across the groups) it is agreed

that the algorithm, although mainly based on changes in CST, seems to have been appropriate for treatment interval adjustment during the clinical trials.

The Applicant chose a fixed dose regimen for the comparator arm. This is in line with the posology of aflibercept in the DME indication which states that treatment should be initiated with one injection per month for five consecutive doses, followed by one injection every two months. Nonetheless, the aflibercept SmPC also states that after the first 12 months of treatment with aflibercept, and based on visual and/or anatomic outcomes, the treatment interval may be extended, such as with a treat-and-extend dose regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes. A T&E regimen for the comparator at year 2 in one of the two pivotal trials would have been preferable for a better evaluation of the conclusions drawn from the T&E dose regimen of the faricimab PTI arm, especially in terms of number of required injections. However, at the time of the initiation of the YOSEMITE and RHINE studies, the Q8W interval for aflibercept was regarded as the most efficacious regimen and the T&E regimen for aflibercept was only approved after initiation of the YOSEMITE and RHINE studies.

The primary endpoint for the phase III studies was the change from baseline in BCVA averaged over Weeks 48, 52, and 56. The BCVA outcome measure was based on the ETDRS VA chart assessed at a starting distance of four meters. The key secondary endpoint was the proportion of patients with a ≥ 2-step DRS improvement from baseline on the ETDRS DRSS at Week 52. There were a number of other secondary endpoints related to visual acuity and DRS changes as well as changes in the CST and absence or intra-retinal fluid.

The choice of endpoints is considered to be relevant to the indication. However, the timepoint for the evaluation of the primary endpoint (the change from baseline in BCVA averaged over weeks 48, 52, and 56) was considered too early. With regard to the faricimab PTI arm, patients received initially 4 monthly injections and then their dosing intervals could be increased based on BCVA/OCT assessment. This happened with 4 week increments. Therefore, with the primary analysis based on the week 48/52/56 assessment, only two injections of the week 16 interval and three injections of the week 12 interval were covered. This was not regarded as optimal for properly informing the posology of the product. Thus, a later time point for the primary analysis would have been preferred. This has also been discussed in a Scientific Advice procedure (EMA/CHMP/SAWP/784935/2017). At that time, the Applicant proposed a fixed 8-week and 12-week interval for faricimab. It was stated by the CHMP that the primary evaluation conducted at week 52 would be insufficient in order to conclude on the adequacy of the Q12W regimen (with three Q12W administrations at that time point). In such a scenario, the data generated during the second year are of outmost importance. These data have been provided with the responses to questions.

In addition there were concerns with regard to the averaging of the results across three time points (weeks 48, 52 and 56). In conjunction with the three different treatment schemes having different number of initial doses (faricimab 6 mg Q8W: 6 initial monthly doses, faricimab 6 mg PTI: 4 initial monthly doses and aflibercept 2 mg Q8W: 5 initial monthly doses), this could have introduced bias. Patients in the aflibercept 2 mg Q8W received doses at week 40, 48 and 56 thus only the week 52 timepoint of the primary endpoint analysis had a temporal distance of 4 weeks to the last injection. On the other hand, patients in the faricimab 6 mg Q8W received doses at week 44 and 52. Thus, there was the week 48 and week 56 timepoint of the primary endpoint analysis that had a temporal distance of 4 weeks to the last injection. This could have been a disadvantage for the Aflibercept 2 mg Q8W arm and was not regarded conservative in a non-inferiority design. The provided additional analyses including a variety of different endpoints with respect to timing of the endpoint assessment. The efficacy results were considered robust despite the different dosing schedules between faricimab Q8W and aflibercept Q8W arms. This applies to both pivotal studies (i.e., YOSEMITE and RHINE).

The primary endpoint was evaluated in the ITT population in both pivotal studies using an MMRM model. A sensitivity analysis was conducted in the ITT population using last observation carried forward. Supplementary analyses included a per protocol analysis; a treatment policy strategy analysis for all intercurrent events and a hypothetical strategy for all intercurrent events. All were conducted using an MMRM model and all except the per protocol analysis were conducted in the ITT population.

Both phase III studies are conducted in tandem and have both been affected by the COVID-19 pandemic, with some patients being unable to attend treatment visits including those at weeks 44, 48 and 52 (DME). Prior to finalisation, the statistical analysis plan was updated to address intercurrent events due to COVID-19.

In the protocol of the Phase III studies, the Applicant defined that if both eyes were considered eligible for the study, the eye with the worse best-corrected visual acuity, as assessed at screening, was selected as the study eye unless the investigator deemed the other eye to be more appropriate for treatment in the study. In a Scientific Advice procedure (EMA/CHMP/SAWP/784935/2017) concerning the design of the pivotal Phase III studies, the Applicant was recommended to select the study eye at random, if both study eyes would have been eligible. This advice was not followed. According to the baseline ocular characteristics, the bilateral eligibility concerned 84 patients in the Yosemite trial and in 53 of these patients, the eye with the worse BCVA was selected. In Rhine, the bilateral eligibility concerned 94 patients and in 60 of these patients, the eye with the worse BCVA was selected. In their response to question, the Applicant justified that the process of selecting the worse eye (based on BCVA) if both eyes were eligible for study treatment, was due to ethical considerations. Testing an investigational drug administered via intravitreal injection on the better seeing eye would not have been ethical. It is also agreed that due to the low number of patients that were affected (in about 10% of the patients both eyes were eligible) and the randomization process that was in place (leading to balanced baseline characteristics among groups), an impact on study results was not expected.

Efficacy data and additional analyses

Both pivotal studies demonstrated non-inferiority of both faricimab treatment schedules to aflibercept in the ITT and treatment naïve populations for change from baseline in BCVA averaged over weeks 48, 52 and 56. Superiority to aflibercept was not shown in the treatment naïve population.

The adjusted mean change from baseline in BCVA at week 48/52/56 in the RHINE study was 11.8 letters in the faricimab Q8W population, 10.8 letters in the faricimab PTI population and 10.3 in the aflibercept population. The difference in adjusted means for the faricimab Q8W dose was 1.5 letters (97.5% CI -0.1, 3.2) and for the PTI dose 0.5 letters (97.5%CI -1.1, 2.1) when compared with the aflibercept Q8W. Similar results were seen in the treatment naïve population. In the YOSEMITE study in the ITT population the adjusted mean change from baseline at week 48/52/56 was 10.7 letters for faricimab Q8W, 11.6 for faricimab PTI and 10.9 for aflibercept. The difference in adjusted means for the faricimab Q8W dose was -0.2 letters (97.5% CI -2.0, 1.6) and for the PTI dose 0.7 letters (97.5%CI -1.1, 2.5) when compared with the aflibercept Q8W. Broadly similar results were seen in the treatment naïve population. In both studies, the lower bound of the 97.5% CI were well above -4 in the treatment naïve and ITT populations. A sensitivity analysis using LOCF and supplementary analyses including per protocol, a treatment policy strategy analysis for all intercurrent events and a hypothetical strategy for all intercurrent events all produced similar results for both studies.

In response to a question, the Applicant provided the requested year 2 data for the pivotal RHINE and YOSEMITE studies. Mean change from baseline in BCVA was comparable across the faricimab Q8W,

faricimab PTI and aflibercept Q8W groups throughout year 2, both in YOSEMITE and in RHINE and BCVA efficacy data at week 92/96/100 were similar to the BCVA efficacy data at week 48/52/56, showing maintenance of the effect beyond year 1.

For the primary analysis, missing data were not imputed. This is acceptable - for inferences based on an MMRM model - assuming that data were missing at random. However, to a large degree, sensitivity and supplementary analyses also require the assumption that a large proportion of data (e.g. for COVID-19 related reasons) are missing at random. Consequently, additional analyses evaluating the robustness of results with respect to deviations from the MAR assumptions were requested. Tipping point analyses were conducted and the results were considered to be sufficiently robust to support the conclusions on the primary endpoint.

While there is little concern that the results of studies YOSEMITE and RHINE support a non-inferiority conclusion with respect to the applied dosing schemes (on average) on BCVA, there remain uncertainties as to what degree the presented results may support conclusions of non-inferior efficacy within subgroups of an individualized treatment schedule with faricimab (i.e. the concern may be that undertreatment with the longest treatment interval is compounded by overtreatment with the shortest interval). This appears especially relevant as a substantial proportion of subjects (~7% through Week 56 and ~4% through Week 96, always on Q4W dosing regimen) in the individualized treatment arm have been dosed more often (see above) compared to a fixed Q8W treatment schedule with unclear implications on efficacy and safety (see also corresponding concern on safety below). In addition, there remain uncertainties with regard to adherence to the fixed dosing schemes of faricimab and aflibercept for the treatment of DME, as there likely have been substantial deviations from the prescribed dosing schedule due to the pandemic situation. Several additional analyses were presented by the Applicant in response to questions raised during the assessment with respect to adherence to and impact of the prescribed treatment intervals on efficacy. These additional analyses did not raise any concerns with regard to the conclusions on non-inferiority.

Secondary endpoint results were generally supportive of the primary endpoint. In the RHINE study, a slightly higher proportion of those in the aflibercept arm achieved a ≥ 2-step improvement than those in the faricimab arms in DRS and non-inferiority was not demonstrated compared to aflibercept whereas in the YOSEMITE study, improvement was greater in both faricimab arms and non-inferiority was demonstrated. However, there were discrepancies in the aflibercept arms regarding this endpoint in the two studies. Faricimab treated patients in both studies demonstrated greater reduction in CST from baseline than aflibercept. However, the improvement in the anatomic outcome CST did not seem to translate into a further improvement in the visual outcomes, where the outcomes were similar between the treatment arms. Sub-group analysis showed similar improvement from baseline in BCVA in treatment naïve and pre-treated patients in both studies.

In the RHINE and YOSEMITE studies 51% and 52.8% respectively of participants on a PTI dosing interval were on a Q16W treatment interval at Week 52 and 20.1% and 21% were on a Q12W treatment interval. Across the two studies approximately 65% maintained a Q12W or Q16W dosing interval without a decrease in injection interval below Q12W. However, the results of this analysis was not considered to be very informative, as it was done at week 52. In the D120 response, the Applicant explained that within the 2-year period of the study, the patients in the faricimab PTI arm could have up to a maximum of four full Q16W dosing cycles and up to a maximum of six full cycles of Q12W dosing. This is considered to be acceptable in order to fully investigate the treatment potential of these intervals in the PTI arm. The Applicant provided further data showing the proportion of patients in the PTI arm on a Q4W, Q8W, Q12W or Q16W treatment interval at week 96. The results were consistent between the YOSEMITE and RHINE study and show that approximately 62% of the patients were on a

Q16W interval and 16% were on a Q12W interval at week 96. The Applicant further corroborated the adequacy of the treat-and-extend regimen by providing additional analyses on proportion of patients in the faricimab PTI arm who achieved a Q12W or Q16W treatment interval without an injection interval decrease below Q12W at Week 96 (being approximately 61%) and proportion of patients at Week 96 who achieved a Q16W treatment interval without an injection interval decrease below Q16W (being approximately 55%). The number of patients who were on a Q16W interval at week 52 and remained on Q16W dosing through week 96 was also high (69.9% in YOSEMITE and 81.8% in RHINE). These results further strengthen the proposed treat-and-extend regimen.

The Applicant provided the mean number of study drug administrations through week 56. The mean number of injections did not differ significantly between the three treatment arms. This is in clear contrast to the argumentation of the Applicant provided throughout the dossier, where it is stated that there might be a reduction in treatment burden.

Analyses were also performed for the "proportion of patients with ≥ 2-Step DRS Improvement". These analyses revealed that in the subgroup of patients with baseline DRSS>53, a higher proportion of patients in the aflibercept arm had an improvement compared to the faricimab arms. This might also be explainable by the small number of patients analysed in this subgroup. In response to a question by the CHMP, the Applicant submitted that the discrepancy regarding the "proportion of patients with ≥2-step DRS improvement from baseline at week 52" observed in the aflibercept arms in the two main studies (35.8% in Yosemite and 46.8% in Rhine) was caused by the variability in this endpoint. The number of patients achieving a ≥2-step DRS improvement across all treatment arms in both pivotal studies was high and similar to historical controls (anti-VEGF pivotal trials). In addition, the newly provided year 2 data show maintenance of the effect regarding this endpoint throughout year 2 and show also more consistent results across aflibercept arms between the studies (42.2% in YOSEMITE and 43.8% in RHINE).

In contrast to the Yosemite trial, in the subgroup of patients with a baseline BCVA <=63 letters a higher proportion of patients in the Aflibercept arm had a ≥ 2-Step DRS improvement compared to the Faricimab Q8W arm in Rhine. It is agreed with the Applicant that this might be a chance finding given variability in the endpoint and the low number of subjects in the sub-group.

It should be noted that the phase III studies were conducted during the COVID-19 pandemic and prior to finalisation, the statistical analysis plan was updated to address intercurrent events due to COVID-19. Further information was sought in order to better understand the potential impact of these intercurrent events on the study results. Further analysis using more conservative approaches were sought. These analyses did not raise any concerns with regard to the robustness of the study results.

Regarding the SmPC the posology proposed in section 4.2 should more closely reflect the approach to dosing for the PTI arm in the clinical studies (see SmPC comments). See SmPC for further comments on the sections 4.2 and 5.1 of the SmPC.

2.4.7. Conclusions on the clinical efficacy

Overall, the clinical development for the nAMD indication was acceptable and the design of both pivotal Phase III studies was appropriate. Efficacy results demonstrate non-inferiority of faricimab 6 mg compared to 2mg aflibercept.

With regard to the diabetic macular oedema indication overall, the results of the Phase III trials (Yosemite and Rhine) demonstrated non-inferiority of Faricimab 6 mg, compared with Aflibercept 2 mg. Data has since been provided for Year 2 which confirms maintenance of effect with regard to best corrected visual acuity. Further data up to two years has also been provided on treatment intervals which support the proposed posology.

2.4.8. Clinical safety

2.4.8.1. Adverse events

nAMD:

The AEs for the pivotal studies TENAYA and LUCERNE were presented individually and pooled.

In addition, for TENAYA and LUCERNE, specific AEs of intraocular inflammation (IOI) and retinal vascular occlusive disease events in the study eye were presented. IOI events include the PTs of anterior chamber flare, chorioretinitis, anterior chamber inflammation, iridocyclitis, iritis, keratic precipitates, keratouveitis, non-infectious endophthalmitis, post procedural inflammation, uveitis, and vitritis.

Retinal vascular occlusive disease events include the PTs of retinal artery embolism, retinal artery occlusion, and retinal vein occlusion.

Table 51. nAMD indication Overview of Safety Through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Patients)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one AE	238 (71.5%)	235 (69.9%)	233 (70.4%)	248 (76.1%)	471 (70.9%)	483 (73.0%)
Total number of AEs	858	812	812	846	1670	1658
Total number of patients with at least one SAE	34 (10.2%)	44 (13.1%)	49 (14.8%)	57 (17.5%)	83 (12.5%)	101 (15.3%)
Total number of SAEs	47	67	68	122	115	189
Total number of deaths	5 (1.5%)	1 (0.3%)	4 (1.2%)	7 (2.1%)	9 (1.4%)	8 (1.2%)
Total number of patients withdrawn from study due to an AE	3 (0.9%)	4 (1.2%)	5 (1.5%)	6 (1.8%)	8 (1.2%)	10 (1.5%)
Total number of patients withdrawn from study treatment due to an AE	3 (0.9%)	3 (0.9%)	8 (2.4%)	1 (0.3%)	11 (1.7%)	4 (0.6%)
Total number of patients with at least one AESI	3 (0.9%)	12 (3.6%)	11 (3.3%)	8 (2.5%)	14 (2.1%)	20 (3.0%)
Ocular events: study eye total number of patients with at least one						
AE	121 (36.3%)	128 (38.1%)	133 (40.2%)	118 (36.2%)	254 (38.3%)	246 (37.2%)
SAE	4 (1.2%)	6 (1.8%)	7 (2.1%)	7 (2.1%)	11 (1.7%)	13 (2.0%)
AE leading to withdrawal from study treatment	1 (0.3%)	0	5 (1.5%)	1 (0.3%)	6 (0.9%)	1 (0.2%)
Treatment related AEs	9 (2.7%)	9 (2.7%)	10 (3.0%)	8 (2.5%)	19 (2.9%)	17 (2.6%)
Treatment related SAEs	3 (0.9%)	0	5 (1.5%)	1 (0.3%)	8 (1.2%)	1 (0.2%)
AE of Special Interest	3 (0.9%)	6 (1.8%)	5 (1.5%)	6 (1.8%)	8 (1.2%)	12 (1.8%)
Drop in VA score >=30	3 (0.9%)	4 (1.2%)	4 (1.2%)	5 (1.5%)	7 (1.1%)	9 (1.4%)
Associated with severe IOI	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.3%)
Intervention req. to prevent permanent vision loss	0	1 (0.3%)	0	0	0	1 (0.2%)
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0
Ocular events: fellow eye total number of patients with at least one						
AE	76 (22.8%)	81 (24.1%)	93 (28.1%)	81 (24.8%)	169 (25.5%)	162 (24.5%)
SAE	0	5 (1.5%)	7 (2.1%)	2 (0.6%)	7 (1.1%)	7 (1.1%)
AE of Special Interest	0	5 (1.5%)	6 (1.8%)	2 (0.6%)	6 (0.9%)	7 (1.1%)
Drop in VA score >=30	0	3 (0.9%)	5 (1.5%)	1 (0.3%)	5 (0.8%)	4 (0.6%)
Associated with severe IOI	0	0	0	0	0	0
Intervention req. to prevent permanent vision loss	0	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.5%)
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Non-ocular events total number of patients with at least one						
AE	174 (52.3%)	174 (51.8%)	172 (52.0%)	189 (58.0%)	346 (52.1%)	363 (54.8%)
SAE	30 (9.0%)	34 (10.1%)	38 (11.5%)	48 (14.7%)	68 (10.2%)	82 (12.4%)
AE leading to withdrawal from study treatment	2 (0.6%)	3 (0.9%)	3 (0.9%)	0	5 (0.8%)	3 (0.5%)
AE of Special Interest	0	1 (0.3%)	0	0	0	1 (0.2%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0	0	0
Adjudicated APTC events	3 (0.9%)	3 (0.9%)	4 (1.2%)	3 (0.9%)	7 (1.1%)	6 (0.9%)
Non-fatal MI	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.3%)
Non-fatal Stroke	0	1 (0.3%)	2 (0.6%)	0	2 (0.3%)	1 (0.2%)
Death	2 (0.6%)	1 (0.3%)	0	2 (0.6%)	2 (0.3%)	3 (0.5%)

AE=Adverse Event; AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA = Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

Common Adverse Events (nAMD)

Ocular AEs in the Study Eye from the Pooled Phase III nAMD Studies

AEs by Frequency through Week 48

Through Week 48, the incidence of ocular AEs in the study eye was comparable between the treatment arms (38.3% in the faricimab arm and 37.2% in the aflibercept arm), with the exception (≥1% difference in any treatment arms: faricimab arm vs. aflibercept arm) of dry eye (13 patients [2.0%]

vs. 22 patients [3.3%]), vitreous floaters (20 patients [3.0%] vs. 11 patients [1.7%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 9 patients [1.4%]).

The difference in frequency of these AEs (95% CI) were -1.37 (-3.31, 0.51) for dry eye, 1.35 (-0.43, 3.21) for vitreous floaters, and 1.50 (-0.19, 3.30) for retinal pigment epithelial tear; the differences were not considered to be clinically significant. The vitreous floaters were all reported as non-serious and mild in severity.

The retinal pigment epithelial tear events were mostly reported as either mild or moderate in severity. There were 5 patients in the faricimab arm and 1 patient in the aflibercept arm with a retinal pigment epithelial tear event in the study eye associated with vision loss ≥ 15 letters (4 patients in the faricimab arm and 1 patient in the aflibercept arm with vision loss ≥ 15 letters; and 1 patient with vision loss ≥ 30 letters in the faricimab arm). Sustained vision loss of ≥ 15 letters or ≥ 30 letters associated with an AE by Week 48 was measured as the change in vision defined as the highest BCVA recorded after the event onset until Week 48 minus the BCVA closest to and strictly before the first event onset;, events with vision loss ≥ 30 letters were counted in both the vision loss ≥ 15 letters and ≥30 letters categories.

The most common ocular AEs in the study eye (≥ 2% incidence in any treatment arm: faricimab arm vs. aflibercept arm) by PT were *conjunctival haemorrhage (6.8% vs. 7.7%), neovascular age-related macular degeneration (verbatim, worsening of nAMD) (5.7% vs. 5.7%), vitreous detachment (3.3% vs. 3.0%), eye pain (2.6% vs. 3.0%), dry eye (2.0% vs. 3.3%), cataract (3.0% vs. 2.1%), intraocular pressure increased (2.6% vs. 2.3%), vitreous floaters (3.0% vs. 1.7%), retinal pigment epithelial tear (2.9% vs. 1.4%), foreign body sensation in eyes (1.5% vs. 2.0%), and punctate keratitis (1.4% vs. 2.0%)* (Table below).

The per-injection rate of ocular AEs in the study eye through Week 48 was 12.24% in the faricimab arm and 9.95% in the aflibercept arm.

The per-injection rate of ocular AEs in the study eye with a ≥ 0.1% higher incidence (in faricimab arm vs. aflibercept arm) by PT were nAMD (verbatim, worsening of nAMD) (1.06% vs. 0.83%), vitreous detachment (0.52% vs. 0.41%), eye irritation (0.75% vs. 0.12%), vitreous floaters (0.50% vs. 0.28%), cataract (0.47% vs. 0.28%), retinal pigment epithelial tear (0.45% vs. 0.18%), ocular discomfort (0.42% vs. 0.16%), ocular hyperaemia (0.38% vs. 0.08%), and eye discharge (0.21% vs. 0).

Table 52. <u>(nAMD)</u> Ocular Adverse Events in the Study Eye Occurring in ≥ 1% in Any Treatment Arm through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	121 (36.3%)	128 (38.1%)	133 (40.2%)	118 (36.2%)	254 (38.3%)	246 (37.2%)
Total number of events	291	254	228	235	519	489
Conjunctival haemorrhage	19 (5.7%)	22 (6.5%)	26 (7.9%)	29 (8.9%)	45 (6.8%)	51 (7.7%)
Neovascular age-related macular degeneration	14 (4.2%)	18 (5.4%)	24 (7.3%)	20 (6.1%)	38 (5.7%)	38 (5.7%)
Vitreous detachment	11 (3.3%)	10 (3.0%)	11 (3.3%)	10 (3.1%)	22 (3.3%)	20 (3.0%)
Eye pain	7 (2.1%)	11 (3.3%)	10 (3.0%)	9 (2.8%)	17 (2.6%)	20 (3.0%)
Dry eye	7 (2.1%)	14 (4.2%)	6 (1.8%)	8 (2.5%)	13 (2.0%)	22 (3.3%)
Cataract	10 (3.0%)	7 (2.1%)	10 (3.0%)	7 (2.1%)	20 (3.0%)	14 (2.1%)
Intraocular pressure increased	8 (2.4%)	8 (2.4%)	9 (2.7%)	7 (2.1%)	17 (2.6%)	15 (2.3%)
Vitreous floaters	13 (3.9%)	7 (2.1%)	7 (2.1%)	4 (1.2%)	20 (3.0%)	11 (1.7%)
Retinal pigment epithelial tear	9 (2.7%)	6 (1.8%)	10 (3.0%)	3 (0.9%)	19 (2.9%)	9 (1.4%)
Foreign body sensation in eyes	5 (1.5%)	6 (1.8%)	5 (1.5%)	7 (2.1%)	10 (1.5%)	13 (2.0%)
Punctate keratitis	5 (1.5%)	5 (1.5%)	4 (1.2%)	8 (2.5%)	9 (1.4%)	13 (2.0%)
Blepharitis	4 (1.2%)	4 (1.2%)	5 (1.5%)	4 (1.2%)	9 (1.4%)	8 (1.2%)
Posterior capsule opacification	4 (1.2%)	2 (0.6%)	6 (1.8%)	5 (1.5%)	10 (1.5%)	7 (1.1%)
Dry age-related macular degeneration	5 (1.5%)	7 (2.1%)	3 (0.9%)	1 (0.3%)	8 (1.2%)	8 (1.2%)
Lacrimation increased	2 (0.6%)	6 (1.8%)	4 (1.2%)	3 (0.9%)	6 (0.9%)	9 (1.4%)
Photopsia	3 (0.9%)	4 (1.2%)	3 (0.9%)	4 (1.2%)	6 (0.9%)	8 (1.2%)
Eye irritation	5 (1.5%)	2 (0.6%)	4 (1.2%)	2 (0.6%)	9 (1.4%)	4 (0.6%)
Corneal abrasion	4 (1.2%)	6 (1.8%)	0	2 (0.6%)	4 (0.6%)	8 (1.2%)
Ocular discomfort	4 (1.2%)	3 (0.9%)	4 (1.2%)	1 (0.3%)	8 (1.2%)	4 (0.6%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

<u>Ocular AEs by Treatment Relationship through Week 48 (nAMD)</u>

Through Week 48, the incidence of ocular AEs suspected by the investigator to be related to faricimab was low (2.9%). The most common treatment-related ocular AEs in the study eye (≥ 0.5%) were retinal pigment epithelial tear (8 patients [1.2%]) and vitritis (3 patients [0.5%]).

The incidence of ocular AEs suspected by the investigator to be related to aflibercept was low (2.6%). The most common treatment-related ocular AE in the study eye (≥ 0.5%) was intraocular pressure increased (3 patients [0.5%]).

Ocular AEs in the Study Eye (nAMD)

At the time of the primary analysis, the Phase III trials continue to be ongoing. Therefore, cumulative safety data available as of the Clinical Cut-Off Date associated with the primary endpoint was also assessed (i.e., the subset of patients with follow-up data beyond Week 48). From baseline to the Clinical Cut-Off Date, 41.0% of patients in the faricimab arm and 40.0% of patients in the aflibercept arm experienced at least one ocular AE in the study eye.

After Week 48 to the Clinical Cut-Off Date, the most common ocular AEs in the study eye (≥ 1% incidence in any treatment arm) by PT was neovascular age-related macular degeneration (verbatim, worsening of nAMD; 7 patients [1.1%] in the faricimab arm). From baseline to the Clinical Cut-Off Date, 2.9% of patients in each treatment arm experienced at least one treatment related ocular AEs in the study eye.

After Week 48 to the Clinical Cut-Off Date, the treatment-related ocular AEs in the study eye were intraocular pressure increased and non-infectious endophthalmitis (1 patient [0.2%] each) in the aflibercept arm. There were no treatment-related ocular AEs in the faricimab arm after Week 48 to the Clinical Cut-Off Date.

Ocular AEs in the Fellow Eye through Clinical Cut-Off Date (nAMD)

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 29.2% in the faricimab arm and 26.9% in the aflibercept arm experienced at least one ocular AE in the fellow eye. After Week 48 to the Clinical Cut-Off Date, the most common ocular AEs in the fellow eye (≥ 2% incidence in any treatment arm) by PT was neovascular age-related macular degeneration (verbatim, worsening of nAMD; 2.1% in the faricimab arm).

Ocular AEs in Study Eye by Severity from the Pooled Phase III nAMD Studies

The majority of ocular AEs in the study eye through Week 48 were mild or moderate in severity in the faricimab and aflibercept treatment arms. Through Week 48, 13 patients (2.0%) in the faricimab arm and 11 patients (1.7%) in the aflibercept arm experienced at least one severe ocular AE in the study eye. The severe ocular AEs in the study eye in the faricimab arm by PT were retinal pigment epithelial tear, uveitis, intraocular pressure increased (2 patients [0.3%] each), neovascular age-related macular degeneration (verbatim, worsening of nAMD), eye pain, cataract, punctate keratitis, subretinal fibrosis, cataract nuclear, hyalosis asteroid, procedural pain, viral uveitis, chorioretinitis (viral) (1 patient [0.2%] each).

The severe ocular AEs in the study eye in the aflibercept arm by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD) (3 patients [0.5%]), eye pain, subretinal fibrosis, vitreoretinal traction syndrome, uveitis, cataract cortical, diplopia, intraocular pressure increased, and blepharal papilloma (1 patient [0.2%] each).

The severe ocular AEs in the study eye that were not resolved by the Clinical Cut-Off Date were retinal pigment epithelial tear (2 events), cataract nuclear, cataract, subretinal fibrosis, and uveitis (1 event each) in the faricimab arm; and vitreoretinal traction syndrome and subretinal fibrosis (1 event each) in the aflibercept arm.

After Week 48 to the Clinical Cut-Off Date, 3 patients (0.5%) in the faricimab arm and 5 patients (0.8%) in the aflibercept arm experienced at least one severe ocular AE in the study eye. The severe ocular AEs in the study eye by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD), blepharitis, and rhegmatogenous retinal detachment (1 patient [0.2%] each) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD), macular fibrosis, visual acuity reduced, cataract operation complication, and cataract traumatic (1 patient [0.2%] each) in the aflibercept arm. After Week 48 to the Clinical Cut-Off Date, the severe

ocular AEs in the study eye were not suspected by the investigator to be related to study treatment. The majority of the severe ocular AEs (62.5% [5/8]) in the study eye that occurred after Week 48 to the Clinical Cut-Off Date resolved or were resolving with the exception of 3 ocular AEs that were not resolved (neovascular age-related macular degeneration [verbatim, worsening of nAMD], visual acuity reduced, and macular fibrosis, all in the aflibercept arm) by the Clinical Cut-Off Date.

Ocular Adverse Events of Special Interest (nAMD)

Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest were required to be reported by the investigator to the Sponsor immediately:

Adverse events of special interest for this study were as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study drug, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: an adverse event is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:

  – It causes a decrease of ≥ 30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.

  – It requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas, or a medication) to prevent permanent loss of sight.

  – It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare, or 4+ vitritis)

All of the above listed sight-threatening adverse events should be reported as serious adverse events, listing the underlying cause (if known) of the event as the primary

Sight-Threatening Adverse Events Through Week 48 (nAMD)

Through Week 48, the incidence of AESIs in the study eye was low and comparable between the treatment arms (8 patients [1.2%] in the faricimab arm and 12 patients [1.8%] in the aflibercept arm; Table 53). Through Week 48, the most common sight-threatening AE in the study eye which caused a decrease of ≥30 letters in VA score lasting more than 1 hour (≥2 patients in any treatment arm) by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD) and retinal pigment epithelial tear (2 patients [0.3%] each) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD; 2 patients [0.3%]) in the aflibercept arm.

Through Week 48, the sight-threatening AEs in the study eye which was associated with severe intraocular inflammation by PT were chorioretinitis (viral; 1 patient [0.2%]) in the faricimab arm; and corneal abrasion and endophthalmitis (1 patient [0.2%] each) in the aflibercept arm. The chorioretinitis event in the faricimab arm was reported as viral choriretinitis based on serology assessment and of herpectic origin.

Through Week 48, the only sight-threatening AE in the study eye which required surgical or medical intervention to prevent permanent loss of sight was neovascular age-related macular degeneration (verbatim, neovascular age-related macular degeneration; 1 patient [0.2%]) in the aflibercept arm; the patient underwent a tissue plasminogen activated vitrectomy. There were no events in the faricimab arm. The majority of the ocular AESIs in the study eye resolved, resolved with sequelae, or were resolving by the Clinical Cut-Off Date. The sight-threatening AEs in the study eye which caused a decrease of ≥ 30 letters in VA score lasting more than 1 hour that were not resolved by Week 48 were retinal pigment epithelial tear (2 events) and cataract in the faricimab arm; and subretinal fibrosis in the aflibercept arm. The per-injection rate of AESIs in the study eye was 0.21% in the faricimab arm and 0.24% in the aflibercept arm.

Table 53. (nAMD) Adverse Events of Special Interest in the Study Eye through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
AE of Special Interest MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	3 (0.9%)	6 (1.8%)	5 (1.5%)	6 (1.8%)	8 (1.2%)	12 (1.8%)
Overall total number of events	4	6	5	6	9	12
CAUSES A DECREASE OF >= 30 LETTERS IN VA SCORE LASTING MORE THAN 1 HOUR						
Total number of patients with at least one adverse event	3 (0.9%)	4 (1.2%)	4 (1.2%)	5 (1.5%)	7 (1.1%)	9 (1.4%)
Total number of events	4	4	4	5	8	9
Neovascular age-related macular degeneration	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	2 (0.3%)	2 (0.3%)
Retinal pigment epithelial tear	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
Uveitis	1 (0.3%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
Age-related macular degeneration	0	1 (0.3%)	0	0	0	1 (0.2%)
Cataract	0	0	1 (0.3%)	0	1 (0.2%)	0
Cataract cortical	0	0	0	1 (0.3%)	0	1 (0.2%)
Corneal oedema	0	0	0	1 (0.3%)	0	1 (0.2%)
Eye allergy	0	0	0	1 (0.3%)	0	1 (0.2%)
Subretinal fibrosis	0	1 (0.3%)	0	0	0	1 (0.2%)
Viral uveitis	1 (0.3%)	0	0	0	1 (0.2%)	0
Vitreous haemorrhage	0	0	0	1 (0.3%)	0	1 (0.2%)
Vitritis	0	0	1 (0.3%)	0	1 (0.2%)	0
ASSOCIATED WITH SEVERE INTRAOCULAR INFLAMMATION						
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.3%)
Total number of events	0	1	1	1	1	2
Chorioretinitis	0	0	1 (0.3%)	0	1 (0.2%)	0
Corneal abrasion	0	1 (0.3%)	0	0	0	1 (0.2%)
Endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
REQUIRES SURGICAL OR MEDICAL INTERVENTION TO PREVENT PERMANENT LOSS OF SIGHT						
Total number of patients with at least one adverse event	0	1 (0.3%)	0	0	0	1 (0.2%)
Total number of events	0	1	0	0	0	1
Neovascular age-related macular degeneration	0	1 (0.3%)	0	0	0	1 (0.2%)

Sight-Threatening Adverse Events up to Clinical Cut-Off Date in the Study Eye (nAMD)

Through cumulative data from baseline to the Clinical Cut-Off Date, 1.7% of patients in the faricimab arm and 2.6% of patients in the aflibercept arm experienced at least one AESI in the study eye.

After Week 48 to the Clinical Cut-Off Date, the sight-threatening AEs in the study eye which caused a decrease of ≥30 letters in VA score lasting more than 1 hour by PT were visual acuity reduced (1 patient [0.2%]) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD), cataract, visual acuity reduced, cataract traumatic, and retinal degeneration (1 patient [0.2%] each) in the aflibercept arm. After Week 48 to the Clinical Cut-Off Date, the sight-threatening AEs in the study eye which required surgical or medical intervention to prevent permanent loss of sight by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD) and rhegmatogenous retinal detachment (1 patient [0.2%] each) in the faricimab arm; and cataract operation complication (1 patient [0.2%]) in the aflibercept arm. After Week 48 to the Clinical Cut-Off Date, there were no sight-threatening AEs in the study eye which was associated with severe intraocular inflammation.

After Week 48 to the Clinical Cut-Off Date, there was 1 patient (0.2%) in the aflibercept arm with a suspected transmission of an infectious agent by the study drug (non-infectious endophthalmitis).

After Week 48 to the Clinical Cut-Off Date, the majority of the ocular AESIs in the study eye resolved or were resolving by the Clinical Cut-Off Date. The sight-threatening AEs in the study eye which caused a decrease of ≥ 30 letters in VA score lasting more than 1 hour that were not resolved by the Clinical Cut-Off Date were neovascular age-related macular degeneration (verbatim, worsening of nAMD), retinal degeneration, and visual acuity reduced in the aflibercept arm.

Ocular Selected Adverse Events Intraocular Inflammation Events through Week 48 (nAMD)

Table 22 Adverse Events of Intraocular Inflammation in the Study Eye through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	5 (1.5%)	2 (0.6%)	8 (2.4%)	6 (1.8%)	13 (2.0%)	8 (1.2%)
Total number of events	6	2	10	7	16	9
Iridocyclitis	0	0	3 (0.9%)	2 (0.6%)	3 (0.5%)	2 (0.3%)
Iritis	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.5%)	2 (0.3%)
Uveitis	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
Vitritis	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.2%)
Chorioretinitis	0	0	1 (0.3%)	0	1 (0.2%)	0
Keratic precipitates	1 (0.3%)	0	0	0	1 (0.2%)	0
Post procedural inflammation	0	0	0	1 (0.3%)	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Intraocular Inflammation events include Anterior Chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Non-infectious Endophthalmitis, Post procedural inflammation, Uveitis, Vitritis and Anterior chamber flare.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes events with onset up to Day 349 (last day of Week 48 analysis visit window).

Through Week 48, the incidence of intraocular inflammation (IOI) events in the study eye was low and comparable between the treatment arms (13 patients [2.0%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm). There were no IOI events associated with retinal vasculitis or occlusive disease in any treatment arms based on the reported preferred terms.

There were 2 patients with an IOI event in the study eye associated with vision loss ≥ 15 letters (1 patient with vision loss ≥ 15 letters and 1 patient with vision loss ≥30 letters); both patients were in the faricimab arm. The IOI event in the study eye associated with the patient with vision loss ≥15 letters was chorioretinitis (viral); this event was considered serious, suspected by the investigator not to be related to study treatment (related to varicella zoster), and resolving by Week 48.

The IOI event in the study eye associated with the patient with vision loss ≥ 30 letters was uveitis; this event was suspected to be related to study treatment, serious, and resolving by Week 48. Sustained vision loss of ≥ 15 letters or ≥ 30 letters associated with an AE by Week 48 was measured as the change in vision defined as the highest BCVA recorded after the event onset until Week 48 minus the BCVA closest to and strictly before the first event onset; in the table, events with vision loss ≥ 30 letters were counted in both the vision loss ≥ 15 letters and ≥30 letters categories.

The most common IOI events in the study eye (≥2 patients in any treatment arm: faricimab arm vs. aflibercept arm) by PT were iridocyclitis (3 patients [0.5%] vs. 2 patients [0.3%]), iritis (3 patients [0.5%] vs. 2 patients [0.3%]), uveitis (2 patients [0.3%] in each arm), and vitritis (3 patients [0.5%] vs. 1 patient [0.2%]).

Through Week 48, 3 patients (0.5%) in the faricimab arm and 1 patient (0.2%) in the aflibercept arm experienced at least one severe IOI event in the study eye. The severe IOI events in the study eye (treatment arm: faricimab arm vs. aflibercept arm) by PT were uveitis (2 patients [0.3%] vs. 1 patient [0.2%]) and chorioretinitis (viral;1 patient [0.2%] vs. 0). The AE severity grading scale is provided in Table 54. Five patients in the faricimab arm and 1 patient in the aflibercept arm experienced a serious

IOI event in the study eye. The serious IOI events by PT were uveitis (2 events), vitritis (2 events), and chorioretinitis (viral) in the faricimab arm; and uveitis in the aflibercept arm. Two of the serious IOI events were associated with vision loss ≥ 15 letters (1 patient with chorioretinitis [viral] with vision loss ≥ 15 letters and 1 patient with uveitis with vision loss ≥ 30 letters); 1 of these serious IOI events (uveitis) in the faricimab arm was not resolved by Week 48. There was no clear relationship between injection day of study treatment and the timing of the IOI events. The majority of the IOI events occurred after the initial loading doses, 4 to 5 injections (range: 1–8) of faricimab and after 4 or 6 injections (range: 3–8) of aflibercept.

Through Week 48, the incidence of IOI events occurring in the fellow eye was low (3 patients [0.5%] in the faricimab arm and 4 patients [0.6%] in the aflibercept arm). The IOI events in the fellow eye (treatment arm: faricimab arm vs. aflibercept arm) by PT were post procedural inflammation (2 patients [0.3%] vs. 1 patient [0.2%]), iritis (1 patient [0.2%] in each arm), iridocyclitis (0 vs. 1 patient [0.2%]), and uveitis (0 vs. 1 patient [0.2%]).

Table 23 Analysis of Intraocular Inflammation, Retinal Vasculitis and Retinal Vascular Occlusive Events in the Study Eye through Week 48 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Number of Patients with IOI, Retinal Vasculitis, or Retinal Vascular Occlusive Events	14 (2.1%)	8 (1.2%)
Number of Patients with IOI and Retinal Vasculitis	0	0
Number of Patients with IOI, Retinal Vasculitis and Retinal Vascular Occlusive Events	0	0
Number of Patients with IOI and Available BCVA through Week 48		
n	12	7
Vision Loss >=15 Letters*	2 (16.7%)	0
Vision Loss >=30 Letters*	1 (8.3%)	0

* Use the number of patients with IOI and Available Change in vision as the denominator.
IOI = Intraocular Inflammation.
Intraocular Inflammation events include Anterior Chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Non-infectious Endophthalmitis, Post procedural inflammation, Uveitis, and Vitritis. Retinal vascular occlusive events include Retinal artery embolism, Retinal artery occlusion, Retinal vein occlusion. Vision loss is calculated as the difference in BCVA between the highest BCVA recorded after the event onset until W48 and the closest BCVA recorded before the event onset (BCVA before). For events with no post-baseline BCVA prior to event onset, BCVA measured at baseline/day of event onset used.
For a patient with multiple events of interest, BCVA before is the BCVA closest to and strictly before the onset of the first event.

Intraocular Inflammation Events up to Clinical Cut-Off Date (nAMD)

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 2.3% in the faricimab arm and 1.5% in the aflibercept arm experienced at least one IOI event in the study eye. The 2 IOI events in the study eye associated with vision loss ≥15 letters through Week 48 (chorioretinitis and uveitis) were still resolving by the Clinical Cut-Off Date. After Week 48 to the Clinical Cut-Off Date, there were no additional patients with an IOI in the study eye associated with vision loss ≥ 15 letters.

After Week 48 to the Clinical Cut-Off Date, the IOI events in the study eye by PT were iritis and vitritis (1 patient [0.2%] each) in the faricimab arm; and post procedural inflammation (i.e., post-cataract operation inflammation) and non-infectious endophthalmitis (1 patient [0.2%] each) in the aflibercept arm.

After Week 48 to the Clinical Cut-Off Date, all of the IOI events in the study eye were mild or moderate in severity.

After Week 48 to the Clinical Cut-Off Date, there were no additional IOI events in the fellow eye.

Retinal Vascular Occlusive Disease Through Week 48 (nAMD)

Through Week 48, 1 patient [0.2%] in the faricimab arm was found to have a retinal artery embolism AE (Hollenhorst plaque) in the study eye during clinical examination. The finding was not associated with any retinal vascular occlusion, and was noted during the clinical examination and confirmed with fundus fluorescein angiography. There was no anterior or posterior segment inflammation noted at any visit from the date of AE onset through follow up. The retinal artery embolism AE (Hollenhorst plaque)

had no impact on vision (BCVA immediately before the event: 70 letters; on day of onset: 70 letters; from AE onset to Clinical Cut-Off Date, range 63–70 letters). It was reported that on follow-up with the cardiologist, no abnormality was found. The retinal artery embolism AE (Hollenhorst plaque) was considered non-serious, suspected by the investigator not to be related to study treatment, and not resolved by the Clinical Cut-Off Date.

After Week 48 to the Clinical Cut-Off Date, there were no additional retinal vascular occlusive disease AEs in the study eye.

Intraocular Pressure Mean (nAMD)

Pre-dose IOP and mean IOP change from baseline over time through the Clinical Cut-Off Date in the study eye were comparable between the faricimab and aflibercept arms.

There was no observable increase in pre-dose IOP over time. Overall, mean IOP changes from pre-dose to post-dose by visit in the treatment arms were similar.

There were no clinically meaningful differences in the mean change from pre-dose to post-dose IOP across the treatment arms. Through the Clinical Cut-Off Date, 18 patients (2.7%) in each treatment arm experienced an intraocular pressure increased AE in the study eye. One of the intraocular pressure increased AEs (in the faricimab arm) was considered serious, suspected by the investigator not to be related to study treatment, and resolved by the Clinical Cut-Off Date.

Through the Clinical Cut-Off Date, 4 patients (0.6%) in the faricimab arm and 5 patients (0.8%) in the aflibercept arm developed ocular hypertension in the study eye. One of the patients in the faricimab arm experienced worsening of pre-existing ocular hypertension. Two of the ocular hypertension AEs in the study eye (both in the aflibercept arm) were suspected by the investigator to be related to study treatment and not resolved by the Clinical Cut-Off Date. None of these ocular hypertension AEs were considered serious.

Through the Clinical Cut-Off Date, 3 patients (0.5%) in the faricimab arm and 5 patients (0.8%) in the aflibercept arm developed glaucoma in the study eye. Two of the patients in the faricimab arm and 1 of the patients in the aflibercept arm experienced worsening of pre-existing glaucoma.

