EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2024
EMA/333706/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Vabysmo

International non-proprietary name: faricimab

Procedure No. EMEA/H/C/005642/II/0005

Marketing authorisation holder (MAH): Roche Registration GmbH

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List of abbreviations

ADA Anti-Drug Antibody

ADR Adverse Drug Reaction

AE Adverse Event

AEMPS Spanish Agency of Medicines and Medical Devices

AH Aqueous Humor

ANCOVA Analysis Of Covariance

Ang-2 Angiopoietin-2 (Protein)

BASG/AGES Austrian Federal Office for Safety in Health Care/ Medicines and Medical Devices Agency

BCVA Best-Corrected Visual Acuity

BRVO Branch Retinal Vein OcclusionCCOD Clinical Cutoff Date

CFDI Center for Food and Drug Inspection

CFP colour Fundus Photography

CHMP Committee for Medicinal Products for Human Use

CI Confidence Interval

CL/F Apparent Plasma Clearance

CMO Cystoid Macular Oedema

CNV Choroidal Neovascularization

CO Clinical overview

COVID-19 Coronavirus Disease

CRC Central Reading Center

CRVO Central Retinal Vein Occlusion

CSR Clinical Study Report

CST Central Subfield Thickness

DME Diabetic Macular Edema

DR Diabetic Retinopathy

EMA European Medicines Agency

ETDRS Early Treatment Diabetic Retinopathy Study

FDA US Food & Drug Administration

FFA Fundus Fluorescein Angiography

GCP Good Clinical Practice

HCP Health Care Provider

HRVO Hemiretinal Vein Occlusion

ICE Intercurrent Event

IgG1 Immunoglobulin G1

IMA Icelandic Medicines Agency

IOI Intraocular Inflammation

IOP Intraocular Pressure

ITT Intent-To-Treat (population)

LTE Long-Term Extension (study)

MI Multiple Imputation

MMRM Mixed-Effect Model With Repeated Measures

MNAR Missing Not At Random

nAMD Neovascular Age-Related Macular Degeneration

NEI/NHI US National Eye Institute/National Institutes of Health

NEI VFQ-25 National Eye Institute 25-Item Visual Functioning Questionnaire

NI Non-Inferiority (margin)

(China's) National Medical Products Administration (NMPA)

OCT Optical Coherence Tomography

OCTA Optical Coherence Tomography Angiography

PD Pharmacodynamics

PK Pharmacokinetics

PMP Pre-Meeting Package

PoC Proof Of Concept

popPK Population Pharmacokinetic

PP Per-Protocol (population)

PRAC Pharmacovigilance Risk Assessment Committee

PTI Personalized Treatment Interval

Q4w Every 4 Weeks

Q16W Every 16 Weeks

RAO Retinal Artery Occlusion

RVO Retinal Vein Occlusion

RWE Real World Evidence

RWD Real World Data

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SBP Summary of Biopharmaceutic Studies and Associated Analytical Methods

sBLA Supplemental Biologic License Application

SCE Summary of Clinical Efficacy

SCORE2 Study of Comparative Treatments for Retinal Vein Occlusion 2

SCP Summary of Clinical Pharmacology Studies

SCS Summary of Clinical Safety

SD Standard Deviation

t1/2 Half-Life

VEGF Vascular Endothelial Growth Factor

VH Vitreous Humor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 24 July 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) for Vabysmo, based on results from the two phase 3 studies: GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and GR41986 (COMINO) in patients with central retinal vein occlusion (CRVO) or hemi-retinal vein occlusion (HRVO). These are global, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety, and PK of faricimab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision on the granting of a product-specific waiver for all subsets of the paediatric population with RVO (P/0333/2020).

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

Not applicable.

Scientific advice

During the development of faricimab for the treatment of patients with RVO, the MAH sought Scientific Advice (SA) from the EMA Scientific Advice Working Party (SAWP).

In February 2020 the MAH received SA on clinical aspects **(EMEA/H/SA/3552/4/2020/II).** The main recommendations were as follows.

In relation to the planned **study population**, it was supported that patients with ischemic RVO are not excluded. It was recommended to include patients with hemi-retinal vein occlusion and this recommendation was followed by the MAH. External validity was considered to be reduced, as the study was planning to enrol patients with less than 3 months history of RVO.
The proposal to exclude patients with visually significant vitreous haemorrhage was questioned. The proposal to exclude patients with diabetic retinopathy was supported. The stratification on BCVA was endorsed but it was considered that the cut-off (i.e. 55 letters for stratification) needed to be justified.

In relation to the **treatment dose and regimen** for faricimab, it was highlighted that, as there are no phase II data in the treatment of RVO, it is difficult to comment regarding the appropriateness of the proposed dose regimen and therefore it was considered that the dose would need to be justified at the stage of the MAA. In relation to the dose of the comparator it was agreed that the monthly regimen for the comparator could be accepted.

In relation to the **non–inferiority margin,** the 4-letter proposed by the MAH was considered to be a margin in the range that could be acceptable.

In relation to the **treatment regimen beyond the primary endpoint** it was agreed that individualised treatment regimen after primary efficacy could be explored. However, it was highlighted that the development programme in RVO does not robustly address the potential to reduce the number of faricimab injections as no comparative data are available after 6 months of treatment. Even if it can be shown that BCVA is maintained with a reduced number of injections compared to the evaluation at month 6, this will be a descriptive analysis only. It was recommended to continue the trial in a controlled and masked setting where a T&E dosing is evaluated in both treatment arms. However, this aspect of the scientific advice (SA) was not followed by the MAH.

There was no objection that the MAH would provide at the stage of MAA the Real-World Data (RWD) supplementary analysis. However, due to methodological limitations (as highlighted to the MAH) this was foreseen to introduce a bias in favour of faricimab and of concern, with regard to a fair comparison.

The EMA endorsed the proposed **safety** monitoring plan and the overall size of the safety database (> 2800 subjects). The approximate number of 540 patients with RVO exposed to faricimab at the time of filing this application was considered sufficient to draw an initial conclusion on the benefit/risk in the treatment of RVO. However, the Agency expected that safety data, including some long-term data would be available from other indications (in particular DME) at the time of submission. While the Agency did not object to supplementary analysis with RWD, the downsides associated with these types of data, specifically under-reporting of adverse events and handling of post-baseline treatment decisions, were highlighted.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Jayne Crowe (IE) Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	24 July 2023
Start of procedure	12 Aug 2023
CHMP Rapporteur Assessment Report	06 Oct 2023
PRAC Rapporteur Assessment Report	13 Oct 2023
PRAC members comments	18 Oct 2023
Updated PRAC Rapporteur Assessment Report	N/A (pAR=uAR)
PRAC outcome	26 Oct 2023
CHMP members comments	30 Oct 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	31 Oct 2023
Request for Supplementary Information (RfSI)	09 Nov 2023
MAH re-submission deadline	19 Jan 2024
Re-start of procedure	22 Jan 2024
CHMP Rapporteur Assessment Report	20 Feb 2024
PRAC Rapporteur Assessment Report	23 Feb 2024
PRAC members comments	28 Feb 2024
Updated PRAC Rapporteur Assessment Report	29 Feb 2024
PRAC outcome	07 Mar 2024
CHMP members comments	11 Mar 2024
Updated CHMP Rapporteur Assessment Report	14 Mar 2024
2nd Request for Supplementary Information (RfSI)	21 Mar 2024
MAH re-submission deadline	26 April 2024
Re-start of procedure	29 April 2024
CHMP Rapporteur Assessment Report	28 May 2024
PRAC Rapporteur Assessment Report	29 May 2024
PRAC members comments	05 June 2024
Updated PRAC Rapporteur Assessment Report	N/A
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	20 June 2024
CHMP Opinion	27 June 2024

2. Scientific discussion

2.1. Introduction

Faricimab (also known as RO6867461 and VABYSMO) is the first humanised bispecific immunoglobulin G1 (IgG1) antibody developed for intravitreal use that selectively binds to and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A).
Vabysmo is currently approved for the treatment of adult patients with:

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

With this application, the Sponsor seeks an additional indication for the use of faricimab to treat patients with macular oedema due to retinal vein occlusion (RVO). Clinical evidence supporting the efficacy, safety, and favourable benefit-risk assessment of faricimab is mainly based on the primary analysis results of two pivotal Phase III studies:

- Study GR41984 (hereafter referred to as BALATON) in patients with macular edema due to branch retinal vein occlusion (BRVO)
- Study GR41986 (hereafter referred to as COMINO) in patients with macular edema due to central retinal vein occlusion or hemiretinal vein occlusion (C/HRVO).

2.1.1. Problem statement

Disease or condition

RVO is one of the most common retinal vascular disorders and is associated with varying degrees of visual loss (Hayreh et al. 1994). RVO has been reported as the second leading cause of blindness for patients with retinal vascular disease, following diabetic retinopathy (DR) (Cugati et al. 2006; Klein et al. 2008; Rogers et al. 2010; Yasuda et al. 2010). The main types of RVO include BRVO, HRVO, and CRVO. As of 2015, approximately 28.06 million adults worldwide were affected by any type of RVO, of which 4.67 million are CRVO patients and 23.38 million are BRVO patients. The estimated global prevalence of RVO increased with advanced age but did not show significant differences between sexes (Song et al. 2019).

State the claimed the therapeutic indication

Vabysmo is indicated for the treatment of adult patients with:

- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Epidemiology and risk factors, screening tools/prevention

The most recognised risk factors for RVO are age and systemic vascular disorders. In over half of the cases, the age of onset is over 65 years. Systemic diseases such as hypertension, hyperlipidaemia, and diabetes mellitus are very strongly associated with the development of RVO (Kolar 2014). The most common ocular risk factor associated with RVO is glaucoma.

Aetiology and pathogenesis

The pathogenesis of macular oedema in patients with RVO starts with an increase in intraluminal pressure within the retinal vein caused by vascular obstruction, which leads to areas of reduced retinal perfusion and ischemia. Ischemia leads to up-regulation and secretion of vascular endothelial growth factor (VEGF) (Boyd et al. 2002; Noma et al. 2006) and angiopoietin-2 (Ang-2), both well-known proangiogenic and vessel hyperpermeability cytokines with Ang-2 contributing additional pro-inflammatory and vessel destabilization properties (Maisonpierre at al. 1997; Hackett et al 2000; Fiedler et al 2006).

Patients with RVO were found to have some of the highest vitreous and/or aqueous levels of both Ang-2 and VEGF among patients with retinal vascular diseases (Aiello et al 1994; Regula et al. 2016).

Increased levels of Ang-2 and VEGF in retinal tissue result in pathological changes in the retina, and in many patients, also leads to macular oedema that is accompanied with a decrease in vision. A hallmark of RVO is the characteristic pattern of retinal haemorrhages, tortuous and dilated retinal veins across the affected area of retina (one quadrant in BRVO, two quadrants in HRVO and the entire retina in CRVO). In more severe cases, patients can develop retinal ischemia with subsequent retinal neovascularisation, haemorrhages, neovascularisation in the anterior segment leading to rubeosis or neovascular glaucoma, and some patients may develop optic disc oedema.

Clinical presentation, diagnosis

The most common presenting complaint of RVO is an abrupt, painless decrease of central vision, due to macular oedema. Less frequently, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over several days to weeks before being followed by a permanent decrease in vision. Metamorphopsia and visual field defects have also been described (Achiron et al. 2015; Manabe et al. 2017).

Management

Anti-VEGF pharmacotherapy is the current mainstay of treatment in macular oedema due to RVO and has demonstrated efficacy across several pivotal, randomised clinical studies, although macular laser and intravitreal steroids especially steroid implants are also used in some cases.

2.1.2. About the product

Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).

Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation.

By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

During the development of faricimab for the treatment of patients with RVO, the MAH sought Scientific Advice (SA) from the EMA Scientific Advice Working Party (SAWP). In February 2020 the MAH received SA on clinical aspects (EMEA/H/SA/3552/4/2020/II).

2.1.4. General comments on compliance with GCP

The MAH provided confirmation that all clinical trials conducted outside the European Union meet the ethical requirements of the EU Clinical Trial Directive [2001/20/EC].

For studies conducted in the EU/EEA countries, the investigators ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. The pivotal studies were conducted in the following countries:

Table 1. List of countries involved in each study included in the dossier

Study Number	Protocol Number	EU Countries	Non-EU Countries
RVO studies			
GR41984 (BALATON) A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion	GR41984	Austria, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Spain	Argentina, Australia, Brazil, China, Hongkong, Israel, Japan, Russian Federation, Republic of Korea, Singapore, Taiwan, UK, US
GR41986 (COMINO) A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients With Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion	GR41986	Austria, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Spain	Argentina, Australia, Brazil, China, Hongkong, Israel, Japan, Russian Federation, Republic of Korea, Singapore, Taiwan, UK, US

There were two site GCP inspections each for BALATON (GR41984) and COMINO (GR41986), respectively, conducted in China by the Center for Food and Drug Inspection (CFDI) under China's National Medical Products Administration (NMPA). There were no major or critical findings for the BALATON and COMINO site inspections. A summary of these site GCP inspections are provided in **Table 2**.

Table 2. Summary of site GCP inspections

Inspection Type	Health Authority	Study/Location	Date	Findings
Site GCP Inspection	CFDI (China NMPA)	BALATON Affiliated Eye Hospital of Nanjing Medical University, Nanjing	16-18 August 2023	No major or critical findings.
		BALATON He Eye Specialist Shenyang Hospital, Shenyang	21-23 August 2023	No major or critical findings.
Site GCP Inspection	CFDI (China NMPA)	COMINO Eye Hospital, Wenzhou Medical University	30 November – 2 December 2023	No major or critical findings.
		COMINO He Eye Specialist Shenyang Hospital, Shenyang	14-16 December 2023	No major or critical findings.

CFDI = Center for Food and Drug Inspection; GCP = Good Clinical Practice; NMPA = China's National Medical Products Administration

2.2. Non-clinical aspects

No new nonclinical data have been submitted in support of this application.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance is a natural substance (protein) 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.

2.2.2. Conclusion on the non-clinical aspects

No new nonclinical data have been submitted in support of this application, which was acceptable for the CHMP.

Considering the above, faricimab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

In the initial marketing application for use of faricimab for the indications of neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DME), the clinical pharmacology of faricimab was characterised in nine clinical studies. These included one Phase I, two Phase II and two Phase III studies in patients with nAMD, one Phase I in patients with nAMD and DME and one Phase II and two Phase III studies in patients with DME.

For the present extension of indication application, two Phase III studies in patients with macular oedema due to retinal vein occlusion (RVO) were conducted; Study GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and Study GR41986 (COMINO) in patients with central/hemiretinal retinal vein occlusion (C/HRVO). The pharmacokinetic (PK), pharmacodynamic (PD) and anti-drug antibody (ADA) results from all 11 faricimab clinical studies were pooled for the population PK analysis. Exposure-response analyses (efficacy and safety) in patients with RVO were also conducted.

The proposed dose of faricimab is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for 3 or more consecutive doses, followed by a treat-and-extend approach for macular oedema secondary to RVO.

Table 3 below gives an overview of the studies contributing new data to support the RVO indication through Week 24:

Table 3. Summary of RVO Studies contributing to PK, PD and Immunogenicity data

Study Name (Number)	Study Design	Patient Population	Number of Patients Enrolled	Route and Dose Regimen(s)	Analytes Measured: Faricimab PK	PD	ADA
Pivotal Phase III Studies							
BALATON (GR41984) **COMINO** (GR41986)	Phase III, Two-Part, Multicenter, Randomized, Double–Masked, Active Comparator-Controlled[a], Parallel-Group Study	Patients with RVO: BRVO (BALATON) or C/HRVO (COMINO)	**BALATON** = 553 Faricimab:N=276 Aflibercept: N=277 **COMINO** = 729 Faricimab: N=366 Aflibercept: N=363	Part 1 (Q4W Dosing): Arm A: 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Arm B: 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Part 2 (PTI Regimen)[b]: Patients in both Arms A and B received 6 mg faricimab intravitreal injections to a PTI dosing regimen from Week 24 through Week 68	AH and plasma	Ang-2: AH and plasma VEGF-A: AH and plasma	Plasma

ADA = anti-drug antibodies; AH = aqueous humor; Ang-2 = angiopoietin-2; BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CST= central subfield thickness; HRVO = hemiretinal vein occlusion; PD=pharmacodynamic; PK=pharmacokinetic; PTI=personalized treatment interval; Q4W=every 4 weeks; Q16W = every 16 weeks; RVO = retinal vein occlusion; VEGF-A = vascular endothelial growth factor-A.

[a] Studies BALATON and COMINO are only active comparator-controlled during Part 1.

[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 Q16W or a minimum of Q4W based on the relative change of the CST and BCVA compared with the patient's reference CST and reference BCVA.

GCP

The MAH provided a statement of GCP compliance for both the BALATON and COMINO studies. There were two site GCP inspections each for these two studies, conducted in China by the Center for Food and Drug Inspection (CFDI) under China's National Medical Products Administration (NMPA). There were no major or critical findings for both BALATON and COMINO site(s) inspections.

2.3.2. Pharmacokinetics

Bioanalytical methods

PK was evaluated using the same validated bioanalytical assays for measuring free faricimab aqueous humour (AH) and plasma concentrations as described for the previous Phase III trials in the initial MAA. Immunogenicity was evaluated using the same validated faricimab ADA assay as described for the previous Phase III trials in the initial MAA. PD was evaluated using the same validated bioanalytical methods to measure AH Ang-2 and free Ang-2 in plasma, and the same validated methods to measure free VEGF in AH and plasma, as were used for the previous Phase III trials.

A table summarising the bioanalytical method studies for the analysis of PK, PD, and anti-drug antibodies for all Phase III clinical studies is noted below. All bioanalytical methods used in this study were previously validated for the initial MAA.

Table 4. Summary of Bioanalytical Methods for the Analysis of Pharmacokinetics, Pharmacodynamics, and Anti-Drug Antibodies in Phase III Clinical Studies

Clinical Study [Indication]	Free Faricimab Pharmacokinetics		Faricimab ADAs	Ang-2		Free VEGF	
	AH	Plasma	Plasma	AH	Plasma	AH	Plasma
Phase III							
TENAYA [nAMD]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
LUCERNE [nAMD]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
YOSEMITE [DME]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
RHINE [DME]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
BALATON [BRVO]	1106459 [a]	1061938	1061515	1105680	free Ang-2: 1105351	1085875	1105710
COMINO [C/HRVO]	1106459 [a]	1061938	1061515	1105680	free Ang-2: 1105351	1085875	1105710

ADA = anti-drug antibody; AH = aqueous humor Ang-2 = angiopoietin-2; DME = diabetic macular edema; NA = not applicable; nAMD = neovascular age-related macular degeneration; PD =pharmacodynamics; PK = pharmacokinetics; VEGF = vascular endothelial growth factor; X = assay performed using other method (see footnotes).