Slitlamp Examination (nAMD)

The proportion of patients by grade for the worst post-baseline outcome in the study eye through the Clinical Cut-Off Date on slitlamp examination including intraocular inflammation, cataract and vitreous haemorrhage were generally comparable between the treatment arms.

A small proportion of patients developed new or worsened cataracts by Week 84 (latest visit corresponding to the Clinical Cut-Off Date), and the distribution of cataract by grade was generally comparable between the treatment arms.

Slitlamp Findings in the Study Eye through Clinical Cut-Off Date from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population) (nAMD)

			Pooled(TENAYA and LUCERNE) (N=1326)	
Visit	Assessment	Grade	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Baseline	Anterior Chamber Cell	n	664	662
		0	664 (100%)	662 (100%)
	Anterior Chamber Flare	n	663	662
		0	663 (100%)	662 (100%)
	Cataract	n	661	657
		1+	208 (59.6%)	195 (60.0%)
		2+	133 (38.1%)	122 (37.5%)
		3+	8 (2.3%)	8 (2.5%)
		Not Applicable	312	332
	Vitreous Cell	n	664	662
		0	664 (100%)	662 (100%)
	Vitreous Hemorrhage	n	664	662
		0	664 (100%)	662 (100%)
Worst post-baseline outcome through CCOD	Anterior Chamber Cell	n	664	661
		0	650 (97.9%)	650 (98.3%)
		0.5+	3 (0.5%)	3 (0.5%)
		1+	6 (0.9%)	4 (0.6%)
		2+	5 (0.8%)	2 (0.3%)
		3+	0	1 (0.2%)
		4+	0	1 (0.2%)
	Anterior Chamber Flare	n	664	661
		0	658 (99.1%)	659 (99.7%)
		1+	2 (0.3%)	0
		2+	4 (0.6%)	2 (0.3%)
		2+	1 (0.6%)	2 (0.3%)
	Cataract	n	663	656
		1+	198 (55.6%)	181 (54.5%)
		2+	134 (37.6%)	126 (38.0%)
		3+	23 (6.5%)	23 (6.9%)
		4+	1 (0.3%)	2 (0.6%)
		Not Applicable	307	324
	Vitreous Cell	n	664	661
		0	655 (98.6%)	655 (99.1%)
		0.5+	1 (0.2%)	1 (0.2%)
		1+	2 (0.3%)	1 (0.2%)
		2+	3 (0.5%)	4 (0.6%)
		3+	2 (0.3%)	0
		4+	1 (0.2%)	0
	Vitreous Hemorrhage	n	664	661
		0	664 (100%)	658 (99.5%)
		1+	0	1 (0.2%)
		2+	0	2 (0.3%)

Baseline for safety analyses is defined as the last available measurement prior to first exposure to study drug. Patients with Not Applicable result are excluded from the denominator for percentage calculation.

Indirect Ophthalmoscopy (nAMD)

The proportion of patients having any post-baseline retinal break or retinal detachment through the Clinical Cut-Off Date in the study eye were low and comparable between the treatment arms (see Table below).

At baseline, 1 patient (0.2%) in the faricimab arm was reported to have developed a new retinal break in the study eye since their Screening visit, which was attributed to a new serous macular detachment secondary to nAMD. Through the Clinical Cut-Off Date, 2 patients (0.3%) in the faricimab arm experienced any post-baseline retinal break in the study eye (1 patient attributed to a serous macular detachment secondary to nAMD and 1 patient with posterior vitreal detachment and peripheral retinal break which was repaired by photocoagulation). There were no patients in the aflibercept arm that experienced a retinal break in the study eye at baseline or through the Clinical Cut-Off Date. At baseline, 14 patients (2.1%) in the faricimab arm and 11 patients (1.7%) in the aflibercept arm were reported to have a retinal detachment in the study eye. These baseline detachments were serous macular detachments secondary to nAMD. 2.4% of patients in the faricimab arm and 1.7% of patients in the aflibercept arm developed any post-baseline retinal detachment in the study eye; the majority of these were serous macular detachments secondary to nAMD. One patient had a rhegmatogenous retinal detachment in the study eye (faricimab arm), which occurred after the Week 52 visit and was repaired prior to the Week 56 visit.

Table 54: (nAMD) Indirect Ophthalmoscopy: Summary of Baseline and any Post-Baseline Retinal Break or Detachment through Clinical Cut-Off Date from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	Pooled (TENAYA and LUCERNE) (N=1326)	
Eye Assessment	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Study Eye		
Baseline		
Retinal Break	1/664 (0.2%)	0/661
Retinal Detachment	14/664 (2.1%)	11/661 (1.7%)
Any Post-Baseline		
Retinal Break	2/664 (0.3%)	0/660
Retinal Detachment	16/664 (2.4%)	11/660 (1.7%)
Fellow Eye		
Baseline		
Retinal Break	0/664	0/661
Retinal Detachment	1/664 (0.2%)	0/661
Any Post-Baseline		
Retinal Break	0/664	3/660 (0.5%)
Retinal Detachment	4/664 (0.6%)	3/660 (0.5%)

PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For baseline, a patient was counted as having a retinal break or retinal detachment present if one was observed at any point during the screening or baseline assessments (up to and including the day of first exposure to study drug). Post-baseline refers to any timepoint after the day of first exposure to study drug.

Ocular safety from Supportive Phase II nAMD Study STAIRWAY (CR39521)

STAIRWAY is a completed Phase II, multicenter, randomised, active comparator-controlled, subject and outcome-assessor masked, parallel group (three treatment arms), 52-week study investigating the efficacy, safety, and pharmacokinetics of 6-mg faricimab administered by intravitreal injection at Q12W and Q16W in treatment-naive patients with nAMD.

A total of 76 patients from 25 sites in the United States were randomized in a 2:2:1 ratio to one of three treatment arms (29 patients to the 6 mg faricimab Q12W arm, 31 patients to the 6 mg faricimab Q16W arm, and 16 patients to the 0.5 mg ranibizumab Q4W arm).

Overall, 6 mg of faricimab administered Q12W or Q16W was generally well tolerated, and no new safety signals were observed. Treatment with 6 mg of faricimab resulted in generally consistent overall ocular and non-ocular safety in nAMD patients compared with 0.5 mg of ranibizumab administered Q4W through Week 52.

Treatment exposure and the key safety results are summarized below:

- The median duration of treatment exposure in the study eye was comparable across the three treatment arms: 339 days (range: 57– 344) in the faricimab Q12W arm, 311 days (range: 30–341) in the faricimab Q16W arm, and 338 days (range: 330–344) in the ranibizumab Q4W arm.
- The incidence of AEs was generally similar across the three treatment arms (75.0%, 74.2%, and 81.3% in the faricimab Q12W, faricimab Q16W, and ranibizumab Q4W arms, respectively).
- The incidence of ocular AEs occurring in the study eye was numerically lower in the faricimab treatment arms compared to the ranibizumab arm (37.5% and 35.5% in the faricimab Q12W and Q16W arms compared with 50.0% in the ranibizumab Q4W arm); all ocular AEs occurring in the study eye in the faricimab and ranibizumab arms were of mild or moderate intensity, with the exception of one severe AE (eye pain) reported in the ranibizumab arm.
- The most common ocular AEs in the study eye (≥2 patients: faricimab Q12W, faricimab Q16W, and ranibizumab Q4W arms, respectively) were conjunctival haemorrhage (5 patients, 4 patients, and 4 patients), eye pain (2 patients, no patients, and 2 patients), and retinal haemorrhage (2 patients, no patients, and no patients).
- There were no serious ocular AEs reported in the study or fellow eye.
- No AEs were reported that led to discontinuation of treatment. Two patients experienced 4 AEs that led to a dose interruption of the study drug in the 6 mg faricimab Q12W arm including the AEs of fall, headache and mental status changes for one patient and chalazion for the other patient.

One patient in the faricimab Q12W arm had a sight-threatening event (AESI) of visual acuity reduced (BCVA score at AE onset on Study Day 46: 24 letters, BCVA score from previous assessment: 59 letters) in the study eye, which was considered unrelated to study treatment and resolved (BCVA score at AE resolution on Study Day 88: 58 letters). No non-ocular AESIs were reported in the study.

- Two mild ocular inflammatory events (iritis and anterior chamber flare) were reported in the study eye in the faricimab arms, both of which resolved within 3 weeks of onset.

Supportive Phase II nAMD Study AVENUE (BP29647)-ocular safety:

AVENUE is a completed Phase II multicenter, multiple-dose and regimen, randomized, active comparator controlled, double masked, parallel group (five treatment arms), 36-week study investigating the efficacy, safety, tolerability, and pharmacokinetics of 1.5 mg and 6 mg faricimab administered by intravitreal injection at Q4W and Q8W in treatment-naive and anti-VEGF-incomplete-responder patients with nAMD.

A total of 273 treatment-naive patients with nAMD at 58 sites in the United States were enrolled in the study and randomized (Arm A: 68 patients, Arm B: 47, Arm C: 42, Arm D: 47, and Arm E: 69).

Non-Ocular AEs from the Pooled Phase III nAMD Studies

Through Week 48, the incidence of non-ocular AEs was comparable between the treatment arms (52.1% of patients in the faricimab arm and 54.8% of patients in the aflibercept arm), with the exception (≥ 1% difference in any treatment arms: faricimab arm vs. aflibercept arm) of hypertension (3.6% vs. 2.4%), arthralgia (3.0% vs. 1.7%), fall (1.8% vs. 2.9%), bronchitis (2.6% vs. 1.4%), blood pressure increased (0.2% vs. 1.2%), and dyspnoea (0.2% vs. 1.2%).

The most common non-ocular AEs (≥5% incidence in any treatment arm) by PT was nasopharyngitis (6.3% in the faricimab arm and 6.6% in the aflibercept arm). The majority of non-ocular AEs were mild or moderate in severity in both the faricimab arm and aflibercept arm.

Through Week 48, 5.6% of patients in the faricimab arm and 10.0% of patients in the aflibercept arm experienced at least one severe non-ocular.

Table (nAMD) Non-Ocular Adverse Events (≥2%) through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	174 (52.3%)	174 (51.8%)	172 (52.0%)	189 (58.0%)	346 (52.1%)	363 (54.8%)
Total number of events	462	445	452	479	914	924
Nasopharyngitis	18 (5.4%)	28 (8.3%)	24 (7.3%)	16 (4.9%)	42 (6.3%)	44 (6.6%)
Urinary tract infection	17 (5.1%)	10 (3.0%)	10 (3.0%)	11 (3.4%)	27 (4.1%)	21 (3.2%)
Hypertension	16 (4.8%)	7 (2.1%)	8 (2.4%)	9 (2.8%)	24 (3.6%)	16 (2.4%)
Upper respiratory tract infection	6 (1.8%)	6 (1.8%)	9 (2.7%)	11 (3.4%)	15 (2.3%)	17 (2.6%)
Arthralgia	11 (3.3%)	6 (1.8%)	9 (2.7%)	5 (1.5%)	20 (3.0%)	11 (1.7%)
Fall	4 (1.2%)	10 (3.0%)	8 (2.4%)	9 (2.8%)	12 (1.8%)	19 (2.9%)
Bronchitis	9 (2.7%)	4 (1.2%)	8 (2.4%)	5 (1.5%)	17 (2.6%)	9 (1.4%)
Headache	7 (2.1%)	5 (1.5%)	8 (2.4%)	6 (1.8%)	15 (2.3%)	11 (1.7%)
Sinusitis	6 (1.8%)	5 (1.5%)	7 (2.1%)	6 (1.8%)	13 (2.0%)	11 (1.7%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 56.8% of patients in the faricimab arm and 59.1% of patients in the aflibercept arm experienced at least one non-ocular AE.

After Week 48 to the Clinical Cut-Off Date, the most common non-ocular AEs (≥1% incidence in any treatment arm: faricimab vs. aflibercept arm) by PT were urinary tract infection (10 patients [1.5%] vs. 8 patients [1.2%]) and fall (11 patients [1.7%] in each arm).

Serious Non-Ocular AEs Through Week 48 (nAMD)

Through Week 48, the incidence of serious non-ocular AEs was comparable between the treatment arms (10.2% of patients in the faricimab arm and 12.4% of patients in the aflibercept arm). The most common serious non-ocular AEs through Week 48 (≥ 0.5% incidence in any treatment arm) are presented in the Table below.

Table 55. (nAMD)_Serious Non-Ocular Adverse Events Occurring in ≥0.5% in Any Treatment Arm through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

MedDRA Preferred Term	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	30 (9.0%)	34 (10.1%)	38 (11.5%)	48 (14.7%)	68 (10.2%)	82 (12.4%)
Total number of events	42	56	51	113	93	169
Atrial fibrillation	3 (0.9%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	4 (0.6%)	5 (0.8%)
Cardiac failure congestive	1 (0.3%)	1 (0.3%)	2 (0.6%)	4 (1.2%)	3 (0.5%)	5 (0.8%)
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	3 (0.5%)	4 (0.6%)
Pneumonia	1 (0.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	5 (0.8%)
COVID-19	1 (0.3%)	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	2 (0.3%)
Cardiac failure	1 (0.3%)	0	1 (0.3%)	3 (0.9%)	2 (0.3%)	3 (0.5%)
Syncope	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	3 (0.5%)
Constipation	1 (0.3%)	0	0	3 (0.9%)	1 (0.2%)	3 (0.5%)
Osteoarthritis	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.2%)
Dyspnoea	0	1 (0.3%)	0	2 (0.6%)	0	3 (0.5%)
Gastrointestinal haemorrhage	0	2 (0.6%)	0	1 (0.3%)	0	3 (0.5%)
Sepsis	0	1 (0.3%)	0	2 (0.6%)	0	3 (0.5%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

nAMD: SAFETY DATA THROUGH WEEK 60

The extent of exposure and safety results based on the pooled data from the two pivotal Phase III Studies TENAYA and LUCERNE up to Week 60 and up to the Week 60 Clinical Cut-Off Date of 19 January 2021 for TENAYA and 28 December 2020 for LUCERNE are presented below. The safety results up to Week 48 are presented below for comparison and are based on the original Week 48 results for Clinical Cut-Off Date of 26 October 2020 for TENAYA and 05 October 2020 for LUCERNE. The safety profile of faricimab up to Week 60 is consistent with the safety profile up to Week 48 with no new or unexpected safety signals identified for the study through the Week 60 Clinical Cut-Off Date.

Table 56 (nAMD) Overview of Safety from Phase III nAMD Studies through Week 48 and Week 60 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Patients)

	Pooled (TENAYA and LUCERNE)			
	Baseline through Week 48		Baseline through Week 60	
	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one AE	471 (70.9%)	483 (73.0%)	508 (76.5%)	510 (77.0%)
Total number of AEs	1670	1658	2022	1947
Total number of patients with at least one SAE	83 (12.5%)	101 (15.3%)	94 (14.2%)	117 (17.7%)
Total number of SAEs	115	189	144	215
Total number of deaths	9 (1.4%)	8 (1.2%)	12 (1.8%)	8 (1.2%)
Total number of patients withdrawn from study due to an AE	8 (1.2%)	10 (1.5%)	14 (2.1%)	13 (2.0%)
Total number of patients withdrawn from study treatment due to an AE	11 (1.7%)	4 (0.6%)	16 (2.4%)	9 (1.4%)
Total number of patients with at least one AESI	14 (2.1%)	20 (3.0%)	20 (3.0%)	26 (3.9%)
Ocular events: study eye total number of patients with at least one				
AE	254 (38.3%)	246 (37.2%)	278 (41.9%)	266 (40.2%)
SAE	11 (1.7%)	13 (2.0%)	14 (2.1%)	17 (2.6%)
AE leading to withdrawal from study treatment	6 (0.9%)	1 (0.2%)	9 (1.4%)	5 (0.8%)
Treatment related AEs	19 (2.9%)	17 (2.6%)	19 (2.9%)	18 (2.7%)
Treatment related SAEs	8 (1.2%)	1 (0.2%)	8 (1.2%)	2 (0.3%)
AE of Special Interest	8 (1.2%)	12 (1.8%)	11 (1.7%)	16 (2.4%)
Drop in VA score >=30	7 (1.1%)	9 (1.4%)	8 (1.2%)	12 (1.8%)
Associated with severe IOI	1 (0.2%)	2 (0.3%)	1 (0.2%)	2 (0.3%)
Intervention req. to prevent permanent vision loss	0	1 (0.2%)	2 (0.3%)	2 (0.3%)
Suspected transmission of infectious agent by study drug	0	0	0	1 (0.2%)

Non-ocular events total number of patients with at least one				
AE	346 (52.1%)	363 (54.8%)	388 (58.4%)	398 (60.1%)
SAE	68 (10.2%)	82 (12.4%)	76 (11.4%)	94 (14.2%)
AE leading to withdrawal from study treatment	5 (0.8%)	3 (0.5%)	7 (1.1%)	4 (0.6%)
AE of Special Interest	0	1 (0.2%)	0	1 (0.2%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	7 (1.1%)	6 (0.9%)	13 (2.0%)	10 (1.5%)
Non-fatal MI	3 (0.5%)	2 (0.3%)	3 (0.5%)	2 (0.3%)
Non-fatal Stroke	2 (0.3%)	1 (0.2%)	3 (0.5%)	3 (0.5%)
Death	2 (0.3%)	3 (0.5%)	7 (1.1%)	5 (0.8%)

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 433 (last day of Week 60 analysis visit window).

Non-Ocular Adverse Events by Frequency (nAMD)

Through Week 60, the incidence of non-ocular AEs was comparable between the treatment arms and generally consistent with the Week 48 dataset considering the increase in exposure duration (faricimab: 58.4% [Week 60] and 52.1% [Week 48] vs. aflibercept: 60.1% [Week 60] and 54.8% [Week 48].

Non-Ocular Adverse Events of Special Interest (nAMD)

Between Week 48 and Week 60, there were no additional non-ocular AESIs.

Through Week 60, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) remained low and was comparable between the treatment arms (faricimab: 2.0% [Week 60] and 1.1% [Week 48] vs. aflibercept: 1.5% [Week 60] and 0.9% [Week 48].

Between Week 48 and Week 60, the death adjudicated APTC-defined ATEs were cardiac failure congestive, ill-defined disorder, pneumonia bacterial, pulmonary oedema, and subarachnoid haemorrhage (1 patient [0.2%] each) in the faricimab arm; and cardiac failure and glioblastoma multiforme (1 patient [0.2%] each) in the aflibercept arm. None of the death adjudicated APTC ATEs were suspected to be related to study treatment. Between Week 48 and Week 60, there was 1 patient (0.2%) in the faricimab arm and 2 patients (0.3%) in the aflibercept arm who experienced a non-fatal stroke (cerebrovascular accident in all patients). None of the non-fatal stroke adjudicated APTC ATEs were suspected to be related to study treatment. Two of the cerebrovascular accident events (1 in the faricimab arm and 1 in the aflibercept arm) occurred prior to the Week 48 data cutoff but the adjudication information for these events were not available until the Week 60 data cutoff; hence, these events were not included in the Week 48 dataset but rather the Week 60 dataset. Between Week 48 and Week 60, there were no non-fatal MI adjudicated APTC-defined ATEs in both treatment arms.

Non-ocular events from supportive Phase II study STAIRWAY- nAMD indication

The incidence of non-ocular AEs was comparable between the treatment arms (58.3%, 64.5%, and 56.3% in the faricimab Q12W, faricimab Q16W, and ranibizumab Q4W arms, respectively). None of the non-ocular AEs reported were considered related to study treatment.

In total, 7 patients experienced a non-ocular SAE across the faricimab arms; no patients in the ranibizumab arm experienced a non-ocular SAE. There were two APTC events reported in the study:

non-fatal cerebral infarction and fatal ischemic stroke, both of which were reported in the faricimab Q12W arm. Of note these events were not part of the external APTC adjudication process which was subsequently established.

Supportive Phase II nAMD Study AVENUE (BP29647)

Overall, 170 patients (64.9%) experienced non-ocular AEs. The incidence was generally comparable between treatment arms (55.2%, 80.4%, 59.0%, 65.2%, and 67.2% for 0.5 mg ranibizumab Arm A, 1.5 mg faricimab Arm B, 6 mg faricimab Arm C, 6 mg faricimab Q4W/6 mg faricimab Q8W Arm D, 0.5 mg ranibizumab/6 mg faricimab Arm E, respectively); however, the percentage was higher in the 1.5 mg faricimab Arm B. • 33 (12.6%) patients reported non-ocular SAEs. None of the non-ocular AEs reported were considered related to study treatment.

There were four APTC events reported during the study: 1 event in the 6 mg faricimab Arm C (acute myocardial infarction), 1 in the 6 mg faricimab Q4W/Q8W Arm D (basal ganglia infarction), and 2 in the 0.5 mg ranibizumab/6 mg faricimab Arm E (cerebrovascular accident during ranibizumab treatment and fatal cardio-respiratory arrest during faricimab treatment). Of note these events were not part of the external APTC adjudication process which was subsequently established.

Phase III nAMD and DME: ADVERSE DRUG REACTIONS

The ocular ADRs in the study eye through Week 48 for nAMD and Week 56 for DME were pooled across indications. The list of ADRs is presented in Table 57.

The most common pooled ADRs (≥ 2% incidence in any treatment arm: combined faricimab arms vs. aflibercept arm) by PT were conjunctival haemorrhage (6.7% vs. 6.9%), vitreous floaters (3.3% vs. 1.6%), intraocular pressure increased (2.8% vs. 2.2%), and eye pain (2.3% vs. 3.0%).

The most common pooled serious ADRs (≥ 2 patients in any treatment arm: combined faricimab arms vs. aflibercept arm) by PT were uveitis (5 patients [0.3%] vs. 1 [0.1%]), retinal pigment epithelial tear (nAMD only; 4 patients [0.6%] vs. 0), endophthalmitis (4 patients [0.2%] vs. 2 patients [0.2%]), vitreous haemorrhage (3 patients [0.2%] vs. 2 patients [0.2%]), vitritis (2 patients [0.1%] vs. 0), visual acuity reduced transiently (2 patients [0.1%] vs. 1 patient [0.1%]), intraocular pressure increased (2 patients [0.1%] vs. 0) and retinal tear (2 patients [0.1%] vs. 0).

The majority of the serious ADRs resolved, resolved with sequelae, or were resolving by Week 48 for nAMD events and Week 56 for DME events.

The serious ADRs that were not resolved by Week 48 for the nAMD events were retinal pigment epithelial tear (4 events) and uveitis (1 event); and retinal tear (1 event) by Week 56 for the DME event.

The most common pooled sight-threatening ADRs which caused a decrease of ≥ 30 letters in VA score lasting more than 1 hour (≥2 patients in any treatment arm: combined faricimab arms vs. aflibercept arm) by PT were retinal pigment epithelial tear (2 patients [0.1%] vs. 0) and vitreous haemorrhage (2 patients [0.1%] vs. 2 patients [0.2%]).

The pooled sight-threatening ADRs which was associated with severe intraocular inflammation (≥ 2 patients in any treatment arm: combined faricimab arms vs. aflibercept arm) by PT were endophthalmitis (2 patients [0.1%] vs. 2 patients [0.2%]) and uveitis (2 patients [0.1%] vs. 0).

The most common pooled sight-threatening ADR which required surgical or medical intervention to prevent permanent loss of sight (≥ 2 patients in any treatment arm: combined faricimab arms vs. aflibercept Q8W arm) was retinal tear (2 patients [0.1%] vs. 0).

The majority of the pooled sight-threatening ADRs resolved, resolved with sequelae, or were resolving by Week 48 for the nAMD events and by Week 56 for the DME events. The pooled sight-threatening ADRs that were not resolved by Week 48 for the nAMD events were retinal pigment epithelial tear (2 events) and vitreous haemorrhage (1 event), all in the faricimab arm; and by Week 56 for the DME events was retinal tear (1 event) in the faricimab PTI arm.

Table 57. Adverse Drug Reactions in the Study Eye Identified from Pooled Phase III Studies through Week 48 for nAMD and Week 56 for DME (Pooled Safety-Evaluable Population)

	nAMD (N=1326)		DME (N=1887)		POOLED (nAMD, DME) (N=3213)	
MedDRA Preferred Term	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1926)	Aflibercept (N=1287)
Total number of patients with at least one adverse event	124 (18.7%)	119 (18.0%)	218 (17.3%)	95 (15.2%)	342 (17.8%)	214 (16.6%)
Total number of events	232	191	349	136	581	327
Conjunctival haemorrhage	45 (6.8%)	51 (7.7%)	84 (6.7%)	38 (6.1%)	129 (6.7%)	89 (6.9%)
Vitreous floaters	20 (3.0%)	11 (1.7%)	43 (3.4%)	10 (1.6%)	63 (3.3%)	21 (1.6%)
Intraocular pressure increased	17 (2.6%)	15 (2.3%)	37 (2.9%)	13 (2.1%)	54 (2.8%)	28 (2.2%)
Eye pain	17 (2.6%)	20 (3.0%)	27 (2.1%)	19 (3.0%)	44 (2.3%)	39 (3.0%)
Retinal pigment epithelial tear	19 (2.9%)	9 (1.4%)	0	0	19 (1.0%)	9 (0.7%)
Eye irritation	9 (1.4%)	4 (0.6%)	8 (0.6%)	5 (0.8%)	17 (0.9%)	9 (0.7%)
Ocular discomfort	8 (1.2%)	4 (0.6%)	8 (0.6%)	2 (0.3%)	16 (0.8%)	6 (0.5%)
Vitreous haemorrhage	1 (0.2%)	3 (0.5%)	14 (1.1%)	3 (0.5%)	15 (0.8%)	6 (0.5%)
Eye pruritus	5 (0.8%)	3 (0.5%)	9 (0.7%)	5 (0.8%)	14 (0.7%)	8 (0.6%)
Lacrimation increased	6 (0.9%)	9 (1.4%)	8 (0.6%)	3 (0.5%)	14 (0.7%)	12 (0.9%)
Corneal abrasion	4 (0.6%)	8 (1.2%)	8 (0.6%)	2 (0.3%)	12 (0.6%)	10 (0.8%)
Ocular hyperaemia	4 (0.6%)	4 (0.6%)	7 (0.6%)	1 (0.2%)	11 (0.6%)	5 (0.4%)
Vision blurred	3 (0.5%)	3 (0.5%)	8 (0.6%)	9 (1.4%)	11 (0.6%)	12 (0.9%)
Iritis	3 (0.5%)	2 (0.3%)	5 (0.4%)	2 (0.3%)	8 (0.4%)	4 (0.3%)
Uveitis	2 (0.3%)	2 (0.3%)	6 (0.5%)	0	8 (0.4%)	2 (0.2%)
Iridocyclitis	3 (0.5%)	2 (0.3%)	4 (0.3%)	0	7 (0.4%)	2 (0.2%)
Sensation of foreign body	0	0	7 (0.6%)	3 (0.5%)	7 (0.4%)	3 (0.2%)
Vitritis	3 (0.5%)	1 (0.2%)	4 (0.3%)	2 (0.3%)	7 (0.4%)	3 (0.2%)
Endophthalmitis	0	1 (0.2%)	4 (0.3%)	1 (0.2%)	4 (0.2%)	2 (0.2%)
Visual acuity reduced transiently	0	0	3 (0.2%)	1 (0.2%)	3 (0.2%)	1 (<0.1%)
Retinal tear	0	0	2 (0.2%)	0	2 (0.1%)	0
Rhegmatogenous retinal detachment	0	0	1 (<0.1%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
For nAMD: Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
For DME: Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
ADR terms: Uveitis, Iritis, Vitritis, Iriodcyclitis, Endophthalmitis, Rhegmatogenous retinal detachment, Retinal tear, Retinal Pigment Epithelial tear, Intraocular Pressure Increased, Conjunctival haemorrhage, Ocular hyperaemia, Lacrimation increased, Vision blurred, Visual acuity reduced transiently, Vitreous hemorrhage, Vitreous floaters, Eye pruritus, Eye irritation, Ocular discomfort, Eye pain, Sensation of foreign body, Corneal abrasion

Diabetic macular edema (DME)

<u>Common TEAEs - the Pooled Phase III DME Studies</u>

The incidence of AEs was generally comparable across treatment arms (513/630 [81.4%], 486/632 [76.9%], and 488/625 [78.1%] patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

Table 58: Overview of Safety through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Patients)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one AE	257 (82.1%)	253 (80.8%)	244 (78.5%)	256 (80.8%)	233 (73.0%)	244 (77.7%)	513 (81.4%)	486 (76.9%)	999 (79.2%)	488 (78.1%)
Total number of AEs	1062	1016	938	1107	875	914	2169	1891	4060	1852
Total number of patients with at least one SAE	82 (26.2%)	77 (24.6%)	56 (18.0%)	67 (21.1%)	49 (15.4%)	58 (18.5%)	149 (23.7%)	126 (19.9%)	275 (21.8%)	114 (18.2%)
Total number of SAEs	171	114	96	101	79	95	272	193	465	191
Total number of deaths	8 (2.6%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	0	5 (1.6%)	13 (2.1%)	9 (1.4%)	22 (1.7%)	9 (1.4%)
Total number of patients withdrawn from study due to an AE	10 (3.2%)	11 (3.5%)	6 (1.9%)	6 (1.9%)	1 (0.3%)	3 (1.0%)	16 (2.5%)	12 (1.9%)	28 (2.2%)	9 (1.4%)
Total number of patients withdrawn from study treatment due to an AE	6 (1.9%)	8 (2.6%)	3 (1.0%)	4 (1.3%)	4 (1.3%)	4 (1.3%)	10 (1.6%)	12 (1.9%)	22 (1.7%)	7 (1.1%)
Total number of patients with at least one AESI	12 (3.8%)	15 (4.8%)	6 (1.9%)	15 (4.7%)	11 (3.4%)	7 (2.2%)	27 (4.3%)	26 (4.1%)	53 (4.2%)	13 (2.1%)

<u>Ocular events through Week 56- the Pooled Phase III DME Studies- DME indication</u>

The incidence of ocular AEs occurring in the study eye was comparable across treatment arms (37.3%, 35.6%, and 34.4% of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), with the exception (≥ 2% difference in any treatment arms) of vitreous floaters (30

patients [4.8%], 13 patients [2.1%], and 10 patients [1.6%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively), which were mainly mild and all non-serious.

The most common ocular AEs in the study eye (≥ 2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were conjunctival haemorrhage (7.3%, 6.0%, and 6.1%), cataract (5.1%, 4.1%, and 4.8%), vitreous detachment (3.7%, 2.8%, and 3.2%), vitreous floaters (4.8%, 2.1%, 1.6%), intraocular pressure increased (3.7%, 2.2%, and 2.1%), dry eye (3.5%, 2.2%, and 1.8%), and eye pain (1.9%, 2.4%, and 3.0%).

Ocular AEs in the study eye occurring in ≥ 1% in any treatment arm through Week 56 are summarized in Table 60.

Ocular AEs with a difference of ≥ 1% between the faricimab Q8W and faricimab PTI arms, respectively, were conjunctival haemorrhage (7.3% vs. 6.0%), vitreous floaters (4.8% vs. 2.1%), intraocular pressure increased (3.7% vs. 2.2%), dry eye (3.5% vs. 2.2%), cataract cortical (0.6% vs. 1.6%), and blepharitis (1.7% vs. 0.6%).

Ocular AEs with a difference of ≥1% between the faricimab Q8W and aflibercept Q8W arms, respectively, were conjunctival haemorrhage (7.3% vs. 6.1%), vitreous floaters (4.8% vs. 1.6%), intraocular pressure increased (3.7% vs. 2.1%), dry eye (3.5% vs. 1.8%), eye pain (1.9% vs. 3.0%), and blepharitis (1.7% vs. 0.3%).There were no ocular AEs with a difference of ≥ 1% between the faricimab PTI and aflibercept Q8W arms

Table 59: Overview of Safety through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Patients)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Ocular events: study eye total number of patients with at least one										
AE	98 (31.3%)	106 (33.9%)	102 (32.8%)	137 (43.2%)	119 (37.3%)	113 (36.0%)	235 (37.3%)	225 (35.6%)	460 (36.5%)	215 (34.4%)
SAE	6 (1.9%)	9 (2.9%)	2 (0.6%)	9 (2.8%)	10 (3.1%)	6 (1.9%)	15 (2.4%)	19 (3.0%)	34 (2.7%)	8 (1.3%)
AE leading to withdrawal from study treatment	2 (0.6%)	5 (1.6%)	1 (0.3%)	0	3 (0.9%)	1 (0.3%)	2 (0.3%)	8 (1.3%)	10 (0.8%)	2 (0.3%)
Treatment related AEs	11 (3.5%)	8 (2.6%)	5 (1.6%)	8 (2.5%)	8 (2.5%)	14 (4.5%)	19 (3.0%)	16 (2.5%)	35 (2.8%)	19 (3.0%)
Treatment related SAEs	0	4 (1.3%)	0	0	1 (0.3%)	0	0	5 (0.8%)	5 (0.4%)	0
AE of Special Interest	6 (1.9%)	8 (2.6%)	1 (0.3%)	9 (2.8%)	9 (2.8%)	5 (1.6%)	15 (2.4%)	17 (2.7%)	32 (2.5%)	6 (1.0%)
Drop in VA score >=30	2 (0.6%)	2 (0.6%)	1 (0.3%)	6 (1.9%)	6 (1.9%)	2 (0.6%)	8 (1.3%)	8 (1.3%)	16 (1.3%)	3 (0.5%)
Associated with severe IOI	2 (0.6%)	5 (1.6%)	0	1 (0.3%)	0	1 (0.3%)	3 (0.5%)	5 (0.8%)	8 (0.6%)	1 (0.2%)
Intervention req. to prevent permanent vision loss	3 (1.0%)	2 (0.6%)	0	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.8%)	5 (0.8%)	10 (0.8%)	2 (0.3%)
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0	0	0	0	0
Ocular events: fellow eye total number of patients with at least one										
AE	89 (28.4%)	104 (33.2%)	106 (34.1%)	128 (40.4%)	91 (28.5%)	105 (33.4%)	217 (34.4%)	195 (30.9%)	412 (32.6%)	211 (33.8%)
SAE	7 (2.2%)	7 (2.2%)	5 (1.6%)	6 (1.9%)	4 (1.3%)	3 (1.0%)	13 (2.1%)	11 (1.7%)	24 (1.9%)	8 (1.3%)
AE of Special Interest	7 (2.2%)	7 (2.2%)	4 (1.3%)	6 (1.9%)	2 (0.6%)	2 (0.6%)	13 (2.1%)	9 (1.4%)	22 (1.7%)	6 (1.0%)
Drop in VA score >=30	6 (1.9%)	4 (1.3%)	2 (0.6%)	6 (1.9%)	2 (0.6%)	2 (0.6%)	12 (1.9%)	6 (0.9%)	18 (1.4%)	4 (0.6%)
Associated with severe IOI	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Intervention req. to prevent permanent vision loss	1 (0.3%)	3 (1.0%)	2 (0.6%)	0	0	0	1 (0.2%)	3 (0.5%)	4 (0.3%)	2 (0.3%)
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0	0	0	0	0

Table 60: Ocular Adverse Events in the Study Eye Occurring in ≥ 1% in Any Treatment Arm through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety Evaluable Population)

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	98 (31.3%)	106 (33.9%)	102 (32.8%)	137 (43.2%)	119 (37.3%)	113 (36.0%)	235 (37.3%)	225 (35.6%)	460 (36.5%)	215 (34.4%)
Total number of events	196	208	169	250	211	181	446	419	865	350
Conjunctival haemorrhage	20 (6.4%)	22 (7.0%)	19 (6.1%)	26 (8.2%)	16 (5.0%)	19 (6.1%)	46 (7.3%)	38 (6.0%)	84 (6.7%)	38 (6.1%)
Cataract	14 (4.5%)	11 (3.5%)	17 (5.5%)	18 (5.7%)	15 (4.7%)	13 (4.1%)	32 (5.1%)	26 (4.1%)	58 (4.6%)	30 (4.8%)
Vitreous detachment	10 (3.2%)	11 (3.5%)	9 (2.9%)	13 (4.1%)	7 (2.2%)	11 (3.5%)	23 (3.7%)	18 (2.8%)	41 (3.2%)	20 (3.2%)
Vitreous floaters	15 (4.8%)	6 (1.9%)	2 (0.6%)	15 (4.7%)	7 (2.2%)	8 (2.5%)	30 (4.8%)	13 (2.1%)	43 (3.4%)	10 (1.6%)
Intraocular pressure increased	10 (3.2%)	5 (1.6%)	5 (1.6%)	13 (4.1%)	9 (2.8%)	8 (2.5%)	23 (3.7%)	14 (2.2%)	37 (2.9%)	13 (2.1%)
Dry eye	8 (2.6%)	3 (1.0%)	4 (1.3%)	14 (4.4%)	11 (3.4%)	7 (2.2%)	22 (3.5%)	14 (2.2%)	36 (2.9%)	11 (1.8%)
Eye pain	8 (2.6%)	7 (2.2%)	9 (2.9%)	4 (1.3%)	8 (2.5%)	10 (3.2%)	12 (1.9%)	15 (2.4%)	27 (2.1%)	19 (3.0%)
Conjunctivitis	2 (0.6%)	4 (1.3%)	3 (1.0%)	6 (1.9%)	6 (1.9%)	4 (1.3%)	8 (1.3%)	10 (1.6%)	18 (1.4%)	7 (1.1%)
Cataract cortical	1 (0.3%)	2 (0.6%)	7 (2.3%)	3 (0.9%)	8 (2.5%)	2 (0.6%)	4 (0.6%)	10 (1.6%)	14 (1.1%)	9 (1.4%)
Diabetic retinal oedema	5 (1.6%)	1 (0.3%)	3 (1.0%)	4 (1.3%)	5 (1.6%)	3 (1.0%)	9 (1.4%)	6 (0.9%)	15 (1.2%)	6 (1.0%)
Medication error	3 (1.0%)	0	0	5 (1.6%)	9 (2.8%)	4 (1.3%)	8 (1.3%)	9 (1.4%)	17 (1.3%)	4 (0.6%)
Punctate keratitis	3 (1.0%)	3 (1.0%)	4 (1.3%)	5 (1.6%)	4 (1.3%)	2 (0.6%)	8 (1.3%)	7 (1.1%)	15 (1.2%)	6 (1.0%)
Posterior capsule opacification	2 (0.6%)	4 (1.3%)	6 (1.9%)	5 (1.6%)	1 (0.3%)	2 (0.6%)	7 (1.1%)	5 (0.8%)	12 (1.0%)	8 (1.3%)
Blepharitis	2 (0.6%)	0	1 (0.3%)	9 (2.8%)	4 (1.3%)	1 (0.3%)	11 (1.7%)	4 (0.6%)	15 (1.2%)	2 (0.3%)
Vision blurred	4 (1.3%)	3 (1.0%)	3 (1.0%)	1 (0.3%)	0	6 (1.9%)	5 (0.8%)	3 (0.5%)	8 (0.6%)	9 (1.4%)
Vitreous haemorrhage	5 (1.6%)	4 (1.3%)	1 (0.3%)	2 (0.6%)	3 (0.9%)	2 (0.6%)	7 (1.1%)	7 (1.1%)	14 (1.1%)	3 (0.5%)
Cataract nuclear	2 (0.6%)	3 (1.0%)	3 (1.0%)	4 (1.3%)	3 (0.9%)	0	6 (1.0%)	6 (0.9%)	12 (1.0%)	3 (0.5%)
Diabetic retinopathy	2 (0.6%)	4 (1.3%)	1 (0.3%)	2 (0.6%)	4 (1.3%)	2 (0.6%)	4 (0.6%)	8 (1.3%)	12 (1.0%)	3 (0.5%)
Cataract subcapsular	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (1.3%)	4 (1.3%)	0	6 (1.0%)	6 (0.9%)	12 (1.0%)	2 (0.3%)
Macular fibrosis	1 (0.3%)	1 (0.3%)	3 (1.0%)	1 (0.3%)	0	4 (1.3%)	2 (0.3%)	1 (0.2%)	3 (0.2%)	7 (1.1%)
Sensation of foreign body	2 (0.6%)	1 (0.3%)	1 (0.3%)	4 (1.3%)	0	2 (0.6%)	6 (1.0%)	1 (0.2%)	7 (0.6%)	3 (0.5%)
Ocular hypertension	1 (0.3%)	3 (1.0%)	0	0	4 (1.3%)	1 (0.3%)	1 (0.2%)	7 (1.1%)	8 (0.6%)	1 (0.2%)

Ocular AEs by Treatment Relationship through Week 56 DME indication

Ocular AEs Suspected to be Related to Faricimab by the Investigator Through Week 56, the incidence of ocular AEs suspected by the investigator to be related to faricimab was low (3.0% in the faricimab Q8W arm and 2.5% in the faricimab

The most common treatment-related ocular AEs in the study eye (≥ 0.5% incidence in either of the faricimab arms) were intraocular pressure increased (7 patients [1.1%]) and vitreous floaters (6 patients [1.0%]) in the faricimab Q8W arm; and intraocular pressure increased, uveitis, and ocular hypertension (3 patients [0.5%] each) in the faricimab PTI arm.

Ocular AEs in the Study Eye through Clinical Cut-Off Date DME indication

At the time of the primary analysis, the Phase III trials were ongoing. Therefore, cumulative safety data available as of the Clinical Cut-Off Date associated with the primary endpoint was also assessed (i.e., the subset of patients with follow-up data beyond Week 56). From baseline to the Clinical Cut-Off Date, 41.4%, 41.6%, and 38.4% of patients experienced at least one ocular AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. After Week 56 to the Clinical Cut-Off Date, the most common ocular AEs in the study eye (≥ 2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT was cataract (2.2%, 2.2%, and 1.8%).

From baseline to the Clinical Cut-Off Date, 3.3%, 2.8%, and 3.0% of patients experienced at least one treatment-related ocular AEs in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. After Week 56 to the Clinical Cut-Off Date, the treatment-related ocular AEs in the study eye were cataract and Sjogren's syndrome (1 patient [0.2%] each) in the faricimab Q8W arm; and cataract (2 patients [0.3%]), uveitis and endophthalmitis (1 patient [0.2%] each) in the faricimab PTI arm.

There were no treatment-related ocular AEs in the study eye in the aflibercept Q8W arm.

Adverse Events of Special Interest - the Pooled Phase III DME Studies -DME indication

Sight-Threatening Adverse Events Through Week 56 -DME indication

Sight-Threatening Adverse Events in the Study Eye Through Week 56

Through Week 56, a higher incidence of AESIs in the study eye occurred in both faricimab arms compared to the aflibercept Q8W arm (15 patients [2.4%], 17 patients [2.7%], and 6 patients [1.0%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively). While the difference in AESI trends toward favouring aflibercept, the overall incidence was low for all treatment arms.

Through Week 56, the most common sight-threatening AEs in the study eye which caused a decrease of ≥ 30 letters in VA score lasting more than 1 hour (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 3 patients [0.5%], 2 patients [0.3%], and 0) and cataract (2 patients [0.3%], 0, and 1 patient [0.2%]).

Through Week 56, the most common sight-threatening AEs in the study eye which required surgical or medical intervention to prevent permanent loss of sight (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) was retinal tear (0, 2 patients [0.3%], and 0).

Through Week 56, the most common sight-threatening AE in the study eye which was associated with severe intraocular inflammation (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) was uveitis (0, 2 patients [0.3%], and 0).

Sight-Threatening Adverse Events up to Clinical Cut-Off Date DME indication

Sight-Threatening Adverse Events in the Study Eye Through Clinical Cut-Off Date

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 3.2%, 3.8%, and 1.6% of patients experienced at least one AESI in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.

After Week 56 to the Clinical Cut-Off Date, the most common sight-threatening AE in the study eye which caused a decrease of ≥30 letters in VA score lasting more than 1 hour (≥2 patients in any treatment arm) was cataract (2 patients [0.3%] each in the faricimab Q8W and faricimab PTI arms).

After Week 56 to the Clinical Cut-Off Date, the sight-threatening AEs in the study eye which required surgical or medical intervention to prevent permanent loss of sight were retinal tear, endophthalmitis, and corneal abrasion (1 patient [0.2% each) in the faricimab PTI arm; and cataract subcapsular (1 patient [0.2%]) in the aflibercept Q8W arm. There were no additional events in the faricimab Q8W arm.

After Week 56 to the Clinical Cut-Off Date, there were no sight-threatening AEs in the study eye which were associated with severe intraocular inflammation in any treatment arms.

After Week 56 to the Clinical Cut-Off Date, half of the ocular AESIs (9/18) in the study eye resolved or were resolving by the Clinical Cut-Off Date. The sight-threatening AEs in the study eye which caused a decrease of ≥30 letters in VA score lasting more than 1 hour that were not resolved by the Clinical Cut-Off Date were cataract (2 events), diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema), retinal haemorrhage, ocular ischaemic syndrome, and visual impairment in the faricimab PTI arm; and diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema) in the aflibercept Q8W arm.

The sight-threatening AEs in the study eye which required surgical or medical intervention to prevent permanent loss of sight that were not resolved by the Clinical Cut-Off Date were retinal tear in the faricimab PTI arm; and cataract subcapsular in the aflibercept Q8W arm.

Table 61. Adverse Events of Special Interest in Study Eye through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

AE of Special Interest MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	6 (1.9%)	8 (2.6%)	1 (0.3%)	9 (2.8%)	9 (2.8%)	5 (1.6%)	15 (2.4%)	17 (2.7%)	32 (2.5%)	6 (1.0%)
Overall total number of events	7	9	1	12	9	5	19	18	37	6
CAUSES A DECREASE OF >= 30 LETTERS IN VA SCORE LASTING MORE THAN 1 HOUR										
Total number of patients with at least one adverse event	2 (0.6%)	2 (0.6%)	1 (0.3%)	6 (1.9%)	6 (1.9%)	2 (0.6%)	8 (1.3%)	8 (1.3%)	16 (1.3%)	3 (0.5%)
Total number of events	2	2	1	9	6	2	11	8	19	3
Diabetic retinal oedema	1 (0.3%)	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	0	3 (0.5%)	2 (0.3%)	5 (0.4%)	0
Cataract	0	0	0	2 (0.6%)	0	1 (0.3%)	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
Vitreous haemorrhage	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
Cataract subcapsular	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Diabetic retinopathy	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Dry eye	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Endophthalmitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Influenza	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Retinal artery occlusion	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Retinal vein occlusion	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Visual acuity reduced transiently	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Visual impairment	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
REQUIRES SURGICAL OR MEDICAL INTERVENTION TO PREVENT PERMANENT LOSS OF SIGHT										
Total number of patients with at least one adverse event	3 (1.0%)	2 (0.6%)	0	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.8%)	5 (0.8%)	10 (0.8%)	2 (0.3%)
Total number of events	3	2	0	2	3	2	5	5	10	2
Retinal tear	0	1 (0.3%)	0	0	1 (0.3%)	0	0	2 (0.3%)	2 (0.2%)	0
Visual acuity reduced transiently	0	0	0	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
Chorioretinitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Device dislocation	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Endophthalmitis	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Intraocular pressure increased	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Macular fibrosis	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Narrow anterior chamber angle	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Ocular hypertension	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Rhegmatogenous retinal detachment	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
ASSOCIATED WITH SEVERE INTRAOCULAR INFLAMMATION										
Total number of patients with at least one adverse event	2 (0.6%)	5 (1.6%)	0	1 (0.3%)	0	1 (0.3%)	3 (0.5%)	5 (0.8%)	8 (0.6%)	1 (0.2%)
Total number of events	2	5	0	1	0	1	3	5	8	1
Endophthalmitis	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
Uveitis	0	2 (0.6%)	0	0	0	0	0	2 (0.3%)	2 (0.2%)	0
Keratouveitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0

Intraocular Inflammation Events (IOI) until week 56- the Pooled Phase III DME Studies DME indication

Through Week 56, the incidence of IOI events in the study eye was low and generally comparable across all treatment arms (8 patients [1.3%], 9 patients [1.4%], and 4 patients [0.6%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). There were no IOI events associated with retinal vasculitis or occlusive disease in any treatment arms based on the reported preferred terms.

There were 2 patients with at least one IOI event in the study eye associated with vision loss ≥ 15 letters (1 patient with vision loss ≥15 letters and 1 patient with vision loss ≥ 30 letters); both patients were in the faricimab PTI arm.

- The IOI events in the study eye associated with vision loss ≥ 15 letters were uveitis and chorioretinitis. Prior to these events, the patient received a total of 9 injections of study treatment with the uveitis event occurring 21 days after the last injection followed by chorioretinitis 6 days after. Both were suspected by the investigator to be related to study treatment, serious, and resolving by Week 56.
- The IOI events in the study eye associated with vision loss ≥ 30 letters were keratic precipitates and uveitis. Prior to the keratic precipitates event, the patient received a total of 9 injections of study treatment with the event occurring 77 days after the last injection; this event was suspected by the investigator to be related to study treatment, non-serious, and not resolved by Week 56. Prior to the uveitis event, the patient received a total of 11 injections of study treatment with the event occurring 4 days after the last injection; this event was suspected by the investigator to be related to study treatment, serious, and resolving by Week 56.

The most common IOI events in the study eye (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were iritis (2 patients [0.3%], 3 patients [0.5%], and 2 patients [0.3%]), uveitis (2 patients [0.3%], 4 patients [0.6%], and 0), vitritis (3

patients [0.5%], 1 patient [0.2%], and 2 patients [0.3%]), and iridocyclitis (2 patients [0.3%], 2 patients [0.3%], and 0).

Through Week 56, the per-injection rate of IOI events in the study eye was low and generally comparable (0.17%, 0.28%, and 0.10% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

The majority of IOI events in the study eye were mild or moderate in severity in the combined faricimab arms and aflibercept Q8W arms.

Severe IOI events - the Pooled Phase III DME Studies- DME indication

Through Week 56, 1 patient (0.2%) and 2 patients (0.3%) experienced at least one severe IOI event in the study eye in the faricimab Q8W and faricimab PTI, respectively.

The severe IOI events in the study eye by PT were vitritis (1 patient [0.2%]) in the faricimab Q8W arm and uveitis (2 patients [0.3%]) in the faricimab PTI arm. There were no severe IOI events in the study eye in the aflibercept Q8W arm.

There was one IOI SAE of reported keratouveitis suspected to be related to possible herpetic origin.

There was no clear relationship between injection day of study treatment and the timing of the IOI events. The majority of the IOI events occurred after the initial loading doses, 6 or 8 injections (range: 28) of faricimab (in the Q8W arm) and 4 to 5 injections (range: 4-11) of faricimab (in the PTI arm); and all IOI events occurred after 3 to 7 injections of aflibercept.

Intraocular Inflammation Events (IOI) after week 56 DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 8 patients (1.3%), 11 patients (1.7%), and 7 patients (1.1%) experienced at least one IOI event in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively. After Week 56 to the Clinical Cut-Off Date, there were no additional IOI events associated with retinal vasculitis or occlusive disease in any treatment arms. After Week 56 to the Clinical Cut-Off Date, there was 1 additional patient with an IOI event in the study eye associated with vision loss ≥ 30 letters in the aflibercept Q8W arm; the IOI event was iridocyclitis and was considered non-serious, suspected by the investigator not to be related to study treatment, and not resolved by the Clinical Cut-Off Date.

After Week 56 to the Clinical Cut-Off Date, the IOI events in the study eye by PT were iritis (1 patient [0.2%]) in the faricimab Q8W arm; uveitis (2 patients [0.3%]) and iritis (1 patient [0.2%]) in the faricimab PTI arm; and post procedural inflammation (2 patients [0.3%]) and iridocyclitis (1 patient [0.2%]) in the aflibercept Q8W arm.

After Week 56 to the Clinical Cut-Off Date, the majority of the IOI events in the study eye were mild or moderate in severity across all treatment arms, with 1 patient (0.2%) with a severe IOI event of uveitis in the faricimab PTI arm.

Table 62: Adverse Events of Intraocular Inflammation in the Study Eye through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	5 (1.6%)	7 (2.2%)	3 (1.0%)	3 (0.9%)	2 (0.6%)	1 (0.3%)	8 (1.3%)	9 (1.4%)	17 (1.3%)	4 (0.6%)
Total number of events	6	13	5	4	2	1	10	15	25	6
Iritis	0	3 (1.0%)	1 (0.3%)	2 (0.6%)	0	1 (0.3%)	2 (0.3%)	3 (0.5%)	5 (0.4%)	2 (0.3%)
Uveitis	2 (0.6%)	3 (1.0%)	0	0	1 (0.3%)	0	2 (0.3%)	4 (0.6%)	6 (0.5%)	0
Vitritis	2 (0.6%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	0	3 (0.5%)	1 (0.2%)	4 (0.3%)	2 (0.3%)
Iridocyclitis	2 (0.6%)	1 (0.3%)	0	0	1 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)	0
Anterior chamber inflammation	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Chorioretinitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Keratic precipitates	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Keratouveitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).Intraocular Inflammation events include Anterior Chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Non-infectious Endophthalmitis, Post procedural inflammation, Uveitis, and Vitritis. Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes events with onset up to Day 405 (last day of Week 56 analysis visit window).

Retinal Vascular Occlusive Disease Through Week 56 - the Pooled Phase III DME Studies- DME indication

Through Week 56, 1 patient [0.2%], 2 patients [0.3%], and 2 patients [0.3%] experienced a retinal vascular occlusive disease AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The retinal vascular occlusive disease AEs in the study eye (by faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) were retinal vein occlusion (1 patient [0.2%],

2 patients [0.3%], and 0), retinal artery embolism (0, 0, and 1 patient [0.2%]), and retinal artery occlusion (0, 0, and 1 patient [0.2%]).

Two of the retinal vascular occlusive disease AEs in the study eye were considered serious (retinal vein occlusion in the faricimab PTI arm and retinal artery occlusion in the aflibercept Q8W arm). The serious retinal vein occlusion and serious retinal artery occlusion AEs were both suspected by the investigator not to be related to study treatment and resolved or resolved with sequelae by the Clinical Cut-Off Date, respectively.

Upon slitlamp examination, no findings of inflammation (no cells or flare) were reported for the retinal vein occlusions in the faricimab arms. For the retinal artery embolism in the aflibercept Q8W arm there was minimal (trace) inflammation reported. For the retinal artery occlusion in the aflibercept Q8W arm, conjunctival hyperaemia, corneal edema, rubeosis iridis, and hyphema were found on slitlamp examination, and there were no cells or flare reported.

Retinal Vascular Occlusive Disease up to Clinical Cut-Off Date DME indication

After Week 56 to the Clinical Cut-Off Date, there was 1 additional patient with a retinal vascular occlusive disease AE in the study eye (retinal artery occlusion [1 patient, 0.2%] in the faricimab Q8W arm; The retinal artery occlusion AE was considered non-serious, suspected by the investigator not to be related to study treatment, and not resolved by the Clinical Cut-Off Date.

For the retinal artery occlusion, dry cornea and cataract were found on slitlamp examination, with trace cells in the anterior chamber.

Slitlamp examination

Table 63.

The proportion of patients by grade for the worst post-baseline outcome in the study eye through the CCOD on slitlamp examination including intraocular inflammation, cataract and vitreous hemorrhage were generally comparable across treatment arms.

Table 52 Baseline and Worst Post-Baseline Grade Slitlamp Findings in the Study Eye through CCOD from Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

			Pooled(YOSEMITE and RHINE) (N=1887)			
Visit	Assessment	Grade	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Baseline	Anterior Chamber Cell	n	630	632	1262	625
		0	627 (99.5%)	631 (99.8%)	1258 (99.7%)	625 (100%)
		Trace	2 (0.3%)	0	2 (0.2%)	0
		1+	0	1 (0.2%)	1 (<0.1%)	0
		2+	1 (0.2%)	0	1 (<0.1%)	0
	Anterior Chamber Flare	n	628	631	1259	625
		0	627 (99.8%)	630 (99.8%)	1257 (99.8%)	625 (100%)
		Trace	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
	Cataract	n	628	627	1255	622
		1+	280 (70.9%)	268 (69.3%)	548 (70.1%)	265 (67.4%)
		2+	108 (27.3%)	114 (29.5%)	222 (28.4%)	117 (29.8%)
		3+	6 (1.5%)	5 (1.3%)	11 (1.4%)	11 (2.8%)
		4+	1 (0.3%)	0	1 (0.1%)	0
		Not Applicable	233	240	473	229
	Neovascularization Of Iris	n	629	630	1259	624
		Present	3 (0.5%)	3 (0.5%)	6 (0.5%)	1 (0.2%)
		Absent	626 (99.5%)	627 (99.5%)	1253 (99.5%)	623 (99.8%)
	Vitreous Cell	n	630	632	1262	625
		0	627 (99.5%)	631 (99.8%)	1258 (99.7%)	622 (99.5%)
		Trace	2 (0.3%)	1 (0.2%)	3 (0.2%)	2 (0.3%)
		0.5	0	0	0	1 (0.2%)
		1	1 (0.2%)	0	1 (<0.1%)	0
	Vitreous Hemorrhage	n	630	632	1262	625
		0	628 (99.7%)	631 (99.8%)	1259 (99.8%)	624 (99.8%)
		0.5+	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
		1+	1 (0.2%)	0	1 (<0.1%)	0
Worst post-baseline outcome through CCOD	Anterior Chamber Cell	n	629	632	1261	625
		0	609 (96.8%)	614 (97.2%)	1223 (97.0%)	614 (98.2%)
		Trace	3 (0.5%)	1 (0.2%)	4 (0.3%)	2 (0.3%)
		0.5+	3 (0.5%)	6 (0.9%)	9 (0.7%)	4 (0.6%)
		1+	11 (1.7%)	6 (0.9%)	17 (1.3%)	2 (0.3%)
		2+	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
		3+	1 (0.2%)	2 (0.3%)	3 (0.2%)	2 (0.3%)
		4+	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)

Table 52 Baseline and Worst Post-Baseline Grade Slitlamp Findings in the Study Eye through CCOD from Pooled Phase III DME Studies (Pooled Safety-Evaluable Population) (cont.)

			Pooled(YOSEMITE and RHINE) (N=1887)			
Visit	Assessment	Grade	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Worst post-baseline outcome through CCOD	Anterior Chamber Flare	n	627	631	1258	625
		0	621 (99.0%)	623 (98.7%)	1244 (98.9%)	621 (99.4%)
		Trace	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
		1+	2 (0.3%)	4 (0.6%)	6 (0.5%)	1 (0.2%)
		2+	2 (0.3%)	2 (0.3%)	4 (0.3%)	0
		3+	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
		4+	0	0	0	1 (0.2%)
	Cataract	n	628	629	1257	622
		1+	241 (58.6%)	235 (58.8%)	476 (58.7%)	235 (57.9%)
		2+	131 (31.9%)	140 (35.0%)	271 (33.4%)	134 (33.0%)
		3+	34 (8.3%)	22 (5.5%)	56 (6.9%)	33 (8.1%)
		4+	5 (1.2%)	3 (0.8%)	8 (1.0%)	4 (1.0%)
		Not Applicable	217	229	446	216
	Neovascularization Of Iris	n	628	631	1259	625
		Present	3 (0.5%)	5 (0.8%)	8 (0.6%)	5 (0.8%)
		Absent	625 (99.5%)	626 (99.2%)	1251 (99.4%)	620 (99.2%)
	Vitreous Cell	n	629	632	1261	625
		0	616 (97.9%)	620 (98.1%)	1236 (98.0%)	618 (98.9%)
		Trace	3 (0.5%)	1 (0.2%)	4 (0.3%)	1 (0.2%)
		0.5	0	3 (0.5%)	3 (0.2%)	3 (0.5%)
		1	7 (1.1%)	2 (0.3%)	9 (0.7%)	2 (0.3%)
		2	2 (0.3%)	3 (0.5%)	5 (0.4%)	1 (0.2%)
		3	1 (0.2%)	3 (0.5%)	4 (0.3%)	0
	Vitreous Hemorrhage	n	629	632	1261	625
		0	619 (98.4%)	620 (98.1%)	1239 (98.3%)	619 (99.0%)
		Trace	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
		0.5+	2 (0.3%)	4 (0.6%)	6 (0.5%)	1 (0.2%)
		1+	8 (1.3%)	5 (0.8%)	13 (1.0%)	4 (0.6%)
		3+	0	1 (0.2%)	1 (<0.1%)	0

Ocular AEs in the Fellow Eye from the Pooled Phase III DME Studies

AEs by Frequency through Week 56

Through Week 56, 34.4%, 30.9%, and 33.8% of patients experienced at least one ocular AE in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most common ocular AEs in the fellow eye (≥2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were diabetic retinal oedema (verbatim, worsening

of diabetic retinal oedema; 5.4%, 5.7%, and 5.1%), cataract (5.2%, 3.5%, and 4.6%), vitreous detachment (2.4%, 1.9%, and 2.7%), conjunctival haemorrhage (2.4%, 2.4%, and 2.1%), diabetic retinopathy (1.9%, 1.7%, and 2.7%), dry eye (2.4%, 2.1%, and 1.9%), vitreous haemorrhage (2.5%, 1.1%, and 1.4%), and retinal haemorrhage (1.0%, 2.1%, and 1.0%).

Ocular AEs in the Fellow Eye through Clinical Cut-Off Date DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 37.9%, 36.7%, and 39.0% of patients experienced at least one ocular AE in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

After Week 56 to the Clinical Cut-Off Date, the most common ocular AEs in the fellow eye (≥2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 5 patients [0.8%], 8 patients [1.3%], and 13 patients [2.1%]) and cataract (9 patients [1.4%] 14 patients [2.2%], and 9 patients [1.4%]).

From baseline to the Clinical Cut-Off Date, 11 patients (1.7%), 7 patients (1.1%), and 13 patients (2.1%) experienced at least one ocular AE in the fellow eye related to fellow eye treatment in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. After Week 56 to the Clinical Cut-Off Date, the ocular AE in the fellow eye related to fellow eye treatment were Sjogren's syndrome (1 patient [0.2%]) in the faricimab Q8W arm; and intraocular pressure increased in the faricimab PTI and aflibercept Q8W arms (1 patient [0.2%] in each).

Table 64: Most Frequent Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population Protocol: GR40349 & GR40398 DME indication

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	89 (28.4%)	104 (33.2%)	106 (34.1%)	128 (40.4%)	91 (28.5%)	105 (33.4%)
Total number of events	155	172	164	216	150	170
Diabetic retinal oedema	9 (2.9%)	18 (5.8%)	18 (5.8%)	25 (7.9%)	18 (5.6%)	14 (4.5%)
Cataract	13 (4.2%)	12 (3.8%)	17 (5.5%)	20 (6.3%)	10 (3.1%)	12 (3.8%)
Vitreous detachment	8 (2.6%)	8 (2.6%)	6 (1.9%)	7 (2.2%)	4 (1.3%)	11 (3.5%)
Conjunctival haemorrhage	8 (2.6%)	10 (3.2%)	6 (1.9%)	7 (2.2%)	5 (1.6%)	7 (2.2%)
Diabetic retinopathy	6 (1.9%)	9 (2.9%)	8 (2.6%)	6 (1.9%)	2 (0.6%)	9 (2.9%)
Dry eye	5 (1.6%)	5 (1.6%)	5 (1.6%)	10 (3.2%)	8 (2.5%)	7 (2.2%)
Vitreous haemorrhage	8 (2.6%)	4 (1.3%)	3 (1.0%)	8 (2.5%)	3 (0.9%)	6 (1.9%)
Intraocular pressure increased	4 (1.3%)	2 (0.6%)	4 (1.3%)	6 (1.9%)	5 (1.6%)	4 (1.3%)
Retinal haemorrhage	2 (0.6%)	4 (1.3%)	3 (1.0%)	4 (1.3%)	9 (2.8%)	3 (1.0%)
Retinal exudates	5 (1.6%)	7 (2.2%)	3 (1.0%)	2 (0.6%)	2 (0.6%)	5 (1.6%)
Conjunctivitis	3 (1.0%)	1 (0.3%)	3 (1.0%)	8 (2.5%)	2 (0.6%)	6 (1.9%)
Vitreous floaters	3 (1.0%)	2 (0.6%)	3 (1.0%)	0	6 (1.9%)	8 (2.5%)
Cataract cortical	2 (0.6%)	3 (1.0%)	4 (1.3%)	3 (0.9%)	6 (1.9%)	3 (1.0%)
Macular oedema	3 (1.0%)	4 (1.3%)	4 (1.3%)	2 (0.6%)	4 (1.3%)	4 (1.3%)
Eye pain	4 (1.3%)	3 (1.0%)	5 (1.6%)	2 (0.6%)	1 (0.3%)	5 (1.6%)
Posterior capsule opacification	3 (1.0%)	6 (1.9%)	2 (0.6%)	3 (0.9%)	2 (0.6%)	4 (1.3%)
Blepharitis	1 (0.3%)	1 (0.3%)	2 (0.6%)	8 (2.5%)	3 (0.9%)	1 (0.3%)
Punctate keratitis	2 (0.6%)	1 (0.3%)	3 (1.0%)	5 (1.6%)	4 (1.3%)	1 (0.3%)
Cataract subcapsular	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (1.3%)	3 (0.9%)	0
Eye pruritus	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.9%)	3 (0.9%)	3 (1.0%)
Cataract nuclear	1 (0.3%)	5 (1.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	0
Macular fibrosis	0	3 (1.0%)	3 (1.0%)	4 (1.3%)	2 (0.6%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Sight-Threatening Adverse Events in the Fellow Eye Through Clinical Cut-Off Date DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 2.5%, 1.7%, and 1.8% experienced at least one AESI in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.

After Week 56 to the Clinical Cut-Off Date, the most common sight-threatening AE in the fellow eye which caused a decrease of ≥ 30 letters in VA score lasting more than 1 hour (≥2 patients in any treatment arm) was diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 2 patients [0.3%]) in the aflibercept Q8W arm.

After Week 56 to the Clinical Cut-Off Date, the sight-threatening AEs in the fellow eye which required surgical or medical intervention to prevent permanent loss of sight were foreign body in eye and macular fibrosis (1 patient [0.2%] each) in the faricimab PTI arm. There were no events in the faricimab Q8W or aflibercept Q8W arms.

IOI Events in the Fellow eye Through Clinical Cut-off Date DME indication

Through Week 56, the incidence of IOI events occurring in the fellow eye was low (4 patients [0.6%], 2 patients [0.3%], and 5 patients [0.8%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively;

The IOI events in the fellow eye (treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were iritis (3 patients [0.5%], 1 patient [0.2%], and 0), uveitis (0, 1 patient [0.2%], and 2 patients [0.3%]), vitritis (0, 0, and 3 patients [0.5%]), and iridocyclitis (1 patient [0.2%], 0, and 1 patient [0.2%]).

Fellow eye DME indication

From baseline to the Clinical Cut-Off Date, 5 patients (0.8%), 3 patients (0.5%), and 7 patients (1.1%) experienced at least one IOI event in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively. After Week 56 to the Clinical Cut-Off Date, the IOI events in the fellow eye by PT were iritis and uveitis (1 patient [0.2%] each) in the faricimab Q8W arm; iritis (1 patient [0.2%]) in the faricimab

PTI arm; and iritis and post procedural inflammation (1 patient [0.2%] each) in the aflibercept Q8W arm.

Non-ocular events - from the Pooled Phase III DME Studies

The incidence of non-ocular AEs was comparable across all treatment arms (62.4%, 60.9%, and 62.4% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The following events with a ≥ 2% difference (in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively) by PT were nasopharyngitis (7.0%, 5.9%, and 8.5%), urinary tract infection (3.2%, 3.0%, and 5.4%), and vomiting (2.9%, 0.8%, and 1.6%).

Table: Overview of Safety through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Patients)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Non-ocular events total number of patients with at least one										
AE	204 (65.2%)	210 (67.1%)	203 (65.3%)	189 (59.6%)	175 (54.9%)	187 (59.6%)	393 (62.4%)	385 (60.9%)	778 (61.6%)	390 (62.4%)
SAE	75 (24.0%)	64 (20.4%)	50 (16.1%)	52 (16.4%)	39 (12.2%)	52 (16.6%)	127 (20.2%)	103 (16.3%)	230 (18.2%)	102 (16.3%)
AE leading to withdrawal from study treatment	4 (1.3%)	3 (1.0%)	2 (0.6%)	4 (1.3%)	1 (0.3%)	3 (1.0%)	8 (1.3%)	4 (0.6%)	12 (1.0%)	5 (0.8%)
AE of Special Interest	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Adjudicated APTC events	9 (2.9%)	10 (3.2%)	9 (2.9%)	4 (1.3%)	2 (0.6%)	5 (1.6%)	13 (2.1%)	12 (1.9%)	25 (2.0%)	14 (2.2%)
Non-fatal MI	4 (1.3%)	2 (0.6%)	4 (1.3%)	0	0	2 (0.6%)	4 (0.6%)	2 (0.3%)	6 (0.5%)	6 (1.0%)
Non-fatal Stroke	3 (1.0%)	2 (0.6%)	3 (1.0%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	4 (0.6%)	4 (0.6%)	8 (0.6%)	4 (0.6%)
Death	2 (0.6%)	6 (1.9%)	2 (0.6%)	3 (0.9%)	0	2 (0.6%)	5 (0.8%)	6 (0.9%)	11 (0.9%)	4 (0.6%)

2.4.8.2. Serious adverse event/deaths/other significant events

nAMD

Deaths

In total, through Week 48, death was reported in 17 patients (9 patients [1.4%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm). The most common primary cause of death (≥2 patients in any treatment arm) was cardiac failure (2 patients [25.0%], both in the aflibercept arm). None of the deaths were suspected by the investigator to be related to study treatment.

Table 16 Patient Deaths through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of deaths	5 (1.5%)	1 (0.3%)	4 (1.2%)	7 (2.1%)	9 (1.4%)	8 (1.2%)
Primary Cause of Death						
n	5	1	4	7	9	8
Cardiac failure	0	0	0	2 (28.6%)	0	2 (25.0%)
Fall	0	0	1 (25.0%)	1 (14.3%)	1 (11.1%)	1 (12.5%)
Acute kidney injury	0	1 (100%)	0	0	0	1 (12.5%)
Brain oedema	0	0	1 (25.0%)	0	1 (11.1%)	0
Cardiac failure congestive	1 (20.0%)	0	0	0	1 (11.1%)	0
Cardiopulmonary failure	0	0	0	1 (14.3%)	0	1 (12.5%)
Cerebrovascular accident	1 (20.0%)	0	0	0	1 (11.1%)	0
Death	0	0	0	1 (14.3%)	0	1 (12.5%)
Glioblastoma multiforme	0	0	0	1 (14.3%)	0	1 (12.5%)
Ill-defined disorder	0	0	1 (25.0%)	0	1 (11.1%)	0
Metastases to liver	0	0	0	1 (14.3%)	0	1 (12.5%)
Multiple organ dysfunction syndrome	1 (20.0%)	0	0	0	1 (11.1%)	0
Pancreatic carcinoma	0	0	1 (25.0%)	0	1 (11.1%)	0
Pneumonia	1 (20.0%)	0	0	0	1 (11.1%)	0
Pneumonia bacterial	1 (20.0%)	0	0	0	1 (11.1%)	0

Percentages for Total Number of Deaths are relative to total N. All other percentages are relative to n within each module.
Include deaths that occurred on or prior to Day 349 (last day of Week 48 analysis visit window).

Deaths up to Clinical Cut-Off Date (nAMD)

After Week 48 to the Clinical Cut-Off Date, death was reported in an additional 4 patients (2 patients in each treatment arm). The primary cause of death after Week 48 to the Clinical Cut-Off Date were pulmonary oedema and respiratory failure (1 patient [50.0%] each) in the faricimab arm; and bile duct cancer and pulmonary embolism (1 patient [50.0%] each) in the aflibercept arm. None of the deaths were suspected by the investigator to be related to study treatment.

Table. (nAMD)__Patient Deaths through the Clinical Cut-Off Date from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

Pooled(TENAYA and LUCERNE)
(N=1326)

	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of deaths	2 (0.3%)	11 (1.7%)	2 (0.3%)	10 (1.5%)
Primary Cause of Death				
n	2	11	2	10
Cardiac failure	0	0	0	2 (20.0%)
Fall	0	1 (9.1%)	0	1 (10.0%)
Acute kidney injury	0	0	0	1 (10.0%)
Bile duct cancer	0	0	1 (50.0%)	1 (10.0%)
Brain oedema	0	1 (9.1%)	0	0
Cardiac failure congestive	0	1 (9.1%)	0	0
Cardiopulmonary failure	0	0	0	1 (10.0%)
Cerebrovascular accident	0	1 (9.1%)	0	0
Death	0	0	0	1 (10.0%)
Glioblastoma multiforme	0	0	0	1 (10.0%)
Ill-defined disorder	0	1 (9.1%)	0	0
Metastases to liver	0	0	0	1 (10.0%)
Multiple organ dysfunction syndrome	0	1 (9.1%)	0	0
Pancreatic carcinoma	0	1 (9.1%)	0	0
Pneumonia	0	1 (9.1%)	0	0
Pneumonia bacterial	0	1 (9.1%)	0	0
Pulmonary embolism	0	0	1 (50.0%)	1 (10.0%)
Pulmonary oedema	1 (50.0%)	1 (9.1%)	0	0
Respiratory failure	1 (50.0%)	1 (9.1%)	0	0

Percentages for Total Number of Deaths are relative to total N. All other percentages are relative to n within each module.

Through Week 48, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committeewas low and comparable between the treatment arms (7 patients [1.1%] in the faricimab arm and 6 patients [0.9%] in the aflibercept arm).

The death adjudicated APTC ATEs were reported in 2 patients (0.3%) in the faricimab arm and 3 patients (0.5%) in the aflibercept arm. All death adjudicated APTC ATEs were reported in 1 patient each. None of the death adjudicated APTC ATEs were suspected by the investigator to be related to study treatment. The non-fatal myocardial infarction adjudicated APTC ATEs were reported in 3 patients (0.5%) in the faricimab arm and 2 patients (0.3%) in the aflibercept arm. The most common non-fatal myocardial infarction adjudicated APTC ATEs (≥2 patients in any treatment arm: faricimab arm vs. aflibercept arm) by PT was acute myocardial infarction (2 patients [0.3%] vs. 1 patient [0.2%]). None of the non-fatal myocardial infarction adjudicated APTC ATEs were suspected by the investigator to be related to study treatment. The non-fatal stroke adjudicated APTC ATEs were reported in 2 patients (0.3%) in the faricimab arm and 1 patient (0.2%) in the aflibercept arm. All non-fatal stroke adjudicated APTC ATEs were reported in 1 patient each.

Two of the non-fatal stroke adjudicated APTC ATEs were suspected by the investigator to be related to study treatment: thrombotic cerebral infarction in the faricimab arm and cerebrovascular accident in the aflibercept arm.

Supporting data from phase II study STAIRWAY in nAMD indication:

Three patients experienced AEs with a fatal outcome (1 patient in the faricimab Q12W arm with cause of death due to ischemic stroke [APTC event] and 2 patients in the faricimab Q16W arm with cause of death as sepsis and metastatic neoplasm, respectively). None of the fatal AEs reported were considered related to study treatment.

Serious Ocular AEs in the Study Eye from the Pooled Phase III nAMD Studies

Through Week 48, the incidence of serious ocular AEs occurring in the study eye was low and comparable between the treatment arms (1.7% in the faricimab arm and 2.0% in the aflibercept arm), with the exception (≥ 0.5% difference in any treatment arms) of retinal pigment epithelial tear (4 patients [0.6%] in the faricimab arm and no patients in the aflibercept arm).

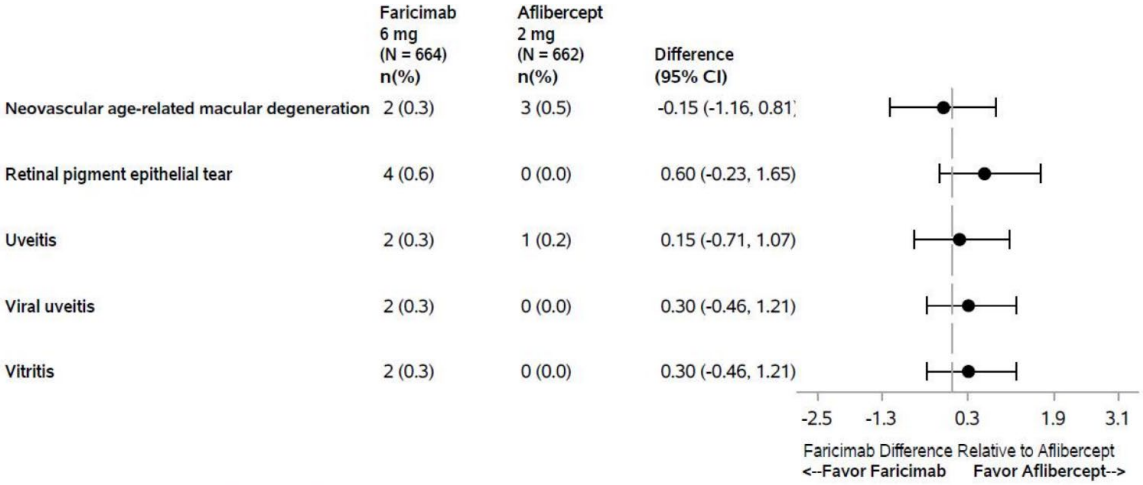
The most common serious ocular AEs in the study eye (≥ 2 patients in any treatment arm) by PT were retinal pigment epithelial tear (4 patients [0.6%]), neovascular age-related macular degeneration (verbatim, worsening of nAMD), uveitis, viral uveitis, and vitritis (2 patients [0.3%] each) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD; 3 patients [0.5%]) in the aflibercept arm (Figure 60). Four patients experienced a serious retinal pigment epithelial tear event in the study eye; all patients were in the faricimab arm.

Table. (nAMD)__Serious Ocular Adverse Events in the Study Eye through Week 48 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

MedDRA Preferred Term	GR40306 (TENAYA) (N=669)		GR40844 (LUCERNE) (N=657)		Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	4 (1.2%)	6 (1.8%)	7 (2.1%)	7 (2.1%)	11 (1.7%)	13 (2.0%)
Total number of events	5	6	10	7	15	13
Neovascular age-related macular degeneration	1 (0.3%)	3 (0.9%)	1 (0.3%)	0	2 (0.3%)	3 (0.5%)
Retinal pigment epithelial tear	2 (0.6%)	0	2 (0.6%)	0	4 (0.6%)	0
Uveitis	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Viral uveitis	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
Vitritis	0	0	2 (0.6%)	0	2 (0.3%)	0
Age-related macular degeneration	0	1 (0.3%)	0	0	0	1 (0.2%)
Cataract	0	0	1 (0.3%)	0	1 (0.2%)	0
Cataract cortical	0	0	0	1 (0.3%)	0	1 (0.2%)
Chorioretinitis	0	0	1 (0.3%)	0	1 (0.2%)	0
Corneal abrasion	0	1 (0.3%)	0	0	0	1 (0.2%)
Corneal oedema	0	0	0	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Eye allergy	0	0	0	1 (0.3%)	0	1 (0.2%)
Facial bones fracture	0	0	0	1 (0.3%)	0	1 (0.2%)
Intraocular pressure increased	0	0	1 (0.3%)	0	1 (0.2%)	0
Subretinal fibrosis	0	1 (0.3%)	0	0	0	1 (0.2%)
Vitreous haemorrhage	0	0	0	1 (0.3%)	0	1 (0.2%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

Figure 60. Safety Plot of Serious Ocular AEs in the Study Eye reported in any Arm with ≥2 Patients through Week 48 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)



Investigator text for AEs encoded using MedDRA version 23.1. n = Number of patients with at least one applicable adverse event.
Percentages are based on N in the column headings. Includes events with onset up to Day 349 (last day of Week 48 analysis visit window).
Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 2.1% of patients in the faricimab arm and 2.7% of patients in the aflibercept arm experienced at least one serious ocular AE in the study eye. After Week 48 to the Clinical Cut-Off Date, the serious ocular AEs in the study eye by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD), visual acuity reduced, and rhegmatogenous retinal detachment (1 patient [0.2%] each) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD), cataract, visual acuity reduced, cataract operation complication, cataract traumatic, non-infectious endophthalmitis, and retinal degeneration (1 patient [0.2%] each) in the aflibercept arm. The non-infectious endophthalmitis serious ocular AE in the study eye in the aflibercept arm was suspected by the investigator to be related to study treatment and had resolved by the Clinical Cut-Off Date.

Through Week 48, the incidence of serious ocular AEs occurring in the fellow eye was low in the treatment arms (7 patients [1.1%] in each treatment arm). The most common serious ocular AEs in the fellow eye (≥2 patients in any treatment arm) by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD; 3 patients [0.5%]) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD) and rhegmatogenous retinal detachment (2 patients [0.3%] each) in the aflibercept arm.

Diabetic macular edema (DME)

Deaths through Week 56- from the Pooled Phase III DME Studies

In total, through Week 56, death was reported in 31 patients (13 patients [2.1%], 9 patients [1.4%], and 9 patients [1.4%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively;). The most common primary cause of death (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) were death (cause unknown) (1 patient [7.7%], 3 patients [33.3%], and 0), acute myocardial infarction (1 patient [7.7%], 0, and 2 patients [22.2%]), bladder cancer (2 patients [15.4%], 0, and 0), cardiac arrest (2 patients [15.4%], 0, and 0), and cardiac failure (0, 2 patients [22.2%], and 0). None of the deaths were suspected by the investigator to be related to study treatment.

Table: Patient Deaths through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of deaths	8 (2.6%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	0	5 (1.6%)	13 (2.1%)	9 (1.4%)	22 (1.7%)	9 (1.4%)
Primary Cause of Death										
n	8	9	4	5	0	5	13	9	22	9
Death	1 (12.5%)	3 (33.3%)	0	0	0	0	1 (7.7%)	3 (33.3%)	4 (18.2%)	0
Acute myocardial infarction	1 (12.5%)	0	1 (25.0%)	0	0	1 (20.0%)	1 (7.7%)	0	1 (4.5%)	2 (22.2%)
Myocardial infarction	0	1 (11.1%)	1 (25.0%)	1 (20.0%)	0	0	1 (7.7%)	1 (11.1%)	2 (9.1%)	1 (11.1%)
Bladder cancer	1 (12.5%)	0	0	1 (20.0%)	0	0	2 (15.4%)	0	2 (9.1%)	0
Cardiac arrest	0	0	0	2 (40.0%)	0	0	2 (15.4%)	0	2 (9.1%)	0
Cardiac failure	0	2 (22.2%)	0	0	0	0	0	2 (22.2%)	2 (9.1%)	0
Adenocarcinoma of colon	0	0	1 (25.0%)	0	0	0	0	0	0	1 (11.1%)
COVID-19	0	1 (11.1%)	0	0	0	0	0	1 (11.1%)	1 (4.5%)	0
Cerebral haemorrhage	0	0	0	1 (20.0%)	0	0	1 (7.7%)	0	1 (4.5%)	0
Completed suicide	0	0	1 (25.0%)	0	0	0	0	0	0	1 (11.1%)
Coronary artery disease	0	0	0	0	0	1 (20.0%)	0	0	0	1 (11.1%)
Diabetic complication	1 (12.5%)	0	0	0	0	0	1 (7.7%)	0	1 (4.5%)	0
Diabetic gangrene	0	0	0	0	0	1 (20.0%)	0	0	0	1 (11.1%)
Embolism	1 (12.5%)	0	0	0	0	0	1 (7.7%)	0	1 (4.5%)	0
General physical health deterioration	1 (12.5%)	0	0	0	0	0	1 (7.7%)	0	1 (4.5%)	0
Hypotension	0	0	0	0	0	1 (20.0%)	0	0	0	1 (11.1%)
Left atrial dilatation	1 (12.5%)	0	0	0	0	0	1 (7.7%)	0	1 (4.5%)	0
Leukaemia	0	1 (11.1%)	0	0	0	0	0	1 (11.1%)	1 (4.5%)	0
Pneumonia aspiration	0	1 (11.1%)	0	0	0	0	0	1 (11.1%)	1 (4.5%)	0
Sepsis	1 (12.5%)	0	0	0	0	0	1 (7.7%)	0	1 (4.5%)	0
Type 1 diabetes mellitus	0	0	0	0	0	1 (20.0%)	0	0	0	1 (11.1%)

PTI = Personalized Treatment Interval (from Q4W up to Q16W). Percentages for Total Number of Deaths are relative to total N. All other percentages are relative to n within each module.
Includes death occurred on or prior to Day 405 (last day of Week 56 analysis visit window).

Deaths up to Clinical Cut-Off Date from the Pooled Phase III DME Studies- DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, death was reported in 2.7%, 2.8%, and 1.9% of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The primary cause of death after Week 56 to the Clinical Cut-Off Date were death (cause unknown), chronic kidney disease, pneumonia, and renal failure (1 patient [25.0%] each) in the faricimab Q8W arm; death, myocardial infarction, COVID-19, cerebral haemorrhage, anaemia, dyspnoea, ischaemic stroke, not reported, and pulmonary fibrosis (1 patient [11.1%] each) in the faricimab PTI arm; and myocardial infarction, drug abuse, and pancreatic carcinoma metastatic (1 patient [33.3%] each) in the aflibercept Q8W arm. None of the deaths were suspected by the investigator to be related to study treatment.

Table: Patient Deaths through the Clinical Cut-Off Date from Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of deaths	4 (0.6%)	17 (2.7%)	9 (1.4%)	18 (2.8%)	13 (1.0%)	35 (2.8%)	3 (0.5%)	12 (1.9%)
Primary Cause of Death								
n	4	17	9	18	13	35	3	12
Death	1 (25.0%)	2 (11.8%)	1 (11.1%)	4 (22.2%)	2 (15.4%)	6 (17.1%)	0	0
Myocardial infarction	0	1 (5.9%)	1 (11.1%)	2 (11.1%)	1 (7.7%)	3 (8.6%)	1 (33.3%)	2 (16.7%)
Acute myocardial infarction	0	1 (5.9%)	0	0	0	1 (2.9%)	0	2 (16.7%)
Bladder cancer	0	2 (11.8%)	0	0	0	2 (5.7%)	0	0
COVID-19	0	0	1 (11.1%)	2 (11.1%)	1 (7.7%)	2 (5.7%)	0	0
Cardiac arrest	0	2 (11.8%)	0	0	0	2 (5.7%)	0	0
Cardiac failure	0	0	0	2 (11.1%)	0	2 (5.7%)	0	0
Cerebral haemorrhage	0	1 (5.9%)	1 (11.1%)	1 (5.6%)	1 (7.7%)	2 (5.7%)	0	0
Adenocarcinoma of colon	0	0	0	0	0	0	0	1 (8.3%)
Anaemia	0	0	1 (11.1%)	1 (5.6%)	1 (7.7%)	1 (2.9%)	0	0
Chronic kidney disease	1 (25.0%)	1 (5.9%)	0	0	1 (7.7%)	1 (2.9%)	0	0
Completed suicide	0	0	0	0	0	0	0	1 (8.3%)
Coronary artery disease	0	0	0	0	0	0	0	1 (8.3%)
Diabetic complication	0	1 (5.9%)	0	0	0	1 (2.9%)	0	0
Diabetic gangrene	0	0	0	0	0	0	0	1 (8.3%)
Drug abuse	0	0	0	0	0	0	1 (33.3%)	1 (8.3%)
Dyspnoea	0	0	1 (11.1%)	1 (5.6%)	1 (7.7%)	1 (2.9%)	0	0
Embolism	0	1 (5.9%)	0	0	0	1 (2.9%)	0	0
General physical health deterioration	0	1 (5.9%)	0	0	0	1 (2.9%)	0	0
Hypotension	0	0	0	0	0	0	0	1 (8.3%)
Ischaemic stroke	0	0	1 (11.1%)	1 (5.6%)	1 (7.7%)	1 (2.9%)	0	0
Left atrial dilatation	0	1 (5.9%)	0	0	0	1 (2.9%)	0	0
Leukaemia	0	0	0	1 (5.6%)	0	1 (2.9%)	0	0
Not reported	0	0	1 (11.1%)	1 (5.6%)	1 (7.7%)	1 (2.9%)	0	0
Pancreatic carcinoma metastatic	0	0	0	0	0	0	1 (33.3%)	1 (8.3%)
Pneumonia	1 (25.0%)	1 (5.9%)	0	0	1 (7.7%)	1 (2.9%)	0	0
Pneumonia aspiration	0	0	0	1 (5.6%)	0	1 (2.9%)	0	0
Pulmonary fibrosis	0	0	1 (11.1%)	1 (5.6%)	1 (7.7%)	1 (2.9%)	0	0
Renal failure	1 (25.0%)	1 (5.9%)	0	0	1 (7.7%)	1 (2.9%)	0	0
Sepsis	0	1 (5.9%)	0	0	0	1 (2.9%)	0	0
Type 1 diabetes mellitus	0	0	0	0	0	0	0	1 (8.3%)

<u>Other Serious Adverse Events-</u> from the Pooled Phase III DME Studies

<u>Diabetic macular edema (DME)-</u>Serious Ocular AEs in the Study Eye Through Week 56

A higher incidence of serious ocular AEs in the study eye occurred in both faricimab arms compared with the aflibercept Q8W arm (15 patients [2.4%], 19 patients [3.0%], and 8 patients [1.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively; However, the incidence was overall low, and there was no consistent pattern observed at the individual PT level between the treatment arms.