[a]: The same method was used for all studies; however, for Phase I and II (1062732) this method was considered qualified. For Phase III this method underwent complete validation (1106459).

Study GR41984 (BALATON)

BALATON (Study GR41984) is a Phase III, multicentre, randomised, double-masked, active comparator−controlled, parallel-group, 2-part study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24, followed by a period of study without active control to evaluate faricimab administered according to a personalized treatment interval (PTI) dosing regimen in patients with macular edema due to BRVO where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment and faricimab treatment interval in Part 2.
This study is comprised two parts: Part 1 (Day 1 through Week 24) compared faricimab every 4 weeks (Q4W) versus aflibercept Q4W; Part 2 (Week 24 through Week 72) evaluated faricimab administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on PTI dosing criteria.

The Primary Clinical Study Report (CSR) submitted with this application provides the results of the primary analysis through Week 24.

In Part 1 (Q4W dosing), 570 patients were planned to be randomized during the global enrolment phase of the study in a 1:1 ratio to one of two treatment arms: Arm A (n = 285) received 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections) and Arm B (n = 285) received 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections).

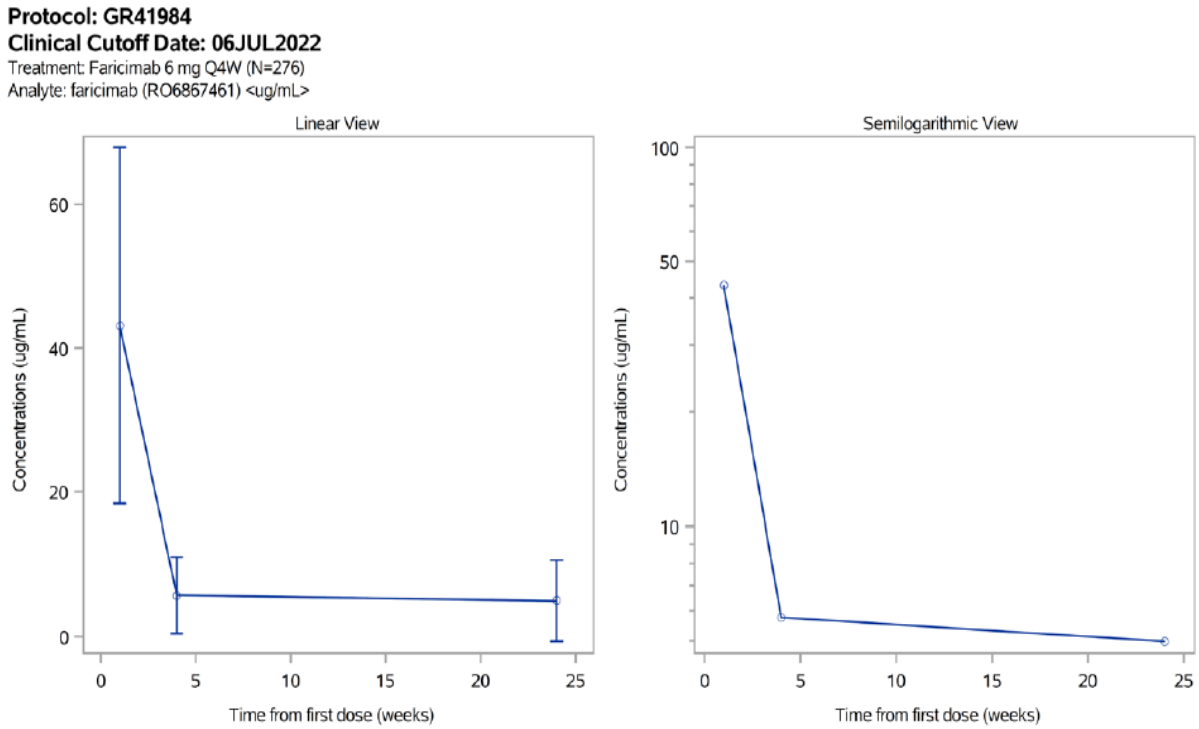
Mandatory blood samples for plasma concentrations for faricimab PK, PD, and ADA were taken at Day 1, Day 7, Week 4, and Week 24 for the study period in this report. Optional aqueous humour (AH) samples were taken at Day 1, Day 7, and Week 4, and Week 24 for the study period in this report. Optional PK plasma samples if an AH sample was collected were at Day 7, and optional PD plasma Samples were at Day 7 and Week 4.

Pharmacokinetic Results

Ocular Pharmacokinetics
Aqueous humour faricimab concentrations from 23 patients consenting to optional aqueous humour sampling were included in the PK data analysis.
Faricimab was measurable throughout the study. Medium to high inter-patient variability was observed in faricimab aqueous humour concentrations through Week 24 (CV: 57.4% to 113.4%). The maximum observed concentration was observed at the first time point collected (i.e., 1-week post-dose).

The observed mean (±SD) faricimab aqueous humour concentration was 43.2 (±24.8) µg/mL at Week 1 (1 week after the first administration). The observed mean faricimab 4 week-post-dose aqueous humour concentrations were 5.8 (±5.3) µg/mL at Week 4 and 5.0 (±5.6) µg/mL at Week 24.
The mean aqueous humour concentration-time profiles are shown in Figure 1 below.

Figure 1. Mean (± SD) Aqueous Humor faricimab Concentration-Time Profiles though Week 24 (Lineal and semi-Log scale), faricimab PK-Evaluable Population



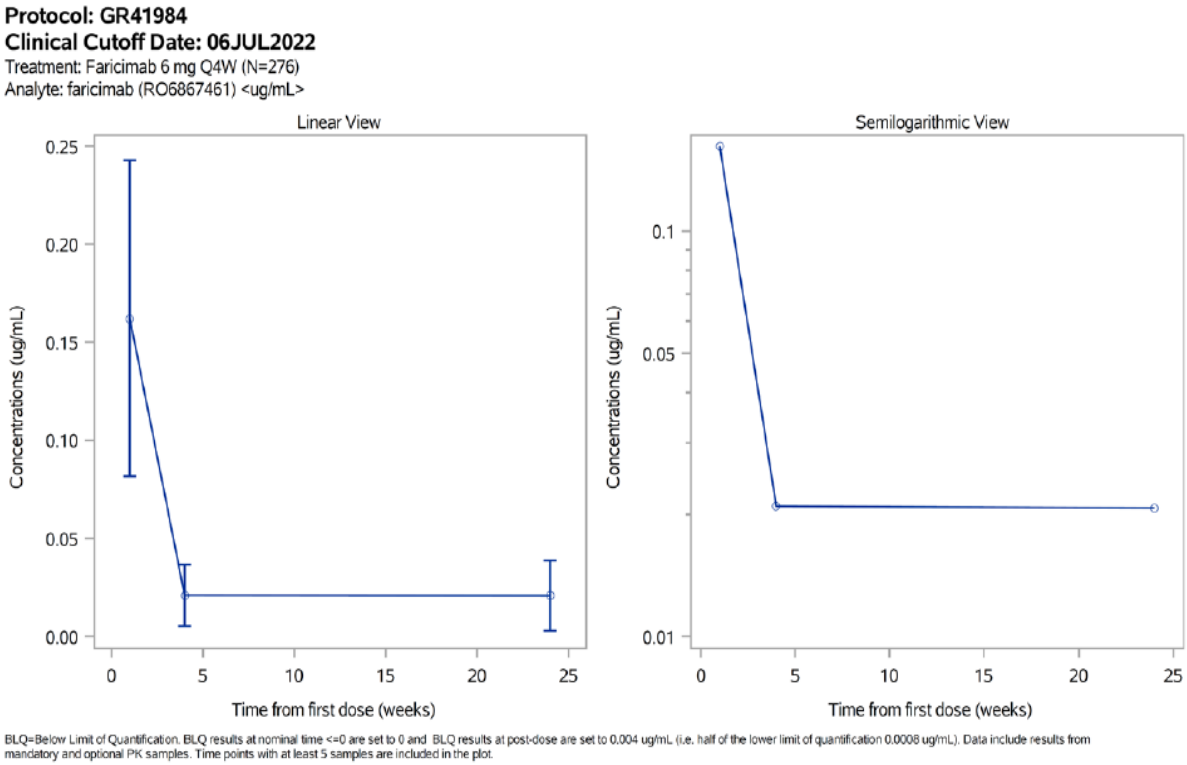
BLQ=Below Limit of Quantification. BLQ results at nominal time <=0 are set to 0 and BLQ results at post-dose are set to 0.003905 ug/mL (i.e. half of the lower limit of quantification 0.00781 ug/mL). Data include results from mandatory and optional PK samples. Time points with at least 5 samples are included in the plot.

Plasma Pharmacokinetics

Plasma data from 269 patients were included in the PK data analysis. High inter-patient variability was observed in faricimab plasma concentrations through Week 24 (coefficient of variation [CV] of 49.7% to 86.0%). The maximum observed concentration was 1-week post-dose (first time point collected after drug administration). The observed mean (±SD) faricimab plasma concentration was 0.162 (±0.0806) µg/mL at Week 1 (1 week after the first administration). The observed mean faricimab 4 week-post-dose plasma concentrations were 0.0209 (±0.0157) µg/mL at Week 4 and 0.0207 (±0.0178) at Week 24.
The faricimab aqueous humor-to-plasma ratio on Day 7 was ~266.

The mean plasma concentration-time profiles based on the faricimab PK-evaluable population are shown in Figure 2 below.

Figure 2. Mean (± SD) Plasma faricimab concentration-time profiles though week 24 (Lineal and semi-Log scale), faricimab PK-evaluable population



Study GR41986 (COMINO)

COMINO (Study GR41986) is a Phase III, multicentre, randomised, double-masked, active comparator controlled, parallel-group, 2-part study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24, followed by a period of study without active control to evaluate faricimab administered according to a personalized treatment interval (PTI) dosing regimen in patients with macular edema due to CRVO or HRVO where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment and faricimab treatment interval in Part 2.

This study is comprised two parts: Part 1 (Day 1 through Week 24) compared faricimab every 4 weeks (Q4W) versus aflibercept Q4W; Part 2 (Week 24 through Week 72) evaluated faricimab administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on PTI dosing criteria.

The Primary Clinical Study Report (CSR) submitted with this application provides the results of the primary analysis through Week 24.

In Part 1 (Q4W dosing), 750 patients were planned to be randomized during the global enrolment phase of the study in a 1:1 ratio to one of two treatment arms: Arm A (n = 375) received 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections) and Arm B (n = 375) received 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections).

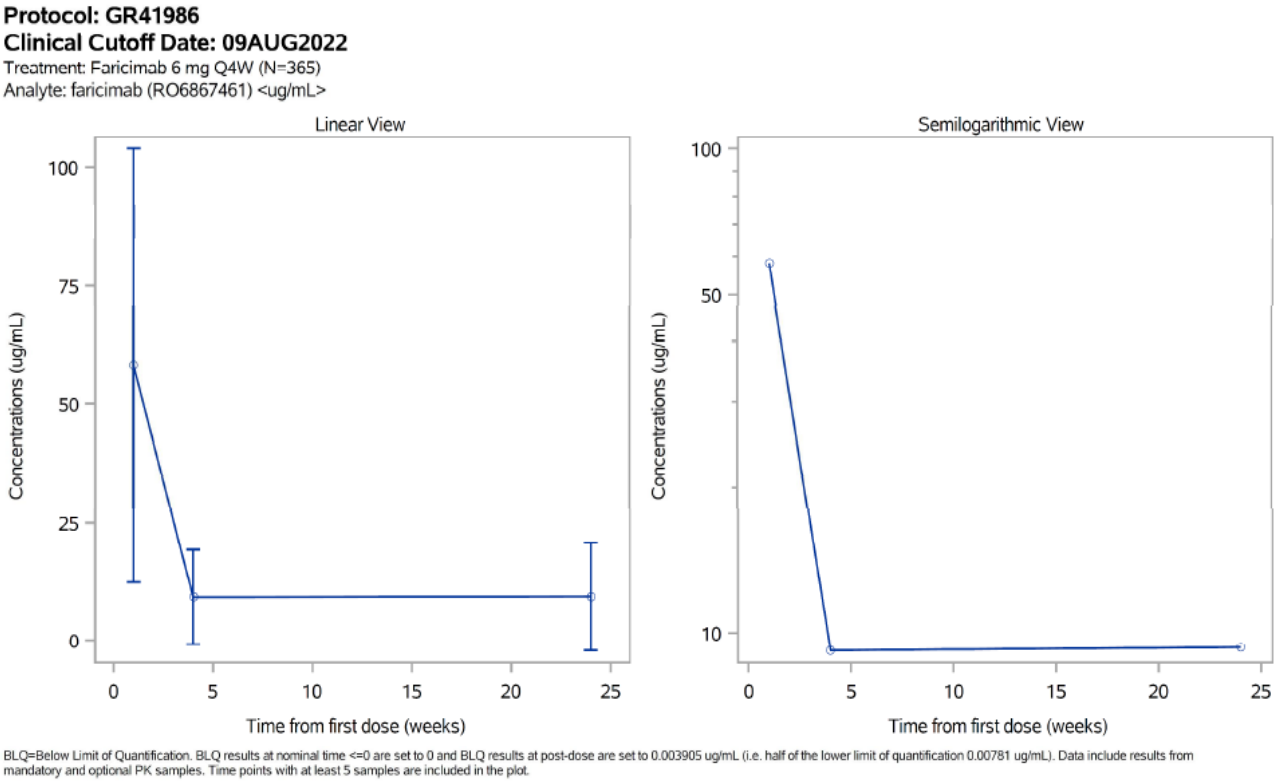
Mandatory blood samples for plasma concentrations for faricimab PK, PD, and ADA were taken at Day 1, Day 7, Week 4, and Week 24 for the study period in this report. Optional aqueous humour (AH) samples were taken at Day 1, Day 7, and Week 4, and Week 24 for the study period in this report. Optional PK plasma samples if AH samples were collected were at Day 7 and optional PD plasma samples were at Day 7 and Week 4.

Pharmacokinetic Results

Ocular Pharmacokinetics
Aqueous humour faricimab concentrations from 33 patients consenting to optional aqueous humour sampling were included in the PK data analysis. Faricimab was measurable throughout the study. High inter-patient variability was observed in faricimab aqueous humour concentrations through Week 24 (CV: 78.8% to 1233%). The maximum observed concentration was observed at the first time point collected (i.e., 1-week post-dose). The observed mean (±SD) faricimab aqueous humour concentrations were 58.1 (±45.8) µg/mL at Week 1 (1 week after the first administration). The observed mean faricimab 4 week-post-dose aqueous humour concentrations was 9.2 (±10.1) µg/mL at Week 4 and 9.3 (±11.5) µg/mL at Week 24.

The mean aqueous humour concentration-time profiles are shown in the Figure 3 below.

Figure 3. Mean (± *SD*) Aqueous Humor faricimab Concentration-Time Profiles though Week 24 (Lineal and semi-Log scale), faricimab PK-Evaluable Population

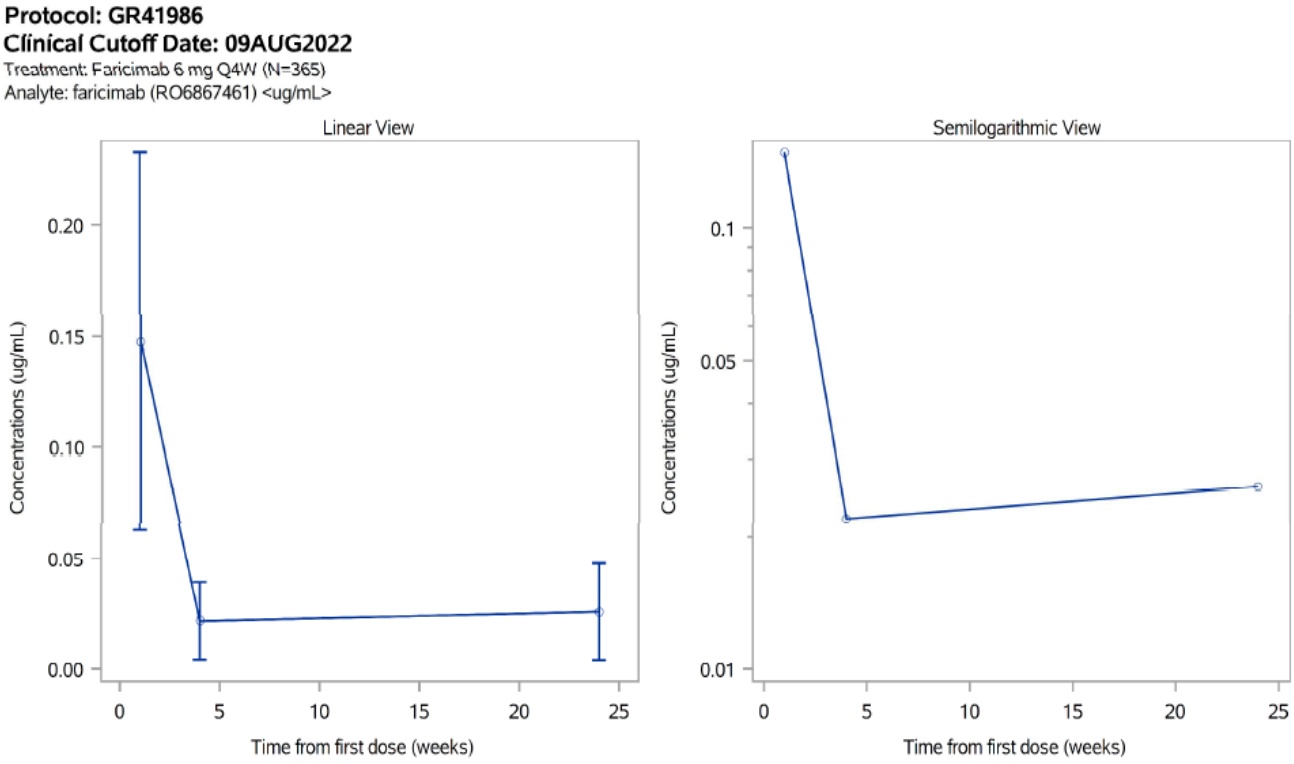


Plasma Pharmacokinetics
Plasma data from 349 patients were included in the PK data analysis. High inter-patient variability was observed in faricimab concentrations through Week 24 (CV% of 57.3% to 83.9%). The maximum observed concentration was 1-week post-dose (first time point collected after drug administration). The observed mean (±SD) faricimab plasma concentration was 0.148 (±0.0846) µg/mL at Week 1 (1 week after the first administration). The observed mean faricimab 4-week post-dose plasma concentrations were 0.0219 (±0.0175) µg/mL at Week 4 and 0.0260 (±0.0218) µg/mL at Week 24.