The most common serious ocular AEs in the study eye (≥ 2 patients in the combined faricimab arms or aflibercept Q8W arm) by PT were diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 5 patients [0.4%] vs. 0), endophthalmitis (4 patients [0.3%] vs. 1 patient [0.2%]), cataract (2 patients [0.2%] vs. 2 patients [0.3%]), vitreous haemorrhage (3 patients [0.2%] vs. 1 patient [0.2%]), uveitis (3 patients [0.2%] vs. 0), visual acuity reduced transiently (2 patients [0.2%] vs. 1 patient [0.2%]), ocular hypertension (2 patients [0.2%] vs. 0), and retinal tear (2 patients [0.2%] vs. 0).

The majority of the serious ocular AEs in the study eye resolved, resolved with sequelae, or were resolving by Week 56. The serious ocular AEs in the study eye that were not resolved by Week 56 were cataract (2 events), uveitic glaucoma, dry eye, and retinal tear (1 event each).

Through Week 56, 5 patients (0.8%) in the faricimab PTI arm experienced at least one serious ocular AE suspected by the investigator to be related to faricimab. The serious ocular AEs related to faricimab in the PTI arm were uveitis (3 patients [0.5%]), chorioretinitis, keratouveitis, and ocular hypertension (1 patient [0.2% each]). All of these serious ocular AEs related to faricimab in the PTI

arm were either resolved, resolved with sequelae, or resolving by Week 56. There were no serious ocular AEs suspected by the investigator to be related to study treatment in the faricimab Q8W or aflibercept Q8W arms.

The per-injection rate of serious ocular AEs in the study eye was 0.34%, 0.39%, and 0.14% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.

Diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 0.06% in the combined faricimab arms vs. 0 in the aflibercept Q8W arm) was the only serious ocular AE in the study eye with a ≥ 0.05% per-injection rate difference in the combined faricimab arms compared to the aflibercept Q8W arm.

Table: Serious Ocular Adverse Events in the Study Eye through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	6 (1.9%)	9 (2.9%)	2 (0.6%)	9 (2.8%)	10 (3.1%)	6 (1.9%)	15 (2.4%)	19 (3.0%)	34 (2.7%)	8 (1.3%)
Total number of events	8	11	2	12	10	6	20	21	41	8
Diabetic retinal oedema	1 (0.3%)	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	0	3 (0.5%)	2 (0.3%)	5 (0.4%)	0
Endophthalmitis	0	2 (0.6%)	0	2 (0.6%)	0	1 (0.3%)	2 (0.3%)	2 (0.3%)	4 (0.3%)	1 (0.2%)
Cataract	0	0	1 (0.3%)	2 (0.6%)	0	1 (0.3%)	2 (0.3%)	0	2 (0.2%)	2 (0.3%)
Vitreous haemorrhage	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.2%)	3 (0.2%)	1 (0.2%)
Uveitis	0	3 (1.0%)	0	0	0	0	0	3 (0.5%)	3 (0.2%)	0
Visual acuity reduced transiently	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
Ocular hypertension	0	1 (0.3%)	0	0	1 (0.3%)	0	0	2 (0.3%)	2 (0.2%)	0
Retinal tear	0	1 (0.3%)	0	0	1 (0.3%)	0	0	2 (0.3%)	2 (0.2%)	0
Cataract subcapsular	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Chemical burns of eye	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Chorioretinitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Device dislocation	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Diabetic retinopathy	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Dry eye	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Glaucoma	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Influenza	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Intraocular pressure increased	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Keratouveitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Macular fibrosis	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Narrow anterior chamber angle	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Retinal artery occlusion	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Retinal neovascularisation	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Retinal vein occlusion	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Rhegmatogenous retinal detachment	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Uveitic glaucoma	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Viral keratouveitis	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Visual impairment	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W)

<u>Diabetic macular edema (DME)-</u>Serious Ocular AEs in fellow Eye Through Week 56

Through Week 56, the incidence of serious ocular AEs occurring in the fellow eye was low across treatment arms (13 patients [2.1%], 11 patients [1.7%], and 8 patients [1.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).
The most common serious ocular AEs in the fellow eye (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, aflibercept Q8W arm, respectively) by PT were vitreous haemorrhage (5 patients [0.8%], 1 patient [0.2%], and 1 patient [0.2%]), diabetic retinopathy (2 patients [0.3%], 2 patients [0.3%], and 1 patient [0.2%]), and diabetic retinal oedema (verbatim, worsening of diabetic retinal oedema; 3 patients [0.5%], 1 patient [0.2%], and 0).

Table: Serious Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population Protocol: GR40349 & GR40398

MedDRA Preferred Term	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	7 (2.2%)	7 (2.2%)	5 (1.6%)	6 (1.9%)	4 (1.3%)	3 (1.0%)
Total number of events	8	8	5	7	4	3
Vitreous haemorrhage	2 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	0	0
Diabetic retinopathy	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0
Diabetic retinal oedema	0	0	0	3 (0.9%)	1 (0.3%)	0
Visual acuity reduced	1 (0.3%)	0	0	0	1 (0.3%)	1 (0.3%)
Cataract traumatic	1 (0.3%)	1 (0.3%)	0	0	0	0
Corneal abrasion	1 (0.3%)	0	0	0	0	1 (0.3%)
Angle closure glaucoma	0	0	1 (0.3%)	0	0	0
Cataract	0	1 (0.3%)	0	0	0	0
Chemical burns of eye	0	0	0	0	0	1 (0.3%)
Endophthalmitis	0	1 (0.3%)	0	0	0	0
Eye haemorrhage	0	0	0	0	1 (0.3%)	0
Intraocular pressure increased	0	0	0	1 (0.3%)	0	0
Macular fibrosis	0	0	1 (0.3%)	0	0	0
Macular oedema	0	1 (0.3%)	0	0	0	0
Narrow anterior chamber angle	1 (0.3%)	0	0	0	0	0
Retinal haemorrhage	0	1 (0.3%)	0	0	0	0
Retinal neovascularisation	0	0	1 (0.3%)	0	0	0
Uveitis	0	1 (0.3%)	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Diabetic macular edema (DME)-Serious Non-Ocular Adverse Events- from the Pooled Phase III DME Studies

Through Week 56, the incidence of serious non-ocular AEs was generally comparable across all treatment arms (20.2%, 16.3%, and 16.3% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Table: Serious Non-Ocular Adverse Events (≥1%) through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

MedDRA Preferred Term	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	75 (24.0%)	64 (20.4%)	50 (16.1%)	52 (16.4%)	39 (12.2%)	52 (16.6%)	127 (20.2%)	103 (16.3%)	230 (18.2%)	102 (16.3%)
Total number of events	155	95	89	82	65	86	237	160	397	175
Pneumonia	4 (1.3%)	3 (1.0%)	5 (1.6%)	5 (1.6%)	4 (1.3%)	3 (1.0%)	9 (1.4%)	7 (1.1%)	16 (1.3%)	8 (1.3%)
Cellulitis	3 (1.0%)	4 (1.3%)	2 (0.6%)	3 (0.9%)	1 (0.3%)	7 (2.2%)	6 (1.0%)	5 (0.8%)	11 (0.9%)	9 (1.4%)
Sepsis	4 (1.3%)	0	6 (1.9%)	5 (1.6%)	0	1 (0.3%)	9 (1.4%)	0	9 (0.7%)	7 (1.1%)
Cardiac failure congestive	4 (1.3%)	0	4 (1.3%)	4 (1.3%)	2 (0.6%)	1 (0.3%)	8 (1.3%)	2 (0.3%)	10 (0.8%)	5 (0.8%)
Myocardial infarction	1 (0.3%)	3 (1.0%)	4 (1.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	4 (0.6%)	4 (0.6%)	8 (0.6%)	6 (1.0%)
Acute kidney injury	4 (1.3%)	1 (0.3%)	3 (1.0%)	2 (0.6%)	2 (0.6%)	1 (0.3%)	6 (1.0%)	3 (0.5%)	9 (0.7%)	4 (0.6%)
Osteomyelitis	3 (1.0%)	1 (0.3%)	3 (1.0%)	2 (0.6%)	1 (0.3%)	3 (1.0%)	5 (0.8%)	2 (0.3%)	7 (0.6%)	6 (1.0%)
Acute myocardial infarction	2 (0.6%)	2 (0.6%)	4 (1.3%)	0	1 (0.3%)	2 (0.6%)	2 (0.3%)	3 (0.5%)	5 (0.4%)	6 (1.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Up to Clinical Cut-Off Date DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 23.8%, 19.9%, and 21.1% of patients experienced at least one serious non-ocular AE in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

After Week 56 to the Clinical Cut-Off Date, the most common serious non-ocular AEs (≥ 1% incidence in any treatment arm) by PT was cardiac failure congestive (8 patients [1.3%] in the faricimab Q8W arm

Table: Serious Non-Ocular Adverse Events ((≥1%) by Preferred Term through Clinical Cut-Off Date, Safety-Evaluable Population Protocol: GR40349 & GR40398 Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020 DME indication

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	33 (5.2%)	150 (23.8%)	35 (5.5%)	126 (19.9%)	68 (5.4%)	276 (21.9%)	40 (6.4%)	132 (21.1%)
Total number of events	52	289	56	216	108	505	55	230
Pneumonia	4 (0.6%)	13 (2.1%)	1 (0.2%)	8 (1.3%)	5 (0.4%)	21 (1.7%)	1 (0.2%)	8 (1.3%)
Cardiac failure congestive	8 (1.3%)	14 (2.2%)	2 (0.3%)	4 (0.6%)	10 (0.8%)	18 (1.4%)	0	5 (0.8%)
Cellulitis	0	6 (1.0%)	1 (0.2%)	6 (0.9%)	1 (<0.1%)	12 (1.0%)	1 (0.2%)	10 (1.6%)
Sepsis	2 (0.3%)	11 (1.7%)	0	0	2 (0.2%)	11 (0.9%)	1 (0.2%)	8 (1.3%)
Acute kidney injury	2 (0.3%)	8 (1.3%)	2 (0.3%)	5 (0.8%)	4 (0.3%)	13 (1.0%)	1 (0.2%)	5 (0.8%)
Myocardial infarction	0	4 (0.6%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	9 (0.7%)	1 (0.2%)	7 (1.1%)
Osteomyelitis	0	5 (0.8%)	0	2 (0.3%)	0	7 (0.6%)	1 (0.2%)	7 (1.1%)
Acute myocardial infarction	2 (0.3%)	4 (0.6%)	0	3 (0.5%)	2 (0.2%)	7 (0.6%)	0	6 (1.0%)
Cerebrovascular accident	0	3 (0.5%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	7 (0.6%)	3 (0.5%)	5 (0.8%)
Coronary artery disease	0	3 (0.5%)	0	5 (0.8%)	0	8 (0.6%)	0	3 (0.5%)
COVID-19	1 (0.2%)	1 (0.2%)	4 (0.6%)	7 (1.1%)	5 (0.4%)	8 (0.6%)	2 (0.3%)	2 (0.3%)
Ischaemic stroke	2 (0.3%)	5 (0.8%)	2 (0.3%)	2 (0.3%)	4 (0.3%)	7 (0.6%)	2 (0.3%)	3 (0.5%)
Acute respiratory failure	0	2 (0.3%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	1 (0.2%)	4 (0.6%)
Cardiac failure	1 (0.2%)	2 (0.3%)	0	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	4 (0.6%)
Gangrene	1 (0.2%)	2 (0.3%)	3 (0.5%)	4 (0.6%)	4 (0.3%)	6 (0.5%)	3 (0.5%)	3 (0.5%)
Hypoglycaemia	0	1 (0.2%)	2 (0.3%)	7 (1.1%)	2 (0.2%)	8 (0.6%)	1 (0.2%)	1 (0.2%)
Urinary tract infection	1 (0.2%)	3 (0.5%)	2 (0.3%)	2 (0.3%)	3 (0.2%)	5 (0.4%)	2 (0.3%)	4 (0.6%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: root/clinical studies/RO6867461/CDT70122/share/pool DME CSR Primary/prod/program/t ae pt cod.sas

<u>Diabetic macular edema (DME)-</u>Adjudicated APTC-Defined ATEs- from the Pooled Phase III DME Studies

For this study, potential Antiplatelet Trialists' Collaboration (APTC) events were identified and forwarded to an Independent Clinical Events Committee (CEC), with event source documents on an ongoing basis for proactive adjudication of APTC-defined ATEs. The role of the CEC was to adjudicate potential APTC events in a blinded, consistent, and unbiased manner throughout the course of the study. APTC events described in the CSR are based on external adjudication.

Through Week 56 DME indication

Through Week 56, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was low and comparable across treatment arms (2.1%, 1.9%, and 2.2% in the faricimab Q8W, and faricimab PTI, and aflibercept Q8W arms,).

The death adjudicated APTC ATEs were reported in 5 patients (0.8%), 6 patients (0.9%), and 4 patients (0.6%) in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most common death adjudicated APTC ATEs (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively) by PT were myocardial infarction (1 patient [0.2%], 2 patients [0.3%], and 1 patient [0.2%]) and death (1 patient [0.2%], 2 patients [0.3%], and 0). None of the death adjudicated APTC ATEs were suspected by the investigator to be related to study treatment.

The non-fatal myocardial infarction adjudicated APTC ATEs were reported in 4 patients (0.6%), 2 patients (0.3%), and 6 patients (1.0%) in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The most common non-fatal myocardial infarction adjudicated APTC ATEs by PT were acute myocardial infarction (1 patient [0.2%], 1 patient [0.2%], and 3 patients [0.5%]) and myocardial infarction (1 patient [0.2%], 1 patient [0.2%], and 3 patients [0.5%]). One of the non-fatal myocardial infarction adjudicated APTC ATEs was suspected by the investigator to be related to study treatment: acute myocardial infarction in the aflibercept Q8W arm.

The non-fatal stroke adjudicated APTC ATEs were reported in 4 patients (0.6%) in each treatment arm (faricimab Q8W, faricimab PTI, and aflibercept Q8W arms). The most common non-fatal stroke adjudicated APTC ATEs (≥ 2 patients in any treatment arm: faricimab Q8W, faricimab PTI, and

aflibercept Q8W arms, respectively) by PT was cerebrovascular accident (2 patients [0.3%], 3 patients [0.5%], and 2 patients [0.3%]).

Three of the non-fatal stroke adjudicated APTC ATEs were suspected by the investigator to be related to study treatment: ischaemic stroke in the faricimab Q8W arm, lacunar stroke in the faricimab PTI arm, and cerebrovascular accident in the aflibercept Q8W arm.

Table: Adjudicated APTC-Defined ATE Events through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
Adjudicated APTC events MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	9 (2.9%)	10 (3.2%)	9 (2.9%)	4 (1.3%)	2 (0.6%)	5 (1.6%)	13 (2.1%)	12 (1.9%)	25 (2.0%)	14 (2.2%)
Overall total number of events	9	10	9	4	2	5	13	12	25	14
DEATH										
Total number of patients with at least one adverse event	2 (0.6%)	6 (1.9%)	2 (0.6%)	3 (0.9%)	0	2 (0.6%)	5 (0.8%)	6 (0.9%)	11 (0.9%)	4 (0.6%)
Total number of events	2	6	2	3	0	2	5	6	11	4
Myocardial infarction	0	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	2 (0.3%)	3 (0.2%)	1 (0.2%)
Death	1 (0.3%)	2 (0.6%)	0	0	0	0	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
Acute myocardial infarction	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Anaemia	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Cardiac arrest	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Cardiac failure	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Cerebral haemorrhage	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
General physical health deterioration	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Hypotension	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Type 1 diabetes mellitus	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
NON-FATAL MI										
Total number of patients with at least one adverse event	4 (1.3%)	2 (0.6%)	4 (1.3%)	0	0	2 (0.6%)	4 (0.6%)	2 (0.3%)	6 (0.5%)	6 (1.0%)
Total number of events	4	2	4	0	0	2	4	2	6	6
Acute myocardial infarction	1 (0.3%)	1 (0.3%)	2 (0.6%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	3 (0.5%)
Myocardial infarction	1 (0.3%)	1 (0.3%)	2 (0.6%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	3 (0.5%)
Cardiac arrest	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Myocardial ischaemia	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
NON-FATAL STROKE										
Total number of patients with at least one adverse event	3 (1.0%)	2 (0.6%)	3 (1.0%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	4 (0.6%)	4 (0.6%)	8 (0.6%)	4 (0.6%)
Total number of events	3	2	3	1	2	1	4	4	8	4
Cerebrovascular accident	2 (0.6%)	2 (0.6%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (0.5%)	5 (0.4%)	2 (0.3%)
Ischaemic stroke	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
Cerebral infarction	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
Lacunar stroke	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Transient ischaemic attack	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)

Up to Clinical Cut-Off Date DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 2.2%, 1.9%, and 2.4% of patients experienced at least one externally adjudicated APTC-defined ATE in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

After Week 56 to the Clinical Cut-Off Date, there were no death adjudicated APTC-defined ATEs across all treatment arms; 1 patient (0.2%) with a non-fatal MI adjudicated APTC-defined ATE (cardiogenic shock in the faricimab Q8W arm suspected by the investigator not to be related to study treatment); and 1 patient (0.2%) with a non-fatal stroke adjudicated APTC-defined ATE (cerebrovascular accident in the aflibercept Q8W arm suspected by the investigator not to be related to study treatment;

90-Day Safety Update Report

The 90-Day Safety Update Report (SUR) provided updated cumulative pooled safety data from the ongoing Phase III studies for each indication (nAMD and DME/DR) up to the Clinical Cut-Off Date of 09 April 2021 (i.e., an additional median of 8 months for nAMD and median of 9 months for DME/DR of safety data compared to the primary analysis presented in the BLA SCS which supports the initial BLA).

nAMD indication

Key pooled safety results provided by the Applicant through the SUR Clinical Cut-Off Date were as follows:

• The overall incidence of AEs remained comparable between the treatment arms (548/664 patients [82.5%] in the faricimab arm and 550/662 patients [83.1%] in the aflibercept arm).

• The incidence of ocular AEs in the study eye through the SUR Clinical Cut-Off Date remained comparable between the treatment arms (48.0% in the faricimab and 46.5% in the aflibercept arm), with an increase of approximately 10 percentage points in the incidence in both arms compared with SCS (Week 48). The ocular AEs with ⩾1% difference between the treatment arms remained similar to those reported in the

SCS (Week 48), with the newly added events as of the SUR Clinical Cut-Off Date (faricimab arm vs. aflibercept arm): cataract (5.7% vs 4.1%) and eye irritation (1.7% vs. 0.6%);

• The most common ocular AEs in the study eye (⩾2% incidence in either treatment arm) by PT were generally consistent with the events reported in the SCS (Week 48), with the newly added events (faricimab arm vs. aflibercept arm): blepharitis (2.3% vs. 2.4%) and posterior capsule opacification (2.3% vs 2.1%);

• The most common treatment-related ocular AEs in the study eye (⩾0.5% in either treatment arm) were generally consistent with those reported in the SCS (Week 48), with the newly added event of uveitis (3 patients [0.5%]) in the faricimab arm.

• The incidence of AEs leading to study treatment discontinuation through the SUR Clinical Cut-Off Date was higher in the faricimab arm compared with that in the aflibercept arm but was still considered low in both treatment arms (3.3% in the faricimab arm and 1.5% in the aflibercept arm; The incidence of ocular AEs leading to study treatment discontinuation remained low in both treatment arms (13 patients [2.0%] in the faricimab arm and 5 patients [0.8%] in the aflibercept arm). The incidence of IOI events leading to treatment discontinuation was higher in the faricimab arm than that in the aflibercept arm (5 patients [0.8%] in the faricimab arm and 1 patient [0.2%] in the aflibercept arm);

• The incidence of AEs leading to study discontinuation remained low (4.7% in the faricimab arm and 3.5% in the aflibercept arm;The incidence of ocular AEs leading to study discontinuation was low and comparable in both treatment arms (2 patients [0.3%] in the faricimab arm and 3 patients [0.5%] in the aflibercept arm).
• The incidence of ocular AESIs in the study eye remained comparable between the treatment arms (13 patients [2.0%] in the faricimab arm and 22 patients [3.3%] in the aflibercept arm);

• The incidence of intraocular inflammation (IOI) events remained low and comparable between the treatment arms (18 patients [2.7%] in the faricimab arm and 12 patients [1.8%] in the aflibercept arm). There were no new IOI events reported as retinal vasculitis or occlusive disease in any treatment arms;

• The incidence and nature of non-ocular AEs through the SUR Clinical Cut-Off Date was generally comparable to that reported in the SCS (Week 48) and between the treatment arms (66.1% in the faricimab arm and 67.7% in the aflibercept arm);

• The incidence of serious non-ocular AEs through the SUR Clinical Cut-Off Date remained comparable between treatment arms (15.8% in the faricimab arm and 18.3% in the aflibercept arm)l

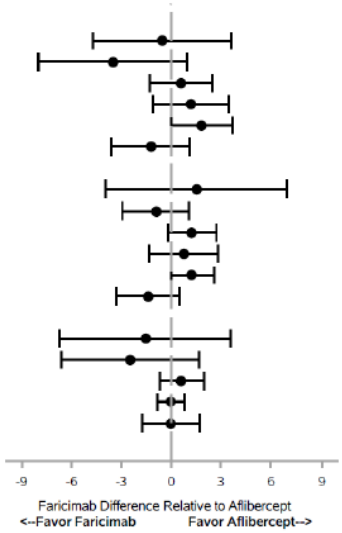
• A total of 34 patients died through the SUR Clinical Cut-Off Date (2.9% in the faricimab arm and 2.3% in the aflibercept arm). No deaths were suspected by the investigator to be related to study treatment.

Table 4 Overview of Safety Through Week 48 and SUR CCOD from the Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	SCS (Week 48) Pooled (TENAYA and LUCERNE) (N=1326)		SUR CCOD (9 April 2021) Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one AE	471 (70.9%)	483 (73.0%)	548 (82.5%)	550 (83.1%)
Total number of AEs	1670	1658	2621	2626
Total number of patients with at least one SAE	83 (12.5%)	101 (15.3%)	127 (19.1%)	150 (22.7%)
Total number of SAEs	115	189	203	290
Total number of deaths	9 (1.4%)	8 (1.2%)	19 (2.9%)	15 (2.3%)
Total number of patients withdrawn from study due to an AE	8 (1.2%)	10 (1.5%)	31 (4.7%)	23 (3.5%)
Total number of patients withdrawn from study treatment due to an AE	11 (1.7%)	4 (0.6%)	22 (3.3%)	10 (1.5%)
Total number of patients with at least one AESI	14 (2.1%)	20 (3.0%)	25 (3.8%)	33 (5.0%)
Ocular events: study eye total number of patients with at least one				
AE	254 (38.3%)	246 (37.2%)	319 (48.0%)	308 (46.5%)
SAE	11 (1.7%)	13 (2.0%)	17 (2.6%)	23 (3.5%)
AE leading to withdrawal from study treatment	6 (0.9%)	1 (0.2%)	13 (2.0%)	5 (0.8%)
Treatment related AEs	19 (2.9%)	17 (2.6%)	24 (3.6%)	19 (2.9%)
Treatment related SAEs	8 (1.2%)	1 (0.2%)	10 (1.5%)	2 (0.3%)
AE of Special Interest	8 (1.2%)	12 (1.8%)	13 (2.0%)	22 (3.3%)
Drop in VA score >=30	7 (1.1%)	9 (1.4%)	8 (1.2%)	17 (2.6%)
Associated with severe IOI	1 (0.2%)	2 (0.3%)	3 (0.5%)	2 (0.3%)
Intervention req. to prevent permanent vision loss	0	1 (0.2%)	2 (0.3%)	3 (0.5%)
Suspected transmission of infectious agent by study drug	0	0	0	1 (0.2%)
Non-ocular events: total number of patients with at least one				
AE	346 (52.1%)	363 (54.8%)	439 (66.1%)	448 (67.7%)
SAE	68 (10.2%)	82 (12.4%)	105 (15.8%)	121 (18.3%)
AE leading to withdrawal from study treatment	5 (0.8%)	3 (0.5%)	9 (1.4%)	5 (0.8%)
AE of Special Interest	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	7 (1.1%)	6 (0.9%)	14 (2.1%)	14 (2.1%)
Non-fatal MI	3 (0.5%)	2 (0.3%)	3 (0.5%)	2 (0.3%)
Non-fatal Stroke	2 (0.3%)	1 (0.2%)	4 (0.6%)	5 (0.8%)
Death	2 (0.3%)	3 (0.5%)	8 (1.2%)	7 (1.1%)

Figure 4 Safety Plot of AE Safety Summary Events Through the SUR CCOD from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	Faricimab 6 mg (N = 664) n (%)	Aflibercept 2 mg (N = 662) n (%)	Difference (95% CI)
All Patients			
Patients with at least one AE	548 (82.5)	550 (83.1)	-0.6 (-4.7, 3.6)
Patients with at least one SAE	127 (19.1)	150 (22.7)	-3.5 (-8.0, 1.0)
Deaths	19 (2.9)	15 (2.3)	0.6 (-1.3, 2.5)
Patients withdrawn from study due to AE	31 (4.7)	23 (3.5)	1.2 (-1.1, 3.5)
Patients withdrawn from study treatment due to AE	22 (3.3)	10 (1.5)	1.8 (0.0, 3.7)
Patients with at least one AESI	25 (3.8)	33 (5.0)	-1.2 (-3.6, 1.1)
Ocular events: study eye			
AE	319 (48.0)	308 (46.5)	1.5 (-4.0, 7.0)
SAE	17 (2.6)	23 (3.5)	-0.9 (-3.0, 1.1)
AE leading to withdrawal from study treatment	13 (2.0)	5 (0.8)	1.2 (-0.2, 2.7)
Treatment related AEs	24 (3.6)	19 (2.9)	0.7 (-1.3, 2.8)
Treatment related Serious Treatment AEs	10 (1.5)	2 (0.3)	1.2 (0.0, 2.6)
AE of Special Interest	13 (2.0)	22 (3.3)	-1.4 (-3.3, 0.5)
Non-ocular events			
AE	439 (66.1)	448 (67.7)	-1.6 (-6.7, 3.6)
SAE	105 (15.8)	121 (18.3)	-2.5 (-6.6, 1.7)
AE leading to withdrawal from study treatment	9 (1.4)	5 (0.8)	0.6 (-0.7, 2.0)
AE of Special Interest	1 (0.2)	1 (0.2)	-0.0 (-0.8, 0.8)
Adjudicated APTC Events	14 (2.1)	14 (2.1)	-0.0 (-1.8, 1.7)



AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; SAE = Serious Adverse Event; n = Number of patients with at least one applicable adverse event. Newcombe with continuity correction method is used for the difference and 95% CI.

The Applicant also provided preliminary data summary to week 112 from the ongoing nAMD clinical studies.
Overall, based on the pooled safety data from 1326 patients from the TENAYA and LUCERNE studies, the safety data indicate that faricimab has a comparable safety profile to aflibercept. In addition, faricimab was generally well tolerated as evidenced by the low incidence (less than 5%) of AEs leading to treatment withdrawal, and AEs were generally manageable (mainly mild/moderate, non-serious, and resolved with or without treatment). The data remains consistent with that observed through the primary endpoint analysis at Week 48.

Key pooled safety results through Week 112 were the following:

- The incidence of AEs was comparable between the treatment arms (575/664 patients [86.6%] in the faricimab arm and 587/662 patients [88.7%] in the aflibercept arm);

- Through Week 112, the incidence of ocular AEs in the study eye was comparable between the treatment arms (358 patients [53.9%] in the faricimab arm and 345 patients [52.1%] in the aflibercept arm), with the exception (> 1% difference in any treatment arm: faricimab arm vs. aflibercept arm) of cataract (58 patients [8.7%] vs. 50 patients [7.6%]), dry eye (29 patients [4.4%] vs. 45 patients [6.8%]), vitreous floaters, (30 patients [4.5%] vs. 17 patients [2.6%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 10 patients [1.5%] ;

– The majority of cataract events were reported as progression of pre-existing condition and unrelated to study treatment or procedure.
– The events of vitreous floaters were non-serious and mild in severity, except for one severe case in each arm. These events of vitreous floaters were not associated with any IOI event.
– No new retinal pigment epithelial tear events were reported in the faricimab arm since the primary analysis (at Week 48). The majority of these events were reported during the loading phase, after 1 - 4 treatment injections.
- Through Week 112, the most common ocular AEs in the study eye (> 0.5%) suspected by the investigator to be related to faricimab were retinal pigment epithelial tear (8 patients [1.2%]), intraocular pressure increased (4 patients [0.6%]), and uveitis (4 patients [0.6%]). The most common ocular AE in the study eye (> 0.5%) suspected by the investigator to be related to aflibercept was intraocular pressure increased (4 patients [0.6%]).

- Through Week 112, the overall incidence of serious ocular AEs in the study eye was low and comparable across treatment arms (4.4% in both treatment arms), with the exception (> 0.5% difference between treatment arms) of retinal pigment epithelial tear (4 patients [0.6%] in the faricimab arm and 0 patients in the aflibercept arm).

- The incidence of AEs leading to study treatment discontinuation was low in both treatment arms (28 patients [4.2%] in the faricimab arm and 18 patients [2.7%] in the aflibercept arm). The incidence of ocular AEs leading to study treatment discontinuation through Week 112 was also low (17 patients [2.6%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm), which was 11 more patients in the faricimab arm and 7 more patients in the aflibercept arm since the primary analysis (at Week 48). No pattern was observed in ocular AEs leading to study treatment discontinuation in terms of timing and per regimen. The most common ocular AE leading to study treatment discontinuation was neovascular age-related macular degeneration (verbatim, worsening of nAMD; 9 patients [1.4%] in the faricimab arm and 4 patients [0.6%] in the aflibercept arm);

- All events of worsening of nAMD were assessed as related to the underlying disease (nAMD) or other cause in the faricimab arm, and a causal relationship to the study drug was ruled out. One event in the aflibercept arm that was assessed related to aflibercept treatment;

- The incidence of AEs leading to study discontinuation was low in both treatment arms (33 patients [5.0%] in the faricimab arm and 35 patients [5.3%] in the aflibercept arm). The incidence of ocular AEs leading to study discontinuation through Week 112 was also low (1 patient [0.2%] in the faricimab arm and 5 patients [0.8%] in the aflibercept arm).

- Through Week 112, the incidence of AESIs in the study eye was low and comparable between the treatment arms (25 patients [3.8%] in the faricimab arm and 27 patients [4.1%] in the aflibercept arm).

- Through Week 112, the incidence of IOI events in the study eye was low in both treatment arms (20 patients [3.0%] in the faricimab arm and 15 patients [2.3%] in the aflibercept arm.

- In total, through Week 112, 44 deaths were reported (23 patients [3.5%] in the faricimab arm and 21 patients [3.2%]) in the aflibercept arm). None of the deaths were suspected to be related to study treatment by investigators.

- Through Week 112, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was low and comparable across treatment arms (3.3% and 3.0% in the faricimab and aflibercept Q8W arms, respectively) and remained as expected in this patient population.

Table 2 Overview of Safety Through Week 112 from Individual and Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Patients)

	Week 48 Pooled(TENAYA and LUCERNE) (N=1326)		During entire study (Week 112) Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one AE	471 (70.9%)	483 (73.0%)	575 (86.6%)	587 (88.7%)
Total number of AEs	1670	1658	3284	3321
Total number of patients with at least one SAE	83 (12.5%)	101 (15.3%)	171 (25.8%)	194 (29.3%)
Total number of SAEs	115	189	280	380
Total number of deaths	9 (1.4%)	8 (1.2%)	23 (3.5%)	21 (3.2%)
Total number of patients withdrawn from study due to an AE	8 (1.2%)	10 (1.5%)	33 (5.0%)	35 (5.3%)
Total number of patients withdrawn from study treatment due to an AE	11 (1.7%)	4 (0.6%)	28 (4.2%)	18 (2.7%)
Total number of patients with at least one AESI	14 (2.1%)	20 (3.0%)	40 (6.0%)	43 (6.5%)
Ocular events: study eye total number of patients with at least one				
AE	254 (38.3%)	246 (37.2%)	358 (53.9%)	345 (52.1%)
SAE	11 (1.7%)	13 (2.0%)	29 (4.4%)	29 (4.4%)
AE leading to withdrawal from study treatment	6 (0.9%)	1 (0.2%)	17 (2.6%)	8 (1.2%)
Treatment related AEs	19 (2.9%)	17 (2.6%)	26 (3.9%)	19 (2.9%)
Treatment related SAEs	8 (1.2%)	1 (0.2%)	10 (1.5%)	2 (0.3%)
AE of Special Interest	8 (1.2%)	12 (1.8%)	25 (3.8%)	27 (4.1%)
Drop in VA score >=30	7 (1.1%)	9 (1.4%)	18 (2.7%)	20 (3.0%)
Associated with severe IOI	1 (0.2%)	2 (0.3%)	3 (0.5%)	2 (0.3%)
Intervention req. to prevent permanent vision loss	0	1 (0.2%)	4 (0.6%)	5 (0.8%)
Suspected transmission of infectious agent by study drug	0	0	0	1 (0.2%)
Ocular events: fellow eye total number of patients with at least one				
AE	169 (25.5%)	162 (24.5%)	284 (42.8%)	285 (43.1%)
SAE	7 (1.1%)	7 (1.1%)	16 (2.4%)	19 (2.9%)
AE of Special Interest	6 (0.9%)	7 (1.1%)	14 (2.1%)	17 (2.6%)
Drop in VA score >=30	5 (0.8%)	4 (0.6%)	10 (1.5%)	13 (2.0%)
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	1 (0.2%)	3 (0.5%)	4 (0.6%)	4 (0.6%)
Suspected transmission of infectious agent by study drug	0	0	0	0

Table 3 Overview of Safety through Week 48 and during the Entire Study from Pooled Phase III DME Studies (Pooled Safety-Evaluable Patients) (cont.)

	Week 48 Pooled (TENAYA and LUCERNE) (N=1326)		During entire study (Week 112) Pooled (TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Non-ocular events total number of patients with at least one				
AE	346 (52.1%)	363 (54.8%)	487 (73.3%)	492 (74.3%)
SAE	68 (10.2%)	82 (12.4%)	138 (20.8%)	162 (24.5%)
AE leading to withdrawal from study treatment	5 (0.8%)	3 (0.5%)	11 (1.7%)	10 (1.5%)
AE of Special Interest				
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0 0	1 (0.2%) 0	1 (0.2%) 0	1 (0.2%) 0
Adjudicated APTC events	7 (1.1%)	6 (0.9%)	22 (3.3%)	20 (3.0%)
Non-fatal MI	3 (0.5%)	2 (0.3%)	3 (0.5%)	3 (0.5%)
Non-fatal Stroke	2 (0.3%)	1 (0.2%)	4 (0.6%)	6 (0.9%)
Death	2 (0.3%)	3 (0.5%)	16 (2.4%)	11 (1.7%)

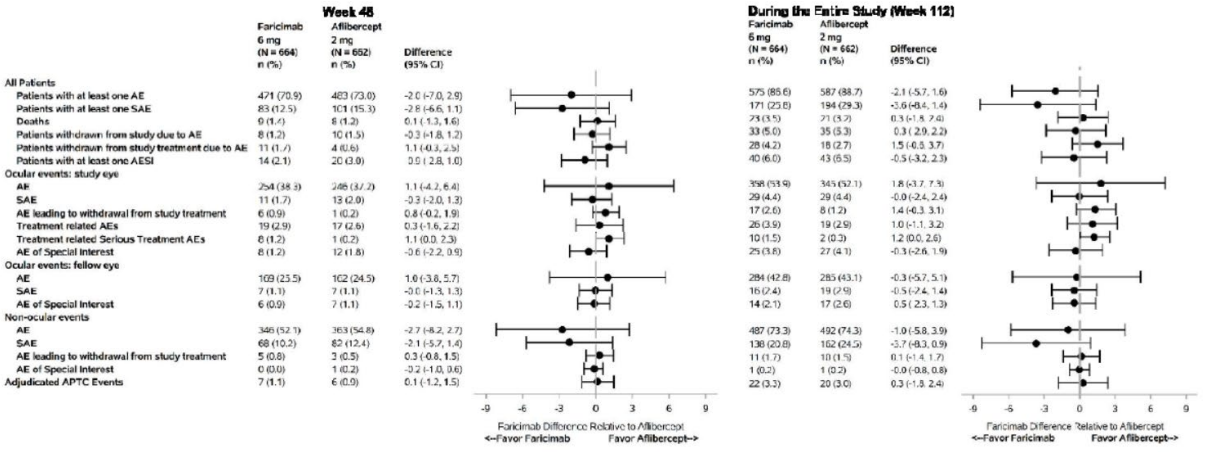
AE=Adverse Event; AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA = Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).

Week 48 footnote: Investigator text for AEs encoded using MedDRA version 23.1. Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

During entire study footnote: Investigator text for AEs encoded using MedDRA version 24.1. Includes events with onset from the first dose of study drug through the end of study.

Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Figure 3 Safety Plot of AE Safety Summary Events Through Week 112 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)



AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; SAE = Serious Adverse Event; n = Number of patients with at least one applicable adverse event. Includes events with onset from the first dose of study drug through the end of study. Percentages are based on N in the column headings. **Week 48 footnote:** Includes events with onset up to Day 349 (last day of Week 48 analysis visit window). **Week 112 footnote:** Includes events with onset from the first dose of study drug through the end of study. Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

DME indication:

Updated safety data was provided by the applicant in the Safety update report (SUR):

Key pooled safety results through the SUR Clinical Cut-Off Date in the pooled Parent Studies were the Following:

• The incidence of AEs remained generally comparable across all treatment arms (567/630 [90.0%], 551/632 [87.2%], and 545/625 [87.2%] patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

• The incidence of ocular AEs in the study eye was 47.5%, 47.3%, and 43.7% of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively, with an increase of approximately 10 percentage points in the incidence in all treatment arms compared with SCS (Week 56). There were a small number of ocular AEs with ⩾2% difference between the faricimab Q8W or PTI arms and the aflibercept Q8W arm (faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively): cataract (12.1%, 9.5%, and 9.3%; newly added), dry eye (4.6%, 4.1%, and 2.6%;

newly added), intraocular pressure increased (4.9%, 3.3%, and 2.6%; newly added), and vitreous floaters (5.1%, 2.5%, and 2.7%).

• The most common ocular AEs in the study eye (⩾2% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were generally consistent with those reported in the SCS (Week 56), with the newly added events: cataract subcapsular (3.0%, 2.2%, and 1.4%; newly added), diabetic retinal oedema (verbatim, worsening of DME; 1.6%, 2.5%, and 2.2%; newly added),conjunctivitis (1.4%, 2.1%, and 1.3%; newly added), cataract nuclear (1.6%, 2.1%, and 1.3%; newly added), blepharitis (2.4%, 1.4%, and 0.8%; newly added), and diabetic retinopathy (verbatim, worsening of DR; 0.6%, 2.1%, and 1.1%; newly added).

• The most common treatment-related ocular AEs in the study eye (⩾0.5% in either of the faricimab arms) were consistent with those reported in the SCS (Week 56); ocular hypertension in the faricimab PTI arm reported in the SCS (Week 56) no longer met the threshold of ⩾0.5% in either of the faricimab arms by the SUR Clinical Cut-Off Date due to updates in the database.

• The incidence of serious ocular AEs in the study eye remained higher in both faricimab arms compared with the aflibercept Q8W arm (4.0%, 4.9%, and 2.9% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

However, the overall incidence remained low, and there was no consistent pattern observed at the individual PT level between the treatment arms. There were two newly added serious ocular AEs with ⩾0.5% difference between any two of the treatment arms; uveitis and retinal tear (0, 3 patients [0.5%], and 0 each in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The most common serious ocular AEs in the study eye (⩾ 2 patients in the combined faricimab arms or aflibercept Q8W arm) by PT were generally consistent with those reported in the SCS (Week 56), with the newly added events (faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively): diabetic retinopathy (verbatim, worsening of DR; 2 patients [0.2%] vs. 3 patients [0.5%]), cataract subcapsular (2 patients[0.2%] vs. 2 patients [0.3%]), retinal vein occlusion (3 patients [0.2%] vs. 0), posterior capsule opacification (2 patients [0.2%] vs. 0), retinal artery occlusion (1 patient [<0.1%] vs. 2 patients [0.3%]), and visual impairment (2 patients [0.2%] vs. 0); visual acuity reduced transiently and ocular hypertension reported in SCS (Week 56) no longer met the threshold of ⩾ 2 patients by the SUR Clinical Cut-Off Date due to updates in the database.

• The incidence of AEs leading to study treatment discontinuation through the SUR Clinical Cut-Off Date remained low (2.4%, 3.2%, and 1.8% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The incidence of ocular AEs leading to study treatment discontinuation remained low and generally comparable across all treatment arms (5 patients [0.8%], 12 patients [1.9%], and 2 patients [0.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). No pattern was observed in ocular AEs leading to study treatment discontinuation in terms of timing and per regimen.

• The incidence of AEs leading to study discontinuation through the SUR Clinical Cut-Off Date remained low (4.3%, 4.4%, and 3.7% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively; The incidence of ocular AEs leading to study discontinuation remained low and comparable across treatment arms (4 patients [0.6%], 5 patients [0.8%], and 2 patients [0.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). No pattern was observed in ocular AEs leading to study discontinuation in terms of timing and per regimen.

• The incidence of ocular AESIs in the study eye remained higher in both faricimab arms than that in the aflibercept Q8W arm as of the SUR Clinical Cut-Off Date (3.8%, 4.7%, and 2.6% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively). However, the difference in AESIs was small and the overall incidence was low for all treatment arms.

• The incidence of IOI events in the study eye remained low and comparable across all treatment arms (9 patients [1.4%], 11 patients [1.7%], and 7 patients [1.1%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

• The incidence and nature of non-ocular AEs through the SUR Clinical Cut-Off Date was generally comparable to that reported in the SCS (Week 56) and across all treatment arms (72.4%, 73.1%, and 73.9% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

The incidence of serious non-ocular AEs remained generally comparable across all treatment arms (27.3%, 24.2%, and 25.8% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

• A total of 73 patients died through the SUR Clinical Cut-Off Date (25 patients [4.0%], 26 patients [4.1%], and 22 patients [3.5%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). No deaths were suspected by the investigator to be related to study treatment.

• The incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) through the SUR Clinical Cut-Off Date remained comparable across treatment arms (4.3%, 4.1%, and 4.2% in the faricimab Q8W, and faricimab PTI, and aflibercept Q8W arms, respectively).