The faricimab AH-to-plasma ratio on Day 7 was ~394.

The mean plasma concentration-time profiles based on the faricimab PK-evaluable population are shown below.

Figure 4. Mean (±SD) Plasma faricimab Concentration-Time Profiles though Week 24 (Lineal and semi-Log scale), faricimab PK-Evaluable Population



BLQ=Below Limit of Quantification. BLQ results at nominal time <=0 are set to 0 and BLQ results at post-dose are set to 0.004 ug/mL (i.e. half of the lower limit of quantification 0.0008 ug/mL). Data include results from mandatory and optional PK samples. Time points with at least 5 samples are included in the plot.

The overall study design for BALATON and COMINO studies to assess the PK of faricimab following an intravitreal injection are overall acceptable for the CHMP.

The ocular and plasma PK are similar between both the BALATON and COMINO studies. The Q4W interval for injection resulted in the highest concentration being seen at the 7-day sampling time-point and low concentrations shown pre-dose at Week 4 and Week 24 for both the ocular and plasma faricimab concentrations. The faricimab AH-to-plasma ratios were ~266 and ~394 for the BALATON and COMINO studies respectively.

The low number of patients that consented to provide AH samples means the data should be interpreted with caution.
Overall, the PK for the plasma and AH exposure from the BALATON and COMINO studies are in line with the Phase III studies from the initial MAA.

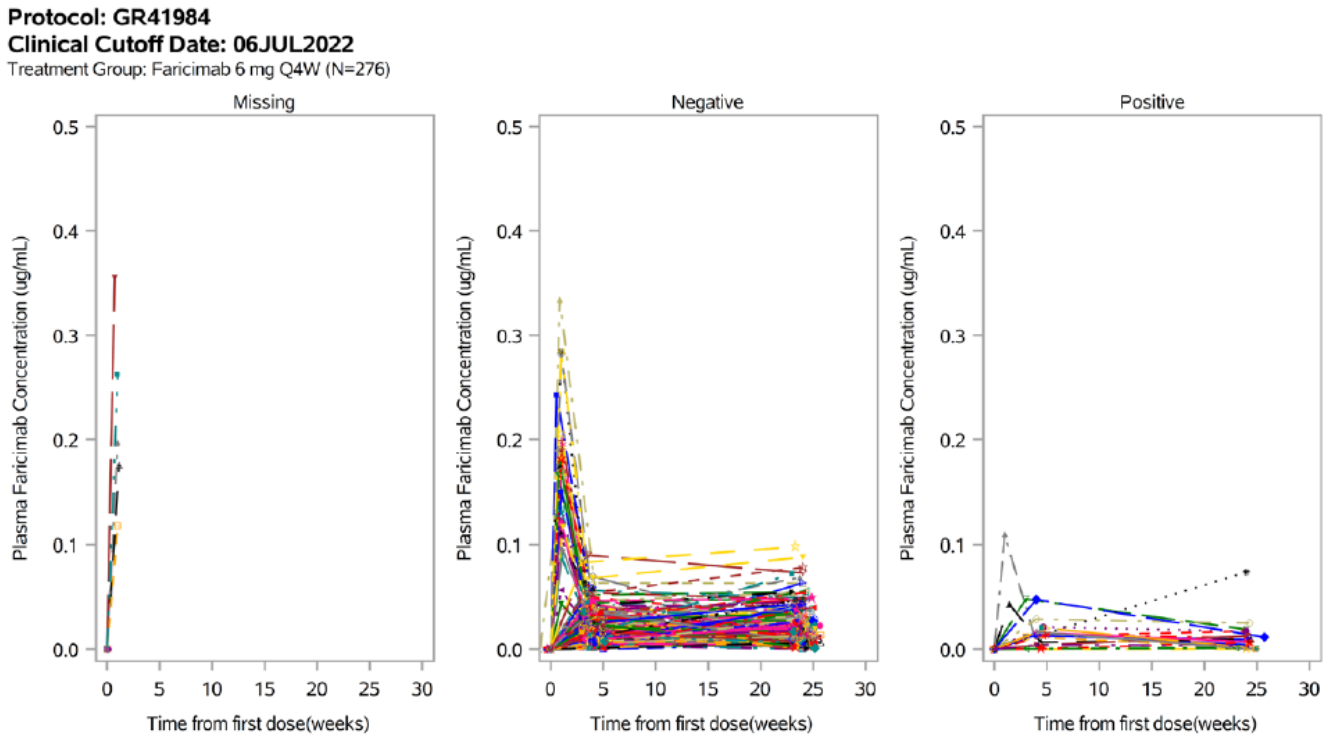
Immunogenicity

Study GR41984 (BALATON)

The ADA analyses were based on the immunogenicity-analysis population for patients in the faricimab Q4W arm in Part 1. The following properties of each sample are listed by patient: ADA status (from the confirmatory assay): ADA positive (yes) or ADA negative (no) and titer value for the ADA positive sample. ADAs were assessed in K3EDTA specimens of faricimab-treated patients at baseline and at Weeks 4 and 24.
The baseline prevalence of ADAs to faricimab in the study was 1.1% (3/264). Incidence of immunogenicity to faricimab is based on patients with treatment-emergent ADAs (the sum of treatment-induced and treatment-boosted ADA-positive patients). Overall, 18/259 patients (6.9%) in BALATON receiving faricimab had treatment-emergent ADAs, of which all were treatment-induced, no patients were treatment-boosted. Persistence was defined as an ADA positive result that was detected

at the last post-baseline sampling timepoint, or at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of 16 weeks, irrespective of any negative samples in between. The observed median time to onset was 24.0 weeks, and ADA positivity was persistent in 94.4% of patients with treatment-induced ADA. ADA titer ranged from 10 to 20480.
The MAH was of the view that visual inspection of the faricimab plasma concentration-time profiles grouped by ADA status did not suggest a difference in plasma exposure in ADA-positive patients compared with ADA-negative patients, in Figure 5 (GR41984) below.

Figure 5. Faricimab plasma concentration-time profiles by ADA status though week 24 (Log scale), faricimab PK-evaluable population



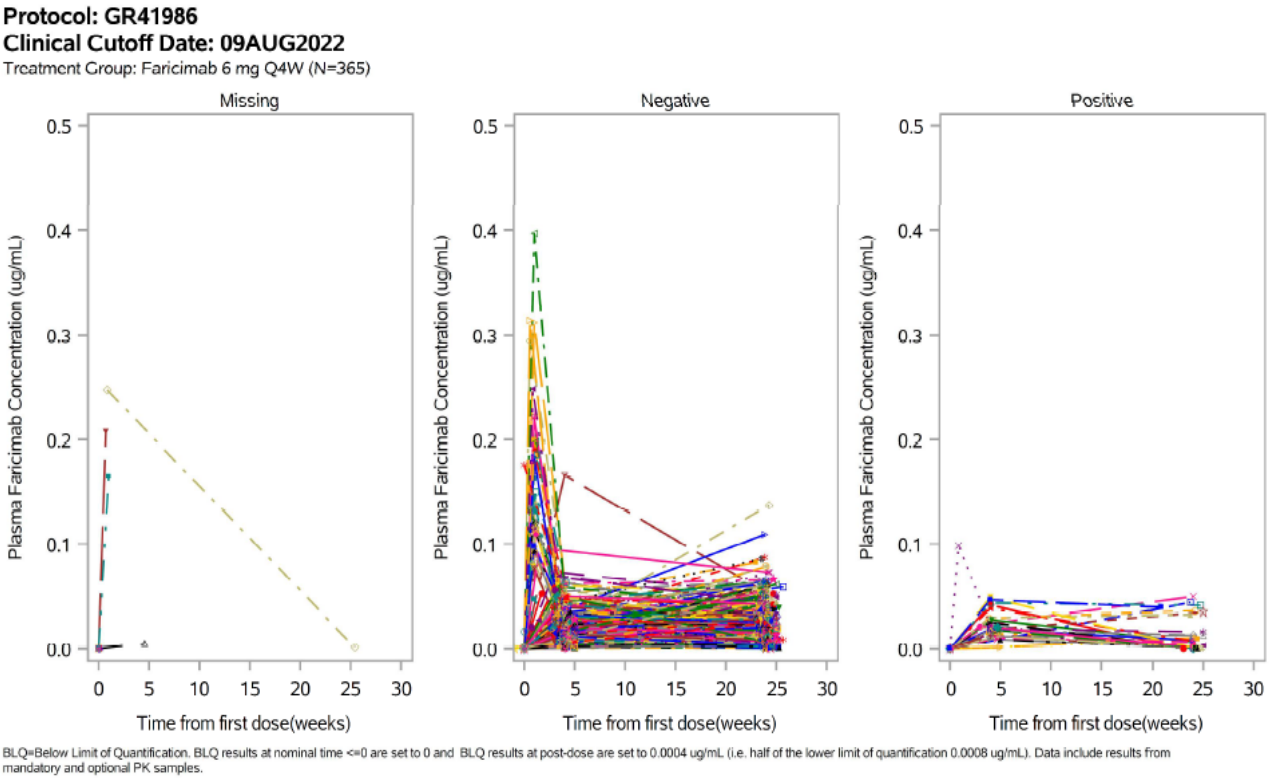
BLQ=Below Limit of Quantification. BLQ results at nominal time <=0 are set to 0 and BLQ results at post-dose are set to 0.0004 ug/mL (i.e. half of the lower limit of quantification 0.0008 ug/mL). Data include results from mandatory and optional PK samples.

Study GR41986 (COMINO)

The ADA analyses were based on the immunogenicity-analysis population for patients in the faricimab Q4W arm in Part 1. The following properties of each sample are listed by patient: ADA status (from the confirmatory assay): ADA positive (yes) or ADA negative (no) and titer value for the ADA positive sample. ADAs were assessed in K3EDTA specimens of faricimab-treated patients at baseline and at Weeks 4 and 24.
The baseline prevalence of ADAs to faricimab in the study was 1.1% (4/343). The incidence of immunogenicity to faricimab is based on patients with treatment emergent-ADAs (the sum of treatment-induced and treatment-boosted ADA-positive patients as described in the SAP, Section 5.7.5). Overall, 30/338 patients (8.9%) receiving faricimab had treatment-emergent ADAs, of which all were treatment-induced, and no patients were treatment-boosted. Persistence was defined as an ADA positive result that was detected at the last post-baseline sampling timepoint, or at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of 16 weeks, irrespective of any negative samples in between. The observed median time to onset was 24.0 weeks and ADA positivity was persistent in 96.7% of patients with treatment-induced ADA. ADA titer ranged from 10 to 10240.

The MAH was of the view that visual inspection of the faricimab plasma concentration-time profiles grouped by ADA status did not suggest a difference in plasma exposure in ADA-positive patients compared with ADA-negative patients, in Figure 6 (GR41986) below.

Figure 6. Faricimab plasma concentration-time profiles by ADA status though week 24 (Log scale), faricimab PK-evaluable population



The immunogenicity timepoints for BALATON and COMINO studies were acceptable for the CHMP. The Committee noted that there was a low baseline prevalence of ADAs to faricimab of 1.1% in both the BALATON and COMINO studies. The incidence of immunogenicity to faricimab was based on patients with treatment emergent-ADAs in both BALATON (18/259 patients; 6.9%) and COMINO (30/338 patients; 8.9%) was low. The median onset time of ADA response was 24 weeks.

In both studies the MAH was of the view that a visual inspection of the faricimab plasma concentration-time profiles do not suggest a difference in plasma exposure between ADA-positive and ADA-negative patients. In the BALATON study (GR41984) it appeared to be a trend of lower plasma concentration in the ADA positive patients compared to ADA negative patients. However, as this was not seen in the COMINO study, and as the incidence of ADA positive patients was low in both Phase III studies, the CHMP considered that these results should be interpreted with caution.

Overall, there was a low incidence of ADAs, and low impact of ADA positive status on faricimab PK in RVO. This is in line with the Summary of Clinical Pharmacology from the initial MAA.

Population PK Analysis

Population PK of faricimab (RO6867461) in patients with neovascular age-related macular degeneration, diabetic macular oedema, or macular oedema secondary to branch retinal, central retinal, or hemiretinal vein occlusion.

Methods

The data from the faricimab treatment arms of the 2 RVO studies (supplemented by the data from 9 studies in patients with nAMD and DME) were used in the population PK analysis. For GR41984 and

GR41986, the PK data available at Clinical Cut-off Date (CCOD) were included in the analysis. Both plasma and AH faricimab concentrations were used for the analysis.
Faricimab concentration values before the first dose were excluded from the PK analysis. Post-dose observations that were below the limit of quantification (BQL) were used in the analysis and the likelihood-based M3 method for handling BQL observations was applied.

The analysis was conducted via nonlinear mixed-effects modelling with the NONMEM software, Version 7.5.1 (ICON Development Solutions). The first-order conditional estimation method of NONMEM with LAPLACIAN and INTERACTION options was used. Model-based simulations were performed by a combination of R and NONMEM software.

A popPK model of intravitreal-administered faricimab was developed previously based on plasma and AH faricimab concentration data from patients with DME and nAMD (legacy model popPK report, Report 1105763). There are no mechanistic reasons to expect the PK of faricimab to be different in patients with RVO. Therefore, initially, external evaluation of the legacy model (developed for patients with nAMD and DME) was performed using data from patients with RVO. Specifically, goodness-of-fit (GOF) diagnostic plots for plasma and AH were assessed, for all RVO patients as well as stratified by RVO type (BRVO, CRVO, and HRVO). Post-hoc estimates of individual PK parameters were used while all population parameters were fixed to the parameters of the legacy model. Visual predictive check plots as well as the plots of individual random effects versus covariates were also assessed. Investigation of disease-related covariates was performed graphically. Covariates were selected based on scientific interest, mechanistic plausibility and exploratory graphics. Subsequently, the data from all faricimab clinical trials in nAMD, DME and RVO patients were pooled, and the model parameters were re-estimated.

The joint (nAMD, DME, and RVO) dataset included 1379 patients (46.3%) who had DME, 881 patients (29.6%) who had nAMD, and 717 patients (24.1%) who had RVO. A total of 1842 AH observations from 365 patients and 13389 plasma observations from 2973 patients were available for the analysis. Patients with RVO provided 246 AH observations from 79 patients and 1919 plasma observations from 713 patients.

Summaries of baseline continuous and categorical covariates in patients with nAMD, DME and RVO are presented in Table 5 and Table 6, respectively. The percentage of patients who were ADA-positive at any time during the trial was comparable between nAMD, DME and RVO populations (approximately 11%).

Table 5. Summary of Continuous Covariates at Baseline, Overall and by Disease

Covariate	All Patients N=2977 Median [Range]	nAMD N=881 Median [Range]	DME N=1379 Median [Range]	RVO N=717 Median [Range]
Weight (kg)	79 [37–209]	73.5 [37.3–172]	83.9 [40.5–209]	75.5 [37–200]
BSA (m^2)	1.91 [1.21–3.14]	1.83 [1.21–2.87]	1.98 [1.28–3.14]	1.88 [1.25–3.12]
Age (years)	67 [22–100]	77 [50–99]	63 [24–91]	66 [22–100]
CRCL (mL/min)	79.3 [2–381]	65.5 [2–189]	87.3 [10.3–381]	83.3 [7.8–234]
AST (U/L)	19 [6–175]	20 [8–175]	18 [6–86]	20 [8–147]
ALT (U/L)	18 [5–287]	16 [5–144]	18 [5–215]	18 [5–287]
Total bilirubin (µmol/L)	7 [1.5–51]	7 [1.5–51]	6 [1.5–35]	8 [1.5–32]
BCVA (# letters)	62 [8–86]	62 [8–83]	65 [15–86]	57 [19–76]
CST (µm)	445 [124–1500]	335 [124–1010]	456 [234–1170]	598 [266–1500]
Free AH VEGF-A (pg/mL)	75.9 [1.46–2540]	53.3 [1.46–182]	102 [3.69–1120]	99.7 [3.07–2540
Free AH Ang-2 (pg/mL)	6.67 [1.12–119]	4.39 [1.12–56.3]	8.51 [1.12–55.9]	15 [4.04–119]
Free Plasma VEGF-A (pg/mL)	20.6 [0–429]	19.3 [0–423]	21.4 [0–391]	20.6 [7.77–429]
Free Plasma Ang-2 (ng/mL)	1.45 [0–20.8]	1.47 [0–13.6]	1.54 [0–20.8]	1.26 [0.3–18.6]

AH = aqueous humor; Ang-2 = angiopoietin-2 (protein); BCVA = best-corrected visual acuity ; BSA = body surface area; CRCL = creatinine clearance; CST = central subfield thickness; DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; RVO = retinal vein occlusion; VEGF-A = vascular endothelial growth factor-A.
Source: popPK Report, Report 1120410, Table 4.

Table 6. Summary of Categorical Covariates at Baseline, Overall by Disease, (for Patients with RVO): Number (Percent) of Subjects

Covariate Name	Level	All Patients N=2977 n (%)	nAMD N=881 n (%)	DME N=1379 n (%)	RVO N=717 n (%)
Dose (mg)	0.5	3 (0.1%)	3 (0.3%)	0 (0.0%)	0 (0.0%)
	1.5	110 (3.7%)	51 (5.8%)	59 (4.3%)	0 (0.0%)
	3	9 (0.3%)	9 (1.0%)	0 (0.0%)	0 (0.0%)
	6	2855 (95.9%)	818 (92.8%)	1320 (95.7%)	717 (100%)
Treatment-naive	Naive, nAMD	880 (39.2%)	880 (100%)	0 (0.0%)	0 (0.0%)
	Not naive, DME	309 (13.8%)	0 (0.0%)	309 (22.6%)	0 (0.0%)
	Naive, DME	1057 (47.1%)	0 (0.0%)	1057 (77.4%)	0 (0.0%)
ADA	No	2650 (89%)	762 (86.5%)	1243 (90.1%)	645 (90%)
	Yes	327 (11%)	119 (13.5%)	136 (9.9%)	72 (10%)
Sex	Male	1548 (52%)	347 (39.4%)	828 (60%)	373 (52%)
	Female	1429 (48%)	534 (60.6%)	551 (40%)	344 (48%)
Race	White	2339 (78.6%)	787 (89.3%)	1066 (77.3%)	486 (67.8%)
	Black	127 (4.3%)	3 (0.3%)	106 (7.7%)	18 (2.5%)
	Asian	380 (12.8%)	69 (7.8%)	133 (9.6%)	178 (24.8%)
	Am. Ind. or Alaska	21 (0.7%)	3 (0.3%)	13 (0.9%)	5 (0.7%)
	Hawaiian or Pacific	6 (0.2%)	0 (0.0%)	4 (0.3%)	2 (0.3%)
	Unknown	104 (3.5%)	19 (2.2%)	57 (4.1%)	28 (3.9%)

	Ph. 1-2	365 (12.3%)	220 (25%)	145 (10.5%)	-
	Ph. 3	2612 (87.7%)	661 (75%)	1234 (89.5%)	717 (100%)
Formulation	Normal (CRCL <90 mL/min)	1074 (36.1%)	167 (19%)	620 (45%)	287 (40%)
	Mild (CRCL <90–≥60 mL/min)	1115 (37.5%)	379 (43%)	484 (35.1%)	252 (35.1%)
	Moderate (CRCL <60–≥30 mL/min)	669 (22.5%)	297 (33.7%)	237 (17.2%)	135 (18.8%)
Renal Impairment	Severe (CRCL <30–≥15 mL/min)	54 (1.8%)	24 (2.7%)	14 (1%)	16 (2.2%)
	Kidney Failure (CRCL < 15 mL/min)	5 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.4%)
	Missing	60 (2%)	13 (1.5%)	23 (1.7%)	24 (3.3%)
	Normal (bilirubin and AST ≤ ULN)	2738 (92%)	807 (91.6%)	1280 (92.8%)	651 (90.8%)
	Mild (bilirubin > 1–1.5 × ULN or AST > ULN)	163 (5.5%)	51 (5.8%)	71 (5.1%)	41 (5.7%)
	Missing	12 (0.4%)	4 (0.5%)	8 (0.6%)	0 (0.0%)
Use of IOP-lowering medication	No	2868 (96.3%)	852 (96.7%)	1323 (95.9%)	693 (96.7%)
	Yes, study eye	92 (3.1%)	25 (2.8%)	43 (3.1%)	24 (3.3%)
	Yes, unknown eye	5 (0.2%)	0 (0.0%)	5 (0.4%)	0 (0.0%)

ADA=anti-drug antibody; AST = aspartate transaminase at baseline; CRCL=creatinine clearance; DME=diabetic macular edema; IOP=intraocular pressure; nAMD=neovascular age-related macular degeneration; RVO=retinal vein occlusion; ULN=upper limit of normal.

All patients in RVO studies were treatment naïve.

Source: popPK Report, Report 1120410, Table 6

Results

The model tested the effect of disease: nAMD, DME, CRVO, HRVO, BRVO and there was no effect of disease on the PK of faricimab. The structural model was a 3-compartment catenary model, Vv, VA, and Vc/F are the volumes of the vitreous, aqueous and plasma compartments and kVH is the first order rate constant from the vitreous to the aqueous compartment, kAH the first order rate constant from the aqueous to the plasma compartment, and the first order constant of elimination from the plasma compartment k (k = CL/Vc). VV was set to 4.5 mL, while all other parameters were estimated. The parameters for the final model 064 are shown in Table 7. The goodness-of-fit plots and the prediction-corrected visual predictive check for the final model 064 for patients with RVO are shown in Figure 7 and Figure 8.

Table 7. Parameters estimates of the final faricimab population PK model 064

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
V_A (mL)	θ_1	0.252	6.76	0.219; 0.286		
k_V (1/day)	θ_3	0.0901	0.57	0.0891; 0.0911		
k_A (1/day)	θ_4	16.5	7.0	14.2; 18.7		
CL (L/day)	θ_5	2.45	1.1	2.39; 2.5		
σ_{prop}	θ_6	0.452	1.05	0.443; 0.461		
SD_{PhaseI}	θ_7	0.609	4.78	0.552; 0.667		
$SD_{PhaseII}$	θ_8	0.746	2.43	0.711; 0.781		
$V_{C,WT}$	θ_9	0.905	5.11	0.814; 0.995		
CL_{WT}	θ_{10}	0.684	4.22	0.627; 0.74		
CL_{female}	θ_{11}	0.857	1.35	0.834; 0.879		
$CL_{formulation1}$	θ_{12}	0.791	1.71	0.764; 0.817		
$k_{VH,age}$	θ_{13}	-0.514	5.04	−0.565; −0.463		
$k_{VH,ADA}$	θ_{14}	1.25	0.945	1.22; 1.27		
$k_{AH,formulation1}$	θ_{15}	0.68	5.66	0.604; 0.755		
V_C (L)	θ_2	1.29	4.46	1.18; 1.41		
ω^2_{VC}	$\Omega(1,1)$	1.55	4.39	1.42; 1.68	CV=124.5 %	58.8%
ω^2_{kVH}	$\Omega(2,2)$	0.0865	2.52	0.0822; 0.0907	CV=29.4%	5.3%
R ω_{kVH} ω_{kAH}	$\Omega(2,3)$	0.0218	29.6	0.00915; 0.0345	R=0.168	
ω^2_{kAH}	$\Omega(3,3)$	0.195	7.36	0.167; 0.224	CV=44.2%	60.0%
R ω_{kAH} ω_{CL}	$\Omega(3,4)$	0.031	17.7	0.0203; 0.0417	R=0.347	
ω^2_{CL}	$\Omega(4,4)$	0.041	6.02	0.0361; 0.0458	CV=20.2%	52.6%
ω^2_{ε}	$\Omega(5,5)$	0.0865	3.39	0.0808; 0.0922	CV=29.4%	41.0%
σ^2_{AH}	$\Sigma(1,1)$	1	Fixed		4.0%	
σ^2_{plasma}	$\Sigma(2,2)$	1	Fixed		17.0%	
k (1/day)	CL/Vc	1.90				
$t_{1/2,VH}$ (day)	log(2)/ k_{VH}	7.69	7.61; 7.78			

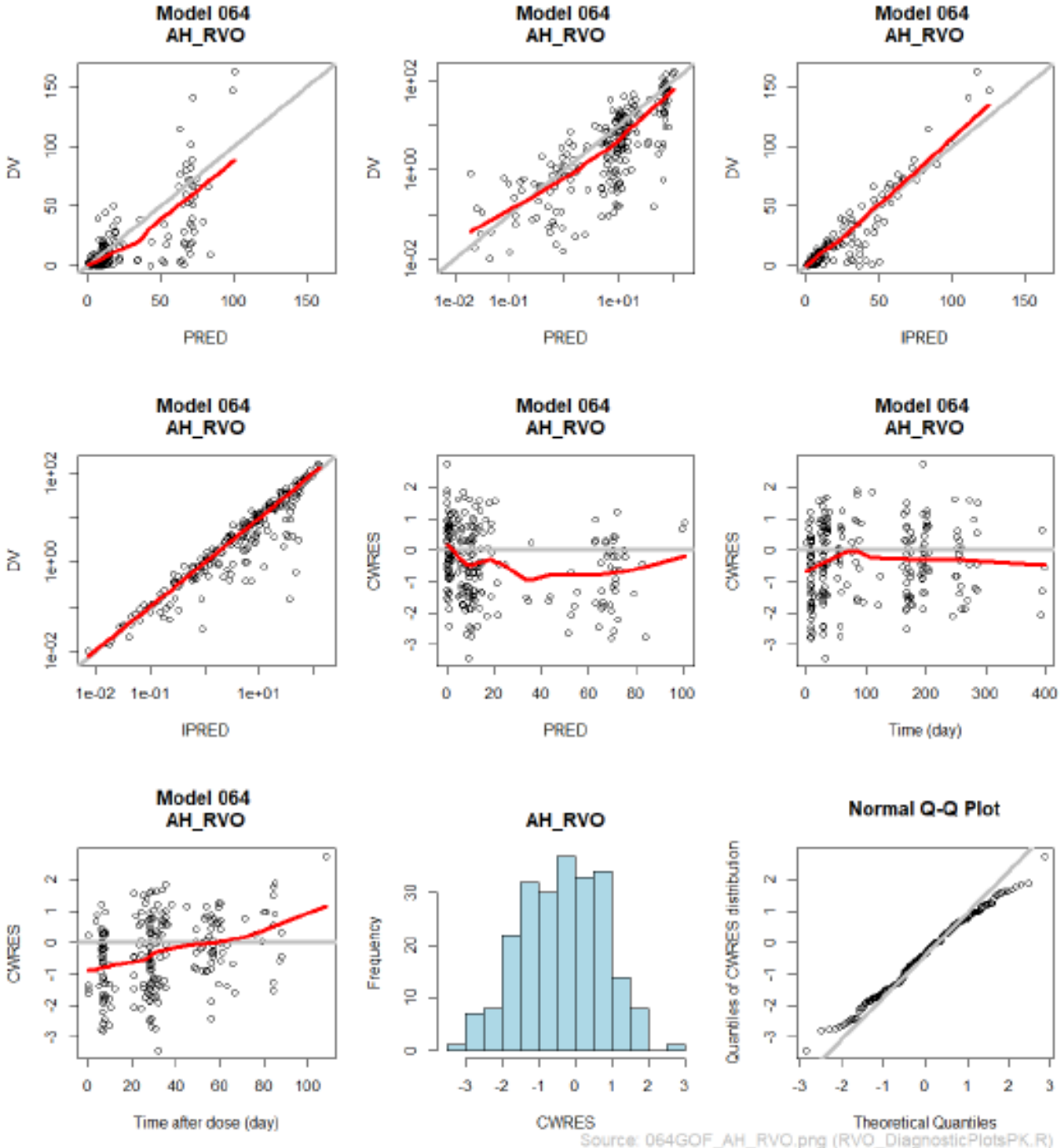
CV=coefficient of variation (100*SD %); k_A=rate constant from aqueous to plasma; k_V=rate constant from vitreous to aqueous; kVH age=rate constant from vitreous to aqueous (age covariate); $k_{V\ ADA}$=rate constant from vitreous to aqueous (ADA covariate); $k_{A\ formulation\ 1}$=rate constant from aqueous to plasma (formulation covariate); N/A=not applicable; σ^2=residual variance; RSE=relative standard error (100·abs[SE/PE]); R ω_{kAH} ω_{CL}=correlation between interindividual variances for kA and CL; R ω_{kVH} ω_{kAH}=correlation between interindividual variances for kV and ke; SD_{phase1}=residual error Phase I; SD_{phase2}=residual error Phase 2; V_A=volume aqueous; Vc=volume central (plasma) compartment; $V_{C,WT}$=power coefficient of the power function between VC and body weight; ω^2=variance ; ω^2_{ε}=interindividual variances; 95%CI =95% confidence interval.

Parameters are 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)

Source: popPK Report 1120410, Table 7

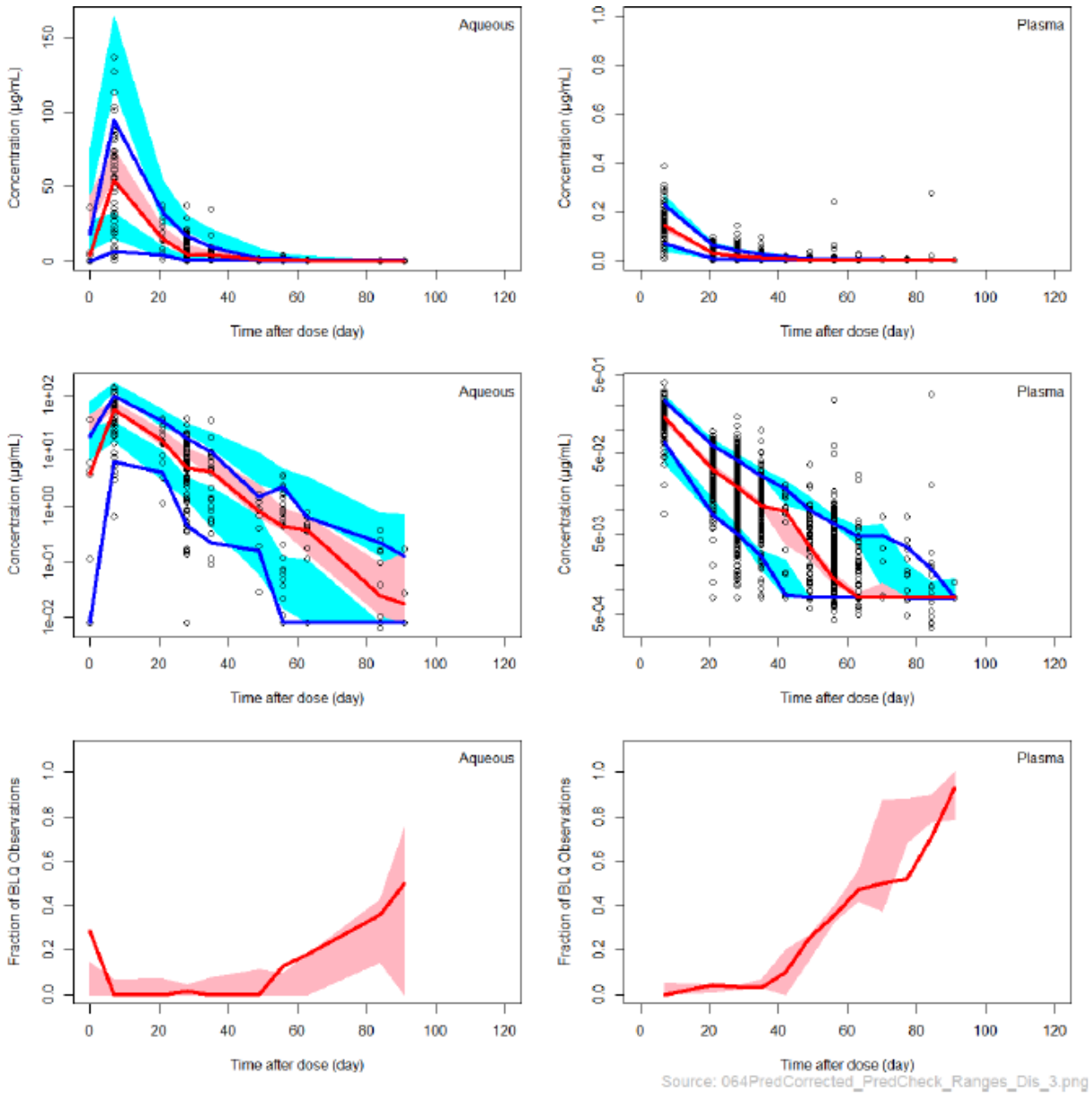
Figure 7. Goodness of Fit for Final Model 064 in Patients with RVO: AH

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: 064GOF_AH_RVO.png (RVO_DiagnosticPlotsPK.R)

Figure 8. Prediction-Corrected Visual Predictive Check for Final Model 064 for Patients with RVO



Source: 064PredCorrected_PredCheck_Ranges_Dis_3.png

The top and middle rows: The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. Bottom 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.

For a reference patient (a 65-year-old, ADA negative, 80 kg male who received the Phase III formulation) the kV was 0.0901 day-1, corresponding to a VH t1/2 of 7.69 days, kA was faster than for the VH rate constant, i.e. 16.5 day-1, corresponding to a t1/2 of 0.04 days. The systemic CL/F was rapid, with a value of 2.45 L/day, corresponding to a plasma t1/2 of 0.36 days.

Covariates affecting the ocular and plasma disposition were identified. For the ocular disposition, the following covariates were retained: plasma ADA on VH rate constant, age on VH rate constant and formulation on aqueous rate constant. For plasma PK, the following covariates were retained: body weight on Vc/F and CL/F, sex on CL/F and formulation on apparent clearance (CL/F). The effects of covariates are presented in the Table below.

Table 8. Covariate effects of faricimab as estimated by the population PK model 064 (Final model)

Parameter	Covariate	Reference	Value	Effect [95%CI]
Central Volume (V_C)	Weight (kg)	80	50	-34.6 [-37.4;-31.8]
			129	54.1 [47.5;60.9]
Clearance (CL)	Weight	80	50	-27.5 [-29.4;-25.5]
			129	38.6 [35;42.4]
	SEXF	Male	Female	-14.3 [-16.6;-12.1]
	Formulation	Phase III	Phase I-II	-20.9 [-23.6;-18.3]
VH elimination rate constant (k_{VH})	Age (years)	65	42	25.2 [22.4;28]
			88	-14.4 [-15.7;-13.1]
	ADA	no ADA	ADA	24.7 [22.4;27]
AH elimination rate constant (k_{AH})	Formulation	Phase III	Phase I-II	-32 [-39.6;-24.5]
Plasma AUC	Weight	80	50	37.9 [34.3;41.6]
			129	-27.9 [-29.8;-25.9]
	SEXF	Male	Female	16.7 [13.7;19.9]
	Formulation	Phase III	Phase I-II	26.4 [22.3;30.8]
VH AUC	Age (years)	65	42	-20.1 [-21.9;-18.3]
			88	16.9 [15.1;18.7]
	ADA	no ADA	ADA	-19.8 [-21.3;-18.3]
AH AUC	Formulation	Phase III	Phase I-II	47.1 [32.4;65.4]

ADA = antidrug antibodies; AH = aqueous humor; AUC = area under the concentration-time curve; VH = Vitreous humor.

Source: popPK Report, Report 1120410, Table 9.

In terms of factors affecting VH disposition, faricimab VH t1/2 increased with increasing age; a typical 42 years' old patient had VH elimination t1/2 approximately 39.6% shorter than a typical 88-year-old patient. The presence of plasma ADA, led to shorter VH t1/2 resulting in a modest (19.8%) decrease in VH exposure. Due to the small (i.e., nearly 20%) magnitude of the effect of the covariates, the influence of the covariates on VH disposition was not considered clinically significant.

In plasma, both CL/F and Vc/F increased with body weight. Plasma volume of distribution increased proportionally with body weight (with the power coefficient of 0.905, (95%CI: 0.814-0.995), consistent with the expected allometric increase. In agreement with allometric scaling, faricimab plasma CL increased with weight with the power coefficient of 0.684 (95%CI: 0.627-0.74). The effect of sex was modest, with 16.7% higher plasma exposure in female patients compared with male patients, while no obvious difference was observed in VH exposure. Due to the small magnitude of the effects of the covariates (~20%) on plasma exposure, they were not considered clinically significant.

Other covariates such as renal and hepatic function, ethnicity and race, prior medications, the effect of disease (nAMD vs DME vs RVO), the different types of RVO (BRVO, HRVO, CRVO) and use of IOP lowering agents had no discernible effect on faricimab disposition.

The individual estimates of the steady-state exposure parameters following 6 mg Q4W doses (AUCQ4W, Cmax, Tmax, and Ctrough,ss) are summarized by disease in Table 9 below. No faricimab accumulation was observed in the vitreous, aqueous and plasma compartments (Figure 9 below).