Table: Overview of Safety through Week 56 and SUR Clinical Cut-Off Date from the Pooled Phase III DME/DR Studies (Pooled Safety-Evaluable Population)

	Parent SCS (Week 56) Pooled (YOSEMITE and RHINE) (N=1887)				Parent SUR CCOD (09 April 2021) Pooled YOSEMITE and RHINE (N=1887)			
	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one AE	513 (81.4%)	486 (76.9%)	999 (79.2%)	488 (78.1%)	567 (90.0%)	551 (87.2%)	1118 (88.6%)	545 (87.2%)
Total number of AEs	2169	1891	4060	1852	3174	2965	6139	2747
Total number of patients with at least one SAE	149 (23.7%)	126 (19.9%)	275 (21.8%)	114 (18.2%)	204 (32.4%)	188 (29.7%)	392 (31.1%)	182 (29.1%)
Total number of SAEs	272	193	465	191	401	336	737	332
Total number of deaths	13 (2.1%)	9 (1.4%)	22 (1.7%)	9 (1.4%)	25 (4.0%)	26 (4.1%)	51 (4.0%)	22 (3.5%)
Total number of patients withdrawn from study due to an AE	16 (2.5%)	12 (1.9%)	28 (2.2%)	9 (1.4%)	27 (4.3%)	28 (4.4%)	55 (4.4%)	23 (3.7%)
Total number of patients withdrawn from study treatment due to an AE	10 (1.6%)	12 (1.9%)	22 (1.7%)	7 (1.1%)	15 (2.4%)	20 (3.2%)	35 (2.8%)	11 (1.8%)
Total number of patients with at least one AESI	27 (4.3%)	26 (4.1%)	53 (4.2%)	13 (2.1%)	41 (6.5%)	42 (6.6%)	83 (6.6%)	30 (4.8%)
Ocular events: study eye total number of patients with at least one								
AE	235 (37.3%)	225 (35.6%)	460 (36.5%)	215 (34.4%)	299 (47.5%)	299 (47.3%)	598 (47.4%)	273 (43.7%
SAE	15 (2.4%)	19 (3.0%)	34 (2.7%)	8 (1.3%)	25 (4.0%)	31 (4.9%)	56 (4.4%)	18 (2.9%
AE leading to withdrawal from study treatment	2 (0.3%)	8 (1.3%)	10 (0.8%)	2 (0.3%)	5 (0.8%)	12 (1.9%)	17 (1.3%)	2 (0.3%
Treatment related AEs	19 (3.0%)	16 (2.5%)	35 (2.8%)	19 (3.0%)	21 (3.3%)	22 (3.5%)	43 (3.4%)	20 (3.2%
Treatment related SAEs	0	5 (0.8%)	5 (0.4%)	0	0	9 (1.4%)	9 (0.7%)	0
AE of Special Interest	15 (2.4%)	17 (2.7%)	32 (2.5%)	6 (1.0%)	24 (3.8%)	30 (4.7%)	54 (4.3%)	16 (2.6%
Drop in VA score >=30	8 (1.3%)	8 (1.3%)	16 (1.3%)	3 (0.5%)	17 (2.7%)	20 (3.2%)	37 (2.9%)	11 (1.8%
Associated with severe IOI	3 (0.5%)	5 (0.8%)	8 (0.6%)	1 (0.2%)	3 (0.5%)	5 (0.8%)	8 (0.6%)	1 (0.2%
Intervention req. to prevent permanent vision loss	5 (0.8%)	5 (0.8%)	10 (0.8%)	2 (0.3%)	6 (1.0%)	8 (1.3%)	14 (1.1%)	4 (0.6%
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0	0	0
Non-ocular events total number of patients with at least one								
AE	393 (62.4%)	385 (60.9%)	778 (61.6%)	390 (62.4%)	456 (72.4%)	462 (73.1%)	918 (72.7%)	462 (73.9%)
SAE	127 (20.2%)	103 (16.3%)	230 (18.2%)	102 (16.3%)	172 (27.3%)	153 (24.2%)	325 (25.8%)	161 (25.8%
AE leading to withdrawal from study treatment	8 (1.3%)	4 (0.6%)	12 (1.0%)	5 (0.8%)	10 (1.6%)	8 (1.3%)	18 (1.4%)	9 (1.4%
AE of Special Interest	0	0	0	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	1 (0.2%
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	1 (0.2%)	0	0	0	1 (0.2%
Adjudicated APTC events	13 (2.1%)	12 (1.9%)	25 (2.0%)	14 (2.2%)	27 (4.3%)	26 (4.1%)	53 (4.2%)	26 (4.2%)
Non-fatal MI	4 (0.6%)	2 (0.3%)	6 (0.5%)	6 (1.0%)	7 (1.1%)	4 (0.6%)	11 (0.9%)	7 (1.1%)
Non-fatal Stroke	4 (0.6%)	4 (0.6%)	8 (0.6%)	4 (0.6%)	10 (1.6%)	8 (1.3%)	18 (1.4%)	7 (1.1%)
Death	5 (0.8%)	6 (0.9%)	11 (0.9%)	4 (0.6%)	10 (1.6%)	14 (2.2%)	24 (1.9%)	12 (1.9%)

AE=Adverse Event. SAE=Serious Adverse Event. AESI=Adverse Event of Special Interest. APTC = Antiplatelet Trialists' Collaboration.
IOI=Intraocular Inflammation. VA = Visual Acuity. MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized
Treatment Interval (from Q4W up to Q16W); CCOD = clinical cutoff date; SCS = Summary of Clinical Safety; SUR = Safety Update Report.

SCS Footnotes: Investigator text for AEs encoded using MedDRA version 23.1. Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
SUR Footnotes: Investigator text for AEs encoded using MedDRA version 24.0.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" ro
in which multiple occurrences of the same AE are counted separately.

2.4.8.3. Laboratory findings

nAMD clinical laboratory evaluations.

There were no clinically relevant imbalances between treatment arms for laboratory parameters.

Diabetic macular edema (DME) clinical laboratory evaluations

There were no clinically relevant imbalances across treatment arms for laboratory parameters.

Non-Ocular Adverse Events of Special Interest DME indication

Through Week 56, 1 patient (0.2%) experienced an elevated ALT or AST with either elevated bilirubin or clinical jaundice (PT of chronic hepatitis) in the aflibercept Q8W arm, the chronic hepatitis event was considered serious, suspected by the investigator not to be related to study treatment, and resolving by the Clinical Cut-Off Date. There were no cases of drug induced liver injuries by the study drug reported in the faricimab arms. After Week 56 to the Clinical Cut-Off Date, there were no additional non-ocular AESIs.

2.4.8.4. Safety in special populations

nAMD: safety in special groups

Intrinsic factors

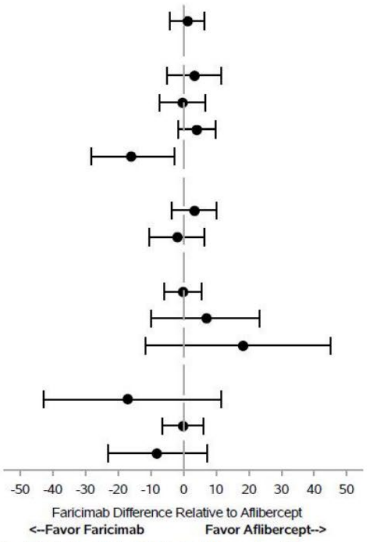
Subgroup Analyses were performed to examine key safety across the subgroups defined by the following intrinsic factors:

- Age (< 75, ≥ 75, <85, ≥85)
- Gender (female and male)
- Race (White, Asian, and Other)
- Medical History (renal disease, cardiac disease, and vascular disease)

Overall, through Week 48, differences in incidences of ocular AEs, incidences of nonocular AEs, incidences of SAEs, and incidences of ocular AESIs between the faricimab and aflibercept arms were generally consistent across subgroups (e.g., by age, gender, race, and medical history) and with incidences between the faricimab and aflibercept arms in the overall safety-evaluable population. Subgroup analyses are provided in forest plots (Figures 61 and 62) for ocular AEs in the study eye through Week 48; for non-ocular AEs through Week 48; for SAEs through Week 48; and for ocular AESIs in the study eye through Week 48.

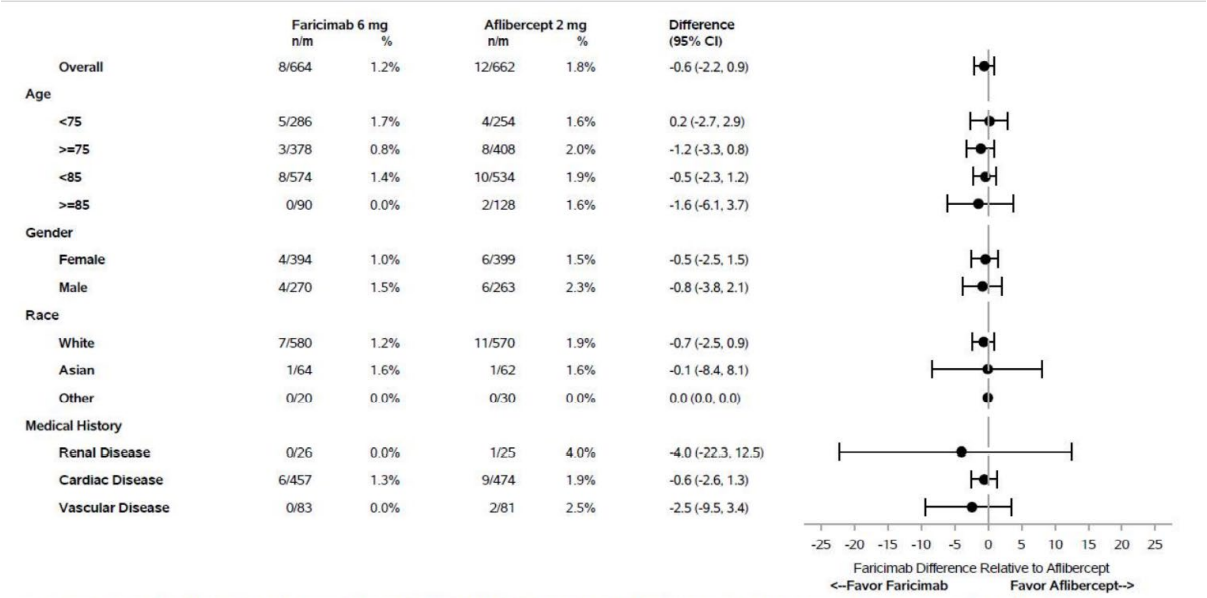
Figure 61. Subgroup Forest Plot of Ocular AEs in the Study Eye through Week 48 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)

	Faricimab 6 mg n/m	%	Aflibercept 2 mg n/m	%	Difference (95% CI)
Overall	254/664	38.3%	246/662	37.2%	1.1 (-4.2, 6.4)
Age					
<75	112/286	39.2%	91/254	35.8%	3.3 (-5.1, 11.7)
>=75	142/378	37.6%	155/408	38.0%	-0.4 (-7.3, 6.5)
<85	232/574	40.4%	194/534	36.3%	4.1 (-1.8, 9.9)
>=85	22/90	24.4%	52/128	40.6%	-16.2 (-28.4, -2.8)
Gender					
Female	158/394	40.1%	147/399	36.8%	3.3 (-3.7, 10.2)
Male	96/270	35.6%	99/263	37.6%	-2.1 (-10.5, 6.3)
Race					
White	222/580	38.3%	219/570	38.4%	-0.1 (-5.9, 5.6)
Asian	21/64	32.8%	16/62	25.8%	7.0 (-9.9, 23.3)
Other	11/20	55.0%	11/30	36.7%	18.3 (-11.7, 44.9)
Medical History					
Renal Disease	8/26	30.8%	12/25	48.0%	-17.2 (-42.8, 11.6)
Cardiac Disease	167/457	36.5%	174/474	36.7%	-0.2 (-6.5, 6.2)
Vascular Disease	27/83	32.5%	33/81	40.7%	-8.2 (-23.2, 7.3)



n = Number of patients with at least one ocular AE; m = Number of patients in the subgroup. Includes events with onset up to Day 349 (last day of Week 48 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

Figure 62. Subgroup Forest Plot of Ocular AEs of Special Interest in the Study Eye through Week 48 from Pooled Phase III nAMD Studies (Pooled Safety-Evaluable Population)



n = Number of patients with at least one ocular AE of special interest; m = Number of patients in the subgroup. Includes events with onset up to Day 349 (last day of Week 48 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

DME: safety in special groups- from the Pooled Phase III DME Studies

Intrinsic factors

Analyses were performed to examine key safety across the subgroups defined by the following intrinsic factors:

- Baseline DR severity (≤ 53 and > 53);
- Baseline HbA1c (≤ 8% and > 8%);
- Age (< 65 and ≥ 65);
- Age (< 75 and ≥ 75);
- Gender (female and male);
- Race (White, Asian and other); and
- Medical history (renal disease, cardiac disease, and vascular disease)

Overall, through Week 56, differences in incidences of ocular AEs, incidences of nonocular AEs, incidences of SAEs, and incidences of ocular AESI between each of the faricimab arms and the aflibercept Q8W arms were consistent across subgroups (e.g., by: age, gender, race, medical history, baseline DR severity, and baseline HbA1c) and with incidences in the overall safety-evaluable population.

Figure: Subgroup Forest Plot of Serious AEs through Week 56, Safety-Evaluable Population DME indication

Protocol: GR40349 & GR40398

	Faricimab 6 mg PTI n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	126/632	19.9%	114/625	18.2%	1.7 (-2.8, 6.2)
Baseline DR severity					
<=53	113/563	20.1%	101/568	17.8%	2.3 (-2.4, 7.0)
>53	10/58	17.2%	9/38	23.7%	-6.4 (-25.3, 10.8)
Baseline HbA1c					
<=8%	74/403	18.4%	68/399	17.0%	1.3 (-4.2, 6.8)
>8%	49/221	22.2%	46/221	20.8%	1.4 (-6.6, 9.3)
Age					
<65	70/352	19.9%	63/362	17.4%	2.5 (-3.4, 8.4)
>=65	56/280	20.0%	51/263	19.4%	0.6 (-6.4, 7.5)
<75	117/577	20.3%	101/570	17.7%	2.6 (-2.1, 7.2)
>=75	9/55	16.4%	13/55	23.6%	-7.3 (-23.2, 9.1)
Gender					
Female	54/236	22.9%	47/262	17.9%	4.9 (-2.4, 12.3)
Male	72/396	18.2%	67/363	18.5%	-0.3 (-6.0, 5.4)
Race					
White	90/489	18.4%	90/504	17.9%	0.5 (-4.4, 5.5)
Asian	11/62	17.7%	10/59	16.9%	0.8 (-14.1, 15.4)
Other	25/81	30.9%	14/62	22.6%	8.3 (-7.6, 23.0)
Medical History					
Renal Disease	20/63	31.7%	14/45	31.1%	0.6 (-18.4, 18.7)
Cardiac Disease	112/511	21.9%	99/497	19.9%	2.0 (-3.2, 7.1)
Vascular Disease	28/91	30.8%	22/97	22.7%	8.1 (-5.3, 21.2)

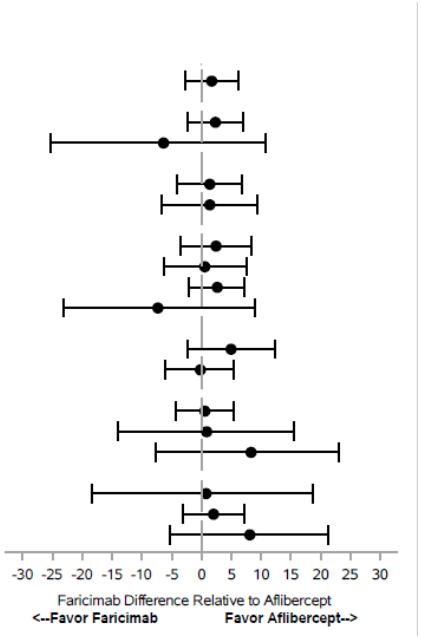
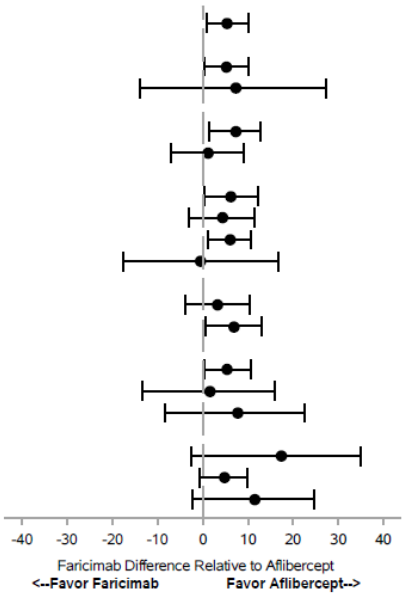


Figure: Subgroup Forest Plot of Serious AEs through Week 56, Safety-Evaluable Population

Protocol: GR40349 & GR40398

	Faricimab 6 mg Q8W n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	149/630	23.7%	114/625	18.2%	5.4 (0.8, 10.0)
Baseline DR severity					
<=53	133/578	23.0%	101/568	17.8%	5.2 (0.4, 10.0)
>53	13/42	31.0%	9/38	23.7%	7.3 (-14.0, 27.3)
Baseline HbA1c					
<=8%	101/417	24.2%	68/399	17.0%	7.2 (1.4, 12.8)
>8%	46/210	21.9%	46/221	20.8%	1.1 (-7.0, 9.2)
Age					
<65	86/363	23.7%	63/362	17.4%	6.3 (0.2, 12.3)
>=65	63/267	23.6%	51/263	19.4%	4.2 (-3.1, 11.4)
<75	137/578	23.7%	101/570	17.7%	6.0 (1.2, 10.8)
>=75	12/52	23.1%	13/55	23.6%	-0.6 (-17.6, 16.7)
Gender					
Female	53/251	21.1%	47/262	17.9%	3.2 (-4.0, 10.3)
Male	96/379	25.3%	67/363	18.5%	6.9 (0.7, 12.9)
Race					
White	114/489	23.3%	90/504	17.9%	5.5 (0.3, 10.6)
Asian	12/65	18.5%	10/59	16.9%	1.5 (-13.4, 15.9)
Other	23/76	30.3%	14/62	22.6%	7.7 (-8.3, 22.6)
Medical History					
Renal Disease	32/66	48.5%	14/45	31.1%	17.4 (-2.6, 35.1)
Cardiac Disease	126/513	24.6%	99/497	19.9%	4.6 (-0.6, 9.9)
Vascular Disease	31/91	34.1%	22/97	22.7%	11.4 (-2.2, 24.6)



Extrinsic factors DME indication

No subgroup analyses by extrinsic factors were performed.

The following tables were provided as part of the response to day 120 list of questions:

In the pooled nAMD data, there were more serious AEs in the oldest age group (> 85 years), with increased incidences noted for fatal events, hospitalization, AEs leading to drop out, nervous system disorders, accidents and injuries, vascular and cerebrovascular disorders, sum of postural hypotension,

falls, black outs, syncope, dizziness, ataxia, fractures, along with small differences in infections, fall, headache, and back pain (Table 65).

Table 65 Pooled Faricimab nAMD Data (TENAYA and LUCERNE): Safety Summary by Age Category through Week 60, Safety-Evaluable Population

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total no. of patients	44 (68.8%)	176 (79.3%)	219 (76.0%)	69 (76.7%)
Total no. of patients with SAE	7 (10.9%)	28 (12.6%)	37 (12.8%)	22 (24.4%)
- Fatal	0	5 (2.3%)	2 (0.7%)	6 (6.7%)
- Hospitalization/prolong existing hospitalization	5 (7.8%)	20 (9.0%)	31 (10.8%)	18 (20.0%)
- Life-threatening	1 (1.6%)	3 (1.4%)	3 (1.0%)	1 (1.1%)
- Disability/incapacity	1 (1.6%)	0	3 (1.0%)	2 (2.2%)
- Other (medically significant)	3 (4.7%)	11 (5.0%)	5 (1.7%)	3 (3.3%)
AE leading to drop-out	0	4 (1.8%)	4 (1.4%)	6 (6.7%)
Psychiatric disorders	1 (1.6%)	5 (2.3%)	11 (3.8%)	2 (2.2%)
Nervous system disorders	4 (6.3%)	15 (6.8%)	29 (10.1%)	14 (15.6%)
Accidents and injuries	5 (7.8%)	29 (13.1%)	38 (13.2%)	20 (22.2%)
Cardiac disorders	1 (1.6%)	8 (3.6%)	18 (6.3%)	6 (6.7%)
Vascular disorders	3 (4.7%)	11 (5.0%)	17 (5.9%)	7 (7.8%)
Cerebrovascular disorders	1 (1.6%)	3 (1.4%)	4 (1.4%)	5 (5.6%)
Infections and infestations	18 (28.1%)	72 (32.4%)	84 (29.2%)	24 (26.7%)
Anticholinergic syndrome	1 (1.6%)	15 (6.8%)	26 (9.0%)	9 (10.0%)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	1 (1.6%)	4 (1.8%)	18 (6.3%)	12 (13.3%)
<other AE appearing more frequently in older patients>				
Fall	1 (1.6%)	1 (0.5%)	8 (2.8%)	9 (10.0%)
Urinary Tract Infection	2 (3.1%)	6 (2.7%)	16 (5.6%)	8 (8.9%)
Pneumonia	0	1 (0.5%)	2 (0.7%)	4 (4.4%)
Headache	1 (1.6%)	5 (2.3%)	7 (2.4%)	4 (4.4%)
Back pain	0	5 (2.3%)	6 (2.1%)	4 (4.4%)
Sinusitis	1 (1.6%)	4 (1.8%)	7 (2.4%)	3 (3.3%)
COVID-19	0	4 (1.8%)	3 (1.0%)	3 (3.3%)

In the pooled DME data, there are no obvious differences in AEs across the <85 year age group categories, though data in the >74 year categories should be interpreted with caution due to the limited number of patients (Table 66).

Table 66 Pooled Faricimab DME Data (YOSEMITE and RHINE): Safety Summary by Age Category through Week 56, Safety-Evaluable Population

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total no. of patients	563 (78.7%)	349 (79.3%)	83 (80.6%)	4 (100%)
Total no. of patients with SAE	156 (21.8%)	98 (22.3%)	19 (18.4%)	2 (50.0%)
- Fatal	10 (1.4%)	10 (2.3%)	3 (2.9%)	1 (25.0%)
- Hospitalization/prolong existing hospitalization	125 (17.5%)	78 (17.7%)	16 (15.5%)	2 (50%)
- Life-threatening	9 (1.3%)	7 (1.6%)	5 (4.9%)	1 (25.0%)
- Disability/incapacity	12 (1.7%)	8 (1.8%)	0	0
- Other (medically significant)	28 (3.9%)	20 (4.5%)	1 (1.0%)	0
AE leading to drop-out	12 (1.7%)	11 (2.5%)	5 (4.9%)	0
Psychiatric disorders	14 (2.0%)	10 (2.3%)	4 (3.9%)	0
Nervous system disorders	85 (11.9%)	50 (11.4%)	13 (12.6%)	1 (25.0%)
Accidents and injuries	96 (13.4%)	61 (13.9%)	18 (17.5%)	1 (25.0%)
Cardiac disorders	46 (6.4%)	39 (80.9%)	8 (7.8%)	0
Vascular disorders	71 (9.9%)	41 (9.3%)	9 (8.7%)	0
Cerebrovascular disorders	16 (2.2%)	10 (2.3%)	3 (2.9%)	0
Infections and infestations	217 (30.3%)	115 (26.1%)	40 (38.8%)	3 (75.0%)
Anticholinergic syndrome	61 (8.5%)	43 (9.8%)	5 (4.9%)	2 (50.0%)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	30 (4.2%)	20 (4.5%)	8 (7.8%)	1 (25.0%)
<other AE appearing more frequently in older patients>	N/A*	N/A*	N/A*	N/A*

2.4.8.5. Immunological events

nAMD

The overall incidence of treatment-emergent ADA-positive patients was low (10.4% [68/657 patients] in the faricimab arm with a median time to onset of ADA of 20.1 weeks. There was no significant impact of ADAs against faricimab observed on overall safety in the nAMD safety population.

Through Week 48, 75 patients were ADA-positive at any point, of which 7 patients were treatment-unaffected ADA-positive.

Through Week 48, with regard to the ADA-positive subgroup, the incidence of SAEs was low (10.7% [8/75 patients] in the faricimab arm) with isolated individual events within SOCs and no specific pattern identified.

Of the patients who were ADA-positive and experienced ocular AEs, they were mainly non-serious, suspected by the investigator not to be related to study treatment, and did not result in vision loss of greater than 30 letters or study withdrawal.

Overall the rate of IOI was higher in the ADA-positive subgroup (6.7% [5/75 patients: 3 patients in TENAYA and 2 patients in LUCERNE) than in the ADA-negative subgroup (1.2% [7/582 patients: 1 patient in TENAYA and 6 patients in LUCERNE.

In the SUR, the incidence of intraocular inflammation (IOI) events remained low and comparable between the treatment arms (18 patients [2.7%] in the faricimab arm and 12 patients [1.8%] in the aflibercept arm). There were no new IOI events reported as retinal vasculitis or occlusive disease in any treatment arms.

Diabetic macular edema

There was no apparent impact of ADAs against faricimab observed on overall safety.

Through Week 56, 113 patients were ADA-positive at any point, of which 8 patients were treatment-unaffected ADA-positive. The incidence of treatment-emergent ADA-positive patients was low and comparable across the faricimab treatment arms (8.2% in the faricimab Q8W arm and 8.7% in the faricimab PTI arm; with a similar median time to onset of ADA (approximately 28 weeks)

Through Week 56, with regard to the ADA-positive subgroup, the incidence of patients with SAEs was 28.1% in the faricimab Q8W arm and 26.8% in the faricimab PTI arm, with isolated individual events within SOCs and no pattern identified. Of the patients who were ADA-positive and experienced ocular AEs, they were mainly non-serious, suspected by the investigator not to be related to study treatment, did not result in vision loss of ≥ 30 letters or study withdrawal, and were not associated with severe IOI events

Overall, the incidence of IOI was higher in the ADA-positive subgroup (9.7%; 11/113): 10 patients in YOSEMITE and 1 patient in RHINE than in the ADA-negative subgroup (0.5%; 6/1130): 2 patients in YOSEMITE and 4 patients in RHINE.

Table: Safety Summary through Week 56: ADA Positive Subgroup, Safety-Evaluable Population Protocol: GR40349 & GR40398 Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349 (YOSEMITE) (N=67)		GR40398 (RHINE) (N=46)		Pooled (YOSEMITE and RHINE) (N=113)		
	Faricimab 6 mg Q8W (N=34)	Faricimab 6 mg PTI (N=33)	Faricimab 6 mg Q8W (N=23)	Faricimab 6 mg PTI (N=23)	Faricimab 6 mg Q8W (N=57)	Faricimab 6 mg PTI (N=56)	Faricimab 6 mg All (N=113)
Total number of patients with at least one AE	28 (82.4%)	27 (81.8%)	17 (73.9%)	16 (69.6%)	45 (78.9%)	43 (76.8%)	88 (77.9%)
Total number of AEs	124	134	94	61	218	195	413
Total number of patients with at least one SAE	12 (35.3%)	9 (27.3%)	4 (17.4%)	6 (26.1%)	16 (28.1%)	15 (26.8%)	31 (27.4%)
Total number of SAEs	25	16	9	8	34	24	58
Total number of deaths	0	0	1 (4.3%)	0	1 (1.8%)	0	1 (0.9%)
Total number of patients withdrawn from study due to an AE	1 (2.9%)	1 (3.0%)	1 (4.3%)	0	2 (3.5%)	1 (1.8%)	3 (2.7%)
Total number of patients withdrawn from study treatment due to an AE	1 (2.9%)	4 (12.1%)	1 (4.3%)	1 (4.3%)	2 (3.5%)	5 (8.9%)	7 (6.2%)
Total number of patients with at least one AESI	3 (8.8%)	6 (18.2%)	0	3 (13.0%)	3 (5.3%)	9 (16.1%)	12 (10.6%)

AE=Adverse Event. SAE=Serious Adverse Event. AESI=Adverse Event of Special Interest. APTC = Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation. VA = Visual Acuity. MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_CSR_Primary/prod/program/t_ae_oview.sas
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04MAR2021 7:58 Page 1 of 4

2.4.8.6. Safety related to drug-drug interactions and other interactions

Since faricimab is a monoclonal antibody, no drug-drug interactions are expected via cytochrome P450, other metabolizing enzymes, or transporters. Therefore, no formal drug-drug interaction studies were conducted for faricimab, which is acceptable (please see PK section of this assessment report). In the population PK analysis, IOP lowering drugs did not have any effect on faricimab ocular PK.

2.4.8.7. Discontinuation due to adverse events

nAMD: AEs that led to Withdrawal of Study Treatment or Study Discontinuation

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 8 patients (1.2%) in the faricimab arm and 3 patients (0.5%) in the aflibercept arm experienced at least one ocular AE that led to study treatment discontinuation.

After Week 48 to the Clinical Cut-Off Date, the ocular AEs leading to study treatment discontinuation by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD; 2 patients [0.3%]) in the faricimab arm; and neovascular age-related macular degeneration (verbatim, worsening of nAMD) and non-infectious endophthalmitis (1 patient [0.2%] each) in the aflibercept arm.

From baseline to the Clinical Cut-Off Date, 2 patients (0.3%) in the faricimab arm and 1 patient (0.2%) in the aflibercept arm experienced at least one ocular AE that led to study discontinuation.

After Week 48 to the Clinical Cut-Off Date, the ocular AEs leading to study discontinuation by PT were neovascular age-related macular degeneration (verbatim, worsening of nAMD; 2 patients [0.3%]) in the faricimab arm; and visual acuity reduced (1 patient [0.2%]) in the aflibercept arm.

Preliminary data to week 112 for the nAMD indication indicates that the overall incidence of AEs leading to treatment discontinuation was balanced across both treatment groups (28 (4.2%)in the faricimab arm and 18 (2.7%)in the aflibercept arm).

The incidence of ocular AEs leading to study treatment discontinuation has previously been noted to be higher for faricimab and through Week 112, the rate was generally low but higher for faricimab (17 patients [2.6%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm). This represents 11 more patients in the faricimab arm and 7 more patients in the aflibercept arm since week 48 data was presented.

No specific pattern in ocular AEs leading to discontinuation has been noted but to date, the most common ocular AE leading to study treatment discontinuation was worsening of nAMD; 9 patients [1.4%] in the faricimab arm and 4 patients [0.6%] for aflibercept.

nAMD: AEs that led to Dose Interruption up to Clinical Cut-Off Date

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 15 patients (2.3%) in the faricimab arm and 9 patients (1.4%) in the aflibercept arm experienced at least one ocular AE that led to dose interruption. After Week 48 to the Clinical Cut-Off Date, the ocular AEs leading to dose interruption by PT were blepharitis, vitritis, ophthalmic herpes simplex, and rhegmatogenous retinal detachment (1 patient [0.2%] each) in the faricimab arm; and cataract operation complication (1 patient [0.2%]) in the aflibercept arm.

Diabetic macular edema

Ocular Adverse Events that led to Withdrawal of Study Treatment or Study Discontinuation Through Week 56-DME indication

Overall through Week 56, the incidence of ocular AEs leading to study treatment discontinuation was low and comparable across treatment arms (2 patients [0.3%], 8 patients [1.3%], and 2 patients [0.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

No pattern was observed in ocular AEs leading to study treatment discontinuation in terms of timing and per regimen. All patients who discontinued from study treatment due to an ocular AE were treatment naive patients.

The ocular AEs leading to study treatment discontinuation by PT were intraocular pressure increased, rhegmatogenous retinal detachment and vitritis (1 patient [0.2%] each) in the faricimab Q8W arm; endophthalmitis (2 patients [0.3%]), uveitis (2 patients [0.3%]), allergy to chemicals, diabetic eye disease, ocular hypertension, and ulcerative keratitis (1 patient [0.2%] each) in the faricimab PTI arm; and endophthalmitis and retinal artery occlusion (1 patient [0.2%] each) in the aflibercept Q8W arm.

Overall, through Week 56, the incidence of ocular AEs leading to study discontinuation was low and comparable across treatment arms (2 patients [0.3%], 2 patients [0.3%], and 1 patient [0.2%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). No pattern was observed in ocular AEs leading to study discontinuation in terms of timing and per regimen. All patients who discontinued from study due to an ocular AE were treatment naive patients.

The ocular AEs leading to study discontinuation by PT were intraocular pressure increased, rhegmatogenous retinal detachment and vitritis (1 patient [0.2%] each) in the faricimab Q8W arm; allergy to chemicals and endophthalmitis (1 patient [0.2%] each) in the faricimab PTI arm; and retinal artery occlusion (1 patient [0.2%]) in the aflibercept Q8W arm.

Table: Ocular Adverse Events Leading to Study Treatment Discontinuation through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	2 (0.6%)	5 (1.6%)	1 (0.3%)	0	3 (0.9%)	1 (0.3%)	2 (0.3%)	8 (1.3%)	10 (0.8%)	2 (0.3%)
Total number of events	3	5	1	0	3	1	3	8	11	2
Endophthalmitis	0	2 (0.6%)	0	0	0	1 (0.3%)	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
Uveitis	0	2 (0.6%)	0	0	0	0	0	2 (0.3%)	2 (0.2%)	0
Allergy to chemicals	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Diabetic eye disease	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Intraocular pressure increased	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Ocular hypertension	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Retinal artery occlusion	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Rhegmatogenous retinal detachment	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Ulcerative keratitis	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
Vitritis	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_CSR_Primary/prod/program/t_ae_pt.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_CSR_Primary/prod/output/t_ae_pt_OCUL_SDSC_W56_SE_DME_HLS.out
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Table: Ocular Adverse Events Leading to Study Discontinuation through Week 56 from Individual and Pooled Phase III DME Studies (Pooled Safety-Evaluable Population)

	GR40349 (YOSEMITE) (N=937)			GR40398 (RHINE) (N=950)			Pooled (YOSEMITE and RHINE) (N=1887)			
MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	2 (0.6%)	2 (0.6%)	1 (0.3%)	0	0	0	2 (0.3%)	2 (0.3%)	4 (0.3%)	1 (0.2%)
Total number of events	3	2	1	0	0	0	3	2	5	1
Allergy to chemicals	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Endophthalmitis	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Intraocular pressure increased	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Retinal artery occlusion	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
Rhegmatogenous retinal detachment	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Vitritis	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Non-Ocular Adverse Events that led to Withdrawal of Study Treatment or Study Discontinuation Through Week 56-DME indication

Overall through Week 56, incidence of non-ocular AEs leading to study treatment discontinuation was low and comparable across treatment arms (8 patients [1.3%], 4 patients [0.6%], and 5 patients [0.8%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively; No pattern was observed in non-ocular AEs leading to study treatment discontinuation in terms of timing, per regimen, or previously treated versus treatment naive population. The non-ocular AEs leading to study treatment discontinuation were breast cancer, lung neoplasm malignant, cerebrovascular accident, ischaemic stroke, cardiac failure congestive, infectious mononucleosis, renal failure, and peripheral artery thrombosis (1 patient [0.2%] each) in the faricimab Q8W arm; colon cancer, neoplasm, plasma cell myeloma, and myocardial infarction (1 patient [0.2%] each) in the faricimab PTI arm; and adenocarcinoma, cerebrovascular accident, dementia Alzheimer's type, spinal cord compression, and contrast media allergy (1 patient [0.2%] each) in the aflibercept Q8W arm.

Overall through Week 56, the incidence of non-ocular AEs leading to study discontinuation was low and comparable across treatment arms (14 patients [2.2%], 10 patients [1.6%], and 8 patients [1.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively; No pattern was observed in non-ocular AEs leading to study discontinuation in terms of timing, per regimen, or previously treated versus treatment naive population.

The non-ocular AEs leading to study discontinuation were myocardial infarction, acute myocardial infarction, cardiac arrest, cardiac failure congestive, left atrial dilatation, left ventricular dilatation, pericarditis, bladder cancer, lung neoplasm malignant, death, general physical health deterioration, cerebral haemorrhage, ischaemic stroke, sepsis, diabetic complication, and embolism (1 patient [0.2%] each) in the faricimab Q8W arm; death (3 patients [0.5%]), cardiac failure (2 patients

[0.2%]), myocardial infarction, colon cancer, neoplasm, plasma cell myeloma, and pneumonia aspiration (1 patient [0.2%] each) in the faricimab PTI arm; and myocardial infarction, acute myocardial infarction, coronary artery disease, adenocarcinoma, dementia Alzheimer's type, spinal cord compression, contrast media allergy, and completed suicide (1 patient [0.2%] each) in the aflibercept Q8W arm.

Up to Clinical Cut-Off Date-DME indication

In assessing cumulative data from baseline to the Clinical Cut-Off Date, 9 patients (1.4%), 4 patients (0.6%), and 7 patients (1.1%) experienced at least one non-ocular AE that led to study treatment discontinuation in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively

Table: Non-Ocular Adverse Events Leading to Study Treatment Discontinuation through Clinical Cut-Off Date, Safety-Evaluable Population Protocol: GR40349 & GR40398 Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020-DME indication

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA System Organ Class MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	1 (0.2%)	9 (1.4%)	0	4 (0.6%)	1 (<0.1%)	13 (1.0%)	2 (0.3%)	7 (1.1%)
Overall total number of events	1	9	0	4	1	13	2	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	0	3 (0.5%)	1 (<0.1%)	6 (0.5%)	0	1 (0.2%)
Total number of events	1	3	0	3	1	6	0	1
Adenocarcinoma	0	0	0	0	0	0	0	1 (0.2%)
Breast cancer	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Colon cancer	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
Colorectal cancer metastatic	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
Lung neoplasm malignant	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Neoplasm	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
Plasma cell myeloma	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
Nervous system disorders								
Total number of patients with at least one adverse event	0	2 (0.3%)	0	0	0	2 (0.2%)	0	3 (0.5%)
Total number of events	0	2	0	0	0	2	0	3
Cerebrovascular accident	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
Dementia Alzheimer's type	0	0	0	0	0	0	0	1 (0.2%)
Ischaemic stroke	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Spinal cord compression	0	0	0	0	0	0	0	1 (0.2%)
Cardiac disorders								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
Total number of events	0	1	0	1	0	2	0	0
Cardiac failure congestive	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Myocardial infarction	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA System Organ Class MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Infections and infestations								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
Total number of events	0	1	0	0	0	1	1	1
Infectious mononucleosis	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Pneumonia	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Immune system disorders								
Total number of patients with at least one adverse event	0	0	0	0	0	0	0	1 (0.2%)
Total number of events	0	0	0	0	0	0	0	1
Contrast media allergy	0	0	0	0	0	0	0	1 (0.2%)
Psychiatric disorders								
Total number of patients with at least one adverse event	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Total number of events	0	0	0	0	0	0	1	1
Confusional state	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Renal and urinary disorders								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
Renal failure	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Vascular disorders								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
Peripheral artery thrombosis	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the

From baseline to the Clinical Cut-Off Date, 2.5%, 2.7%, and 2.2% of patients experienced a non-ocular AE that led to study discontinuation in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Discussion on clinical safety nAMD

The safety evaluation for the nAMD indication is based primarily on the pooled Phase III nAMD safety data from the identical pivotal trials TENAYA and LUCERNE. The primary safety analysis is based on the available data up to Week 48. In addition, the applicant has provided data up to Week 60 to the clinical cutoff date of 19 January 2021 for TENAYA and 28 December 2020 for LUCERNE. A further update in the form of a 90 day Safety Update report (SUR) to April 2021 was provided with the responses and preliminary safety data summary to week 112 was also provided subsequently.

It is highlighted that both pivotal phase III trials in the nAMD indication were ongoing at the time of submission of this application and the final safety data remains outstanding at this time, although an overview of safety data from the nAMD clinical studies to week 112 was provided as a preliminary safety summary. In this context, some uncertainty remains in relation to the overall safety profile of faricimab which is considered to be still evolving at this time, although long term safety will be further followed in the Long term extension study which has been listed in the RMP.

This long-term extension (LTE) study for the nAMD indication is currently planned/ongoing but there is no safety data available from this study at the time of primary safety analysis. An update on the limited data from masked safety data was provided with the responses and while no new safety signals were identified from this limited data, the overall absence of longer term data in this indication remains a concern The Applicant has therefore agreed to include long term safety as missing information in the RMP, which is endorsed.

nAMD- Patient exposure

In total, 664 nAMD patients were exposed to faricimab (331 in LUCERNE and 333 in TENAYA) and 662 patients were exposed to aflibercept (326 in LUCERNE and 336 in TENAYA), the chosen active comparator to study treatment in both studies, in their preselected study eye. Median duration of exposure was 48.1 weeks for both treatment groups (in pooled and individual studies).

The overall patient exposure in the nAMD population is considered generally acceptable. However, as previously highlighted, both pivotal studies in the nAMD indication are ongoing at the time of submission of this application and at the time of the responses to the day 120 list of questions. Also, further data on the longer term safety profile of faricimab is still anticipated with the progression of the LTE study. This is considered an area of uncertainty as the safety profile of faricimab, whilst generally characterised could be considered to be still evolving.

In the nAMD Phase III (TENAYA/LUCERNE) trials, faricimab patients received a dosing regimen (Q8W, Q12W or Q16W) based on their treatment needs, which was determined by an assessment of their disease activity status (at weeks 20 and 24) after the initial loading phase. . According to the Clinical Overview, 45.3%, 33.4% and 21.2% of patients in the nAMD pooled ITT population were on a fixed Q16W, Q12W and Q8W dose regimen at Week 48, respectively. Due to the post randomization patient assignment to treatment schedules based on disease activity asseement, all patients treated with faricimab are reported as a pooled faricimab arm in the provided clinical summary of safety. Considering the new active substance with non-established safety profile for the proposed mode of action (dual inhibition of VEGF and Ang2), some uncertainty remains as to whether the number of evaluated patients is sufficient to conclude safety for each of the dosing groups also with respect to potential rare events, particularly for the most intense 8QW dosing schedule where overall patient

numbers were more limited. This issue will need to be followed closely and further data is expected to be generated for this dosing regimen in the LTE study. Extrapolation from studies that included patients with DME is not expedient due to the distinct disease character with a different profile of potential comorbidities (as also described by the applicant) and due to the differening treatment schedules that were applied in the clinical program for DME (i.e. personalized treatment intervals with dynamic schedule). As noted, the most intense treatment schedule for faricimab, i.e. Q8W, had the least patients included (i.e. n=141 patients). The included numbers for the other treatment schedules appear rather sparse considering the new mode of action (n=222 for Q12W and n=301 for Q16W). The biggest proportion of patients followed Q16W with only two injection events between disease assessment (at weeks 20 and 24) and week 48. Additional data analysis is provided for week 60, which coincides with the time of the third injection for the Q16W schedule.

"*Uncertainties with regard to the amount of data being collected for each dose regimen*" were also expressed in the scope of scientific advice. The applicant was reminded during the procedure that "*there may be insufficient safety data in subsets of patients (e.g. very elderly, cardiovascular risk factors) that might warrant additional (post-approval) studies*" and "*that data collected for the most intense Q8W maintenance regimen will be limited to those (possibly few) patients with disease activity at week 20*".

In this context, the applicant was asked to further justify the extrapolation from other treatment schedules. Safety data up to April 2021 was initially provided in the SUR. Whilst an increased intensity of treatment with faricimab (i.e. Q8W regimen) is associated with an increase in risk for ocular AEs when compared to the other dosing regimens, it was acknowledged that higher frequency of ocular AEs such as procedure-related AEs is likely to occur with more frequent intravitreal administration and the likelihood of more severe ocular disease at baseline (by virtue of the study design). The Applicant presents pooled data on nAMD phase III studies that indicates an increased ocular risk for subjects treated with Q8W faricimab. Nevertheless, there was an increased risk for faricimab (Q8W dosing regimen) treated subjects to experience an AE, AESI or serious AE in the study eye (compared to aflibercept).Still, it is agreed that the applied study design hinders a direct comparison between both treatment options, since patients on faricimab Q8W would have had worse baseline disease, whereas the aflibercept Q8W arm included patients with a range of baseline disease severity

Based on the response provided, the currently available numbers of patients exposed to faricimab in the most intense treatment schedule is considered sufficient for an initial marketing authorisation, provided that the product information is further strengthened to reflect the safety profile of the 8QW dosing regimen for faricimab, and that the safety profile of 8QW dosing of faricimab is further discussed and followed as part of the LTE study.

In relation to the nAMD indication, the Applicant also provided an update through the end of study for the two pivotal nAMD studies for patients enrolled into the global enrollment phase (TENAYA last patient last visit [LPLV] of 18 January 2022 and LUCERNE LPLV of 07 January 2022) in the form of a preliminary safety data summary.

Provision of these data represents the complete safety data from the 2 year pivotal studies for this indication.

On the basis of the preliminary data provided, no new information has emerged since the data-lock point of the Safety Update Report (SUR) from 9 April 2021 for nAMD which would impact on the safety profile for faricimab.

There has not been a change to the list of Important Identified Risks (Infectious Endophthalmitis and Intraocular Inflammation) proposed in the initial submission and the Applicant has agreed to add ATE and non-ocular haemorrhage as Important Potential Risks as outlined in safety specification in the EU RMP Part II Module SVII.1.2 as requested.

Besides data from the two pivotal studies, safety data from two phase II studies (AVENUE and STAIRWAY) are available (AVENUE: n=46 for 1.5mg Q4W, n=39 for 6mg Q4W, n=46 for 6mg Q4W-Q8W, all faricimab and n=67 for 0.5mg ranibizumab; STAIRWAY: n=24 for 6mg Q12W, n=31 for 6mg Q16W, all faricimab and n=16 for 0.5mg ranibizumab Q4W). Data from phase 1 studies is rather limited with n=4 nAMD patients included in study JP39844 and n=24 nAMD patients included in study BP28936. Importantly, the commercial drug product was only used in the pivotal phase 3 studies, after some of the excipients differed as compared to the drug product from previous studies. Due to GCP violations at one study site, data from 10 patients was excluded from AVENUE and five patients were excluded from STAIRWAY. The depicted reasons for study site closure of the affected location and data exclusion can be followed with respect to maintain the integrity of the full data pool. Similarly, exclusion of 3 patients from the safety-evaluable population that never received any treatment after randomization to the pivotal studies (2 in TENAYA and 1 in LUCERNE) can be followed. Importantly, in TENAYA 52 patients and in LUCERNE 23 patients had optional plasma samples or optional aqueous humor samples collected where prior informed consent was either not obtained or withdrawn. These were reported as major protocol deviations and all unconsented sample analyses were removed from the databases used for reporting. The applicant provided reasons for this issue in both pivotal studies and provided an evaluation on the extent of any additional treatment burden and potential safety risk that was caused for these patients. Further clarifications were raised in relation to this issue during the procedure and it was clarified that no specific safety concerns could be identified for the subgroup of patients involved.

nAMD: Patient Population

Baseline demographics as well as ocular characteristics in the study eye appear to be balanced across treatment arms within the individual phase 3 studies and across the two studies for most of the depicted categories. Similarly, no major deviations in distributions were identified for non-ocular characteristics, however, the applicant reports an imbalance in patients with >160 systolic or >90 diastolic blood pressure (11.2% in the faricimab arm vs. 5.2% in the aflibercept arm) in the LUCERNE study only. The mean age of pooled data was 75.9 years with the majority of patients (42.8%) in the ≥75 - <85 year age category (mean age in the faricimab arm was 75.4 years and in the aflibercept arm 76.4 years). However, slightly more patients are reported for the aflibercept arm in the ≥85 year age category (13.7% in the faricimab arm vs. 19.3% in the aflibercept arm), but slightly less patients are reported for the aflibercept arm in the ≥65 - <75 year age category (33.4% in the faricimab arm vs. 28.9% in the aflibercept arm). The patient-reported mean (SD) time since AMD diagnosis across treatment arms was 1.9 (8.1) months with an imbalance across treatment groups with 2.4 (10.8) and 1.4 (3.7) mean months since AMD diagnosis for faricimab and aflibercept, respectively. The range depicts 0-187 months since diagnosis and 34 unknown cases for the faricimab arm, but only 0-51 months and 26 unknown cases for the aflibercept arm. The comparable median (0.6 months and 0.7 months since diagnosis for faricimab and aflibercept arms, respectively) as well as depicted categories that reflect intervals with different times since nAMD diagnosis, both indicate a more balanced distribution than indicated by the mean time since diagnosis. More female patients were included in both pivotal studies for both treatment arms (around 60% females and 40% males included). The applicant provided further discussion on patient numbers in baseline blood pressure categories (low, normal, high) for both studies (see below section on safety in special groups for further discussion in this regard).

Due to the potential to follow a treatment schedule with stretched treatment intervals (depending on disease assessment on weeks 20 and 24 after the initial 4 injections in Q4W), the mean and median numbers of study drug administrations are lower for faricimab as compared to aflibercept (mean: 6.4 and 7.4 injection; median 6 and 8 injections, both for faricimab and aflibercept, respectively) with a

fixed Q8W interval (after initial 3 injections in Q4W). In order to decide for the individual need in treatment exposure also in clinical practice, the need for disease assessment at weeks 20 and 24 was highlighted to inform posology in SmPC. It is also recognised, that the Q8W treatment schedule does not reduce the treatment burden compared to the treatment with aflibercept, but rather requires one additional exposure for the initial steady state exposure (4 injections in Q4W for faricimab compared to 3 injections in Q4W for aflibercept).

All included patients were treated with faricimab only in their dedicated study eye and no data are reported on bilateral treatment with faricimab. However, some patients had a diagnosed bilateral nAMD and were treated with anti-VEGF standard of care in the fellow eye. The proportion of patients with bilateral nAMD can be concluded from the reported treatment for the fellow eye in around 30% of included patients (30.9% of the faricimab arm and 27% of the aflibercept arm across studies). However, clinical practice foresees bilateral treatment for nAMD and the Applicant was encouraged to generate data for bilateral treatment with faricimab. It was clarified that only the availability of reassuring data from bilateral use can allow to potentially omit the warning statement in 4.4 of the SmPC. Furthermore, a statement regarding potentially increased safety risks following bilateral treatment (e.g. due to increased systemic exposure, but also potential bilateral ocular AEs) was added in section 4.4 of the SmPC to reflect these concerns. The Applicant also confirmed that further safety data on bilateral use of faricimab will be generated post-approval specifically in countries where faricimab is already approved for this indication.

nAMD: Adverse events

The overall number of AEs was generally balanced across both pivotal studies in the nAMD indication for both faricimab and the comparator aflibercept for ocular AEs, SAEs and non-ocular events at Week 48.

The safety profile of faricimab up to week 60 appears principally consistent with the safety profile up to week 48. No new or unexpected safety signals are reported for the studies through week 60. In order to estimate the long-term occurrence/latency of safety events and the effect of repeated exposure, the applicant was asked to list AEs, AESI, SAEs and treatment discontinuations due to AEs reported after the week 48 assessment and until the last possible evaluable time point as well as the cumulative pool of events until last available time point until answers are provided for both treatment groups and considering the different schedules in the faricimab arm. Due to the pooling of distinct treatment schedules (Q8W, Q12W and Q16W after disease assessment at weeks 20 and 24), no discrete picture of the safety profile was available for each of the applied dose regimens at the initial submission. Upon request, the Applicant provided a separate safety analysis (including AEs, AESI, SAEs, ADAs and treatment discontinuations due to AEs) for each of the treatment schedules. Based on these data, it was noted that patient numbers in the most intense treatment schedule (i.e. Q8W) appear rather low.

In this context, the Applicant has provided a detailed response to address the question of limitations of the safety data for the faricimab Q8W regimen in the nAMD indication. The Applicant states that there are no clinically meaningful differences in ocular AEs, AESIs, SAEs between the Q8W faricimab subgroup (n=143) and the aflibercept Q8W arm (n=662), as the numerical differences in observed AE rates seen between the different faricimab treatment interval subgroups may be confounded by the fact that patients with greater baseline disease severity would have had more injections (by virtue of the study design).

The Applicant presented pooled data on nAMD phase III studies that support the view that an increased intensity of treatment with faricimab (i.e. higher frequency in dosing) is associated with an increase in risk for ocular AEs in the study eye (70/143 patients (49.0%) for Q8W, 92/219 patients (42.0%) for Q12W, and 113/289 patients (39.1%) for Q16W), AESIs in the study eye (5/143 patients (3.5%) for Q8W, 3/219 patients (1.4%) for Q12W, and 2/289 patients (0.7%) for Q16W) as well as serious ocular AEs in the study eye (143 patients (4.9%) for Q8W, 4/219 patients (1.8%) for Q12W, and 2/289 patients (0.7%) for Q16W).

Also, the Applicant presents pooled data on nAMD phase III studies that do indicate an increased ocular risk for subjects treated with Q8W faricimab compared to the Q8W aflibercept (49% of subjects vs. 40.2% of subjects, respectively). More specifically subjects appear at higher risk to have borderline glaucoma, cataract, retinal pigment epithelial tear and vitritis. Furthermore, also an increased risk of macular fibrosis, nAMD, posterior capsule opacification and vitreous floaters appears rather evident. Still, it is agreed that the applied study design hinders a direct comparison between both treatment options, since patients on faricimab Q8W would have had worse baseline disease, whereas the aflibercept Q8W arm included patients with a range of baseline disease severity.

Nevertheless, as part of the Applicant's response to address this question, they propose to add additional wording in section 4.8 of the SmPC in order to strengthen the existing information for HCPs in relation to RPE tears. This is endorsed.

In response to requests from the CHMP, the Applicant appropriately reports in the SmPC that patients with increased frequency of injections may be at increased risk of procedural complications.

In addition, in response to a request from the CHMP during assessment, section 4.2 of the SmPC has been updated to reflect that data with the Q8W faricimab regimen is limited at this time.

The Applicant has also confirmed that additional safety data from patients with nAMD on a faricimab Q8W dosing regimen could be provided from the long-term extension study AVONELLE-X, although exact patient numbers cannot be confirmed at this time. As also outlined in question 11, the Applicant proposes that the safety evaluation of the faricimab Q8W interval can be addressed within the ongoing LTE study AVONELLE-X, which is a Category 3 PASS in the proposed EU RMP v1.2 to address the missing information of long-term safety. The Final AVONELLE-X CSR is currently planned to be available for submission to the Agency by Q1 2025. The overall approach is considered to be acceptable but the Applicant has been asked to commit to ensuring that emerging safety data relating to this population should be provided regularly through the PSURs**.**

In general, the overall safety profile of the treatment of nAMD with faricimab appears to be sufficiently characterised to inform the intended population in the SmPC, provided the recommended updates are implemented by the Applicant to further strengthen the current wording. Despite the unclear relative risk in comparison to aflibercept, the absolute risk can be reflected in the SmPC and treating physicians (as well as patients) could opt based on this information for an alternative treatment option, in case faricimab does not appear applicable for an individual based on the described risk profile.

nAMD:Ocular AEs

A summary of ocular safety is provided below. This is based on the additional data from the 90 day Safety Update report (SUR) which was provided with the responses, supported by further preliminary safety data to week 112. It is important to highlight that the formal submission of the final data set from the ongoing pivotal clinical trials in the nAMD indication is still outstanding at the time of the responses but a preliminary overview of available data to week 112 has been provided. Overall, based on the pooled safety data from 1326 patients from the TENAYA and LUCERNE studies, the safety data indicate that faricimab has a comparable safety profile to aflibercept. In addition, faricimab was generally well tolerated as evidenced by the low incidence (less than 5%) of AEs leading to treatment withdrawal, and AEs were generally manageable (mainly mild/moderate, non-serious, and resolved with or without treatment). The data remains consistent with that observed through the primary endpoint analysis at Week 48.

At the time of primary safety analysis, up to Week 48, there were 254 patients (38.3%) and 246 patients (37.2%) with ocular AEs for the pooled faricimab and aflibercept arms, respectively.

The incidence of ocular AEs in the study eye up to week 112 was generally comparable between the treatment arms (358 patients [53.9%] in the faricimab arm and 345 patients [52.1%] for aflibercept. There was a > 1% difference in any treatment arm: (faricimab arm vs. aflibercept arm) of cataract (58 patients [8.7%] vs. 50 patients [7.6%]), dry eye (29 patients [4.4%] vs. 45 patients [6.8%]), vitreous floaters, (30 patients [4.5%], vs 17 patients [2.6%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 10 patients [1.5%]. Exposure-adjusted incidence rates for the cumulative pooled data for total ocular AEs in the study eye up to Week 112 were 68.90 per 100PY for faricimab and 64.02 per 100 PY for aflibercept.

In the week 112 preliminary data, the majority of cataract events were reported as progression of pre-existing condition and unrelated to study treatment or procedure.

Treatment related ocular AEs: Up to Week 48 there were 19 patients (2.9%) and 17 patients (2.6%) with treatment related ocular AEs for the pooled faricimab and aflibercept arms, respectively. Beyond Week 48 until the latest available timepoint (SUR), there were a further 7 patients (1.1%) and 2 patients (0.3%), giving a cumulative total of 3.9% (26/664 patients) for faricimab and 2.9% (19/662 patients) for aflibercept. Exposure-adjusted incidence rates for the cumulative pooled data for treatment related ocular AEs were 2.85 per 100 PY for faricimab and 1.97 per 100 PY for aflibercept**.**

Serious Ocular Adverse Events: Up to Week 48 there were 11 patients (1.7%) and 13 patients (2.0%) with serious ocular AEs for the pooled faricimab and aflibercept arms, respectively. Beyond Week 48 until the latest available timepoint, there were a further 6 patients (0.9%) and 11 patients (1.7%), giving a cumulative total of serious ocular AEs 2.6% (17/664 patients) for faricimab and 3.5% (23/662 patients) for aflibercept.

As per SUR cut off date, exposure-adjusted incidence rates for the cumulative pooled data for serious ocular AEs were 2.17 per 100 PY for faricimab and 2.56 per 100 PY for aflibercept.

Treatment related serious ocular adverse events (1.2% for faricimab and 0.2% for aflibercept at week 48 report) were noted to have increased in faricimab arm after 90-days observation when compared to aflibercept (1.5% for faricimab and 0.3% for aflibercept).

Adverse Events of Special Interest (AESI): Up to Week 48 there were 14 patients (2.1%) and 20 patients (3.0%) with AESIs for the pooled faricimab and aflibercept arms, respectively. Beyond Week 48 until the latest available timepoint, there were a further 11 patients (1.7%) and 15 patients (2.3%), giving a cumulative total of 3.8% (25/664 patients) for faricimab and 5.0% (33/662 patients) for aflibercept.

The most frequently reported (> 2 events) AESIs of any category being neovascular age-related macular degeneration (worsening of nAMD), and endophthalmitis.

Exposure-adjusted incidence rates for the cumulative pooled data for study eye AESIs were 1.48 per 100 PY for faricimab and 2.36 per 100 PY for aflibercept.

In the preliminary Week 112, the incidence of AESIs in the study eye was low and comparable between the treatment arms (25 patients [3.8%] in the faricimab arm and 27 patients [4.1%] in the aflibercept arm).

The incidence of IOI events in the study eye was low in both treatment arms (20 patients [3.0%] in the faricimab arm and 15 patients [2.3%] in the aflibercept arm.

Five ocular AEs of endophthalmitis were reported through Week 112 (3 patients [0.5%] in the faricimab arm and 2 patients [0.3%] in the aflibercept arm). All events were assessed as serious. Two cases were considered to be related to faricimab treatment; one of which resulted in discontinuation of study treatment. All events except one case in the aflibercept arm resolved. This event resulted in withdrawal of aflibercept treatment, and the event was considered related to procedure.

Sight-threatening AESIs: There were 15 sight-threatening AESIs that were not resolved at the time of the Week 48 Clinical Cut-Off Date, a total of 7 remained unresolved (5 faricimab and 2 aflibercept) and 8 were resolved or resolving (6 faricimab and 2 aflibercept) by the 90- Day Safety Update Report (SUR) Clinical Cut-Off Date (9 April 2021). The events that remained unresolved at the time of the SUR Clinical Cut-Off Date included vitreous haemorrhage, retinal vein occlusion, macular degeneration, and 2 events of RPE tear (faricimab); and subretinal fibrosis, neovascular age-related macular degeneration (aflibercept).

Treatment discontinuation due to AEs: up to Week 48 there were 11/664 patients (1.7%) and 4/662 patients (0.6%) with AEs leading to study treatment discontinuation for the pooled faricimab and aflibercept arms, respectively. Beyond Week 48 until the latest available timepoint (SUR), there were a further 11 patients (1.7%) and 6 patients (0.9%), giving a cumulative total of 3.3% (22/664 patients) for faricimab and 1.5% (10/662 patients) for aflibercept.

Exposure-adjusted incidence rates for the cumulative pooled data for treatment discontinuations due to Adverse Events were higher for faricimab at 2.17 per 100 PY and 1.18 per 100 PY for aflibercept.

In the 90-day safety update report, more subjects withdrew from study treatment when treated with faricimab compared to aflibercept due to ocular adverse events (2% for faricimab and 0.8% for aflibercept in pooled phase 3 nAMD studies).

RPE Tears: At Week 48, there was a ≥1% difference in the faricimab treatment arm vs. aflibercept arm) for retinal pigment epithelial tear (19 patients [2.9%] vs. 9 patients [1.4%]). These events were mostly reported as either mild or moderate in severity. There were 5 patients in the faricimab arm and 1 patient in the aflibercept arm with a retinal pigment epithelial tear event in the study eye associated with vision loss ≥15 letters (4 patients in the faricimab arm and 1 patient in the aflibercept arm with vision loss ≥15 letters; and 1 patient with vision loss ≥ 30 letters in the faricimab arm. Based on updated SUR, the overall exposure adjusted incidence of RPE tears were slightly higher for faricimab at 1.87 per 100 PY versus 0.98 per 100 PY for aflibercept. Four patients were reported with serious events of retinal pigment epithelial tear in the study eye for the pooled faricimab treatment group (Q8W, Q12W and Q16W) through Week 48 in the initial data submission. No event was reported for aflibercept.In the preliminary safety data to week 112 for retinal pigment epithelial tear (19 patients [2.9%] vs. 10 patients [1.5%] were reported. No new/additional retinal pigment epithelial tear events were reported in the faricimab arm. The majority of these events were previously reported during the loading phase, after 1 - 4 treatment injections.

Vitreous floaters: Through the 90-Day Safety Update Report (SUR) clinical cutoff date (Clinical Cut-Off Date), the incidence of vitreous floaters in the study eye was 3.8% (25 patients) in faricimab arm and 2.1% (14 patients) in aflibercept arm. All events of vitreous floaters were reported as non-serious and mild in severity, with the exception of one patient in the aflibercept arm experiencing severe (but not serious) vitreous floaters.

The exposure-adjusted incidence rate for vitreous floaters events based on cumulative data available to the SUR Clinical Cut-Off Date of 9 April 2021, was slightly higher for faricimab at 2.66 per 100 PYs for faricimab and 1.77 per 100 PY for aflibercept. The events of vitreous floaters reported in the preliminary week 112 data overview (30 patients [4.5%] vs. 17 patients [2.6%]), were non-serious and mild in severity, except for one severe case in each arm. These events of vitreous floaters were not associated with any IOI event.

IOP increase AEs: Using the 90-Day Safety Update Report (SUR) clinical cutoff date (Clinical Cut-Off Date) of 9 April 2021, IOP increase adverse events were reported in 25 patients (3.8%) and 24 patients (3.6%), and ocular hypertension adverse events were reported in 9 patients (1.4%) and 5 patients (0.8%) in faricimab and aflibercept arms. The exposure-adjusted incidence rates for IOP increase ocular AEs in the study eye based on cumulative data available from baseline to SUR Clinical Cut-Off Date is 3.35 per 100 PY for faricimab and 3.25 per 100 PY for aflibercept. Ocular hypertension is less than 1 per 100 PY for both faricimab and aflibercept.

In terms of ocular safety in the nAMD population, there are some parameters where reports of ocular AEs and rates of discontinuation are numerically higher for faricimab when compared to aflibercept. However, this picture is not consistent across all currently available cumulative safety data for faricimab. As can be seen from the currently available cumulative data above, incidences of certain AEs were also higher in the aflibercept population when compared to faricimab.

Whilst the preliminary data to week 112 has been provided for faricimab in this indication, it is highlighted that the formal submission of the full safety data from the nAMD clinical trials is still anticipated. Long term safety data for faricimab will be further followed through the LTE which is listed in the RMP.

Through Week 112, the overall incidence of serious ocular AEs in the study eye was low and comparable across treatment arms (4.4% in both treatment arms), with the exception (> 0.5%

difference between treatment arms) of retinal pigment epithelial tear (4 patients [0.6%] in the faricimab arm and 0 patients in the aflibercept arm).

From the provided 90-day safety update report it was noted that more subjects withdrew from study treatment when treated with faricimab compared to aflibercept due to ocular adverse events (2% for faricimab and 0.8% for aflibercept in pooled phase 3 nAMD studies). However, as indicated above, an overall imbalance in favour of aflibercept was not consistently demonstrated in the currently available safety data in the nAMD population.

Adjudicated APTC events: In the Phase III LUCERNE (GR40844) Study through Week 48, there was a small imbalance in cases reported as adjudicated APTC events in the faricimab treatment group (n=4, 1.2%) compared to aflibercept (n=3, 0.9%) but the numbers are small. The number of adjudicated APTC events reported in TENAYA was the same for both faricimab and aflibercept (n=3, 0.9%) for both treatment arms. Additional clarification was requested in relation to these APTC events.

The preliminary safety data from Week 112, showed that the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was low and comparable across treatment arms (3.3% and 3.0% in the faricimab and aflibercept Q8W arms, respectively).The Applicant submitted a 90 day Safety update report (SUR) with DLP of April 2021 with their responses. The applicant clarified that the overall cumulative rate of APTC events is generally balanced between both treatments at the time of the 90 day SUR. Longer term safety data and the final dataset from the pivotal clinical trials in nAMD is still outstanding however but will be followed closely through the LTE study.

In order to provide a further update on the safety data for the nAMD population in the pivotal clinical studies for faricimab, the applicant presented an overview of safety data in a Safety Update Report (SUR) until the DLP of April 2021 and compared this to the original safety data from week 48.

The available data in the SUR comparing an overview of safety Through Week 48 and SUR from the Pooled Phase III nAMD Studies shows that the total numbers of patients with at least one AE and patients experiencing an SAE are similar between the faricimab and aflibercept treatment groups (and slightly higher in the aflibercept treatment arm).

The total number of fatal cases reported is noted to be similar but numerically higher in the faricimab treatment group (n=19;2.9% versus n=15;2.3%).

More patients withdrew from the studies due to AEs in the faricimab treatment group (n=31;4.7% versus n=23; 3.5% for aflibercept).

Fewer patients in the faricimab nAMD population experienced at least one AESI (n=25;3.8% versus n=33; 5.0% for aflibercept).

The overall rate of ocular AEs was similar between both faricimab and aflibercept treatment groups (n=319;48% versus n=308;46.5%) but noted to be slightly higher in the faricimab group.

Fewer patients treated with faricimab were reported as having an ocular SAE (n=17;2.6% versus n=23; 3.5% for aflibercept). Although the number of treatment-related serious ocular AEs (n=10; 1.5% versus n=2;0.3%) and withdrawals due to ocular AEs was higher for faricimab (n=13; 2.0% versus n=5; 0.8% for aflibercept).

Ocular events of special interest were numerically higher in the aflibercept treatment groups (n=13; 2.0% faricimab versus n=22; 3.3 for aflibercept).

In the SUR, the overall rate of non-ocular AEs was generally balanced between both the faricimab and aflibercept treatment groups and slightly higher for aflibercept (n=439; 66.1% for faricimab versus

n=448; 67.7% for aflibercept). Non-ocular SAEs were higher in the aflibercept treatment group compared with faricimab (n=105; 15.8% versus n=121; 18.3% for aflibercept).

The overall rate of adjudicated APTC events was the same for both groups (n=14; 2.1% for each group).

On the basis of the available updated presented to DLP April 2021, supported by the preliminary overview for safety through to week 112, it is agreed that the safety profile of faricimab in the SUR is generally consistent with that presented in the SCS (Week 48 and Week 60 for nAMD), and remains broadly comparable to aflibercept.

It is highlighted that the total number of withdrawals due to AEs are higher for faricimab versus aflibercept when compared with the earlier week 48 data (1.2% versus 1.5% at week 48 compared to 4.7% faricimab versus 3.5% aflibercept in the SUR). The rate of withdrawals due to ocular AEs is also noted to have risen for faricimab over time when compared to aflibercept (0.9% faricimab versus 0.2% aflibercept at week 48 compared to 2.0% faricimab versus 0.8% aflibercept in the SUR).

Through Week 112, the incidence of AEs leading to study treatment discontinuation was low in both treatment arms (28 patients [4.2%] in the faricimab arm and 18 patients [2.7%] in the aflibercept arm). The incidence of ocular AEs leading to study treatment discontinuation through Week 112 was also low (17 patients [2.6%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm), which was 11 more patients in the faricimab arm and 7 more patients in the aflibercept arm since the primary analysis (at Week 48). No pattern was observed in ocular AEs leading to study treatment discontinuation in terms of timing and per regimen. The most common ocular AE leading to study treatment discontinuation was neovascular age-related macular degeneration (verbatim, worsening of nAMD; 9 patients [1.4%] in the faricimab arm and 4 patients [0.6%] in the aflibercept arm).

The incidence of AEs leading to study discontinuation was low in both treatment arms (33 patients [5.0%] in the faricimab arm and 35 patients [5.3%] in the aflibercept arm). The incidence of ocular AEs leading to study discontinuation through Week 112 was also low (1 patient [0.2%] in the faricimab arm and 5 patients [0.8%] in the aflibercept arm).

In general, the safety profile of faricimab in the nAMD indication can be considered to be sufficiently characterised noting that there is an absence of longer-term safety data for faricimab. This is reflected in the RMP. It is recommended the evolving safety profile of faricimab should continue to be closely monitored. The updated safety data should continue to be presented as data emerges, especially considering the status of faricimab as a new active substance with new mode of action. The applicant has committed to closely following the ongoing safety of faricimab in the LTE study and will provide regular updates on safety in the PSUR.

nAMD:Ocular Selected Adverse Events Intraocular Inflammation Events through Week 48

Intraocular inflammation (IOI) events are a topic of special interest. The overall rate of IOI in the study eye was low in general and while broadly comparable between the treatment arms (13 patients [2.0%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm), it is noted that there was a trend towards a slightly higher incidence of IOI in the faricimab treatment group.

Through Week 48, the per-injection rate of IOI events in the study eye was 0.38% in the faricimab arm and 0.18% in the aflibercept arm.

It is also noted that this trend towards a numerically higher rate of IOI continued past Week 48 as the cumulative data from baseline to the Clinical Cut-Off Date indicates that at least one IOI event was reported in 2.3% of patients in the faricimab arm and 1.5% in the aflibercept arm.

While the majority of IOI events in the study eye were mild or moderate in severity in the faricimab and aflibercept arms, through Week 48, 3 patients (0.5%) in the faricimab arm and 1 patient (0.2%) in the aflibercept arm experienced at least one severe IOI event in the study eye. The IOI events reported past Week 48 have been mild-moderate in intensity with no severe events reported to date.

There were no IOI events associated with retinal vasculitis or occlusive disease in any treatment arms based on currently available data at the time of submission.

In view of the importance of IOI events, the applicant was asked to present a comparative overview of exposure-adjusted incidence rates for IOI events based on the totality of the cumulative data available from baseline to currently available safety available since data DLP.

In the Safety update report (SUR), the incidence of intraocular inflammation (IOI) events remained low and comparable between the treatment arms (18 patients [2.7%] in the faricimab arm and 12 patients [1.8%] in the aflibercept arm). There were no new IOI events reported as retinal vasculitis or occlusive disease in any treatment arms.

In the preliminary overview of safety through Week 112, the incidence of IOI events in the study eye was low in both treatment arms (20 patients [3.0%] in the faricimab arm and 15 patients [2.3%] in the aflibercept arm.

Five ocular AEs of endophthalmitis were reported through Week 112 (3 patients [0.5%] in the faricimab arm and 2 patients [0.3%] in the aflibercept arm). All events were assessed as serious. Two cases were considered to be related to faricimab treatment; one of which resulted in discontinuation of study treatment. All events except one case in the aflibercept arm resolved. This event resulted in withdrawal of aflibercept treatment, and the event was considered related to procedure.

Long term immunogenicity data for faricimab is considered an area of missing information which requires close monitoring going forward. The SmPC should also be further strengthened as recommended in the LoOI.

nAMD:Retinal Vascular Occlusive Disease

There was one case of retinal artery embolism reported with faricimab.

After Week 48 to the Clinical Cut-Off Date, there were no additional retinal vascular occlusive disease AEs in the study eye.

nAMD:Intraocular Pressure Mean

The safety data relating to IOP increased AE in the study eye showed that the overall rate of IOP increased was the same for patients in both the faricimab and aflibercept treatment groups (n= 18 patients (2.7%) in each treatment arm).

One case of IOP increased AEs in the faricimab arm was considered serious but had resolved by the Clinical Cut-Off Date.

Through the Clinical Cut-Off Date, 4 patients (0.6%) in the faricimab arm and 5 patients (0.8%) in the aflibercept arm developed ocular hypertension in the study eye. An update on the cumulative data in respect of IOP increased was provided as part of the request to provide exposure-adjusted incidence rates for ocular AEs, AESIs based on the totality of the currently available data, as outlined above.

As of clinical cut-off point, the number of patients developing new or worsened cataracts and the distribution of cataract by grade was generally similar between the faricimab and aflibercept treatment groups.

nAMD:Retinal Break or Detachment

The number of patients found to have a post-baseline retinal break or retinal detachment in the study eye were low and similar between the faricimab and aflibercept treatment groups based on cumulative available data.

nAMD:Non-Ocular AEs

The overall rates of non-ocular AEs both non-serious and serious are comparable between faricimab and aflibercept treatment arms, the overall rates reported are generally numerically higher in the aflibercept treatment group.

The incidence of non-ocular AEs through week 48 was comparable between the treatment arms (52.1% in the faricimab arm and 54.8% in the aflibercept arm), with the exception (≥1% difference in any treatment arms: faricimab arm vs. aflibercept arm) of hypertension (3.6% vs. 2.4%), arthralgia (3.0% vs. 1.7%), fall (1.8% vs. 2.9%), bronchitis (2.6% vs. 1.4%), blood pressure increased (0.2% vs. 1.2%), and dyspnea (0.2% vs. 1.2%).

The incidence of serious non-ocular AEs through week 48 was comparable between the treatment arms (10.2% in the faricimab arm and 12.4% in the aflibercept arm).

It is noted that the pivotal studies were ongoing at the time of submission of this application. The applicant therefore provided an overview of available safety data up to week 60 and clinical cut off point in the nAMD indication and further data is provided in the 90 day SUR provided with the responses.

The incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was low and comparable between the treatment arms (7 patients [1.1%] in the faricimab arm and 6 patients [0.9%] in the aflibercept arm) at the time of primary analysis at week 48.

In addition, it is noted that there was a trend towards a higher number of fatal cases of adjudicated APTC events reported following treatment with faricimab at week 60 compared with the aflibercept treatment group, with the number of fatal cases reported increasing by 5 for faricimab (n=2 or 0.3% at 48 weeks increasing to n=7 or 1.1% at week 60 for faricimab) versus (n=3 or 0.5% at week 48 for aflibercept increasing to n=5 or 0.8% at week 60).

It is noted that a number of APTC events were reported for faricimab in the Phase II clinical studies but these were not included in the analysis of APTC events which has been justified by the applicant during the procedure.

The applicant provided a cumulative overview of non-fatal and fatal cases of adjudicated APTC events for both treatment groups and presented the exposure adjusted incidence rates for APTC events (including non fatal events).

There was an imbalance between the total number of fatal cases reported for faricimab through to week 60 when compared to aflibercept (faricimab=12 versus aflibercept= 8). A complete listing of total numbers of fatal cases for both treatment groups was presented, including number of treatments administered and detailed causality assessment for any additional fatal cases reported since DLP (see also previous discussion on Fatal cases for DME and nAMD indications). In the SUR, no imbalances in adjudicated APTC events was noted between faricimab and aflibercept. Through Week 112, the incidence of externally adjudicated APTC-defined ATEs was low and comparable across treatment arms (3.3% and 3.0% in the faricimab and aflibercept Q8W arms, respectively).

This topic requires close monitoring and an update should be provided on any new safety data of relevance which emerges from the ongoing clinical trials. The applicant has agreed to add ATE events to the RMP which is endorsed.

nAMD: Fatal cases

In total, through Week 48, death was reported in 17 patients (9 patients [1.4%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm). The most common primary cause of death (greater than 2 patients in any treatment arm) was cardiac failure (2 patients [25.0%], both in the aflibercept arm). None of the deaths were suspected by the investigator to be related to study treatment.

After Week 48 to the Clinical cut-off point, death was reported in an additional 4 patients (2 patients in each treatment arm). The primary cause of death after Week 48 to the Clinical Cut-Off Date were pulmonary oedema and respiratory failure (1 patient [50.0%] each) in the faricimab arm; and bile duct cancer and pulmonary embolism (1 patient [50.0%] each) in the aflibercept arm.

As previously noted, the pivotal studies were ongoing at the time of submission of this application. The applicant therefore provided an overview of available safety data up to week 60 and clinical cut off point in the nAMD indication and further data was provided in the 90 day SUR provided with the responses and further preliminary data to week 112 from the clinical studies which were ongoing.

In addition, in relation to fatal cases arising from APTC events, it is been previously noted that there was a trend towards a higher number of fatal cases of adjudicated APTC events reported following treatment with faricimab at week 60 compared with the aflibercept treatment group, with the number of fatal cases reported increasing by 5 for faricimab (n=2 or 0.3% at 40 weeks increasing to n=7 or 1.1% at week 60 for faricimab) versus 2 for aflibercept (n=3 or 0.5% at week 40 for aflibercept increasing to n=5 or 0.8% at week 60). These findings and any updated results from ongoing clinical studies were further discussed by the applicant. Due to the overall imbalance in fatal cases in the safety data for some studies in the nAMD population (to a lesser extent compared to DME population), this issue was further addressed as part of the previous MO on clinical safety relating to imbalances in overall fatal reports and unexplained deaths with faricimab-please see detailed discussion of this topic for further background.

The reported total number of deaths was 9 cases (1.4%) at week 48, rising to 12 cases (1.8%) at week 60 for faricimab and stable 8 cases (1.2%) at week 48 and week 60 for aflibercept in pivotal nAMD studies. Fatal cases arising from APTC events were reported with 5 additional cases between week 48 and week 60 in the faricimab group (n=2 or 0.3% at 48 weeks increasing to n=7 or 1.1% at week 60 for faricimab) and two additional cases in the aflibercept group in the same time (n=3 or 0.5% at week 48 for aflibercept increasing to n=5 or 0.8% at week 60).

The Applicant clarified why the total number of reported deaths in the faricimab group increased by only 3 cases between week 48 and week 60, despite the 5 additional fatal cases reported for APTC related events already, these cases had already been assessed as part of the initial evaluation. Similarly, the total number of deaths in the aflibercept group remains stable between week 48 and week 60, despite 2 additional fatal cases reported for APTC related events.

A total of 34 patients died through the SUR Clinical Cut-Off Date (2.9% in the faricimab arm and 2.3% in the aflibercept arm). No deaths were suspected by the investigator to be related to study treatment.

In terms of overall fatal reports, a total of 34 patients died through the SUR Clinical Cut-Off Date (2.9% in the faricimab arm and 2.3% in the aflibercept arm). No deaths were suspected by the investigator to be related to study treatment.

In total, through Week 112, 44 deaths were reported (23 patients [3.5%] in the faricimab arm and 21 patients [3.2%]) in the aflibercept arm). None of the deaths were suspected to be related to study treatment by investigators in the preliminary overview of safety data submitted in advance of the formal submission of the final CSRs.

nAMD : Serious Ocular AEs

The number of serious ocular AEs occurring in the evaluable safety population was low and similar between both treatment groups. A slightly higher number of serious ocular AEs were reported in the aflibercept treatment group (2.0%, n=13) compared to the faricimab arm (1.7%, n=11).

In the faricimab treatment arm, n=2 patients reported a serious ocular event of worsening of nAMD compared to n=3 for aflibercept.

Serious ocular AEs in the study eye that were suspected to be related to study treatment by the investigator are reported for 8 patients (1.2%) in the faricimab arm (2 cases of uveitis, 2 cases of vitritis and 4 cases of retinal pigment epithelial tear), but only for 1 patient (0.2%) in the aflibercept arm (1 case of vitritis). Importantly, none of the serious retinal pigment epithelial tear events had resolved by Week 48 and one event of uveitis did not resolve.

There were 2 cases reporting uveitis in the faricimab arm versus 1 case in the aflibercept arm. 2 cases of viral uveitis were also reported in the faricimab arm with none reported in the aflibercept arm.

The Applicant discussed whether the increased load of protein and/or the additional mode of action (i.e. anti-Ang2) compared to aflibercept might be responsible for the increased occurrence in treatment related serious ocular AEs in the study eye for patients treated with faricimab. Despite further discussion in this aspect, it remains unclear whether increased incidences of serious ocular AEs in the study as compared to aflibercept are related to protein content and/or the mechanism of action (including the novel mechanism of Ang-2 inhibition, besides distinct mechanisms of VEGF inhibition between faricimab and aflibercept). It is recognised that the imbalance in treatment related serious ocular adverse events (1.2% for faricimab and 0.2% for aflibercept at week 48 report) became more pronounced after 90-days observation (1.5% for faricimab and 0.3% after aflibercept). However, on the basis of the preliminary safety data through Week 112, it is noted that the overall incidence of serious ocular AEs in the study eye was balanced across treatment arms (4.4% in both treatment arms), with the exception (> 0.5% difference between treatment arms) of retinal pigment epithelial tear (4 patients [0.6%] in the faricimab arm and 0 patients in the aflibercept arm).

nAMD: safety in special groups

The applicant provided subgroup analyses across the various subgroups as outlined-by age, gender, race and medical history.

On the basis of the initial data presented, no major differences were noted across the subgroups presented.

In the Safety Update report, the Applicant reports the requested patient numbers according to baseline blood pressure categories (low: <90/60, normal: ≥90/60 to 139/89 to include high normal, high: ≥140/90) and provides forest plots for subgroup analyses (baseline blood pressure, age categories, gender and time since nAMD diagnosis) on ocular AEs in the study eye. The Applicant concludes that no imbalances were observed across treatment groups in the incidences of ocular AEs, ocular SAEs, non-ocular AEs, and non-ocular SAEs. With respect to provided forest plots it is agreed that no clear negative impact (i.e. more AEs reported) of study treatment is concluded for any of the analysed subgroups with respect to non-ocular AEs, serious non ocular AEs, ocular AEs in the study eye and serious ocular AEs in the study eye in comparison to the comparator treatment (aflibercept). However, it is unclear whether results are compromised by the pooling of less intense treatment schedules in the

faricimab arm (i.e. Q16W and Q12W pooled with the Q8W treatment schedule), compared to the aflibercept arm that maintained all subjects in the most intense treatment schedule.

Patient numbers for the Q8W treatment schedule in the faricimab arm are low (i.e. n=143 subjects for pooled Phase 3 studies TENAYA and LUCERNE) and it is unclear whether any subgroup analyses are meaningful. Thus, the Applicant was asked to elaborate on the safety profile of subgroups (especially baseline blood pressure and age are of interest) that were followed in the Q8W faricimab treatment schedule. The Applicant provided a response outlining that in the TENAYA and LUCERNE studies through Week 60, pooled mean and median age were balanced across treatment interval subgroups and aflibercept. The maximum age in the faricimab Q8W subgroup (91 years) was lower than the faricimab Q12W (99 years) and faricimab Q16W (98 years) subgroups and the aflibercept Q8W (95 years) arm, which corresponds to slightly fewer > 85 year olds in the faricimab Q8W subgroup (9.1%) compared to the Q12W and Q16W subgroups and aflibercept arm (13.2%, 14.9%, and 19.3%, respectively. Within the individual nAMD studies, the mean and median age in the Q8W subgroup in TENAYA (73.3 years and 74.5 years, respectively) were slightly lower than the other faricimab treatment subgroups and aflibercept arm (range: 76.2-76.7 years and 76.0-78.0 years, respectively), with a maximum age of 88 years versus 95-99 years (range). LUCERNE was balanced across the faricimab subgroups and aflibercept arm, both in mean, median, and maximum age.

Of note, there are some differences within the treatment interval subgroups with respect to region. While a conclusion may not definitively be made, this may have an influence on the general reporting of AEs in different regions along with unknowns around the impact of the pandemic in each region, as regions may have been impacted at different times (e.g., lockdown, restrictions, access to general healthcare, etc.), and continues to do so in some areas.

Overall, more than half of patients in TENAYA were located in the United States compared to the LUCERNE study of which more than half were Rest of World/Asia.

Within the individual treatment subgroups, nearly half of patients in the LUCERNE faricimab Q8W were from the United States, which is similar to TENAYA. Systolic and diastolic blood pressure was balanced across subgroups and studies at baseline. High blood pressure at baseline was slightly higher in the faricimab treatment subgroups compared to the aflibercept arm and was balanced across the treatment interval subgroups. The difference was more pronounced between faricimab and aflibercept in LUCERNE, but balanced across both treatment intervals and arms in TENAYA. The Applicant discusses baseline data regarding age and high blood pressure in studies TENAYA and LUCERNE. It is noted that the request was intended to address the safety profile of subgroups within the Q8W treatment schedule. However, it is agreed that any post-hoc analysis regarding AEs in subgroups would suffer from compromised validity due to the low amount of subjects and AEs.

The Applicant has generally outlined that there were fewer > 85 year olds in the faricimab Q8W subgroup (9.1%) compared to the Q12W and Q16W subgroups and aflibercept arm (13.2%, 14.9%, and 19.3%).

For the pivotal nAMD study TENAYA, the mean and median ages were lower in the Q8W subgroup in (73.3 years and 74.5 years, respectively) when compared to the other faricimab treatment subgroups and aflibercept arm (range: 76.2-76.7 years and 76.0-78.0 years, respectively). Nevertheless, the maximum age of was still 88 years when compared to higher range of 95-99 years for the other subgroups.

There were no imbalances in the other pivotal nAMD study LUCERNE in relation to age across faricimab subgroups and aflibercept arm.

The Applicant also highlights that there were some demographic differences across the pivotal nAMD studies whereby >50% of patients in TENAYA were located in the United States whereas in LUCERNE,

more than half of patients were from the Rest of World/Asia. Within the individual treatment subgroups, nearly half of patients in the LUCERNE faricimab Q8W were from the United States, which is similar to TENAYA. The Applicant highlights that, particularly in the context of the global pandemic, this could have had some impact on issues such as reporting and access to general healthcare, but no firm conclusions can be made on the basis of the data presented.

Overall, there were no major imbalances in systolic and diastolic blood pressure across the nAMD pivotal studies, although the number of patients with high blood pressure at baseline was slightly higher in the faricimab treatment subgroups compared to the aflibercept arm.

On the basis of the limited discussion presented, it is difficult to draw any further robust conclusions in relation to the overall safety of the faricimab Q8W dosing regimen, nevertheless, the Applicant has provided a detailed response to address the question of limitations of the safety data for the faricimab Q8W regimen in the nAMD indication in their responses. Strengthening of the SmPC is recommended in relation to this topic and the Applicant has also confirmed that additional safety data from patients with nAMD on a faricimab Q8W dosing regimen could be provided from the long-term extension study, AVONELLE-X.

The Applicant is also asked to commit to ensuring that emerging safety data relating to this population should be provided regularly through the PSURs.

nAMD: Use in pregnancy and lactation

Faricimab has not been studied in pregnant women. It is not known whether faricimab can cross the placenta or cause harm to the fetus when administered to pregnant women.

There were no pregnancies reported in the TENAYA or LUCERNE studies; however, a total of two pregnancies were reported in the YOSEMITE and RHINE studies. In view of the potential teratogenicity of faricimab due to its pharmacological effects, as outlined in section 5.3 of the proposed SmPC, and given the status of faricimab as a new active substance with novel mode of action (and potential for exposure to women of child-bearing potential in the DME indication especially), the Applicant was requested to update the RMP to include pregnancy under 'missing information'. An updated RMP was submitted with the responses to reflect this concern.

nAMD: Immunological events

Anti-drug antibodies were analysed for patients treated with faricimab only, no data were generated for patients treated with aflibercept in pivotal studies or ranibizumab in the previous clinical phase 1/2 program. The incidence of treatment emergent ADAs was 10.4% (68 of 657 evaluated patients) in nAMD studies and an additional 1.8% of patients had ADAs at baseline (in total 75 patients with ADAs). The risk analysis provided by the applicant concludes no meaningful impact of ADA on overall safety. Still, ADA-positive patients had a higher incidence in events of intra-ocular inflammation (6.7% of ADA-positive patients and only 1.2% of ADA-negative patients). A comparable pattern was also seen in the clinical program on DME. Around 10% of patients (113 ADA-positive patients and 1130 ADA-negative patients) developed ADAs upon exposure to faricimab and within this subgroup of ADA-positive patients 9.7% had an event of intra-ocular inflammation. In contrast, only 0.5% of patients had intra-ocular inflammation in the ADA-negative group. The rate of treatment-induced ADA formation in the population treated with faricimab from pivotal studies is also in line with data from phase 2 studies AVENUE (11.3% of patients) and STAIRWAY (10.9% of patients). The general incidence of IOI in the study eye (independent of ADA status) was 2% for patients treated with faricimab and 1.2% for patients treated with aflibercept in pivotal studies on nAMD. These data suggest, that faricimab induces ADA formation in approximately 10% of treated patients and that these ADAs are increasing the chance of IOI. It is agreed with the applicant that a direct comparison of the observed incidences of treatment-induced ADAs to other products (e.g. anti-VEGF agents) might

be misleading, due to differences in sample handling and assays used for detection. Still, no other comparison is possible after no ADA status was tested for patients in the comparator arm. Within the clinical program for aflibercept (as described in the EPAR of Eylea) treatment emergent ADAs were detected to a similar extent as for baseline in around 1-3% of patients across treatment groups.

A requested comparison of the immunogenic potential of other anti-VEGF agents (e.g. aflibercept and ranibizumab) did not indicate reason for concern. Upon request, the applicant also provided a list of patients with treatment induced ADAs for each of the applied faricimab treatment schedules (i.e. Q8W, Q12W and Q16W). No relevant differences were recognized across treatment schedules with respect to the reported incidences of ADAs. Furthermore, the Applicant clarified that 3 of the 75 ADA-positive subjects (across pooled phase 3 studies) were recorded with serious AEs (worsening of nAMD, uveitis and vitritis in the study eye) and provided details on these three subjects . Two of these events (uveitis and vitritis) were considered related to study treatment, but any relation of these adverse events to the presence of anti-faricimab antibodies is not evident. Timing of events (ADA detection and onset of SAEs) does not exclude a potential negative impact of ADAs, but a clear causal relation between the occurrence of ADA and serious AEs cannot be established with the data at hand for the nAMD clinical program.

The applicant has presented cumulative safety data relating to IOI events in the nAMD population up to week 60 in which the exposure adjusted incidence rate for IOI was 2.26 per 100 PY for the faricimab arm and 1.28 per 100 PY for aflibercept, indicating one additional IOI event in the faricimab group per 100 patient years.