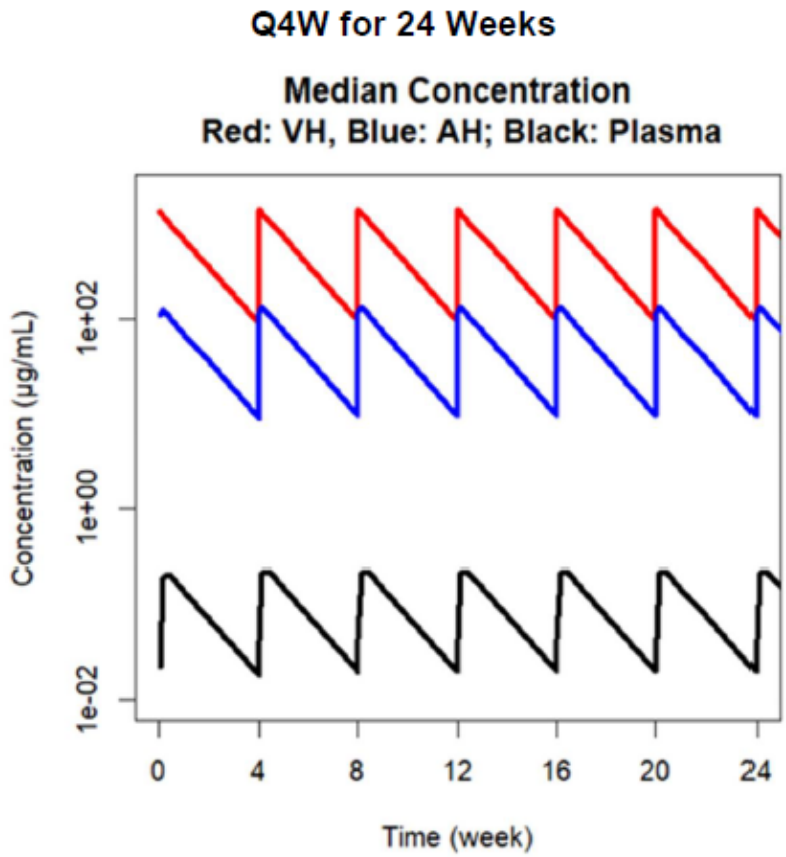
Table 9. Summary of individual estimates of faricimab steady-state exposures for patients from Phase III studies following 6 mg Q4W dosing, by disease

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

Disease	Compartment	N	AUC_{Q4W} (µg/mL*day)	C_{max} (µg/mL)	$C_{trough,ss}$ (µg/mL)	T_{max} (day)
Mean (Standard Deviation)						
DME	VH	1234	14300 (4420)	1450 (99)	120 (99.5)	0 (0)
	AH		1460 (263)	152 (35)	11 (6.76)	0.311 (0.051)
	Plasma		2.56 (0.545)	0.228 (0.0625)	0.0208 (0.0135)	1.95 (0.947)
nAMD	VH	661	15900 (4850)	1490 (117)	156 (117)	0 (0)
	AH		1490 (299)	142 (30)	13.5 (8.38)	0.322 (0.0589)
	Plasma		2.98 (0.621)	0.242 (0.0644)	0.0287 (0.0158)	2.23 (1.19)
RVO	VH	717	14400 (4290)	1450 (94.7)	121 (95.2)	0 (0)
	AH		1420 (213)	146 (26.6)	10.9 (6.55)	0.305 (0.0475)
	Plasma		2.79 (0.613)	0.248 (0.0691)	0.0231 (0.0146)	1.96 (1.04)
Median (95% Prediction Interval)						
DME	VH	1234	13500 (7780-24300)	1420 (1340-1700)	91.1 (11.3-368)	0 (0-0)
	AH		1430 (1140-1940)	147 (106-238)	9.67 (1.73-27)	0.309 (0.229-0.407)
	Plasma		2.49 (1.7-3.82)	0.222 (0.134-0.356)	0.0182 (0.00344-0.0521)	1.73 (1.25-4.69)
nAMD	VH	661	15400 (8360-27100)	1460 (1350-1780)	131 (15.8-453)	0 (0-0)
	AH		1450 (1130-2030)	138 (98.2-212)	12.6 (2.67-30.8)	0.315 (0.236-0.437)
	Plasma		2.94 (1.92-4.25)	0.232 (0.144-0.393)	0.0262 (0.00589-0.0637)	1.87 (1.27-5.71)
RVO	VH	717	13900 (7490-24800)	1430 (1340-1710)	98.1 (9.35-383)	0 (0-0)
	AH		1420 (903-1780)	143 (98.6-206)	9.81 (1.45-25.8)	0.308 (0.203-0.392)
	Plasma		2.72 (1.8-4.11)	0.24 (0.141-0.404)	0.0202 (0.00377-0.0602)	1.73 (1.21-4.39)
Geometric Mean (Coefficient of Variation)						
DME	VH	1234	13600 (0.302)	1450 (0.0651)	83.7 (0.932)	0 (-)
	AH		1440 (0.158)	148 (0.209)	8.89 (0.724)	0.307 (0.155)
	Plasma		2.51 (0.209)	0.221 (0.263)	0.0168 (0.695)	1.83 (0.316)
nAMD	VH	661	15200 (0.3)	1480 (0.0747)	115 (0.852)	0 (NaN)
	AH		1470 (0.17)	139 (0.198)	11.2 (0.656)	0.318 (0.164)
	Plasma		2.91 (0.21)	0.234 (0.262)	0.0244 (0.617)	2.05 (0.376)
RVO	VH	717	13700 (0.299)	1450 (0.0625)	85.4 (0.939)	0 (-)
	AH		1400 (0.167)	143 (0.186)	8.75 (0.76)	0.301 (0.168)
	Plasma		2.72 (0.22)	0.239 (0.275)	0.0186 (0.711)	1.83 (0.315)

Source file: 064aucSim_ExposureSummary_by_Tau.csv (RVO_Simulations_PK_parameters_SS.R)

Figure 9. Prediction of Final Model 064, following 6 mg Q4W doses administered to patients with RVO from Phase III studies



AH = aqueous humor; Q4W–every 4 weeks; VH–vitreous humor.
Solid lines: medians of individual predictions.
Source: popPK Report 1120410, Figure 65.

The methods used for model development and evaluation are acceptable for the CHMP. Data exclusions were well documented and are agreeable. Post-dose BLQ observations were appropriately handled using the M3 method.

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 in patients with RVO. The VH volume was fixed to the literature value of 4.5 mL, as done previously, which is considered acceptable. The updated parameter estimates, after inclusion of RVO data, were close to the parameters of the prior legacy model based on nAMD and DME data.

All final model parameters were estimated with good precision and High IIV shrinkage (~40-60%) of plasma CL and Vc as well as the AH elimination rate constant (K_{AH}) are noted. Therefore, individual estimates for these parameters and predicted exposures of faricimab in the AH and plasma may not be reliable. Importantly, IIV shrinkage of K_{VH} was low (5.3%). As such, predicted VH exposure, which were used as PK metric in the ER analyses, can be considered reliable.

Overall, the goodness-of-fit diagnostic plots indicated that the final model described the observed data adequately. The pcVPC showed that the final model captured both the central tendency and the interindividual variability of faricimab PK in AH and plasma adequately.

Consistent with the prior legacy model, the covariates that influenced faricimab ocular PK parameters were age, formulation, and presence of ADAs, while faricimab systemic PK parameters were influenced

by sex, body weight, and formulation. The effects of these covariates on ocular and plasma PK were not considered to be clinically meaningful, which is agreed by the CHMP.

2.3.3. Pharmacodynamics

The most common presenting complaint of RVO is an abrupt, painless decrease of central vision due to macular oedema. The pathogenesis of macular oedema in these patients starts with an increase in intraluminal pressure due to vascular obstruction, which causes areas of reduced perfusion and ischemia. Ischemia leads to up-regulation and secretion of vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2), both well-known proangiogenic and vessel hyperpermeability cytokines, with Ang-2 contributing to additional proinflammatory and vessel destabilization. Patients with RVO have the highest vitreous levels of both Ang-2 and VEGF among all retinal vascular diseases.

Mechanism of action

Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) that selectively and independently binds VEGF-A and Ang-2. The VEGF binding fragment antigen binding (Fab) of faricimab binds all isoforms of VEGF with high affinity, and the Ang-2 binding Fab binds to Ang-2 also with high affinity. The proposed hypothesis is that simultaneous inhibition of both VEGF-A and Ang-2 has the potential for additional improvements in visual acuity and anatomical outcomes as well as a prolonged duration of treatment effect as compared to targeting only VEGF-A. Faricimab combines the anti-inflammatory and anti-angiogenic mechanism of action through Ang-2 neutralization with the well-established effects of anti-VEGF targeting.

Primary pharmacology

Study GR41984 (BALATON)

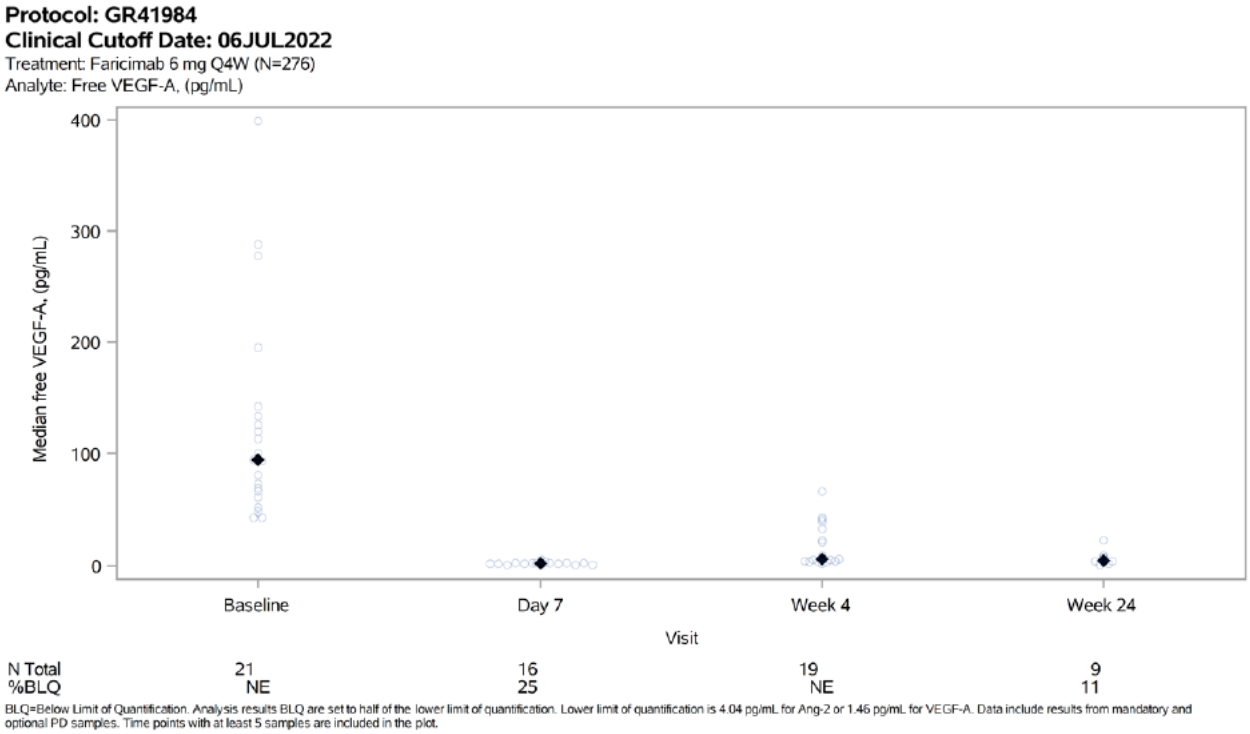
Ocular Pharmacodynamics

AH concentrations from 23 patients treated with faricimab and consenting to optional AH sampling were included in the PD data analysis (AH free Ang-2 and free VEGF-A concentrations). Free VEGF-A samples below the lower limit of quantification (LLOQ; 1.46 pg/mL) and free Ang-2 samples below the LLOQ (4.04 pg/mL) were imputed with LLOQ/2 and mean values were calculated.

High inter-patient variability was observed in aqueous humour Ang-2 (CV: 71.6−268%) and VEGF-A (CV: 56.9−108%) concentrations in the faricimab Q4W arm through Week 24.

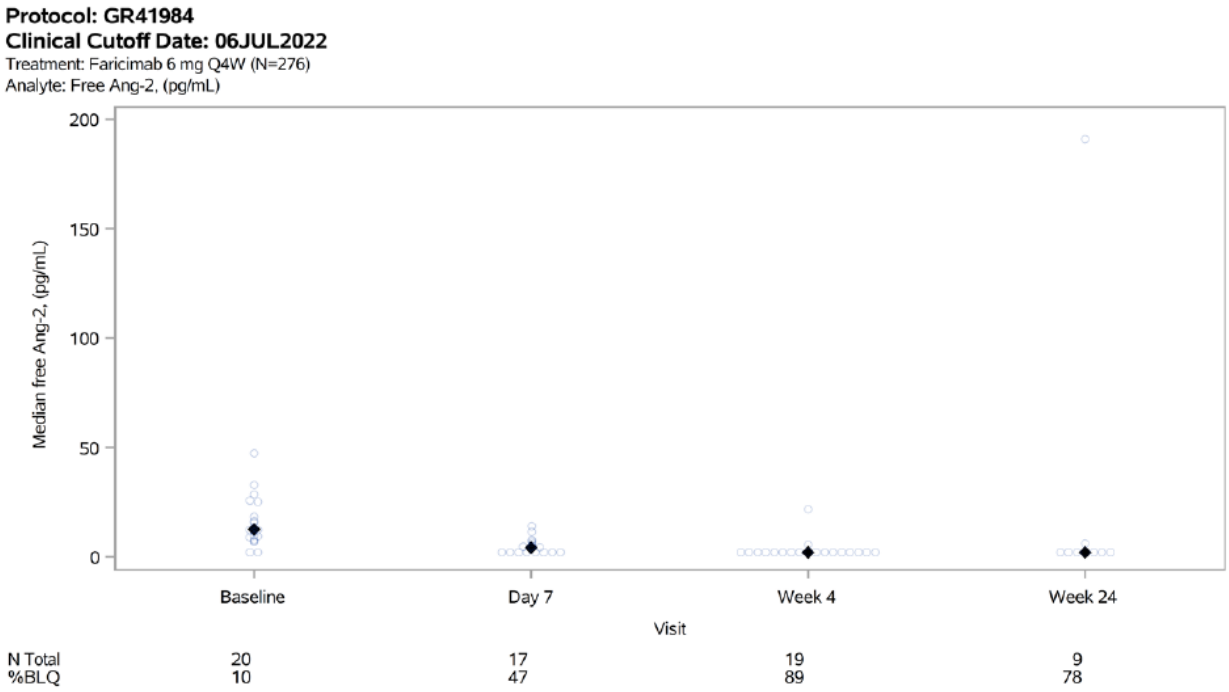
Median (min-max) baseline VEGF-A concentrations were 94.2 (43.3−399) pg/mL for the faricimab Q4W arm. The faricimab treatment arm showed rapid suppression of VEGF-A (median concentration < 3 pg/mL) from Day 7 onwards and thereafter sustained target suppression was observed. Median VEGF-A concentration was < 7 pg/mL up to the last visit (Week 24) (Figure 10 below).

Figure 10. Median Aqueous Humor Free VEGF-A Concentration in the faricimab Q4W Arm though week 24, Safety-evaluation Population



Median (min-max) baseline Ang-2 concentrations were 12.6 (2.0−47.3) pg/mL for the faricimab Q4W arm. Approximately 10% of the aqueous humor samples were below the limit of quantification (BLQ) at baseline and increased up to approximately 89% following faricimab administration. The faricimab Q4W arm showed rapid suppression of Ang-2 starting 7 days post-dose (median 4.2 pg/mL) and median concentrations remained below median baseline up to the last visit (Week 24) (see Figure 11 below).

Figure 11. Median Aqueous Humor Free Ang-2 Concentrations in the faricimab Q4W Arm through week 24, Safety-Evaluable Population



Plasma Pharmacodynamics

Plasma data from 269 and 268 patients treated with faricimab were included in the PD data analysis for VEGF-A and Ang-2, respectively.

No change in free VEGF-A or in free Ang-2 was observed post-dose as compared to baseline in the faricimab Q4W arm through Week 24. The plasma free VEGF-A and free Ang-2 concentrations by visit are shown in Figure 12 and Figure 13 below.