The rate for IOI per individual treatment regime was Q16W faricimab treatment regime (2.06) with a higher overall incidence of IOI events with faricimab dosing regimes Q8W (5.38) and Q12W (4.94) are noted, which are concerning in the context of the evolving safety profile of farcimab, particularly over longer term treatment. The applicant was asked to discuss this finding further and to discuss plans to monitor this issue beyond routine pharmacovigilance, going forward, particularly in relation to the more frequent faricimab posology regimes.

The Applicant clarified that immunogenicity data beyond the primary analysis will be available at the time of the final Week 112 analysis for TENAYA and LUCERNE, which will be submitted after approval.

In TENAYA and LUCERNE, patients in the faricimab arm were on fixed Q8W, Q12W, Q16W treatment intervals until the Week 60 visit; from Week 60 onward, all faricimab patients were treated according to a personalized treatment interval (PTI) dosing regimen. Treatment interval analysis (i.e., analysis by different faricimab 'posology regimes') beyond week 60 cannot be easily performed, since the PTI allows for a more flexible dosing regimen based on patient needs, allowing patients to be dosed at different intervals. As such, patients may not remain on one interval for the remainder of the study.

ADAs were assessed in faricimab treated patients at baseline and at Weeks 4, 20, 48, 76 and 112. ADA occurrence in TENAYA and LUCERNE by treatment interval at Week 24 (Q8W, Q12W, or Q16W) through Week 48 was provided as part of D120 Response to Question (OC 163). Considering median time to ADA occurrence was 20 weeks after start of the treatment, the Applicant believes that ADA data by treatment interval up to Week 48 supports the observation that no relevant differences were recognised across treatment schedules with respect to the reported incidences of ADAs.
As described, a long-term extension (LTE) study is ongoing for the patients who completed TENAYA and LUCERNE through Week 112. This LTE study (AVONELLE-X) will continue to collect safety information, including assessment of immunogenicity, for a further two years, resulting in up to four years of exposure and long-term safety for 991 patients from the baseline of TENAYA/LUCERNE through the end of AVONELLE-X. All patients in AVONELLE-X are treated with faricimab PTI, therefore, the safety data from the LTEs will comprise more frequent dosing regimens. Key safety outcomes include AEs (ocular and non-ocular), SAEs, and AESIs, along with collection of samples for the

assessment of ADA at 5 different time points throughout the LTE study (i.e., Day 1, Week 8, Week 12, Year 1, and Year 2).
The Applicant will continue to monitor the long-term immunogenicity including ocular events, SAEs, and AESIs in ADA-positive patients within the ongoing LTE study AVONELLE-X. The AVONELLE-X final CSR is currently planned to be available for submission to the Agency in Q1 2025 but in the interim, the applicant will provide a more regular update on this topic in the PSURs.

nAMD: Discontinuations due to AEs

The rate of patient discontinuation from treatment up to the week 48 was numerically higher overall in the faricimab treatment group compared to the aflibercept treatment group (1.7% and 0.6% of discontinuations due to AEs as well as 0.9% and 0.2% due to ocular AEs for faricimab and aflibercept at week 48, respectively). Similarly, a numerically higher rate of dose interruption was observed during the pivotal clinical studies in the faricimab treatment arm (1.8% versus 1.2%).

In the SUR, the overall incidence of AEs leading to study treatment discontinuation through the SUR Clinical Cut-Off Date was higher in the faricimab arm compared with that in the aflibercept arm (3.3% in the faricimab arm and 1.5% in the aflibercept arm).

The incidence of AEs leading to study discontinuation through the SUR Clinical Cut-Off Date remained low (4.7% in the faricimab arm and 3.5% in the aflibercept arm).

The incidence of ocular AEs leading to study treatment discontinuation remained low in both treatment arms (13 patients [2.0%] in the faricimab arm and 5 patients [0.8%] in the aflibercept arm).

The incidence of IOI events leading to treatment discontinuation was higher in the faricimab arm than that in the aflibercept arm (5 patients [0.8%] in the faricimab arm and 1 patient [0.2%] in the aflibercept arm).

The overall trend for discontinuation rates based on the available cumulative safety data indicate that discontinuation rates are generally found to be slightly higher for faricimab compared to aflibercept.

In the preliminary safety data from week 112 provided with the responses, the incidence of AEs leading to study treatment discontinuation was low in both treatment arms (28 patients [4.2%] in the faricimab arm and 18 patients [2.7%] in the aflibercept arm).

The incidence of ocular AEs leading to study treatment discontinuation through Week 112 was also low (17 patients [2.6%] in the faricimab arm and 8 patients [1.2%] in the aflibercept arm), which was 11 more patients in the faricimab arm and 7 more patients in the aflibercept arm since the primary analysis (at Week 48). No pattern was observed in ocular AEs leading to study treatment discontinuation in terms of timing and per regimen. The most common ocular AE leading to study treatment discontinuation was neovascular age-related macular degeneration (verbatim, worsening of nAMD; 9 patients [1.4%] in the faricimab arm and 4 patients [0.6%] in the aflibercept arm).

This topic should continue to be closely followed through the LTE study and regular updates on discontinuation rates should be provided in the PSURs.

Diabetic macular edema

DME:Data set

The primary safety data analysis provided by the applicant for the diabetic macular edema indication is based on the pooled Phase III DME safety data (YOSEMITE and RHINE) up to the timepoint of the primary analysis (Week 56). A further update in the form of a 90 day Safety Update report (SUR) to April 2021 was provided with the responses.

It is noted that the following dose schedules were tested in the pivotal studies:

- Faricimab Q8W group: 6 mg faricimab injections Q4W to Week 20, followed by 6 mg faricimab injections Q8W to Week 96, followed by the final study visit at Week 100.
- Faricimab PTI group: 6 mg faricimab injections Q4W to at least Week 12, followed by Personalized Treatment Interval dosing In this arm the frequency of dosing in this arm could range from Q4W to Q16W.)

The faricimab Q8W fixed dose regimen was selected to match the approved dose regimen for the active comparator aflibercept Q8W arm in the control arm. The faricimab PTI regimen incorporates the possibility to extend, as well as reduce dosing intervals according to patient's treatment needs, thereby avoiding overtreatment and reducing burden of excessive check-ups/HCP visits for patients who can maintain their initial vision gains without frequent injections, while providing more intensive treatment to those patients who need it. A reduced need for injection while maintaining visual acuity is seen as highly desirable, as a large proportion of AEs of intravitreally administered VEGF-inhibitors are injection-related. A non-inferior visual acuity outcome vs. aflibercept Q8W while being able to reduce the number of injections would be regarded as relevant. In the scenario of a non-inferior outcome of the faricimab, its safety profile needs to be highly reassuring.

For the SmPC dose schedules are similar to those investigated in the Faricimab PTI group. In line with the SmPC the recommended dose for Vabysmo is 6 mg administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses. Thereafter, based on the physician's judgement of the individual patient's visual and/or anatomic outcomes, the dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks.

In both pivotal studies aflibercept was used as a comparator. Eylea was approved in the EU in 2012 and therefore the safety profile of this treatment is established. There are some differences between mode of action of faricimab and aflibercept which could have some implication for safety. Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that selectively binds to and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

The aflibercept Q8W fixed dose regimen was chosen for the comparator arm, in line with the posology of aflibercept in the DME indication. As per SmPC for aflibercept, the treatment should be initiated with one injection per month for five consecutive doses, followed by one injection every two months. However, after the first 12 months of treatment with aflibercept, and based on visual and/or anatomic outcomes, the treatment interval may be extended, such as with a treat-and-extend dose regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes.

While the comparison between faricimab Q8W and aflibercept Q8W dose regimen is appropriate, the comparison between an unfixed PTI dose regimen of faricimab AND a fixed Q8W dose regimen for aflibercept raises some concerns. As these two dose regimens are inherently different, the interpretation of safety findings is difficult, in particular given that a number of patients in the faricimab PTI arm received more intensive treatments i.e. more injections than the patients in the aflibercept Q8W arm. A PTI regimen for the comparator at year 2 in one of the two pivotal trials, as suggested during a scientific advice procedure, would have been more suitable, however, Applicant's arguments as to why these schedules were chosen can be followed (see discussion on efficacy).

DME: Exposure

In pivotal studies, in total 1262 patients were exposed to faricimab (630 patients received faricimab in the Q8W dosing scheme while 632 patients received faricimab in the PTI dosing scheme) while 625 were exposed to aflibercept (active comparator). Both treatment naïve patients and patients who have been previously treated with IVT anti-VEGF therapy were recruited in the study, which is considered important to improve external validity. The median duration of exposure was the same between all treatment arms (56.1 weeks). At the time of submission, an additional analysis up to clinical cut-off date (Clinical Cut-Off Date) was provided which includes additional 16.1 weeks of treatment duration for 1031 patients in the combined faricimab arms and 15.8 weeks of treatment duration for 506 patients in the aflibercept Q8W arm. It needs to be highlighted that both pivotal studies were ongoing at the time of submission. With the responses to the Day 120 List of Questions the Applicant submitted additional safety data i.e the 90-day safety update report was provided (SUR). As of the SUR Clinical Cut-Off Date, the median duration of exposure was similar in all treatment arms (93.1, 95.1, and 92.9 weeks in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively); approximately an additional 37 weeks (median) of duration of exposure was provided in this SUR compared with SCS (Week 56).

It is noted that the RHONE-X LTE extension study is still ongoing. The applicant is requested to provide regular PSUR updates on emerging long-term safety identified in this study**.**

Dose investigated

The PTI arm comprised a myriad of different individualised treatment schemes, with differences seen not only between patients but also within the same patient in the course of treatment and different treatment regimens have not been investigated systematically. This is of lesser concern for longer intervals i.e. Q12W and Q16W, as they are expected to be associated with less AEs. Contrary to that, a more intensive dosing scheme such as Q4W is expected to be associated with more AEs. By pooling all the data together, the safety of a specific dosing interval is not discernible i.e. likely better safety profile of longer intervals is obscured by the likely worse safety profile of shorter intervals. The applicant was requested to provide separate safety analyses for patients in faricimab PTI arm who received less versus equal or more administrations in comparison to the planned administrations in the fixed Q8W dosing schedule

Furthermore, about 10%-15% of patients in both phase III studies remained in the Q4W dosing interval through Week 56 without a single increase in dosing interval. As this is the most intense dose regimen and it is expected to be associated with more AEs, a separate safety analysis was needed for patients who remained in the Q4W interval through Week 56 and beyond.

The applicant provided the requested analysis. In relation to the safety profile depending on the number of injections, based on presented (limited) data there is no strong evidence to support higher incidence of AE with increased number of injections, however small but consistent trends can be observed, in particular for ocular AEs. Also more ocular SAEs and AESI were reported with higher number of injections, although the interpretation of these results should be cautious due to overall low incidences. Higher incidence of cardiac disorders has also been observed with an increased numbers of injection, but same limitations pertaining to the small numbers apply here as well.

The safety data for the faricimab Q4W dosing interval, albeit limited, indicate a higher risk of both ocular and non-ocular adverse events, including higher risk for serious AEs compared to faricimab Q8W interval but also compared to aflibercept Q8W dosing regimen.

Consequently, the Applicant was requested to include an appropriate statement in the section 4.8 of the SmPC that dosing intervals shorter than Q8W are associated with a higher risk of ocular (AEs, SAEs and AESI) and systemic adverse events, including serious systemic adverse events

The applicant included in the SmPC information that the data in this population is limited (see below) which is insufficient.

"Populations with limited data: *There is only limited experience in the treatment of DME patients with type I diabetes, patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), sustained dosing intervals shorter than Q8W, or nAMD and DME patients with active systemic infections. There is also no experience of treatment with faricimab in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients."*

The Applicant appropriately reflected in the SmPC – upon request of the CHMP- the lack of information on dosing schedules with intervals shorter than 8 weeks.

DME: Common adverse events

In DME pivotal studies through Week 56 treatment-emergent Adverse Events were reported slightly more frequently the faricimab Q8W group (81.4%) as compared to the aflibercept Q8W treatment (78.1%). In the faricimab PTI group the incidences of subjects with any TEAE was lower (76.9%). The incidences of subjects with any SAE was higher in both faricimab (Q8W and PTI) as compared to the aflibercept Q8W group, although the difference was small. 23.7% and 19.9% of patients experienced SAEs in the faricimab Q8W and faricimab PTI respectively. SAEs were reported in 18.2 % in the aflibercept group.

In DME pivotal studies through Week 56 a total 31 deaths were reported. 9 (1.4%) in patients receiving aflibercept and 22 (1.7%) in patients receiving faricimab. Upto the Clinical Cut-Off Date 35 (2.8%) patients treated with faricimab experienced death as compared to 12 patients (1.9%) receiving aflibercept. The number of patients withdrawn from the study or withdrawn from the study treatment was small (2.5% or less in any treatment group)

As per the SUR Clinical Cut-Off Date in the pooled Parent Studies the incidence of AEs remained generally comparable across all treatment arms (567/630 [90.0%], 551/632 [87.2%], and 545/625 [87.2%] patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

DME: Ocular adverse events

General information

Through Week 56 the incidence of ocular adverse events was slightly higher in the faricimab groups (i.e Q8W-37.3%, PTI 35.6%) as compared to the aflibercept group (34.4%). The most common ocular AEs reported were conjunctival haemorrhage (6.7% for faricimab and 6.1% for aflibercept), cataract (4.6% for faricimab and 4.8% for aflibercept), vitreous detachment (3.2% for faricimab and 3.2% for aflibercept) and vitreous floaters (3.4% for faricimab and 1.6% for aflibercept).

As per the SUR Clinical Cut-Off Date in the pooled Parent Studies the incidence of ocular AEs in the study eye was 47.5%, 47.3%, and 43.7% of patients in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively, with an increase of approximately 10 percentage points in the incidence in all treatment arms compared with SCS (Week 56). There were a small number of ocular AEs with ≥2% difference between the faricimab Q8W or PTI arms and the aflibercept Q8W arm such as cataract, dry eye, intraocular pressure increased, and vitreous floaters.

DME: Intraocular pressure increased

Intraocular pressure increased occurred with slightly higher frequency in the faricimab group as compared to the aflibercept group. Through the Clinical Cut-Off Date, 24 patients (3.8%), 18 patients (2.8%), and 14 patients (2.2%) experienced an intraocular pressure increased AE in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. Through the Clinical Cut-Off Date, 2 patients (0.3%), 8 patients (1.3%), and 1 patient (0.2%) developed ocular hypertension in the study eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. Cases of intraocular pressure increased were considered as treatment-related ocular AEs by investigators. In two cases i.e one case of intraocular pressure increased on one case of Ocular hypertension required surgical or medical intervention to prevent permanent loss of sight.

At the time of the final 2-year analysis of YOSEMITE and RHINE the proportion of patients with events with IOP increased was 5.1% and 3.3% in the faricimab Q8W and PTI arms, respectively, and 2.6% in the aflibercept arms difference faricimab Q8W versus aflibercept 2.5% (95%CI: 0.3%, 4.9%); difference faricimab PTI versus aflibercept: 0.8 (95%CI: -1.3, 2.8).

The applicant was requested to discuss cases of intraocular pressure increased reported in pivotal studies.

The applicant considers that volume rather than mode of action is relevant to increase in IOP, and faricimab volume is considered acceptable as evident in the lack of significant findings in pre-dose to postdose IOP fluctuations. Further, the applicant clarified that nearly all intraocular pressure increased AEs were considered non-serious, with the exception of one event in the faricimab PTI arm in RHINE study. This serious case resolved the same day following Anterior Chamber Paracentesis and was considered as mild in severity and not related to study drug.

In addition, there were no clinically meaningful differences in the mean change from pre-dose to post-dose IOP across the treatment arms, and there was no observable increase in pre-dose IOP from baseline over time. Finally, no safety signal has been detected with respect to sustained IOP increases or ocular hypertension to date. This justification provided by the applicant was considered acceptable.

DME: Sight-Threatening Adverse Events

Through Week 56, a higher incidence of sight-threatening adverse events in the study eye occurred in both faricimab arms compared to the aflibercept Q8W arm (15 patients [2.4%], 17 patients [2.7%], and 6 patients [1.0%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively). The per injection rate of AESIs through Week 56 in the study eye was slightly higher in both faricimab arms compared to aflibercept arm (0.32%, 0.33%, and 0.10% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively.)

The applicant was requested to provide the updated safety data and comment on the fact that the majority of sight-threatening adverse events were reported in the faricimab groups (i.e in 32 patients) whereas in the comparator group these events were only reported in 6 patients. The applicant provided the updated safety information.

By Week 100 the incidence of AESIs of sight-threatening events was (defined as decrease of ≥30 letters in visual acuity (VA) score) 18 patients [2.9%], 23 patients [3.6%], and 16 patients [2.6%] the faricimab Q8W, faricimab PTI and aflibercept Q8W arm, respectively

The event requires surgical or medical intervention: (6 patients [0.95%], 8 patients [1.3%], and 4 patients [0.7%] the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively

However, the majority of the ocular AESIs in the study eye resolved, resolved with sequelae, or were resolving by the Week 100, and were considered not related to study drug by the investigator and did

not result in a change to study drug. While drug had to be withdrawn in 3 patients in pooled faricimab arms, there were no cases of drug withdrawal in pooled aflibercept arms.

It can be agreed with the applicant that the sight-threatening events were reported at an overall low incidence however, taking into consideration these imbalances sight-threatening AEs should continue to be closely monitored particularly over longer term treatment with faricimab. The applicant clarified that sight-threatening adverse events will be monitored within the ongoing long-term extension (LTE) study, RHONE-X. This is acceptable.

DME: Intraocular inflammation events

Through Week 56, the incidence of intraocular inflammation events in the study eye was higher in both faricimab groups as compared to the aflibercept groups. These events were reported in 8 patients [1.3%], 9 patients [1.4%], and 4 patients [0.6%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

The following events were most frequently reported: iritis, uveitis, vitritis and iridocyclitis. Although the majority of intraocular inflammation events in the study eye were mild or moderate in severity, severe events were also reported but only in the faricimab groups. These severe events were one case of vitritis in the faricimab Q8W arm and 3 cases of uveitis in the faricimab PTI arm.

There were 2 patients with at least one IOI event in the study eye associated with vision loss ≥15 letters (uveitis and chorioretinitis) and 1 patient with vision loss ≥30 letters keratic precipitates and uveitis)); all events occurred in the faricimab PTI arm and were considered to be related to faricimab.

There was one IOI SAE of reported keratouveitis initially suspected to be related to possible herpetic origin. Again this SAE was reported in the faricimab group, and later on the investigator considered the event of keratouveitis to be related to faricimab and procedures (unspecified). The Applicant's claim on the lack of causality between faricimab and keratouveitis has not been substantiated. The Applicant is asked to provide evidence for the lack of causality or otherwise include keratouveitis in the PI (OC/SmPC).

The provided data seems to indicate that the risk of development of intraocular inflammation/infection could be higher in patients treated with faricimab as compared to those treated with aflibercept. In particular, there are concerns in relation to the higher frequency of endophthalmitis. The applicant was requested to discuss and provide the updated safety data in relation to this safety issue.

Through Week 100 the pooled rate of IOI (uveitis including iritis, iridocyclitis, and vitritis) for YOSEMITE and RHINE was 1.6% (95% CI: 1.03%, 2.44%) for faricimab and 1.1% (95% CI: 0.54%, 2.29%) aflibercept (difference of 0.5% (95% CI: -0.82%, 1.49%. Exposure-adjusted incidence rates for any IOI through Week 100 were low but slightly higher in the PTI group (0.88, 1.38, and 0.88, in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

The pooled rate of endophthalmitis for YOSEMITE and RHINE through the entire studies was 0.5% (95% CI: 0.22%, 1.03%) for faricimab and 0.2% (95%CI: 0.03%, 0.90%) for aflibercept (difference of 0.3% [95% CI: -0.47%, 0.89%]). Exposure-adjusted incidence rates for endophthalmitis through Week 100 were 0.26 per 100 PY and 0.09 per 100 PY for faricimab and aflibercept, respectively.

In addition, IOIs occurred more frequently in ADA positive patients i.e the incidence of IOI in ADA-positive patients was 5/75 [6.7%] in nAMD (Week 48) and 15/128 [11.7%] in DME (Week 100) compared with 7/582 [1.2%] in nAMD (Week 48) and 5/1124 [0.4%] in DME (Week 100) ADA-negative patients.

It can be agreed that the risk of IOI was low however the frequency of IOI in patients treated with faricimab was slightly higher than in patients treated with aflibercept (in particular in the PTI group).

Further, it is noted that IOIs occurred more frequently in ADA positive patients. Therefore, cases of IOI, (including those reported in ADA positive patients), should continue to be closely monitored particularly over longer term treatment with faricimab and updated safety data presented as data emerges, especially considering the status of faricimab as a new active substance with new mode of action. Types of IOI reported in ADA positive patients need to be recorded and compared to those observed in a general population. The applicant was requested to outline plans to monitor this issue going forward (beyond routine pharmacovigilance) taking also into consideration the faricimab posology regimen. The applicant clarified that cases of IOI will be monitored within the ongoing long-term extension (LTE) study, RHONE-X. This is acceptable, and the applicant will present the updated safety data regularly in the PSUR**.**

DME: Retinal Vascular Occlusive Disease

A number of post-marketing cases of retinal vasculitis and/or retinal vascular occlusions typically occurred in the presence of intraocular inflammation have been reported with another anti-VEGF product.

In pivotal studies in patients DME for this application, there were only a few cases of retinal vascular occlusive disease**.**

The Applicant has provided a clear overview of reported cases relating to retinal vascular occlusive disease from the faricimab clinical development programme. It is noted that these cases were confounded by the presence of medical co-morbidities and were not considered by the investigators to be causally related to treatment with faricimab. Of note, no reported cases of retinal vascular occlusive disease were associated with intraocular inflammation. In the majority of cases, treatment with faricimab was not interrupted. However, this topic should continue to be closely monitored and updated safety data presented as data emerges, especially considering the status of faricimab as a new active substance with new mode of action.

DME: Slitlamp examination

The proportion of patients by grade for the worst post-baseline outcome in the study eye through the Clinical Cut-Off Date on slitlamp examination with regard to the anterior chamber cell grade, vitreous cell grade and vitreous haemorrhage grade was slightly higher in the faricimab arms, in particular in the faricimab Q8W arm: anterior chamber cell grade 1+: 11 (1.7%), 6 (0.9%) and 2 (0.3%); vitreous cell grade 1: 7 (1.1%), 2 (0.3%) and 2 (0.3%); vitreous haemorrhage grade 1+: 8 (1.3%), 5 (0.8%) and 4 (0.6%) in the faricimab Q8W, faricimab PTI and aflibercept arm, respectively. The applicant was asked to discuss these differences and potential reasons for their higher incidence with faricimab, however, the latter has not been provided. Updated data (up to Week 100) were in accordance with earlier results i.e. while differences between treatments were small, they were in favour of aflibercept.

DME Ocular Adverse Events in the Fellow Eye

Through Week 56, 34.4%, 30.9%, and 33.8% of patients experienced at least one ocular AE in the fellow eye in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. Also types of AEs reported in the fellow eye were similar to those reported in the study eye

DME: Serious ocular adverse events

A higher incidence of serious ocular AEs in the study eye occurred in both faricimab arms compared with the aflibercept Q8W arm (15 patients [2.4%], 19 patients [3.0%], and 8 patients [1.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. Also the per-injection rate of serious ocular AEs in the study eye was slightly higher in faricimab arms i.e. 0.34%, 0.39%, and 0.14% in faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The applicant was requested to discuss these imbalances

The most common serious ocular AEs in the study eye (≥ 2 patients in the combined faricimab arms or aflibercept Q8W arm) by PT were diabetic retinal oedema, endophthalmitis, cataract, vitreous haemorrhage, uveitis, visual acuity reduced transiently, ocular hypertension and retinal tear.

This higher incidence of serious ocular AEs was also observed during the entire study (through Year 2) in the pooled DME studies and the difference in the incidence of serious ocular adverse events was approx. 1.6%. In the pooled DME data through Year 2, the overall rate of serious ocular AEs in the study eye per 100 PYs of exposure were 2.99, 3.72, and 1.93 in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively.
The applicant indicated that this difference is primary driven by SAEs of cataract, diabetic retinal oedema, endophthalmitis, retinal tear, retinal vein occlusion and events of uveitis.

Although the difference in the incidence of serious ocular AEs was low (approx. 1.6%) taking into consideration these imbalances, serious ocular AEs should continue to be closely monitored particularly over longer term treatment with faricimab and updated safety data presented as data emerges, especially considering the status of faricimab as a new active substance with new mode of action.

DME: Serious intraocular inflammation

There are concerns regarding a higher incidence of inflammation related SAEs reported in the faricimab as compared to the aflibercept group such as endophthalmitis (4 patients [0.3%] vs. 1 patient [0.2%]) and uveitis (3 patients [0.2%] vs. 0), respectively. It is noted that endophthalmitis was classified by the applicant as an AE of special interest In addition, in 4 patients inflammation SAEs were considered as related to the study drug by investigators including cases of uveitis, chorioretinitis and keratouveitis. In all 4 patients treatment with faricimab was permanently discontinued due to these SAE. Cases of serious intraocular inflammation should continue to be closely monitored particularly over longer term treatment.

DME: Rhegmatogenous retinal detachment and retinal tear

One case of rhegmatogenous retinal detachment and two cases of retinal tear were reported in the faricimab groups in DME studies. There were no such events in the aflibercept arm.

The applicant claims that the risk of rhegmatogenous retinal detachment and retinal tear in patients treated with faricimab is consistent with the risks associated with other approved intravitreal anti-VEGF monotherapies. This can be agreed as the incidence of these events (i.e. 0.2%) in DME pivotal studies is not higher than reported for other anti-VEGF agents. The overall incidence of rhegmatogenous retinal detachment after intravitreal injection of anti-VEGF agents was reported to be up to 0.67% (Meyer et al, 2011 and Tolentino M, 2011). These risks are already highlighted in the SmPC.

DME: Ocular haemorrhage

There have been several reports of ocular haemorrhage following the use of intravitreal anti-VEGF drugs. In DME pivotal studies 3 SAEs of vitreous haemorrhage in the study eye were reported in patients with faricimab and one SAE of vitreous haemorrhage was reported in the aflibercept arm. It is noted that vitreous haemorrhage is included as an ADR within Section 4.8 of the SmPC, because of its potential to be injection procedure-related.

DME: Non-ocular adverse events

Through Week 56, the incidence of non-ocular AEs was comparable across all treatment arms (62.4%, 60.9%, and 62.4% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The following non-ocular events occurred in the higher frequency in the faricimab groups: back pain, bronchitis, couth, fall headache, upper respiratory tract infection and vomiting however, the difference between groups was ≥1%.

As per the SUR Clinical Cut-Off Date in the pooled Parent Studies, the incidence and nature of non-ocular AEs through the SUR Clinical Cut-Off Date was generally comparable to that reported in the SCS

(Week 56) and across all treatment arms (72.4%, 73.1%, and 73.9% in the faricimab Q8W, faricimab PTI, and aflibercept
Q8W arms, respectively).

The most common non-ocular AEs (≥5% incidence in any treatment arm: faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively) by PT were generally consistent with those reported in SCS (Week 56), with newly added events of COVID-19 (4.9%, 6.8%, and 4.0%) and fall (5.6%, 4.3%, and 3.5%), and with no appreciable difference between faricimab and aflibercept.

The applicant was asked to present the updated data and discuss the incidence of AEs within the SOC Cardiac, Infections and infestations and Vascular disorders.

At the time of the final 2-year analysis of YOSEMITE and RHINE data, the proportion of patients with events in the Cardiac disorders SOC was 9.8%, 11.1%, and 10.2% in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively. No particular pattern of the reported AEs can be observed.

Nevertheless AEs within the SOC Cardiac disorders (within the definition of the APTC events) need to be monitored taking into consideration the novel mode of action of faricimab.

Through Week 56, in general there was no difference in the incidence of AEs within the SOC Infections and infestations. AEs Infections and infestations were reported in 27.1% in the pooled faricimab groups compared to 32.6% in the aflibercept group. The applicant provided the updated data and highlighted that at the time of the final 2-year analysis of YOSEMITE and RHINE, there were slightly more events in the SOC Infections and Infestations with aflibercept vs faricimab i.e the proportion of patients with events in the infections and infestations SOC was 39.5% in the pooled faricimab groups compared to 42.7% in the aflibercept arm. At the time of the final 2-year analysis, in relation to Bronchitis, Upper Respiratory Tract Infection and pneumonia the difference between the treatment groups (pooled faricimab groups versus aflibercept arm) were less than 1%. For cough the difference between the treatment groups was 1.5%. The applicant considers that based on this data no update to section 4.4 and 4.8 is necessary and this can be agreed.

In general there was no difference in the incidence of AEs within the SOC Vascular disorders. There was no difference in the frequency of hypertension which occurred in 5.5% in the pooled faricimab groups compared to 5.9% in the aflibercept group. There was also no difference in the incidence of SAEs of hypertension AEs within the SOC Vascular disorders (within the definition of the APTC events) are planned to be monitored taking into consideration novel mode of action of faricimab

DME:Non-ocular adverse events related to faricimab

Following AEs were considered related to faricimab by the investigator: hypertension, visual hallucination, sudden hearing loss and rhinorrhoea. Based on the additionally provided data it can be agreed that at present there is insufficient evidence of a causal association between faricimab and hypertension, visual hallucination, sudden hearing loss and rhinorrhoea. No changes in the PI are deemed necessary at this time.

DME: Serious non-ocular AEs

Through Week 56, the incidence of serious non-ocular AEs was higher in the pooled faricimab groups (18.2%) as compared to the aflibercept group (16.3%). In patients treated with faricimab more serious non-ocular AEs were reported in the faricimab Q8W (20.2%) as compared to the faricimab PTI arm (16.3%).

As per the SUR Clinical Cut-Off Date in the pooled Parent Studies, the incidence of serious non-ocular AEs remained generally comparable across all treatment arms (27.3%, 24.2%, and 25.8% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). No particular pattern of the reported serious non-ocular AEs can be observed.

DME: Non-ocular haemorrhage

Cases of non-ocular haemorrhage were reported in pivotal studies in patients with DME. All these cases were reported in the faricimab group. There were no cases in the aflibercept group.

In the faricimab group the following cases were reported: 2 cases of cerebral haemorrhage, 1 case of Haemorrhagic stroke, 2 cases of gastrointestinal haemorrhage, 1 case of rectal haemorrhage, 1 case of upper gastrointestinal haemorrhage. The applicant was requested to discuss the potential role of faricimab in the development of these events. The applicant provided discussion on all haemorrhage cases reported in DME studies. It was highlighted that none of these events were reported to be causally related to study drug by the investigator, nor resulted in a change to study treatment. In addition it was highlighted that cases of non-ocular haemorrhage were also reported in aflibercept treated patients: rectal haemorrhage, lower gastrointestinal haemorrhage, uterine haemorrhage, oesophageal varices haemorrhage, and vaginal haemorrhage.

However, the observation made by Bendell et al. (2020) indicated that systemic Ang-2 inhibition is associated with an increased number of Grade ≥ 3 adverse events when compared to VEGF-A inhibition, such as haemorrhage, and GI perforations. Therefore, taking also into consideration medical importance of these events and the status of faricimab as a new active substance with new mode of action further monitoring is required. Haemorrhagic cases will be monitored in the ongoing long term safety studies.

Deaths- for nAMD and DME indications

At the beginning of the assessment, there was a concern that a numerically higher number of deaths occurred in patients treated with faricimab as compared to patients treated with aflibercept.

The below forest plot of all-cause deaths across the faricimab clinical development program shows consistently higher hazard ratios for faricimab compared to controls. Some differences between studies were observed, most notably in the nAMD indication.]

Importantly, it is highlighted that the clinical studies were not powered for this safety analysis as provided and thus, conclusions on statistical significance have to be interpreted with care.

The applicant was asked to discuss imbalances in deaths reported in patients treated with faricimab and to present the updated data in relation to the number of deaths reported.

For nAMD indication, the Applicant has provided end of study data (until week 112) for fatal events in nAMD studies. Reported deaths for the nAMD indication, considering the preliminary safety data from week 112 pooled data of both phase III studies (TENAYA and LUCERNE), do not raise concerns as the rates are broadly similar (3.5% and 3.2% of subjects for faricimab and aflibercept, respectively), excluding the COVID-19 deaths, the incidence of other deaths is also similar (0.4% difference).

For the **DME indication**, the overall incidence of deaths in the faricimab and aflibercept arms in the DME studies through the end of study were comparable when excluding COVID-19 deaths.

All Deaths Across the Faricimab Clinical Development Program with Rates per 100 Patient Years and Hazard Ratios Between Treatment Arms

Relationship with PK criteria

The applicant was asked whether the systemic concentration reported in patients receiving faricimab was sufficiently high to cause PD/side effects. In the response it was highlighted that maximum free

faricimab plasma concentrations are approximately 600 and 6000-fold lower than in AH and vitreous, respectively. Cmax and Ctrough values are also low i.e Cmax appearing approximately 2-3 days post-dose was 0.2 µg/mL (1.4 nM) and mean Ctrough for Q8W dosing was 0.003 µg/mL (0.02 nM). In addition the applicant indicated the results of affinity and potency investigated in non-clinical experiments also supporting the applicant's claims that the risk of systemic effect is low.

Further, the Applicant has assessed the potential relationship of death with faricimab plasma exposure and systemic target suppression in individual patients.

However, high inter-patient variability was observed in faricimab, free VEGF-A and free Ang-2 aqueous humor and plasma concentrations for DME and nAMD indication. Comparisons of faricimab plasma concentration (in > 1900 pts), free VEGF-A plasma concentrations and free Ang-2 plasma concentrations between DME and nAMD patients who died and those who survived do not indicate a clear pattern and plasma- concentration time-profiles are overlapping for patients who died and those alive. Free Ang-2 in plasma were BLQ post-dose in a small number of pts (up to 3%), however BLQ values were also measured at baseline (in up to 3% of patients), therefore no firm conclusions can be drawn on BLQ values wrt target inhibition and thus there is some uncertainty on the absence of systemic target inhibition in a very small subset of patients. In patients in whom levels of free-Ang2 were BLQ no concerning systemic reactions. Due to the low number of patients with unexplained death, data on systemic target inhibition are limited as compared to the overall study population, Free VEGF or free-Ang2 results for some patients who died from unexplained deaths are incomplete .

The Applicant argues that differences in pharmacological profiles between aflibercept and faricimab are unlikely to cause differences in reported fatal events due to the low systemic exposure and lack of systemic PD (i.e. absence of suppression in Ang-2 and VEGF-A measured in clinical plasma samples of more than 1900 patients across the four Phase III studies).

Temporal relationship

The applicant also presented the temporal relationship between the last dose of faricimab or aflibercept and death events. It was clarified that the half-life determined in plasma after vitreous administration is longer for aflibercept (11.4 days) than for faricimab (7.5 days). The analysis of temporal relationship between the last dose of faricimab or aflibercept and death events using 7 half-lives for both drugs indicated that the higher proportion of deaths which occurred within 7 half-lives were reported in the aflibercept group than in the faricimab group for both indications.

In addition, the applicant has shown that 95% and 93% of deaths did not occur close to the Cmax (within 1 week of dosing) for faricimab and aflibercept, respectively.

Therefore, the assessment of the time of death relative to the time to the maximum plasma concentration (Tmax) and taking the half-life of faricimab into account, do not clearly indicate a temporal relationship of death with the pharmacokinetic characteristics of faricimab.

Conclusion on the imbalance in deaths

Overall, the further analyses presented do not corroborate the hypothesis that the numerical imbalance in deaths can be causally attributed to faricimab.

Nonetheless, the Applicant will provide regular reports for deaths to the EMA on a 6-monthly basis for the initial 3 years post approval. The Agency will also be informed in case a signal or pattern is identified between reporting periods. This is acknowledged and it is highly recommended to put a focus on subjects with high blood pressure and vascular disease (especially relevant for the DME indication) and subjects ⩾85 years (especially relevant for the nAMD indication) in this specific observation.

APTC events for nAMD and DME indications

The applicant indicated that the systemic exposure to faricimab in humans following intravitreal injection is low; maximum plasma free faricimab concentrations are predicted to be approximately 600- and 6000-fold lower than in aqueous and vitreous humor, respectively. No adverse effects on general safety pharmacology endpoints were observed in nonclinical studies up to the highest doses, achieving maximum plasma concentrations (Cmax) of about 10- up to more than 700-fold greater than faricimab human steady-state systemic exposure estimates in nAMD and DME patients (popPK model following 6 mg Q8W dosing).

Nevertheless, taking into consideration that thromboembolic events have been reported after intravitreal injection for other vascular endothelial growth factor (VEGF) inhibitors, APTC-defined events were reviewed in a blinded manner by an Independent Clinical Events Committee (CEC).

Evaluation and adjudication of vascular events and vascular deaths was based on assessment of AEs according to APTC definitions (The CATT Research Group 2011).

Vascular events were defined as non-fatal myocardial infarctions, non-fatal strokes or vascular deaths. Vascular deaths were further defined as definitely or possibly vascular, which includes all deaths attributed to cardiac, cerebral, haemorrhagic, embolic, other vascular or unknown case.

The applicant outlined that the through Week 56 for DME indication, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was low and comparable across treatment arms (2.1%, 1.9%, and 2.2% in the faricimab Q8W, and faricimab PTI, and aflibercept Q8W arms,). In assessing cumulative data from baseline to the Clinical Cut-Off Date, 2.2%, 1.9%, and 2.4% of patients experienced at least one externally adjudicated APTC-defined ATE in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

In the nAMD indication, APTC events were reported as follows through Week 48, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) was n=7 patients [1.1%] in the faricimab arm and n=6 patients [0.9%] in the aflibercept arm).

The death adjudicated APTC ATEs were reported in 2 patients (0.3%) in the faricimab arm and 3 patients (0.5%) in the aflibercept arm. All death adjudicated APTC ATEs were reported in 1 patient each.

In relation to fatal cases arising from APTC events, there was trend towards a higher number of fatal cases of adjudicated APTC events reported following treatment with faricimab at week 60 compared with the aflibercept treatment group, with the number of fatal cases reported increasing by 5 for faricimab (n=2 or 0.3% at 40 weeks increasing to n=7 or 1.1% at week 60 for faricimab) versus (n=3 or 0.5% at week 40 for aflibercept increasing to n=5 or 0.8% at week 60).

Four additional fatal and non-fatal cases relevant to the discussion of APTC events were reported in the Phase II clinical studies with faricimab but note that these events were not included in the overall analysis of adjudicated APTC events.

Three of the non-fatal stroke adjudicated APTC ATEs were suspected by the investigator to be related to study treatment: ischaemic stroke in the faricimab Q8W arm, lacunar stroke in the faricimab PTI arm, and cerebrovascular accident in the aflibercept Q8W arm. The Applicant has provided case narratives for these patients. Based on the additional information, a causal relationship between faricimab and reported non-fatal strokes is unlikely, but due to a close temporal relationship between the last administered dose of faricimab in 2 patients, and the fact that one of them received only 2 doses of faricimab before developing an adverse event, a causal relationship cannot be completely ruled out.

Based on the cumulative exposure-adjusted data presented in the 90 day SUR, there were no apparent imbalances in APTC events between faricimab and aflibercept in the nAMD population.

However, it is highlighted that the final data set from the nAMD pivotal trials is still outstanding at this time and a preliminary safety overview was provided with the responses which indicates that through Week 112, the incidence of externally adjudicated APTC-defined ATEs was low and comparable across treatment arms (3.3% and 3.0% in the faricimab and aflibercept Q8W arms, respectively).

The Applicant has also provided a detailed discussion in response to this request to further elaborate on the imbalances noted between the DME pivotal trials YOSEMITE and RHINE in relation to APTC-adjudicated deaths.

The rate of APTC-defined deaths per 100 patient years (taking into account the whole study periods) was higher in both faricimab arms compared to aflibercept arm in YOSEMITE [i.e. hazard ratio between treatment arms HR 1.58 (95% CI 0.61, 4.08); and HR 1.72 (95% CI 0.68, 4.36) in faricimab Q8W and faricimab PTI arm, respectively]. This finding was not replicated in RHINE, on the contrary, the rates per 100 patient years were lower with both faricimab arms compared to aflibercept [HR 0.71 (95%CI 0.23, 2.24) and 0.41 (95%CI 0.11, 1.59) in faricimab Q8W and faricimab PTI arm, respectively]. The Applicant could not identify potential underlying reasons for this discrepancy. When comparing the baseline characteristics between both of these Phase III studies, it was highlighted by the Applicant that the majority of the patients in the YOSEMITE study were from U.S. and Canada (~53%), whereas in the RHINE study, the majority of the patients were from the 'Rest of the world countries' (56%-57%). The Applicant states that this difference could potentially account for some regional differences between the two DME studies (US vs. Rest of the World) in terms of local treatment practice, AE reporting, and access to general healthcare which could be considered relevant given the COVID19 pandemic. It is agreed that this might be one of the potential reasons for discrepancy, and it is agreed that the discrepancy points towards a lack of causal association with faricimab.

During the assessment, small differences between studies were found as regards smoking history and systolic blood pressure $\geqslant$160 mmHg, but no firm conclusions can be drawn.

The Applicant emphasises that the pattern of a higher incidence of APTC-defined deaths in the faricmab arms compared with the aflibercept arm in YOSEMITE is actually reversed in RHINE (with a similar percentage difference between the faricimab and aflibercept arms) which does not support a signal of less favourable outcomes for faricimab, given the inconsistency across both studies.

In YOSEMITE, there were a higher number of reports of fatal cases of 'unknown cause' when compared to RHINE (7 vs. 1). These cases were included in the overall rate of deaths in line with the APTC criteria. The Applicant has outlined that if the 7 deaths of unknown cause were excluded from YOSEMITE, the overall incidence of death would be 2.9% (9/313), 2.6% (8/313), and 1.9% (6/311) in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms which is broadly comparable to the incidences seen in RHINE and in the literature for the aflibercept pivotal trials. It is possible that the imbalance in 'unexplained death' observed in YOSEMITE could account for the higher overall incidence of APTC-defined deaths in YOSEMITE. Only limited information on some of these deaths could be presented so it is possible that some of these cases do not represent true ATEs.

The Applicant has also presented data from the published literature for aflibercept and ranibizumab which supports the finding that the overall rates of APTC-defined deaths for faricimab sit broadly within the ranges for this population.

It is considered that Applicant's response has explored the possible reasons for differences in fatal APTC events across the DME phase III pivotal studies and this concern is considered resolved. More broadly, the issue of fatal cases reported with faricimab is considered resolved (see above).

It is acknowledged that the long term safety of faricimab will be closely followed through the LTE studies as outlined in the RMP. In addition, the Applicant has added ATE events as important potential risks to the RMP which is agreed.

Safety in subgroups - DME indications

Analyses were performed to examine key safety across the subgroups i.e by age, gender, race, medical history, baseline DR severity, and baseline HbA1c)

Overall, through Week 56, differences in incidences of ocular AEs, incidences of nonocular AEs, incidences of SAEs, and incidences of ocular AESI between the treatment groups were small.

As highlighted previously SAEs occurred more frequently in the faricimab groups than in the aflibercept group. This trend was also seen across analysed subgroups with the highest difference reported for patients with a history of renal and vascular disease.

Pregnancy- nAMD and DME indications

The systemic exposure to faricimab is low after ocular administration, but due to its mechanism of action, faricimab must be regarded as potentially teratogenic and embryo-/foetotoxic, hence effective contraception is recommended for female patients of childbearing potential. The applicant was therefore asked to update the summary of safety concerns in the RMP to include pregnancy on the basis of the potential for exposure to the new active substance faricimab, with a novel mode of action in women of child-bearing potential (particularly in DME indication) and based on the conclusions in section 5.3 that faricimab should be regarded as potentially teratogenic. The updated RMP has been provided which is endorsed.

ADA-positive subgroup- DME indication

Overall, the proportion of patients with treatment-emergent ADA was low in the pooled Phase III DME studies at Week 56, with only a small increase observed during the second year of the studies: at Week 56, 105 patients had treatment-emergent ADA positivity (8.4%) and by Week 100, this rose to 120 patients (9.6%). The incidence of treatment-induced ADA through end of studies (Week 100) was comparable in the two faricimab treatment arms (9.8% [Q8W] and 9.4% [PTI]), therefore there is no indication of disproportionate ADA incidence across the treatment groups. The reported results are however difficult to interpret without an appropriate comparison, as anti-drug antibodies were analysed for patients treated with faricimab only (as only two dosing schedules of faricimab are compared, no data is available on aflibercept). No data were generated for patients treated with aflibercept in pivotal studies or ranibizumab in the previous clinical phase 1/2 program.