Figure 12. Plasma Free VEGF-A Concentrations in the faricimab Q4W Arm through Week 24, Safety-Evaluable Population

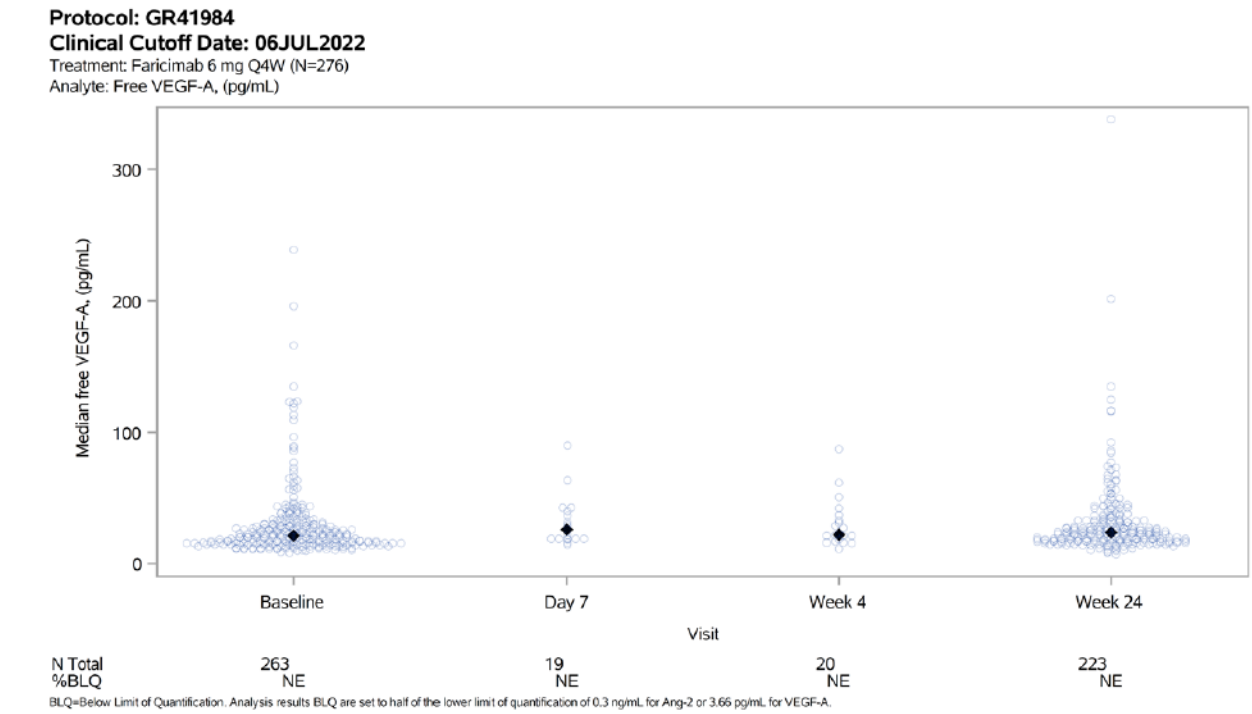
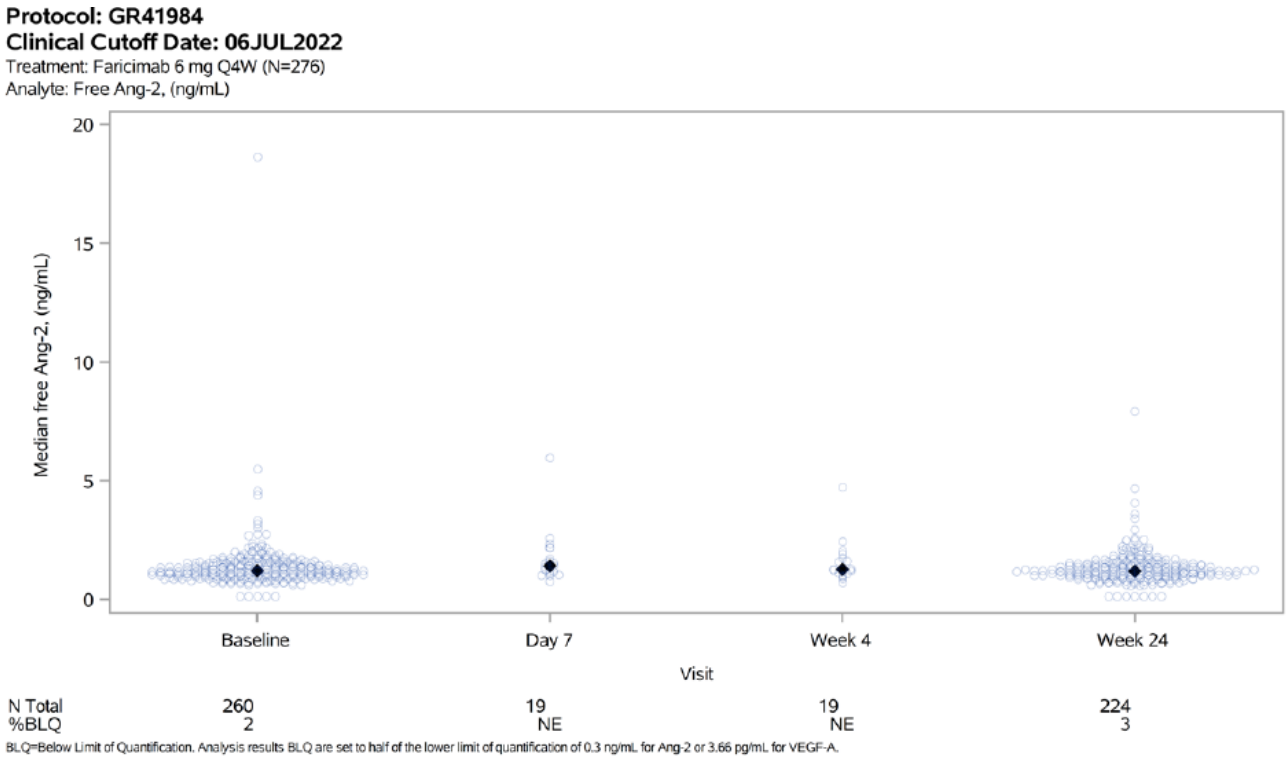


Figure 13. Plasma Free Ang-2 Concentrations in the faricimab Q4W Arm through week 24, Safety-Evaluable Population



Study GR41986 (COMINO)

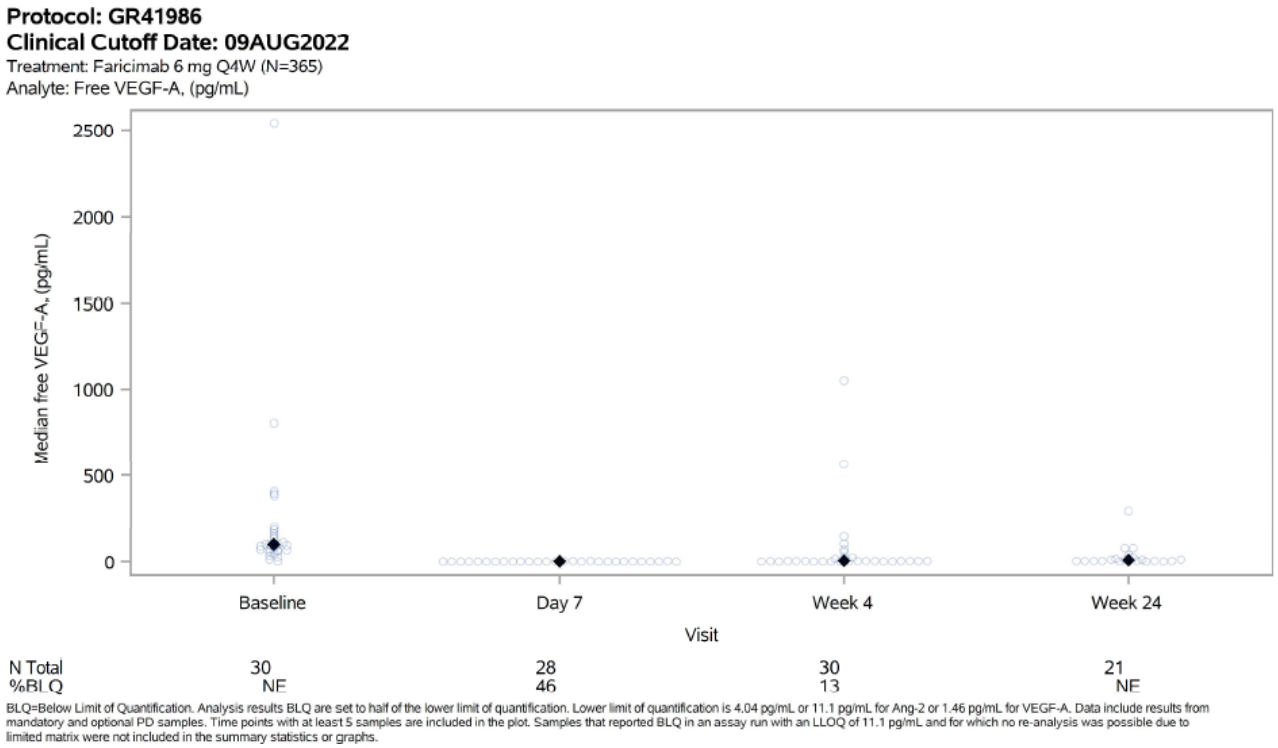
Ocular pharmacodynamics

AH samples from 33 patients treated with faricimab and consenting to optional aqueous humour sampling were included in the PD data analysis (aqueous humour free Ang-2 and free VEGF-A concentrations). Free VEGF-A samples below the lower limit of quantification (LLOQ; 1.46 pg/mL) and free Ang-2 samples below the LLOQ (4.04 pg/mL) were imputed with LLOQ/2 and descriptive statistics were calculated.

High inter-patient variability was observed in aqueous humour Ang-2 (CV 76.6-141%) and VEGF-A (CV 62.2-294%) concentrations in the faricimab Q4W arm through Week 24

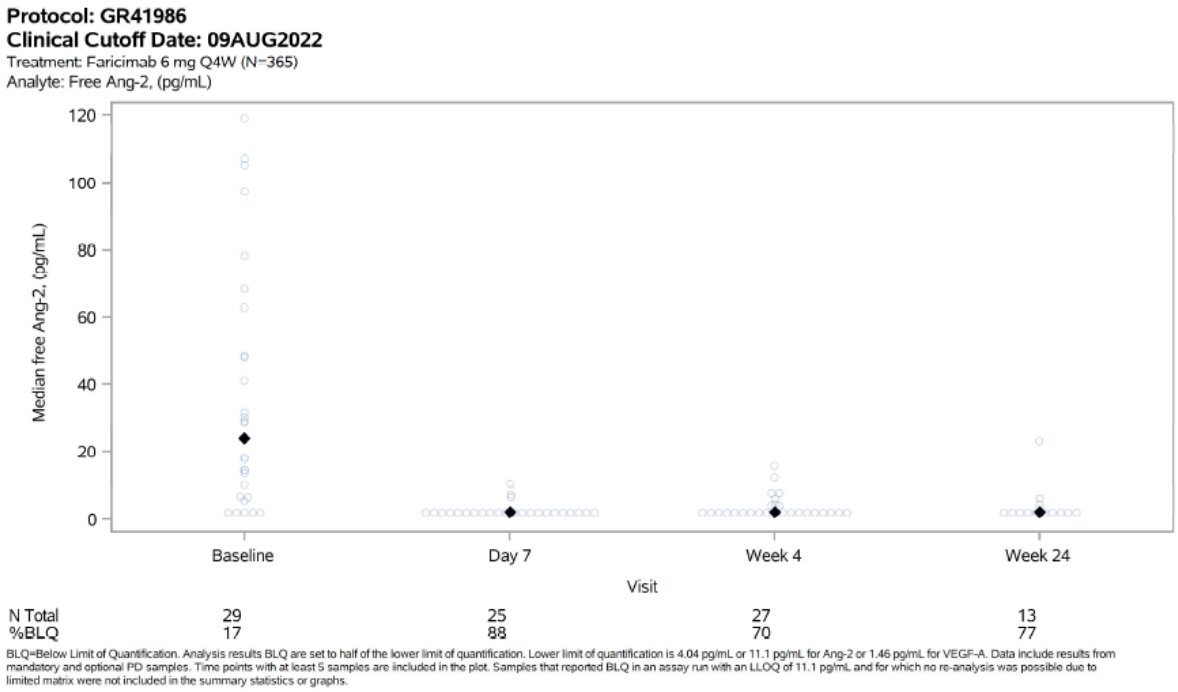
Median (min-max) baseline VEGF-A concentrations were 101 (3.1-2540) pg/mL for the faricimab Q4W arm. The faricimab treatment arm showed rapid suppression of VEGF-A (median concentration < 3 pg/mL) from Day 7 onwards and thereafter sustained target suppression was observed. Median VEGF-A concentration was < 10 pg/mL up to the last visit (Week 24) (Figure 14 below).

Figure 14. Median Aqueous Humor Free VEGF-A Concentrations in the faricimab Q4W Arm through Week 24, Safety-Evaluable Population



Median (min-max) baseline Ang-2 concentrations were 23.8 (2.0-119) pg/mL for the faricimab Q4W arm. Approximately 17% of the aqueous humour samples were below the limit of quantification (BLQ) at baseline which increased up to approximately 88% following faricimab administration. The faricimab Q4W arm showed rapid suppression of Ang-2 starting 7 days post-dose (median 2.0 pg/mL) and median concentrations remained below median baseline up to the last visit (Week 24) (see Figure below).

Figure 15. Median Aqueous Humor Free Ang-2 Concentrations in the faricimab Q4W Arm through week 24, Safety-Evaluable Population



Plasma Pharmacodynamics

Plasma data from 348 and 347 patients treated with faricimab were included in the PD data analysis for VEGF-A and Ang-2, respectively.

No change in free VEGF-A or in free Ang-2 was observed post-dose as compared to baseline in the faricimab Q4W arm through Week 24. The plasma free VEGF-A and free Ang-2 concentrations by visit are shown in the Figures below.

Figure 16. Plasma Free VEGF-A Concentrations in the faricimab Q4W Arm through Week 24, Safety-Evaluable Population

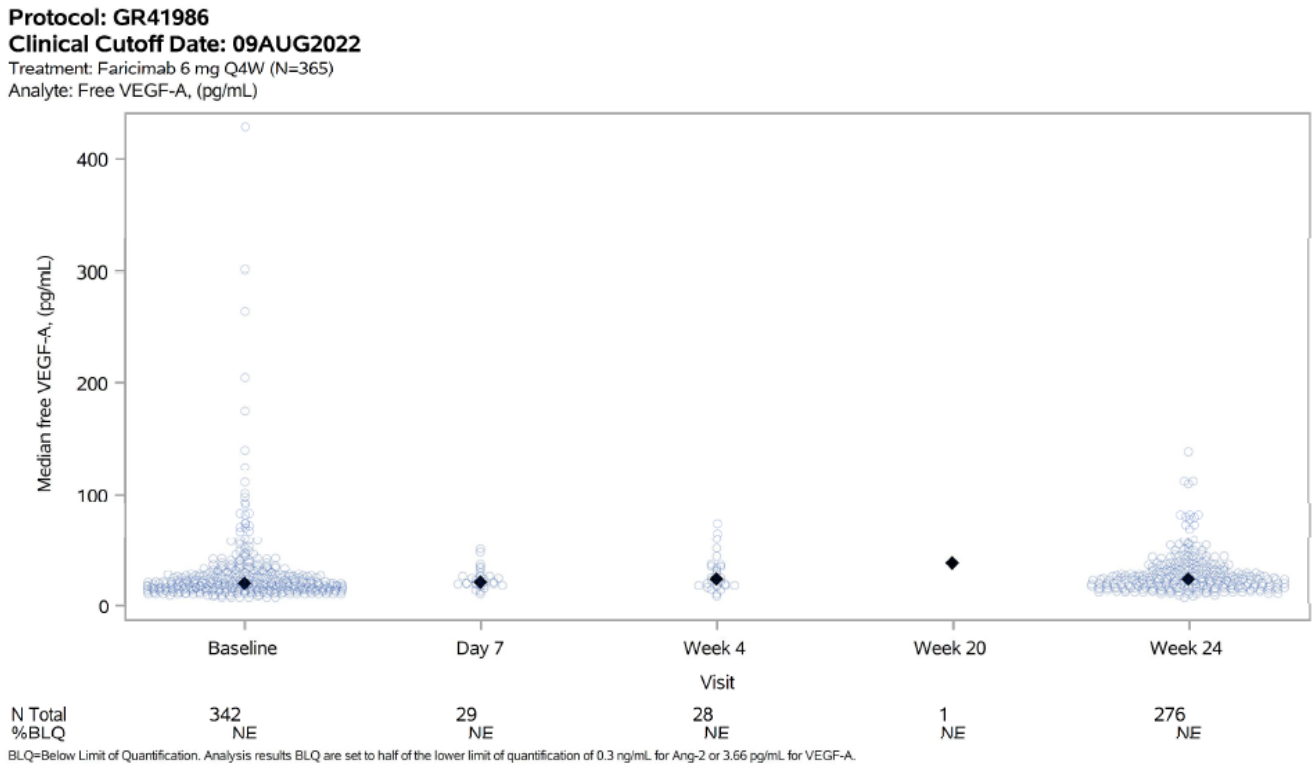
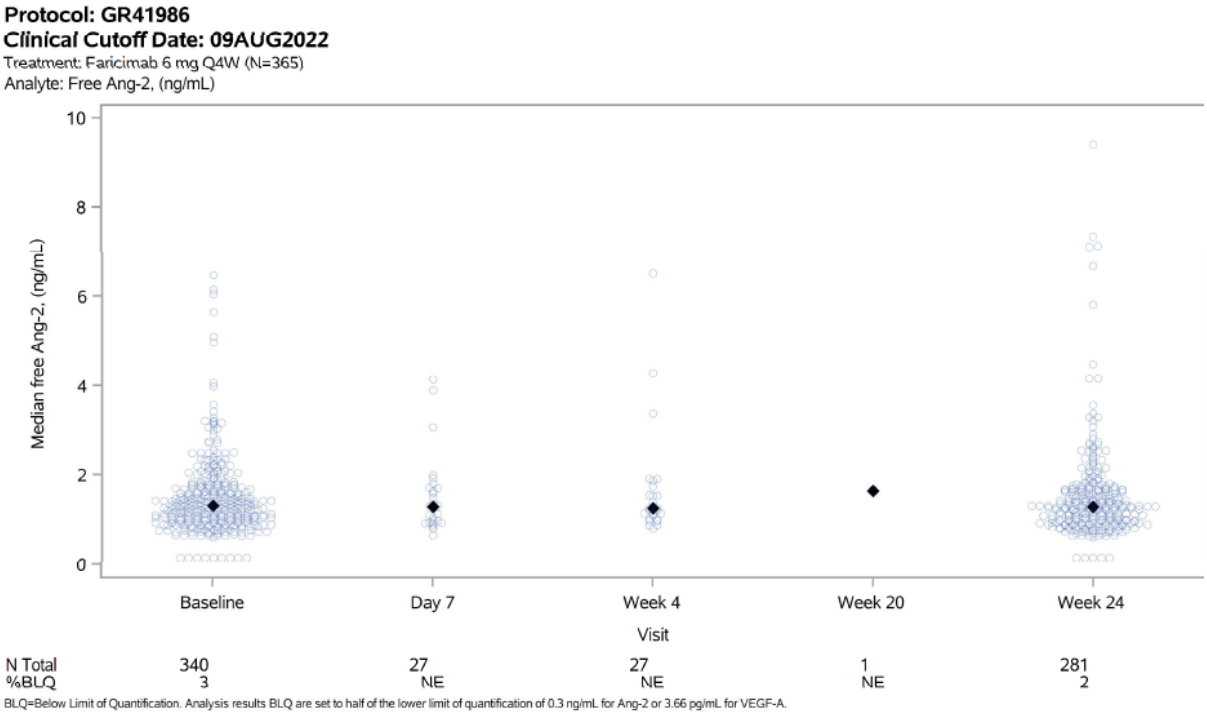


Figure 17. Plasma Free Ang-2- Concentrations in the faricimab Q4W Arm through Week 24, Safety-Evaluable Population



The PD sampling timepoints for the BALATON and COMINO studies are acceptable for the Committee.

The CHMP noted that there was high inter-patient variability in VEGF-A and ANG-2 AH concentrations in both the BALATON (VEGF-A, 56.9−108%; ANG-2, 71.6−268%) and COMINO (VEGF-A, 62.2-294%; ANG-2, 76.6-141%) studies.

The faricimab treatment arm in both the BALATON and COMINO studies showed rapid suppression of both the free VEGF-A and free ANG-2 parameters from Day 7 in the AH. Suppression was maintained up to the Week 24 visit.

There was no change in plasma free VEGF-A or free Ang-2 up to Week 24 when compared with baseline levels.

Overall, the PD for the plasma and AH free VEGF-A and Ang-2 levels from the BALATON and COMINO studies are in line with the Phase III studies from the initial MAA.

2.3.4. PK/PD modelling

Exposure-efficacy analyses in patients with macular oedema secondary to branch retinal, central retinal, or hemiretinal vein occlusion.

Objectives

- To assess the relationships between faricimab VH exposure and best-corrected visual acuity (BCVA) and central subfield thickness (CST).
- To graphically assess the relationships between faricimab exposure in VH and the following pharmacodynamic (PD) endpoints: free VEGF-A and free Ang-2 in AH.

Methods

The exposure-efficacy analyses were performed using the Phase III data from RVO studies GR41984 and GR41986. Efficacy information up to the primary end-point (Week 24) were included. The steady-state trough concentration in VH (Ctrough,ss) following 6 mg Q4W dosing regimen was used as a

metric of exposure to assess the effect of faricimab PK on efficacy. The following continuous endpoints were analysed:

- BCVA, CST, change from baseline of BCVA (dBCVA) or CST (dCST), and percent change from baseline of BCVA (pdBCVA) or CST (pdCST) over time;
- Week 24 change from baseline of BCVA (dBCVAend) and CST (dCSTend);
- Week 24 percent change from baseline of BCVA (pdBCVAend) and CST (pdCSTend).

For the graphical analysis, PD endpoints were observed AH values of free VEGF-A (further called VEGF-A) and observed AH values of free Ang-2 (further called Ang-2).

Results

Exposure Relationship with BCVA in RVO

Linear regression analyses showed a trend suggestive for lower gains in BCVA in patients with higher faricimab VH exposure (Figure 18). This trend is likely explained by the positive correlation between faricimab VH exposure and age (Figure 19).

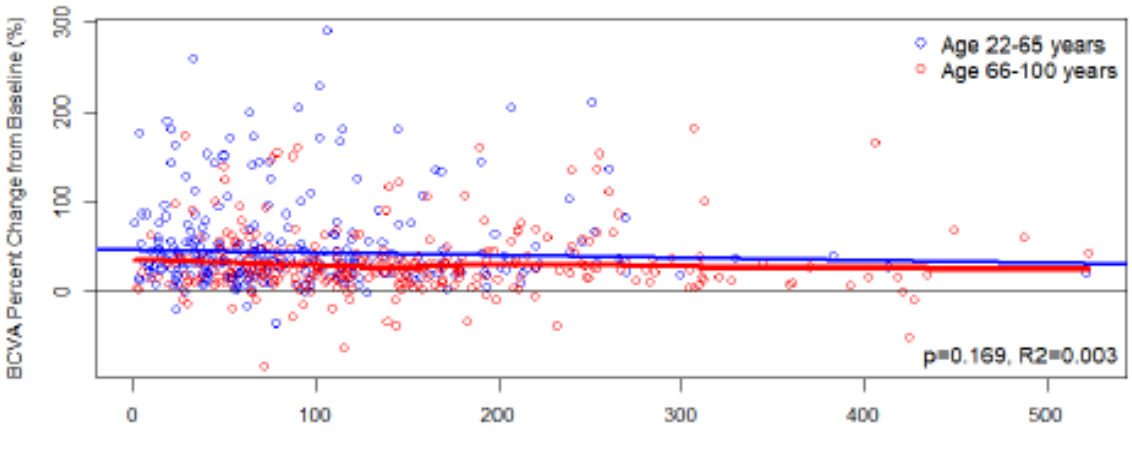
When both age and exposure were included in the linear regression model, only age was found to be a significant predictor of the BCVA response (lower BCVA gains in older patients, [slope 0.370, p-value <0.001]), while there was no significant effect of faricimab exposure [slope 0.003, p-value 0.583].

In the faricimab arm, BCVA response tends to be similar between high age and high exposure groups, and similar between low age and low exposure groups.

A similar tendency for lower BCVA gain with increasing age has been observed for the aflibercept arm. No differences in efficacy have been observed between the faricimab and aflibercept arms within the age subgroups (see Clinical Efficacy).

In conclusion, age-adjusted change in BCVA was similar across the ranges of faricimab exposure. No age-based dose adjustment is needed.

Figure 18. BCVA Change at Weeks 24 by VH trough concentrations for RVO studies BALATON and COMINO



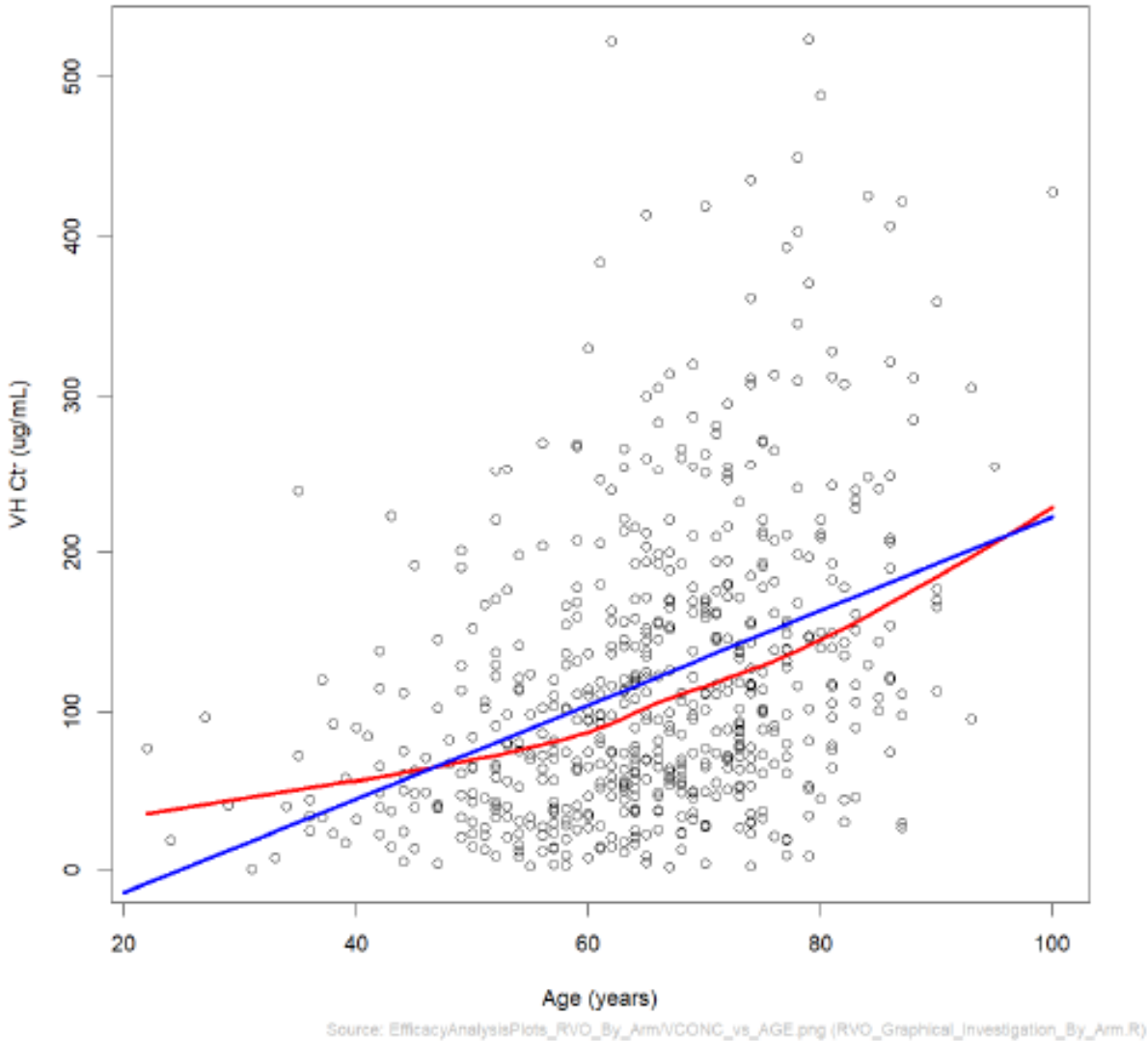
Source: EfficacyAnalysisPlots_RVO/BCVA_versus_VCONC_Q4W.png (RVO_Graphical_Investigation.R)

BCVA = best corrective visual acuity; C_{tr} = C_{trough}; RVO = Retinal Vein Occlusion; VEGF-A = vascular endothelial growth factor-A; VH = vitreous humor.

The individual values are plotted versus ocular Ctrough. Lowess trend line is shown by red color. Linear regression line is shown by blue color. P-value and r2 value of linear regression are shown in the lower right corner of each plot.

Source: popPK Report, Report 1120410, Figure 88

Figure 19. Correlation of exposure (VH C trough) with age for Patients with RVO



C_{tr} = C_{trough}; RVO = Retinal Vein Occlusion; VH = vitreous humor
Red line: lowess smoother; blue line: linear regression line
Source popPK Report, Report 1120410, Figure 73.

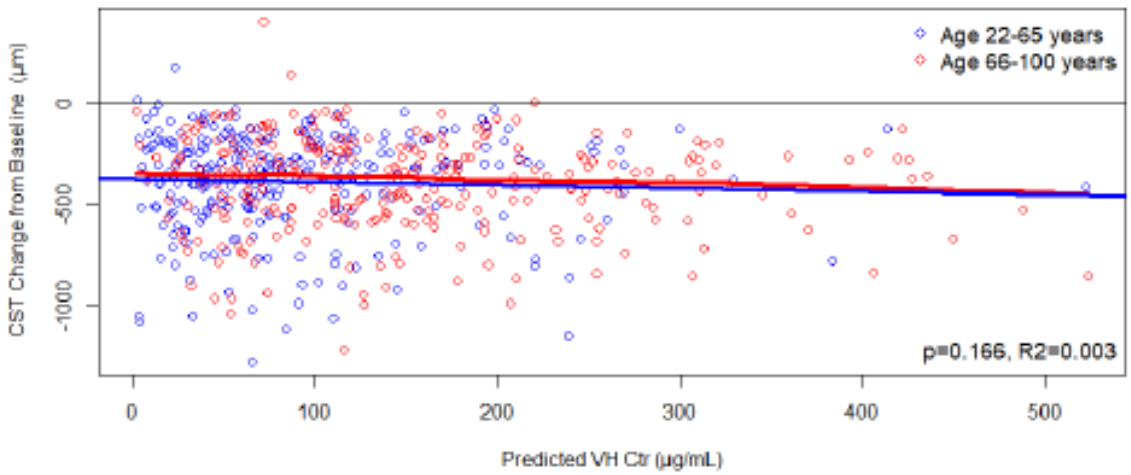
Exposure Relationship with CST in RVO

The relationship between CST and exposure was evaluated using 1) linear regression between VH concentrations vs CST variables at primary endpoint and 2) plots of time-course of CST by VH exposure groups.

There were no apparent differences in the time courses of CST between patients in the different VH exposure groups. The CST-time profiles showed a rapid and persistent decrease in retinal thickness following faricimab administration.

Linear regression analyses show flat relationships between changes in CST and faricimab exposure (Figure 20 below).

Figure 20. CTS Change at Week 24 by VH trough concentrations for RVO studies BALATON and COMINO



CST = central subfield thickness; VH = vitreous humor; Ctr = trough concentration.
The individual CST change from baseline values are plotted versus Ctr. Lowess trend line is shown by red color. Linear regression line is shown by blue color. P-value and r2 value of linear regression are shown in the lower right corner of each plot.
Source: popPK Report, Report 1120410, Figure 89

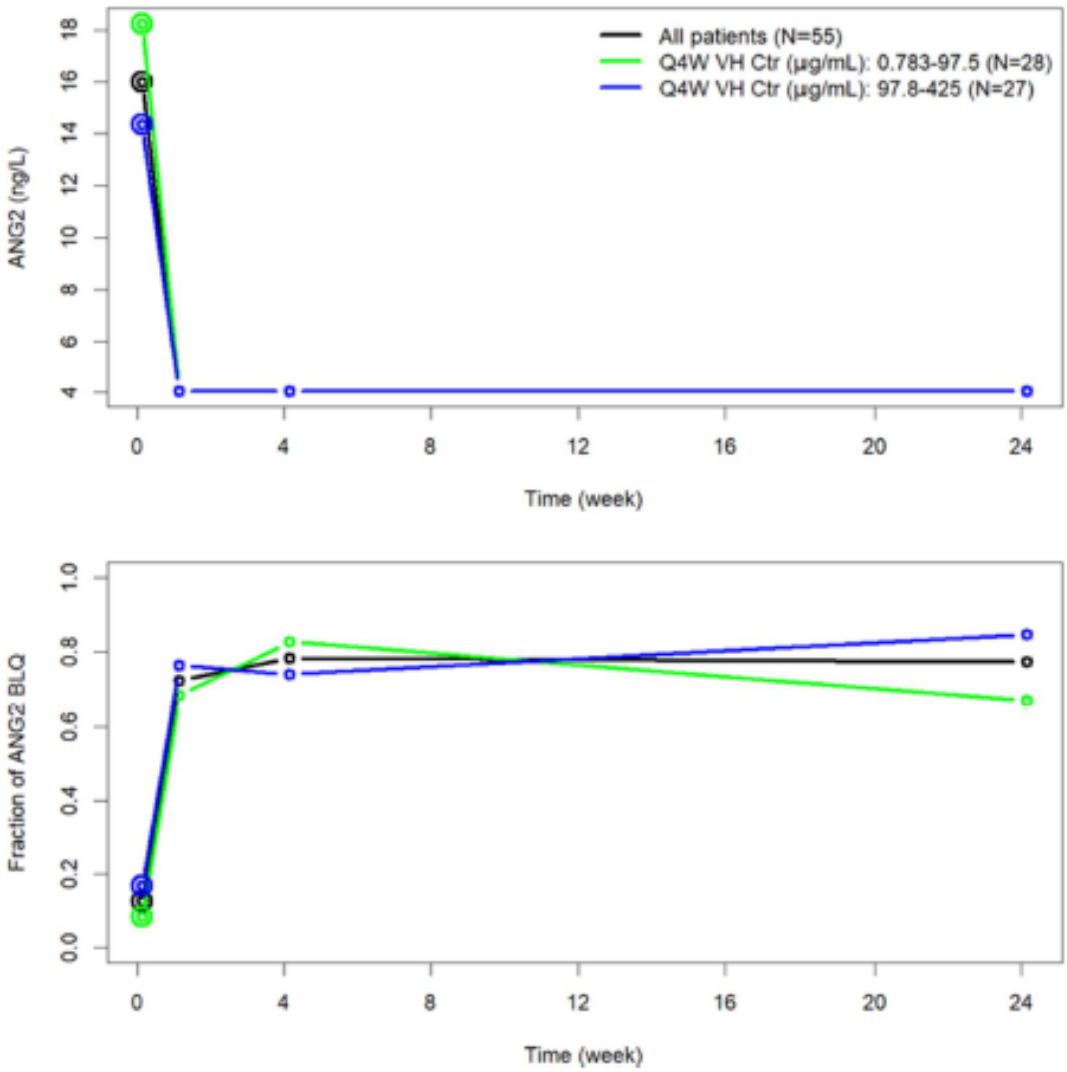
Exposure Relationship with Ocular Ang-2 and Free VEGF-A in RVO

The relationship between aqueous target suppression (Ang-2 and VEGF-A) and VH faricimab exposure in Phase III patients with RVO was explored graphically by plotting the observed AH VEGF-A and Ang-2 concentrations versus time after most recent dose by VH exposure (Ctrough) categories. Patients were divided by low and high exposure categories (below and above median exposure, respectively).

Median free VEGF-A concentration-time profiles and fraction of samples BLQ are displayed in Figure 21 and Figure 22 below.

Ang-2 and VEGF-A were suppressed during the dosing interval and there were no apparent differences in the time courses of VEGF-A and Ang-2 suppression between patients with different VH exposure. The comparable free Ang-2 and free VEGF-A suppression profiles for both exposure categories can be explained by the dosing regimen of Q4W which maintains the target maximally suppressed in all patients during the Q4W dosing interval and therefore no exposure-response is apparent.

Figure 21. Medians and BLQ Fractions of Free Ang-2 AH Concentrations versus Time by Low/High VH trough Concentration in RVO Patients from Studies BALATON and COMINO

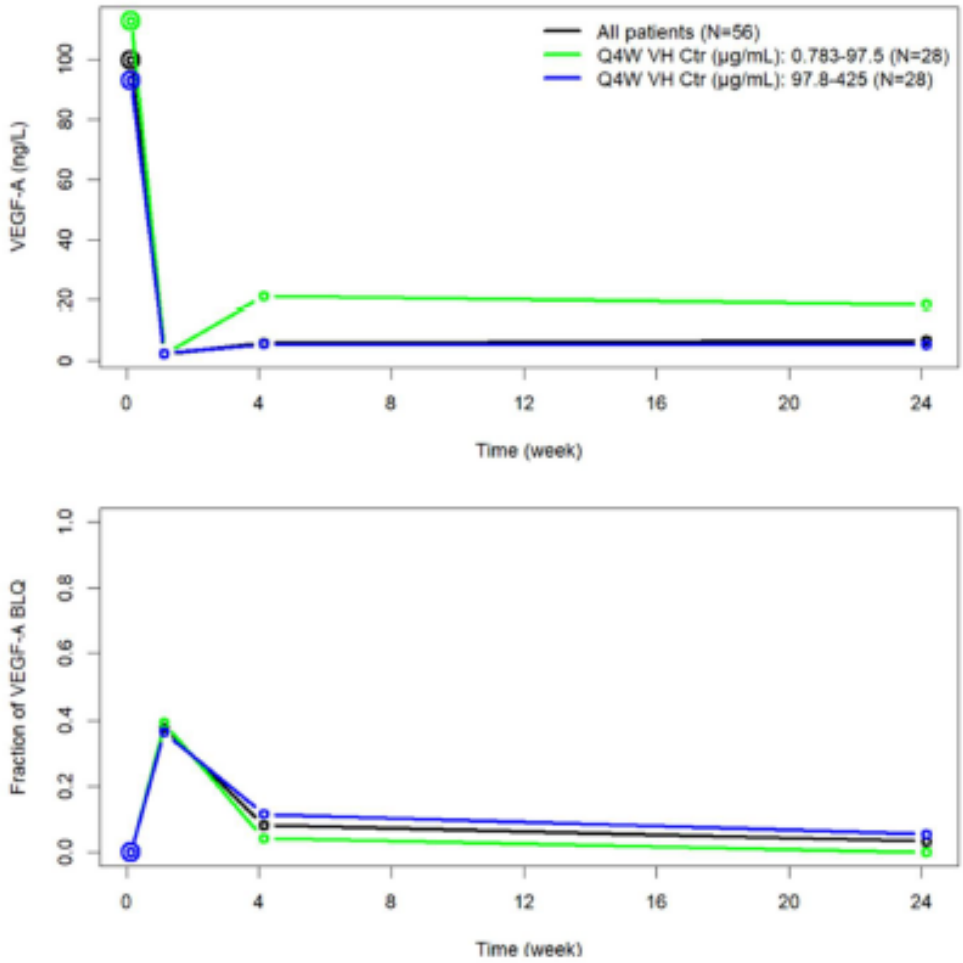


AH = aqueous humor; Ang-2 = angiopoietin-2 (protein); BLQ = below limit of quantification; C_{trough} = trough concentration; LLOQ = lower limit of quantification; RVO = retinal vein occlusion; VH = vitreous humor.