A higher incidence of IOI was observed in ADA-positive patients compared with ADA negative patients.

The total number of IOI events per 1000 injections in the ADA-positive versus ADA-negative population was 13.2 (21 events) versus 0.35 (5 events). This difference was, however, more pronounced in the PTI arm compared to the Q8W arm. Upon enquiry, the Applicant has performed a thorough analysis of the potential underlying cause, however, at present time no firm conclusions can be made. The median time to onset of ADA was not different between Week 56 and Week 100, with 28.3 weeks at Week 56 and 28.6 weeks at Week 100.

There were 45/1124 patients (4.0%) in the ADA-negative population and 14/128 patients (10.9%) in the ADA-positive population with SAEs.

In light of the known risk of immunogenicity towards therapeutic proteins, immunogenicity was added as a potential risk to the RMP, and described within Section 4.4 and Section 4.8 of the draft SmPC as part of the initial MAA.

Study (treatment) discontinuations and dose interruptions

While the incidence of IOI events that led to treatment discontinuation was overall low, more events were reported in pooled faricimab arms compared to aflibercept (5 cases versus no cases). All IOI events which led to faricimab discontinuation were considered related to the study drug by the investigator.

2.4.9. Conclusions on the clinical safety

It is considered that concern in relation to imbalances in the number of deaths is resolved based on the PK/PD characteristic of faricimab and the low risk of systemic effect of faricimab (although the systemic inhibition cannot be completely ruled out). The difference in the number of deaths which was

particularly seen for DME indication (0.9% difference) was less apparent when deaths related to COVID -19 were excluded (0.4% difference). Nevertheless, it is considered that deaths and other systemic AEs potentially associated with faricimab (such as ATE and cerebrovascular haemorrhagic events) need to be monitored in the long-term safety studies. The Applicant has added ATE events to the RMP as important potential risks.

The Applicant has also committed to providing regular reports for deaths to the EMA on a 6-monthly basis for the initial 3 years post approval. The Agency will also be informed in case a worrisome signal or pattern is identified between reporting periods. This commitment is acknowledged and it is highly recommended to focus on subjects with high blood pressure and vascular disease (especially relevant for the DME indication) and subjects' ⩾85 years (especially relevant for the nAMD indication) in this specific observation.

The ocular safety profile of faricimab is noted to be somewhat less favourable in certain aspects of the safety data when compared to aflibercept, particularly with the more frequent administration regimes. However, the overall differences in terms of absolute numbers are relatively small and are not always consistent across all safety parameters in both indications. In addition, these ADRs are well-established for approved products administered by IVT injection, some are procedural and related to the route of administration.

Further, the applicant presented arguments that the observed differences in the safety profile with the most frequent dosing interval (Q8W) used in the nAMD studies may be explained by virtue of the study design – in that patients' who had worse nAMD disease would have received more frequent treatment. In these circumstances, it can be agreed that it is difficult to ascertain whether the numerical differences in the rates of AEs seen in the different faricimab-treatment interval subgroups were as a result of these patients having received more injections, or whether as a result of them having more severe nAMD disease.However, the Applicant's claim that treatment with faricimab requires fewer injections and less frequent trips to the hospital is not agreed, based on data through the first year of the studies. The overall efficacy and treatment burden is considered to be similar to aflibercept.

Furthermore, it is highlighted that long term safety has been added to the RMP as missing information and the longer term ocular safety of faricimab will be closely monitored in the ongoing LTE safety studies and the results will be presented in the PSURs.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation
Important potential risks	Arterial thromboembolic events and Central Nervous System hemorrhagic events
Missing information	Long-term safety Use in pregnancy

2.5.2. Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study GR42691 (AVONELLE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD.	The objective of this study is to evaluate the long-term safety and tolerability of the intravitreal faricimab in patients with nAMD, who have completed either of the Phase III (GR40306 or GR40844) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events	Long-term safety ATE and CNS hemorrhagic events	FPFV	19 April 2021
			Database Lock	Planned April 2024
			Final Clinical Study Report	Planned Q1 2025
Study GR41987 (RHONE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DME.	The objective of this study is to evaluate the long-term safety, tolerability and efficacy of intravitreal faricimab in patients with DME who have completed either of the Phase III (GR40349 or GR40398) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events.	Long-term safety ATE and CNS hemorrhagic events	FPFV	5 August 2020
			Database Lock	Planned December 2023
			Final Clinical Study Report	Planned Q4 2024

ATE=arterial thromboembolic events; CHMP=Committee for Medicinal Products for Human Use; CNS=central nervous system; DME=diabetic macular edema; FPFV=first patient first visit; HCP=health care provider; GR40306=TENAYA; GR40349=YOSEMITE; GR40398=RHINE; GR40644=LUCERNE; LTE=long-term extension; nAMD=neovascular age-related macular degeneration; NCA=National Competent Authority; PRAC=Pharmacovigilance Risk Assessment Committee; PTI=personalized treatment interval; TBD=to be determined.

2.5.3. Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infectious endophthalmitis	**Routine risk minimization measures:** • SmPC Section 4.2 Posology and Method of Administration • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable Effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

	• PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4 Possible side effects Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide	

Intraocular inflammation	**Routine risk minimization measures:** • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable effects • PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4 Possible side effects Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None
Arterial thromboembolic events and Central Nervous System hemorrhagic events	**Routine risk minimization measures:** • SmPC Section 4.4 • PIL Section 2 Vabysmo is a prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Ongoing long-term extension studies: AVONELLE-X (GR42691) RHONE-X (GR41987)

Long-term safety	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ongoing long-term extension studies: AVONELLE-X (GR42691) RHONE-X (GR41987)
Use in pregnancy	**Routine risk minimization measures:** • SmPC Section 4.6 • PIL Section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Roche standard pregnancy follow-up Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

PBRER=Periodic Benefit-Risk Evaluation Report; PIL=Patient Information Leaflet; PSUR=Periodic Safety Update Report; SmPC=Summary of Product Characteristics.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.6. Pharmacovigilance

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study GR42691 (AVONELLE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD.	The objective of this study is to evaluate the long-term safety and tolerability of the intravitreal faricimab in patients with nAMD, who have completed either of the Phase III (GR40306 or GR40844) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events	Long-term safety ATE and CNS hemorrhagic events	FPFV	19 April 2021
			Database Lock	Planned April 2024
			Final Clinical Study Report	Planned Q1 2025
Study GR41987 (RHONE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DME.	The objective of this study is to evaluate the long-term safety, tolerability and efficacy of intravitreal faricimab in patients with DME who have completed either of the Phase III (GR40349 or GR40398) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events.	Long-term safety ATE and CNS hemorrhagic events	FPFV	5 August 2020
			Database Lock	Planned December 2023
			Final Clinical Study Report	Planned Q4 2024

ATE=arterial thromboembolic events; CHMP=Committee for Medicinal Products for Human Use; CNS=central nervous system; DME=diabetic macular edema; FPFV=first patient first visit; HCP=health care provider; GR40306=TENAYA; GR40349=YOSEMITE; GR40398=RHINE; GR40844=LUCERNE; LTE=long-term extension; nAMD=neovascular age-related macular degeneration; NCA=National Competent Authority; PRAC=Pharmacovigilance Risk Assessment Committee; PTI=personalized treatment interval; TBD=to be determined.

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.01.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vabysmo (faricimab) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of adult patients with **Neovascular Age-related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).**

Neovascular Age-related Macular Degeneration (nAMD)

Age-related macular degeneration (AMD) is a chronic, progressive, multifactorial disease of the macula and a leading cause of central vision loss among people over the age of 50 years. nAMD (also known as macular or choroidal neovascularisation [CNV] secondary to AMD) is a form of advanced AMD that causes rapid and severe vision loss. It is characterised by the abnormal proliferation of new blood vessels within the retina, or in the subretinal or sub-retinal pigment epithelium (RPE) spaces.

The diagnosis of nAMD is made clinically by ophthalmoscopy and multimodal retinal imaging techniques, which include optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). The clinical manifestation of nAMD includes the presence of subretinal fluid (SRF) and/or intraretinal fluid (IRF), retinal and subretinal hemorrhage, retinal thickening, and pigment epithelial detachment. Without treatment, progression of the disease results in the formation of a fibrous scar and consequently severely reduced vision.

The prevalence of nAMD increases with age, with estimates in the United States in 2011 ranging from 0.5% among people 65-69 years old to 14.6% among those 90 years old or older (Rudnicka et al. 2012). Of the estimated 253 million people worldwide with visual impairment, more than 10 million (4.1%) were caused by AMD.

In the future, the global population aged 60 years and older is projected to increase dramatically, resulting in a significant increase in the prevalence of nAMD from 23.47 million in 2010 to 80.44 million by 2050.

Diabetic Macular Edema (DME)

Diabetic retinopathy (DR) is regarded as the most common microvascular complication of diabetes and can occur as a complication of both Type 1 and Type 2 diabetes. DME is the most common complication as well as a leading cause of central vision loss in patients with DR and can develop at any stage of DR severity, with increasing frequency as the underlying disease worsens.

Approximately half of patients with DME will lose two or more lines of visual acuity within 2 years if left untreated.

DME and DR are forms of the same underlying pathophysiological processes subsequent to microvasculopathy that is driven by hyperglycaemia in patients with diabetes.

The loss of pericytes, retinal micro-aneurysms, dilated capillaries and vascular inflammation lead to the destabilisation of retinal vasculature, breakdown of the inner blood-retinal barrier and pathological increase in vascular permeability. However, the vision threatening complications of DR are not limited to DME but also include macular ischemia and PDR complications such as vitreous haemorrhage, retinal detachment and neovascular glaucoma.

On a molecular level, DME and DR are characterised by hypoxia-mediated release of pro-angiogenic, hyperpermeability, and pro-inflammatory mediators in the retina, with Ang-2 and VEGF-A playing the key role.

The excess of Ang-2 and VEGF in the vitreous of patients with diabetic eye disease was shown to correlate with disease severity and is thought to mediate vessel destabilisation, vascular leakage, inflammation and, in later stages of disease, neovascularization.

The diagnosis of DR is based on the detection and clinical manifestations of microvascular abnormalities in the retina. NPDR is characterized by microaneurysms, intraretinal haemorrhages, exudates, retinal nerve fibre layer infarcts and in more severe cases, venous beading and intraretinal microvascular abnormalities. PDR is characterized by neovascularization that can be detected anywhere on the retina, optic disc or in the anterior segment.

DME affects 21 million people around the world, including 12% of people with Type 1 diabetes and 28% of those with Type 2 diabetes. In patients diagnosed with insulin-dependent diabetes before the age of 30, the prevalence of DR reaches 97% when diabetes duration exceeds 15 years.

Eventually, nearly all patients with diabetes will develop some form of retinopathy (ADA 2013; Postel et al. 2013). In 2019, the worldwide population of people living with diabetes was approximately 463 million, and this is estimated to grow to 548 million by 2045 (Saeedi et al. 2019). The global burden of DME and DR is expected to increase significantly with considerable public health, socioeconomic, and quality-of-life consequences due to the combined impact on patients, caregivers, family members, and HCPs.

3.1.2. Available therapies and unmet medical need

nAMD

The major goal of treatment is to avoid or recover lost vision and subsequently maintain vision in nAMD patients over time.

The introduction of anti-VEGF therapies has markedly improved vision outcomes and changed the management of nAMD.

The anti-VEGF therapies ranibizumab (Lucentis), aflibercept (Eylea), and brolucizumab (Beovu) are approved and used for the treatment of nAMD in the United States and European Union.

The introduction of anti-VEGF therapy has resulted in an improvement of vision outcomes in patients with nAMD. However, for most patients, the current treatment paradigm involves frequent health care provider (HCP) visits and intravitreal injections in order to maintain vision gains (Heier et al. 2012; Maguire et al. 2016). This imposes a considerable burden on patients, their families, caregivers, and the healthcare system (Jaffe et al. 2018).

Real-world data show that many patients with nAMD do not receive treatment at the perlabel recommended frequency, and the under-treatment in clinical practice may result in lower visual acuity gains compared with those observed in the clinical trials.

Although anti-VEGF therapy is the current mainstay of treatment, nAMD is a multifactorial disease with VEGF being only one of the key drivers; sustained efficacy over time with fewer injections may be achievable by targeting additional drivers of angiogenesis such as Ang-2. In addition, nAMD has an inflammatory component not completely addressed by anti-VEGF treatments alone. New and more durable treatments that target additional pathways to those mediated by VEGF are therefore required, in order to provide visual acuity outcomes with less frequent dosing that are at least as good as those achieved with more frequent anti-VEGF monotherapy regimens.

Current Therapies and Unmet Need for DME

The primary treatment goals in DME are improving or maintaining visual acuity, reducing retinal fluid, improving the underlying diabetic retinopathy and preventing irreversible damage to the macula. The development of anti-VEGF therapy in the last decade has led to dramatic improvements in visual outcomes for patients with DME. Other available approved options for the treatment of DME include periocular or intravitreal steroids and steroid implants which have the limitations of severe side effects such as cataract and glaucoma.

The availability of intravitreal anti-VEGF treatments enabled robust improvements in visual outcomes accompanied by robust improvements in the underlying DR severity in patients with DME and DR severity improvements with anti-VEGF treatments were enabled also in patients with DR, with or without DME (Antoszyk et al. 2020). Ranibizumab (Lucentis) is approved for the treatment of visual impairment due to DME and the treatment of patients with PDR (with or without DME) in the European Union. Aflibercept (Eylea) is approved for the treatment of visual impairment due to DME in the European Union. Although intravitreal anti-VEGF therapies for the treatment of patients with DME and DR represent major advances, there is still an unmet need for improved therapies in these diseases.

In the real world, a significant proportion of DME patients treated with approved therapies do not experience clinically meaningful improvements in vision or are unable to maintain their initial vision gains long-term due to a need for frequent HCP visits for injections or monitoring (Souied et al. 2015; Stefanickova et al. 2018; Shimura et al. 2020; Naujokaitis and Balaciuniene 2021).

Given the multifactorial pathogenesis of DME and DR, treatments targeting additional pathways beyond VEGF are needed to comprehensively address the underlying pathology and to provide more durable efficacy which could reduce the burden of frequent HCP visits and intravitreal injections in these patients.

3.1.3. Main clinical studies

The main evidence of efficacy and safety submitted by the applicant for faricimab is based on the primary analysis results of the pivotal Phase III studies:

Two identically designed Studies GR40306 and GR40844 (referred to as TENAYA and LUCERNE, respectively) in patients with nAMD which are Phase III, Multicentre, Randomised, Double- Masked, Active Comparator- Controlled, 112-week Study.

And

Two identically designed Studies GR40349 and GR40398 (referred to as YOSEMITE and RHINE, respectively) in patients with DME which are Phase III, Multicentre, Randomised, Double-Masked, Active Comparator-Controlled, Three Parallel Groups, 100-week Study.

The safety and efficacy of faricimab is further supported by data from the completed Phase II and Phase I studies.

3.2. Favourable effects

In nAMD both pivotal studies TENAYA and LUCERNE demonstrated non-inferiority of faricimab 6mg given at intervals up to 16 weeks to aflibercept 2mg.

The adjusted mean change from baseline in best corrected visual acuity (BCVA) averaged over weeks 40, 44 and 48 in the TENAYA study was 5.8 and 5.1 letters in the faricimab and aflibercept arms,

respectively. The difference in adjusted mean change from baseline in BCVA between the faricimab arm and aflibercept arm was 0.7 letters (95% CI: - 1.1, 2.5). The adjusted mean change from baseline in BCVA averaged over weeks 40, 44 and48 was 6.6 letters in both the faricimab and aflibercept arms of the LUCERNE study with a difference in adjusted mean change from baseline between the faricimab arm and aflibercept arm of 0.0 letters (95% CI - 1.7, 1.8). In both studies the lower bound of the 95% CI were above the non-inferiority margin of -4.

In the pooled ITT population, 20.1% and 19.0% of patients in the faricimab and aflibercept arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 40/44/48 with a difference of 1.1% (95% CI: -3.2%, 5.4%) between the treatment arms.

In the pooled ITT population, 20.9% and 20.2% of patients in the faricimab and aflibercept arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 52/56/60 with a difference of 0.7% (95% CI: -3.6%, 5.1%) between the treatment arms.

In diabetic macular oedema the RHINE and YOSEMITE studies demonstrated non-inferiority of both faricimab treatment schedules (Q8W and a PTI schedule) to aflibercept in the ITT and treatment naïve populations for improvement from baseline in BCVA averaged over weeks 48, 52 and 56.

The adjusted mean change from baseline in BCVA in the RHINE study was 11.8 letters in the faricimab Q8W population, 10.8 letters in the faricimab PTI population and 10.3 in the aflibercept population. The difference in adjusted means compared to aflibercept arm for the faricimab Q8W dose was 1.5 letters (97.5% CI -0.1, 3.2) and for the PTI dose was 0.5 letters (97.5%CI -1.1, 2.1). Similar results were seen in the treatment naïve population. In the YOSEMITE study in the ITT population the adjusted mean change from baseline was 10.7 lettersfor faricimab Q8W, 11.6 for faricimab PTI and 10.9 for aflibercept. The difference in adjusted means compared to aflibercept arm for the faricimab Q8W dose was -0.2 letters (97.5% CI -2.0, 1.6) and for the PTI dose 0.7 letters (97.5%CI -1.1, 2.5). Broadly similar results were seen in the treatment naïve population. In both studies the lower bound of the 95% CI were well above -4 in the treatment naïve and ITT populations.

In the pooled ITT population, 31.5%, 31.9% and 31.0% of patients in the faricimab Q8W, faricimab PTI and aflibercept arms, respectively, gained ≥15 letters in BCVA score from baseline at Week 48/52/56. The difference in the adjusted proportion of patients who gained ≥15 letters from baseline between the faricimab Q8W and PTI arms when compared with the aflibercept Q8W arm was 0.5% (95% CI: -4.8%, 5.8%) and 0.7% (95% CI: -4.4%, 5.9%) at Week 48/52/56.

3.3. Uncertainties and limitations about favourable effects

nAMD

Only treatment naïve patients were included in the phase III studies. This limits the generalisability of the study results to anti-VEGF pre-treated patients. However, it is noted that the registration studies for other anti-VEGF agents in the nAMD indication only included treatment naïve populations. In addition, the Applicant has also provided data from the AVENUE study showing maintenance of effect on visual acuity in patients switched from ranibizumab to faricimab. Real world data from other anti-VEGF therapies also indicate that vision can be maintained after a therapy switch.

In addition, the inclusion criterion threshold for the focal lesion size of ≤ 9-disc areas (DA) on FFA is likely to exclude a more advanced nAMD population. The VIEW study for aflibercept included patients with a DA of ≤ 12-disc areas. CHMP in the course of scientific advice (EMA/CHMP/SAWP/701753/2018) had advised including patients with a disc area >9 DAs and ≤ 12 DAs. It is noted that currently treatment is initiated earlier because of better outcomes and consequently lesion sizes are not as large as those treated in earlier registration studies Consequently, the proportion of study subjects with a

lesion size between 9 and 12 disc areas is likely to be small. Therefore, the exclusion of the small population with a lesion size between 9 and 12 disc areas should not impact on the generalisability of the study results.

There are uncertainties regarding the durability of the effect, particularly in the longer faricimab treatment intervals, after Week 60. Patients randomised to faricimab could have been assigned from the Week 20/24 treatment visits to one of three treatment intervals (dependent on specific criteria relating to CST and BCVA), namely an 8, 12 or 16 week interval.

There is no data on the durability of the response for the individual faricimab treatment intervals. The period of follow up from Week 20/24 to Week 48 (primary endpoint) or week 60 is inadequate to make any judgement on durability of response particularly in those treated at a 16 week interval. The durability of effect can be fully evaluated once data beyond week 60 is available. Nevertheless, improvements in BCVA from baseline at week 12 were maintained for faricimab 6mg given at Q16W intervals averaged over weeks 52/56/60.

DME

There remain uncertainties as to what degree the presented results may support conclusions of non-inferior efficacy within subgroups of an individualized treatment schedule with faricimab. This is appropriately addressed by the requirement to personalise treatment based on visual and anatomical outcomes in 4.2.

In the RHINE trial, in the subgroup of patients with a baseline BCVA <=63 letters a higher proportion of patients in the Aflibercept arm had a $\geq$ 2-Step DRS improvement compared to the Faricimab Q8W arm in Rhine. It is agreed with the Applicant that this might be a chance finding given variability in the endpoint and the low number of subjects in the sub-group.

3.4. Unfavourable effects

nAMD indication

Exposure-adjusted incidence rates for the cumulative pooled data for total ocular AEs were higher for faricimab at 75.61 per 100PY versus 69.73 per 100 PY for aflibercept.

At Week 48, there was a ≥1% difference in the faricimab treatment arm vs. aflibercept arm) for vitreous floaters (20 patients [3.0%] vs. 11 patients [1.7%]), and retinal pigment epithelial tear (19 patients [2.9%] vs. 9 patients [1.4%]).

The rate of severe ocular AEs to Week 48 was n= 13 patients (2.0%) in the faricimab arm and n=11 patients (1.7%) for aflibercept.

The overall rate of IOI in the study eye was n=13 patients [2.0%] in the faricimab arm and n=8 patients [1.2%] in the aflibercept arm). Through Week 48, 3 patients (0.5%) in the faricimab arm and 1 patient (0.2%) in the aflibercept arm experienced at least one severe IOI event in the study eye. The IOI events reported past Week 48 have been mild-moderate in intensity with no severe events reported to date. All except one IOI event (in the faricimab arm) occurred after treatment day 80.

Through Week 60, the incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee) remained low and was comparable between the treatment arms (faricimab: 2.0% [Week 60] and 1.1% [Week 48] vs. aflibercept: 1.5% [Week 60] and 0.9% [Week 48].

Between Week 48 and Week 60, the death adjudicated APTC-defined ATEs were cardiac failure congestive, ill-defined disorder, pneumonia bacterial, pulmonary oedema, and subarachnoid

haemorrhage (1 patient [0.2%] each) in the faricimab arm; and cardiac failure and glioblastoma multiforme (1 patient [0.2%] each) in the aflibercept arm. None of the death adjudicated APTC ATEs were suspected to be related to study treatment. Between Week 48 and Week 60, there was 1 patient (0.2%) in the faricimab arm and 2 patients (0.3%) in the aflibercept arm who experienced a non-fatal stroke (cerebrovascular accident in all patients).

DME indication

In DME pivotal studies through Week 56 treatment-emergent Adverse Events were reported slightly more frequently in the faricimab Q8W group (81.4%) as compared to the aflibercept Q8W treatment (79.2%). In the Faricimab PTI group the incidences of subjects with any TEAE was lower (76.9%).

Through Week 56 the incidence of ocular AEs reported in the study eye was slightly higher in the faricimab groups (i.e Q8W 37.3%, PTI 35.6%) as compared to the aflibercept group (34.4%). The most common ocular AEs reported were conjunctival haemorrhage (6.7% for faricimab and 6.1% for aflibercept), cataract (4.6% for faricimab and 4.8% for aflibercept), vitreous detachment (3.2% for faricimab and 3.2% for aflibercept) and vitreous floaters (3.4% for faricimab and 1.6% for aflibercept).

Intraocular pressure increased occurred with a slightly higher frequency in the faricimab group as compared to the aflibercept group. At the time of the final 2-year analysis of YOSEMITE and RHINE the proportion of patients with events with IOP increased was 5.1% and 3.3% in the faricimab Q8W and PTI arms, respectively, and 2.6% in the aflibercept arms difference faricimab Q8W versus aflibercept 2.5% (95%CI: 0.3%, 4.9%); difference faricimab PTI versus aflibercept: 0.8 (95%CI: -1.3, 2.8). Nearly all intraocular pressure increased AEs were considered non-serious, with the exception of one event in the faricimab PTI arm in RHINE. This serious case resolved the same day following Anterior Chamber Paracentesis and was considered as mild in severity and not related to study drug.

By Week 100 the incidence of AESIs of sight-threatening events was (defined as decrease of ≥30 letters in visual acuity (VA) score) 18 patients [2.9%], 23 patients [3.6%], and 16 patients [2.6%] in the faricimab Q8W, faricimab PTI and aflibercept Q8W arm, respectively. However, the majority of the ocular AESIs in the study eye resolved, resolved with sequelae, or were resolving by the Week 100, and were considered not related to study drug by the investigator and did not result in a change to study drug.

Through Week 100, the pooled rate of IOI (uveitis including iritis, iridocyclitis, and vitritis) for YOSEMITE and RHINE was 1.6% (95% CI: 1.03%, 2.44%) for faricimab and 1.1% (95% CI: 0.54%, 2.29%); aflibercept difference of 0.5% (95% CI: -0.82%, 1.49%. Exposure-adjusted incidence rates for any IOI through Week 100 were low (0.88, 1.38, and 0.88, in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

Through Week 56, the retinal vascular occlusive disease AEs in the study eye were retinal vein occlusion reported in 3 patients in the faricimab groups and retinal artery embolism and retinal artery occlusion both reported in the aflibercept arm. After Week 56 to the Clinical Cut-Off Date, there was 1 additional patient with a retinal vascular occlusive disease AE in the study eye i.e retinal artery occlusion in the faricimab Q8W arm.

Through Week 56, a higher incidence of serious ocular AEs in the study eye occurred in both faricimab arms compared with the aflibercept Q8W arm (15 patients [2.4%], 19 patients [3.0%], and 8 patients [1.3%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. The per-injection rate of serious ocular AEs in the study eye was 0.34%, 0.39%, and 0.14% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arm, respectively. The most common serious ocular AEs in the study eye (⩾ 2 patients in the combined faricimab arms or aflibercept Q8W arm) by PT were diabetic retinal oedema, endophthalmitis, cataract, vitreous haemorrhage, uveitis, visual acuity reduced

transiently, ocular hypertension and retinal tear. In addition, there were 5 serious IOI events in 4 patients, all of whom were in the faricimab PTI arm. In all 2 patients treatment with faricimab was permanently discontinued due to these SAE, all of which were considered by the investigator as related to faricimab.

This higher incidence of serious ocular AEs was also observed the entire study (through Year 2) and the difference in the incidence of serious ocular adverse events was approx. 1.6%. In the pooled DME data through Year 2, the overall rate of serious ocular AEs in the study eye per 100 PYs of exposure were 2.99, 3.72, and 1.93 in the faricimab Q8W, faricimab PTI, and aflibercept arms, respectively.

Through Week 56 the incidence of non-ocular AEs was comparable across all treatment arms (62.4%, 60.9%, and 62.4% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively). The following non-ocular events occurred in the higher frequency in the faricimab groups: back pain, bronchitis, cough, fall headache and vomiting however, the difference between groups was ≥1%.

As per the SUR Clinical Cut-Off Date in the pooled YOSEMITE and RHINE Studies, the incidence and nature of non-ocular AEs through the SUR Clinical Cut-Off Date was generally comparable to that reported in the SCS (Week 56) and across all treatment arms (72.4%, 73.1%, and 73.9% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

Through Week 56, the incidence of serious non-ocular AEs was higher in the pooled faricimab groups (18.2%) as compared to the aflibercept group (16.3%). As per the SUR Clinical Cut-Off Date in the pooled Parent Studies, the incidence of serious non-ocular AEs remained generally comparable across all treatment arms (27.3%, 24.2%, and 25.8% in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively).

Cases of non-ocular haemorrhage were reported in pivotal studies in patients with DME.

Through Week 56, in the faricimab group the following cases were reported: 2 cases of cerebral haemorrhage, 1 case of Haemorrhagic stroke, 3 cases of gastrointestinal haemorrhage, 1 case rectal haemorrhage, 1 case of Upper gastrointestinal haemorrhage

3.5. Uncertainties and limitations about unfavourable effects

nAMD study conduct

In TENAYA 52 patients and in LUCERNE 23 patients had optional plasma samples or optional aqueous humour samples collected where prior informed consent was either not obtained or withdrawn. These were reported as major protocol deviations and all unconsented sample analyses were removed from the databases used for reporting. The extent of additional treatment burden and safety risk that was caused for these patients was further clarified and no specific safety concerns could be identified arising from the issue.

All included patients were treated with faricimab only in their dedicated study eye and no data are reported on bilateral treatment with faricimab. However, clinical practice foresees bilateral treatment for nAMD and the clinical phase 3 studies included patients with bilateral disease. Implications on the safety profile related to bilateral treatment are currently unknown. The applicant was therefore asked to present proposals to generate further data in order to justify bilateral use in clinical practice going forward. It is envisaged that the ongoing LTE studies will generate relevant data. In the interim, strengthening of the SmPC has been agreed in order to reflect the limitations of the available data.

Deaths - DME and nAMD indication

Despite a numerical unbalance, it is considered that concern in relation to imbalances in the number of deaths is resolved based on the PK/PD characteristics of faricimab, the low risk of systemic effect of faricimab , and the more balanced numbers after COVID-19 related deaths were excluded. Nevertheless, it is considered that deaths and other systemic AEs potentially associated with faricimab (such as ATE and cerebrovascular haemorrhagic events) need to be monitored in the long-term safety studies and in the post-marketing setting. The Applicant will provide regular reports for deaths to the EMA on a 6-monthly basis for the initial 3 years post approval. The Agency will also be informed in case a signal or pattern is identified between reporting periods.

APTC events for nAMD and DME indications

The Applicant has provided a detailed discussion in response to this request to further elaborate on the imbalances noted between the DME pivotal trials YOSEMITE and RHINE in relation to APTC-adjudicated deaths. The Applicant has also presented data from the published literature for aflibercept and ranibizumab which supports the finding that the overall rates of APTC-defined deaths for faricimab sit broadly within the ranges for this population. It is considered that Applicant's response has explored the possible reasons for differences in fatal APTC events across the DME phase III pivotal studies and this concern is considered resolved.

This safety issue will be followed through the LTE studies as outlined in the RMP for both indications. ATE events have also been added to the RMP as important potential risks.

Long-term safety studies - nAMD and DME indications

The long term safety will be followed through the LTE studies as outlined in the RMP. Safety issues such as related to bilateral use safety, safety of the Q8W dosing (for nAMD) and dosing intervals shorter than Q8W, sight-threatening adverse events, IOI, serious ocular adverse events, systemic events potentially related to faricimab, safety issues identified in ADA positive patients should be monitored and presented regularly in the PSUR.

Bilateral use – DME and nAMD

In both indications faricimab was administered only unilaterally. No non-clinical or clinical data have been generated on the bilateral use, although this was recommended during previous scientific advice procedures, as the bilateral treatment is foreseen in the clinical practice for both indications. Moreover, patients with bilateral nAMD and DME were included in the pivotal studies, where their fellow eye was treated with an anti-VEGF treatment, primarily aflibercept. Data on bilateral treatment with faricimab is needed to establish a safe interval between treatments of two eyes. If treatment of both eyes is performed in parallel, this could lead to an increased systemic exposure, which could consequently increase the risk of systemic adverse events. The SmPC was updated to include that bilateral treatment could cause bilateral ocular AEs and/or lead to an increased systemic exposure, which could increase the risk of systemic adverse events. Until data for bilateral use become available, this is a theoretical risk for faricimab. The applicant proposes to generate further relevant data in relation to bilateral use in the ongoing LTE studies.

Safety profile for the different treatment schedules.

<u>DME</u>

The PTI arm comprised a myriad of different individualised treatment schemes, with differences seen not only between patients but also within the same patient in the course of treatment. As patients with different treatment intervals are pooled together in the PTI arm, safety of individual dosing is not discernible i.e. likely better safety profile of longer intervals is obscured by the likely worse safety profile of shorter intervals. As a large proportion of AEs of intravitreally administered VEGF-inhibitors are injection-related, it is anticipated that a Q4W and Q8W intervals are associated with more adverse

events compared to a Q12W or Q16W interval, however the safety of different treatment regimens (other than Q8W) has not been investigated systematically. As no PTI dose regimen was chosen for the comparator, it is difficult to draw conclusions how the faricimab PTI regimen compares to the aflibercept Q8W regimen with respect to the safety. Thus, a separate safety analysis was requested for patients in faricimab PTI arm who received less versus equal or more administrations in comparison to the planned administrations in the fixed Q8W dosing schedule.

The safety data for the faricimab Q4W dosing interval, albeit limited, indicate a higher risk of both ocular and non-ocular adverse events, including higher risk for serious AEs compared to faricimab Q8W interval but also compared to aflibercept Q8W dosing regimen. The applicant included in the SmPC information that the data in this population is limited. This should be updated to state that based on limited information, dosing intervals shorter than Q8W are associated with a higher risk of ocular and systemic adverse events, including serious adverse events.

nAMD

Currently, the number of patients followed for the individual treatment schedules remain somewhat limited and additional safety data is anticipated from the ongoing pivotal and LTE studies in this indication. Of note, the most intense treatment schedule, i.e. Q8W, had the least patients included (i.e. n=143 patients for Q8W, n=219 for Q12W and n=289 for Q16W).

Due to the pooling of distinct treatment schedules (Q8W, Q12W and Q16W after disease assessment at weeks 20 and 24) a limited picture of the safety profile is available for each of the applied dose regimens, although based on the totality of data, the overall safety profile of faricimab can be considered sufficiently characterised and additional data will be generated from the LTE studies. This subgroup of patients should be closely monitored in the LTE studies and relevant safety updates should be provided within the regular PSURs.

The majority of patients (42.8%) across both phase III studies was in the ≥75 - <85 year age category (mean age in the faricimab arm was 75.4 years and in the aflibercept arm 76.4 years). But, slightly more patients are reported for the aflibercept arm in the ≥85 year age category (13.7% in the faricimab arm vs. 19.3% in the aflibercept arm), but slightly less patients are reported for the aflibercept arm in the ≥65 - <75 year age category (33.4% in the faricimab arm vs. 28.9% in the aflibercept arm). More female patients were included in both pivotal studies for both treatment arms (around 60% females and 40% males included). An imbalance in patients with >160 systolic or >90 diastolic blood pressure (11.2% in the faricimab arm vs. 5.2% in the aflibercept arm) is reported for the LUCERNE study only. Clinical implications of these imbalances are currently unknown. This subgroup of patients should be closely monitored in the LTE studies and relevant safety updates should be provided within the regular PSURs.

Intraocular inflammation and intraocular pressure increased events – DME and nAMD indication

For the DME indication, through Week 56, the incidence of intraocular inflammation events in the study eye was slightly higher in both faricimab groups as compared to the aflibercept groups. These events were reported in 8 patients [1.3%], 9 patients [1.4%], and 4 patients [0.6%] in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively. Serious intraocular inflammation events were also reported in the faricimab groups. The reason for such imbalances is not clear. This could be a chance finding however, taking into consideration a novel mode action of faricimab further discussion from the applicant was required.

For DME, at the time of the final 2-year analysis imbalances were less apparent although still noted. Exposure-adjusted incidence rates for any IOI through Week 100 were low (0.88 per 100 PY, 1.38 per

100 PY, and 0.88 per 100 PY, in the faricimab Q8W, faricimab PTI, and aflibercept Q8W arms, respectively.

Exposure-adjusted incidence rates for endophthalmitis through Week 100 were 0.26 per 100 PY and 0.09 per 100 PY for faricimab and aflibercept, respectively.

Therefore, cases of IOI should continue to be closely monitored particularly over longer term treatment with faricimab and updated safety data presented as data emerges, especially considering the status of faricimab as a new active substance with new mode of action.

Immunogenicity - DME and nAMD indication

Taking into consideration that ADA-positive patients experienced more SAEs compared to a general population, the applicant's claim that differences observed between ADA-positive and ADA-negative patients with respect to incidence of IOI events are not clinically relevant is not fully supported. The Applicant considers the clinical relevance is unclear. The SmPC has been updated to reflect the available data and this safety issue needs to be closely monitored

3.6. Effects Table

Effects Table for the nAMD population.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Change from baseline in BCVA averaged over weeks 40, 44 and 48	letters	Faricimab 6mg 4 weekly to W12 and then 8, 12 or 16 weekly from week 20/24 until week 60	Aflibercept 2mg 4 weekly to week 8 followed by 8 weekly injections	Adjusted mean increase from baseline averaged at weeks 40, 44, 48 for the faricimab arm = 5.8 letters Adjusted mean increase for aflibercept = 5.1 letters Difference in adjusted means = 0.7 (95% CI: -1.1, 2.5)	TENAYA phase III study
Secondary endpoint	% patients gaining ≥ 15 letters from baseline averaged over weeks 40, 44, 48	%	Faricimab 6mg 4 weekly to W12 and then 8, 12 or 16 weekly from week 20/24 until week 60	Aflibercept 2mg 4 weekly to week 8 followed by 8 weekly injections	Faricimab = 20% Aflibercept = 15.7%	TENAYA phase III study
Primary endpoint	Change from baseline in BCVA averaged over weeks 40, 44 and 48	letters	Faricimab 6mg 4 weekly to W12 and then 8, 12 or 16 weekly from week 20/24 until week 60	Aflibercept 2mg 4 weekly to week 8 followed by 8 weekly injections	Adjusted mean increase from baseline averaged at weeks 40, 44, 48 for the faricimab arm = 6.6 letters Adjusted mean increase for aflibercept = 6.6 letters Difference in adjusted means = 0.0 (95% CI: -1.7, 1.8)	LUCERNE phase III study
Secondary endpoint	% patients gaining ≥ 15 letters from baseline averaged over weeks 40, 44, 48	%	Faricimab 6mg 4 weekly to W12 and then 8, 12 or 16 weekly from week 20/24 until week 60	Aflibercept 2mg 4 weekly to week 8 followed by 8 weekly injections	Faricimab = 20.2% Aflibercept = 22.2%	LUCERNE phase III study
Unfavourable Effects						
Fatal events	Fatal Events reported through **Week 48**		faricimab pooled up to Q16W **n=9 (1.4%)**	aflibercept Q8W arm **n=8 (1.2%)**	Numerically higher number in the faricimab group as compared to the aflibercept group-cumulative data on total fatal cases was requested, no major imbalances noted	Pooled Phase III nAMD Studies
Ocular Adverse Events	Ocular Adverse Events in the Study Eye through **Week 48**		**faricimab** pooled up to Q16W **n=254 (38.3%)**	**aflibercept** Q8W arm **n=246 (37.2%)**	Numerically higher frequency in the faricimab group as compared to the aflibercept group	Pooled Phase III nAMD Studies
Serious Non-Ocular Adverse Events	Serious Non-Ocular Adverse Events through Week 48		**faricimab** pooled up to Q16W **n=68 (10.2%)**	**aflibercept** Q8W arm **n=82 (12.4%)**	Comparable rate between the faricimab and aflibercept groups	Pooled Phase III nAMD Studies

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
IOI	Intraocular Inflammation in the Study Eye through Week 48 Through Clinical Cut-off point		**faricimab** pooled up to Q16W **n=13 (2.0%)** **2.3%**	**aflibercept** Q8W arms **n=8 (1.2%)** **1.5%**	Numerically higher frequency in the faricimab group as compared to the aflibercept group	Pooled Phase III nAMD Studies primary analysis Week 48 CCoD

Effects table for the DME population.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Change from baseline in BCVA averaged over weeks 48, 52 and 56	letters	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Diff in adj means Faricimab Q8W from aflibercept = 1.5 (97.5% CI -0.1, 3.2) Diff in adj means Faricimab PTI from aflibercept = 0.5 (97.5% CI -1.1, 2.1)	RHINE phase III study
Secondary endpoint	% patients gaining ≥ 2 step improvement in DRS from baseline at Week 52	%	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Faricimab 6m Q8W = 44.2% Faricimab 6 mg PTI =43.7% Aflibercept 2mg = 46.8%	RHINE phase III study
Year 2 data	Change from baseline in BCVA averaged over weeks 92, 96 and 100	letters	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly up to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Diff in adj means Faricimab Q8W from aflibercept = 1.5 (95% CI -0.5, 3.6) Diff in adj means Faricimab PTI from aflibercept = 0.7 (95% CI -1.3, 2.7)	RHINE phase III study
Primary endpoint	Change from baseline in BCVA averaged over weeks 48, 52 and 56	letters	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly up to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Diff in adj means Faricimab Q8W from aflibercept = -0.2 (97.5% CI -2.0, 1.6) Diff in adj means Faricimab PTI from aflibercept = 0.7 (97.5% CI -1.1, 2.5)	YOSEMITE phase III study

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Secondary endpoint	% patients gaining ≥ 2 step improvement in DRS from baseline at Week 52	%	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly up to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Faricimab 6m Q8W = 46.0% Faricimab 6 mg PTI = 42.5% Aflibercept 2mg = 35.8%	YOSEMITE phase III study
Year 2 data	Change from baseline in BCVA averaged over weeks 92, 96 and 100	letters	Faricimab 6mg 4 weekly at least up to week 12 and then PTI **OR** Faricimab 6mg 4 weekly up to week 20 and then 8 weekly	Aflibercept 2mg 4 weekly to week 16 followed by 8 weekly injections	Diff in adj means Faricimab Q8W from aflibercept = -0.7 (95% CI -2.6, 1,2) Diff in adj means Faricimab PTI from aflibercept = -0.7 (95% CI -2.5, 1.2)	YOSEMITE phase III study
Unfavourable Effects						
Fatal evants	Patient Deaths through the Clinical Cut-Off Date		faricimab pooled Q8W and PTI arms **35 (2.8%)**	aflibercept Q8W arms **12 (1.9%)**	a higher frequency in the faricimab group as compared to the aflibercept group. However, overall cumulative difference in fatal cases was 0.4% once COVID19 deaths were excluded	Pooled Phase III DME Studies
Serious Ocular Adverse Events	Serious Ocular Adverse Events in the Study Eye through Week 56		**faricimab** pooled Q8W and PTI arms 34 (2.7%)	**aflibercept** Q8W arm 8 (1.3%)	a higher frequency in the faricimab group as compared to the aflibercept group	Pooled Phase III DME Studies
Serious Non-Ocular Adverse Events	Serious Non-Ocular Adverse Events through Week 56		**faricimab** pooled Q8W and PTI arms **230 (18.2%)**	**aflibercept** Q8W arm **102 (16.3%)**	a higher frequency in the faricimab group as compared to the aflibercept group	Pooled Phase III DME Studies
IOI	Intraocular Inflammation in the Study Eye through Week 56 Intraocular Inflammation in the Study Eye cumulative data from baseline to the Clinical Cut-Off Date		**faricimab** pooled Q8W and PTI arms **17 (1.3%)** **faricimab** Q8W arm: **8 (1.3%)** PTI arm: **11 (1.7%)**	**aflibercept** Q8W arms **4 (0.6%)** **aflibercept** Q8W arm **7 (1.1%)**	a higher frequency in the faricimab group as compared to the aflibercept group	Pooled Phase III DME Studies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, it is considered that efficacy has been demonstrated in the treatment of nAMD and DME. The favourable effects demonstrated in the pivotal Phase III studies provide evidence on the comparable

efficacy of faricimab and aflibercept in visual function, anatomical parameters and visual related quality of life in patients with nAMD and DME.

The most frequent ADRs are well-established for approved products administered by IVT injection, some are procedural and related to the route of administration.

As outlined above, the numerical unbalance in deaths has been investigated with several approaches, and it is not considered causally attributable to faricimab at this stage. In any case, it is highlighted that the overall ocular and non-ocular safety of faricimab, including topics of special interest, will be closely monitored in the ongoing safety studies, and in the post-marketing setting. Regular updates on ocular and non-ocular safety of faricimab will be provided through the PSUR submissions.

3.7.2. Balance of benefits and risks

The overall B/R of Faricimab is positive.

3.8. Conclusions

The overall benefit/risk balance of Vabysmo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vabysmo is favourable in the following indication(s):

Vabysmo is indicated for the treatment of adult patients with:

- neovascular (wet) age-related macular degeneration (nAMD),
- visual impairment due to diabetic macular oedema (DME).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the launch of Vabysmo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at adequately informing patients/carers on the risks of Vabysmo, the key signs and symptoms of those risks, and when to seek urgent attention from their physician with the objective to minimize the risks and any resultant complications by encouraging prompt intervention.

The MAH shall ensure that in each Member State where Vabysmo is marketed, all patients/carers who are expected to use Vabysmo have access to/are provided with the following educational package:

- Patient information pack

The patient information pack consists of the patient information leaflet and a patient/carer guide. The patient guide is provided in written and audio format, and will include the following key elements:

A description of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)

A description of Vabysmo, how it works, and what to expect from Vabysmo treatment

A description of the key signs and symptoms of the key risks associated with Vabysmo, i.e., infectious endophthalmitis and intraocular inflammation

A description of when to seek urgent attention from the health care provider should signs and symptoms of these risks present themselves

Recommendations for adequate care after the injection

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD	Q1 2025
A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DME	Q4 2024

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that faricimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 21 July 2022