The medians of individual values (top) and fraction of BLQ observations (bottom) are plotted versus time after dose by halves of vitreous C_{trough}. Values below quantification limit LLOQ = 4.04 ng/L were assigned LLOQ.

Source: popPK Report, Report 1120410, Figure 97

Figure 22. Medians and BLQ Fractions of Free VEGF-A AH Concentrations versus Time by VH trough Concentration for RVO Studies BALATON and COMINO



AH = aqueous humor; BLQ = below limit of quantification; $C_{tr} = C_{trough}$; LLOQ = lower limit of quantification; RVO = retinal vein occlusion; Q4W = every 4 weeks; VEGF-A = vascular endothelial growth factor-A; VH = vitreous humor.

The medians of individual values (top) and fraction of BLQ observations (bottom) are plotted versus time after dose by halves of vitreous C_{tr}. Values below quantification limit LLOQ = 1.46 ng/L were assigned LLOQ.

Source: popPK Report, Report 1120410, Figure 93

As pointed out by the assessors, the CHMP agreed that the linear regression analysis suggested a trend of lower BCVA response with higher exposure. However, it was determined that this was likely the result of the positive correlation between exposure and age. When both exposure and age were included in the linear regression model, only age was found to be a significant predictor of the BCVA change from baseline (lower BCVA gain in older patients), while there was no significant effect of exposure on BCVA gain (p-value > 0.5). It is agreed that no age-based dose adjustment is needed.

The linear regression analysis did not detect an effect of faricimab exposure on CST changes from baseline.

The observed concentrations of free VEGF-A in AH declined from the median baseline value of about 100 ng/L to nearly undetectable levels shortly after faricimab administration, and stayed low with repeated 6 mg Q4W dosing, slightly increasing by the end of each 4-week dosing interval.

The observed concentrations of free Ang-2 in AH declined from the median baseline value of about 16 ng/L to undetectable levels shortly after faricimab administration and stayed low (below quantification limit of the assay) with repeated 6 mg Q4W dosing.

The comparable free VEGF-A and free Ang-2 suppression profiles for both the lower and higher exposure categories (halves of VH Ctrough,ss) can be explained by the dosing regimen of Q4W which maintained the target maximally suppressed in most patients during the dosing interval and therefore no exposure-response was apparent.

Exposure-safety analyses in patients with macular oedema secondary to branch retinal, central retinal, or hemiretinal vein occlusion.

Objective

To assess the relationships between faricimab VH exposure and the probability of intraocular inflammation (IOI) and any other relevant safety events based on observed data.

Methods

The exposure-safety analysis was performed using the Phase III data from RVO studies GR41984 and GR41986. Safety information up to the primary end-point (Week 24) were included. The steady-state trough concentration in VH (Ctrough,ss) following the 6 mg Q4W dosing regimen was used as a metric of exposure to assess the effect of faricimab PK on the occurrence of intra-ocular inflammation (IOI). The individual PK parameters from the final population PK model were used to predict the individual Ctrough,ss values.

IOI was defined as a binary (0/1) variable indicating absence (0) or presence (1) of IOI at any time before Week 24 irrespectively of the severity of the event or the number of occurrences. The following analyses were performed:

- Event rates were compared between Ctrough,ss exposure groups, for all patients in each indication as well as for ADA-negative and ADA-positive subgroups;
- Logistic regression models were implemented to assess the correlation between the probability of occurrence of IOI and exposure predictors (Ctrough,ss and log(Ctrough,ss)).

Results

The table below shows the incidence rates of intra-ocular inflammation in Part 1 among patients from the faricimab arm (Arm A) by tertile of Ctrough,ss. Overall, IOI incidence rate was low and independent of exposure (1.5%, 2.5%, and 0.5% in Low, Mid, and High exposure groups, respectively).

Table 10. Fraction of RVO patients with intra-ocular inflammation in Part 1 of the studies by Ctrough,ss tertiles

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

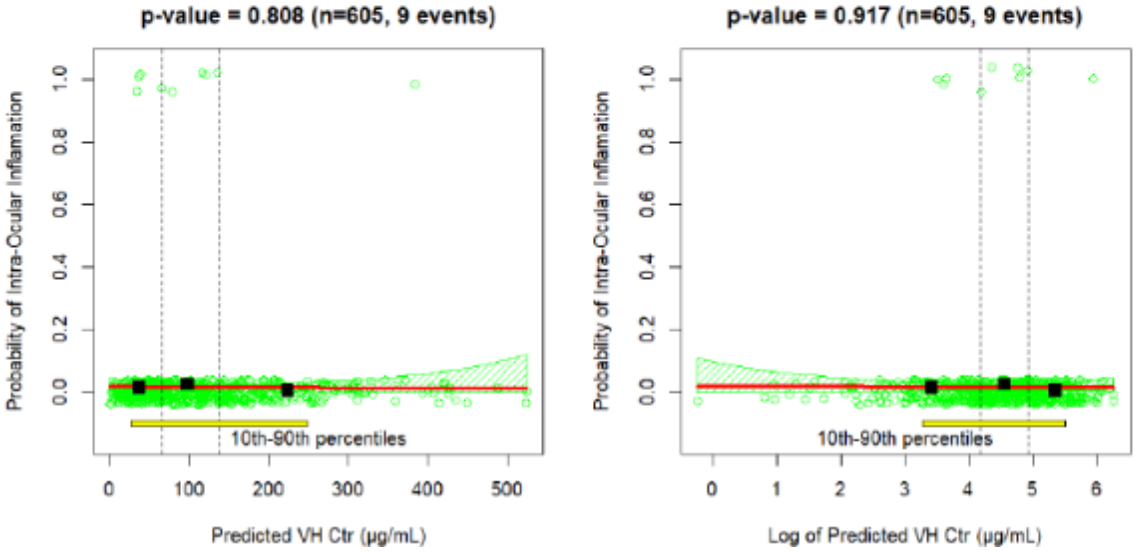
VH $C_{trough,ss}$		Number of		Percent of Patients with Events (%)
Exposure Group	Range (µg/mL)	Patients	Events	
Low	0.783-65	202	3	1.5
Mid	65-138	201	5	2.5
High	138-523	202	1	0.5
Total		605 [a]	9 [b]	1.5

[a] Only subjects with evaluable PK data in Part 1 of the faricimab arm were included in the summary.
[b] Includes all patients with IOI in Part 1, in particular, one patient that had an event of "vitreal cells" reported where the verbatim term was "non-inflammatory vitreous cells"
Source file: RVO_summaryTable_IOIRAO_by_VCONC_Q4W.csv (RVO_Graphical_Investigation.R)

The logistic regression models (Figure 23) confirmed that incidence of IOI did not increase with faricimab exposure (Ctrough,ss and log(Ctrough,ss)).

Figure 23. Logistic Regression for Probability of IOI in RVO Patients receiving faricimab

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. In the BALATON study, 1 patient in the faricimab Q4W arm had 1 event of 'vitreal cells' reported but the verbatim term was "non-inflammatory vitreous cells" and thus not considered an IOI event.



The results showed that the IOI incidence rate did not increase with faricimab VH exposure.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Study GR41984 (BALATON) and Study GR41986 (COMINO)

The overall study design for the BALATON and COMINO studies to assess the PK of faricimab following an intravitreal injection were overall acceptable.

The ocular and plasma PK are similar between both the BALATON and COMINO studies. The Q4W interval for injection resulted in the highest concentration being seen at the 7-day sampling time-point, and low concentrations shown pre-dose at Week 4 and Week 24 for both the ocular and plasma faricimab concentrations. The faricimab AH-to-plasma ratios were ~266 and ~394 for the BALATON and COMINO studies respectively.

The low number of patients that consented to provide AH samples means the data should be interpreted with caution.

Overall, the PK for the plasma and AH exposure from the BALATON and COMINO studies are in line with the Phase III studies from the initial MAA.

Immunogenicity

The immunogenicity timepoints for the BALATON and COMINO studies were acceptable. There was a low baseline prevalence of ADAs to faricimab of 1.1% in both the BALATON and COMINO studies. The incidence of immunogenicity to faricimab is based on patients with treatment emergent-ADAs in both BALATON (18/259 patients; 6.9%) and COMINO (30/338 patients; 8.9%) was low. The median onset time of ADA response was 24 weeks.

In both studies the MAH suggested that a visual inspection of the faricimab plasma concentration-time profiles do not suggest a difference in plasma exposure between ADA-positive and ADA-negative patients. In the BALATON study (GR41984) there does appear to be a trend of lower plasma concentration in the ADA positive patients compared to ADA negative patients. However, as this was not seen in the COMINO study, and as the incidence of ADA positive patients was low in both Phase III studies, the CHMP agreed that these results should be interpreted with caution.

Overall, the CHMP noted that there was a low incidence of ADAs, and low impact of ADA positive status on faricimab PK in RVO, based on the available data. This is in line with the Summary of Clinical Pharmacology from Vabysmo initial MAA. However, most of the patients who developed ADAs still had persistent ADAs at Week 24 (in Balaton, 94.4% and in Comino 96.7%) and possibly beyond Week 24. Further, there were limitations in the strategy for assessment of immunogenicity. The neutralising capacity of antibodies was not investigated, which is not in line with the immunogenicity testing strategy outlined in the Guideline on Immunogenicity assessment of therapeutic proteins. In addition, immunogenicity results were only available for patients randomised to faricimab arm, but not to aflibercept arm.

Therefore, the CHMP conveyed that comparative assessment of immunogenicity is not possible.

Population PK Analysis

The methods used for model development and evaluation are considered acceptable by the CHMP. Data exclusions were well documented and are acceptable. Post-dose BLQ observations were appropriately handled using the M3 method.

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 in patients with RVO. The VH volume was fixed to the literature value of 4.5 mL, as done previously, which is considered acceptable. The updated parameter estimates, after inclusion of RVO data, were close to the parameters of the prior legacy model based on nAMD and DME data.

All final model parameters were estimated with good precision and High IIV shrinkage (~40-60%) of plasma CL and Vc as well as the AH elimination rate constant (K_{AH}) are noted. Therefore, individual estimates for these parameters and predicted exposures of faricimab in the AH and plasma may not be reliable. Importantly, IIV shrinkage of K_{VH} was low (5.3%). As such, predicted VH exposure, which were used as PK metric in the ER analyses, can be considered reliable.

Overall, the goodness-of-fit diagnostic plots indicated that the final model described the observed data adequately.

The pcVPC showed that the final model captured both the central tendency and the interindividual variability of faricimab PK in AH and plasma adequately.

Consistent with the prior legacy model, the covariates that influenced faricimab ocular PK parameters were age, formulation, and presence of ADAs, while faricimab systemic PK parameters were influenced by sex, body weight, and formulation. The effects of these covariates on ocular and plasma PK were not considered to be clinically meaningful, which is agreed by the CHMP.

Pharmacodynamics

Study GR41984 (BALATON) and Study GR41986 (COMINO)

The PD sampling timepoints for the BALATON and COMINO studies were acceptable.

There was high inter-patient variability in VEGF-A and ANG-2 AH concentrations in both the BALATON (VEGF-A, 56.9−108%; ANG-2, 71.6−268%) and COMINO (VEGF-A, 62.2-294%; ANG-2, 76.6-141%) studies.

The faricimab treatment arm in both the BALATON and COMINO studies showed rapid suppression of both the free VEGF-A and free ANG-2 parameters from Day 7 in the AH. Suppression was maintained up to the Week 24 visit. There was no change in plasma free VEGF-A or free Ang-2 up to Week 24 when compared with baseline levels.

Overall, the CHMP noted that the PD for the plasma and AH free VEGF-A and Ang-2 levels from the BALATON and COMINO studies are in line with the Phase III studies from the initial MAA.

Exposure-efficacy analyses
The linear regression analysis suggested a trend of lower BCVA response with higher exposure. However, it was determined that this was likely the result of the positive correlation between exposure and age.

When both exposure and age were included in the linear regression model, only age was found to be a significant predictor of the BCVA change from baseline (lower BCVA gain in older patients), while there was no significant effect of exposure on BCVA gain (p-value > 0.5). The CHMP agreed that no age-based dose adjustment is needed.

The linear regression analysis did not detect an effect of faricimab exposure on CST changes from baseline.

The observed concentrations of free VEGF-A in AH declined from the median baseline value of about 100 ng/L to nearly undetectable levels shortly after faricimab administration, and stayed low with repeated 6 mg Q4W dosing, slightly increasing by the end of each 4-week dosing interval.
The observed concentrations of free Ang-2 in AH declined from the median baseline value of about 16 ng/L to undetectable levels shortly after faricimab administration and stayed low (below quantification limit of the assay) with repeated 6 mg Q4W dosing.

The comparable free VEGF-A and free Ang-2 suppression profiles for both the lower and higher exposure categories (halves of VH Ctrough,ss) can be explained by the dosing regimen of Q4W which maintained the target maximally suppressed in most patients during the dosing interval and therefore no exposure-response was apparent.

Exposure-safety analysis
The results showed that the IOI incidence rate did not increase with faricimab VH exposure.

2.3.6. Conclusions on clinical pharmacology
The CHMP agreed that the pharmacokinetics and pharmacodynamics of faricimab in patients with RVO have been sufficiently characterised.

2.4. Clinical efficacy
This Type II variation seeks approval of faricimab for the treatment of adult patients with *visual impairment due to macular oedema secondary to retinal vein occlusion (**branch RVO or central RVO**).*
The recommended dose in RVO indication is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for 3 or more consecutive doses, followed by a treat-and-extend approach.
Clinical evidence supporting the efficacy, safety, and favourable benefit-risk assessment of faricimab is mainly based on the primary analysis results of two pivotal Phase III studies (Table 11):

- Study GR41984 (hereafter referred to as BALATON) in patients with macular oedema due to branch retinal vein occlusion (BRVO)
- Study GR41986 (hereafter referred to as COMINO) in patients with macular oedema due to central retinal vein occlusion or hemi-retinal vein occlusion (C/HRVO).

The data in this application are primarily based on the data up to Week 24 (Part 1 of the RVO studies). Further data (beyond week 24) supporting this application were provided by the MAH with the day 120 responses including final BALATON Clinical Study Report, Update COMINO CSR, Report 1126075 and Week 72 Addendum Clinical Overview.

Of note, for all efficacy descriptions, 95% is a rounding of 95.03%.

Table 11. Studies supporting RVO indication i.e. the treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Protocol Name/No.	Countries	Study Design	Patient Subset	Criteria for Evaluation	Dose, Duration	No. of Patients	Study Status
Pivotal Studies							
BALATON (GR41984) **COMINO** (GR41986)	Global	Phase III, Two-Part, Multicenter, Randomized, Double–Masked, Active Comparator-Controlled [a], Parallel-Group, 72-Week Study	Patients with RVO: BRVO (BALATON) or C/HRVO (COMINO)	Efficacy, Safety, PK, and PD	Part 1 (Q4W Dosing): Arm A: 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Arm B: 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Part 2 (PTI Regimen) [b]: Patients in both Arms A and B received 6 mg faricimab intravitreal injections to a PTI dosing regimen (up to Q16W treatment intervals) from Week 24 through Week 68	**Total Randomized** = 1282 **Intent-to-Treat** BALATON = 553 COMINO = 729 [c] **Pooled Safety-Evaluable** = 1276 BALATON = 550 COMINO = 726	BALATON: Completed (LPLV: 12 Jun 2023) COMINO: Ongoing (LPLV of global enrollment phase: 12 Jul 2023) [d] Final analysis at Week 72

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CSR = Clinical Study Report; CST = central subfield thickness; HRVO = hemi-retinal vein occlusion; LPLV = last patient last visit; PD = pharmacodynamics; PK = pharmacokinetics; PTI = personalized treatment interval; Q4W = every 4 weeks; Q16W = every 16 weeks.

[a] Studies BALATON and COMINO are only active comparator controlled during Part 1.

[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 Q16W or a minimum of Q4W based on the relative change of the CST and BCVA compared with the patient's reference CST and reference BCVA.

[c] One patient was wrongly randomized to the COMINO study, immediately discontinued and was then subsequently randomized to the BALATON study. This subject's data are only included in the BALATON CSR, resulting in a total of 553 and 729 patients included in BALATON and COMIINO, respectively.

[d] The global enrollment phase of COMINO was completed by the LPLV of 12 Jul 2023. The COMINO China Extension is ongoing. Data from patients enrolled in the China Extension were not included in the analyses for this Clinical Overview Addendum or the COMINO Update CSR, 1126075.

2.4.1. Dose response study(ies)

No dose finding studies were performed for the treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion.

The following dose was proposed for this indication: *6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly); 3 or more consecutive, monthly injections may be needed.*

Thereafter, treatment is individualised using a treat -and-extend approach. Based on the physician's judgement of the patient's anatomic and/or visual outcomes, the dosing interval may be extended, in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate (see section 5.1). Treatment intervals shorter than 4 weeks between injections have not been studied. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion but there is no requirement for monthly monitoring between injections.

No dose finding studies were performed for the treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion. Instead, the same dose as already approved for patients with DME were proposed. This was based on the following considerations:

- The similar pathophysiology of macular oedema and vision loss in patients with DME and RVO,
- Similar faricimab PK and PD characteristics in DME and RVO patients.

Further data supporting dosing regimen:
The combined evidence from the DME (YOSEMITE and RHINE) and RVO (BALATON and COMINO) Phase III studies have shown almost complete suppression of Ang-2 and VEGF-A one week after the first faricimab intravitreal injection and suppression was maintained on average for approximately 12 and 8 weeks, respectively. This was accompanied by robust BCVA gains and CST reductions that were already observed following the first dose.

Implementation of individualised approach to treatment after 3 consecutive monthly doses
The Phase III RVO studies were exploring less frequent dosing regimens (up to Q16W) by applying a PTI algorithm comparable to that successfully applied in the faricimab DME Phase III trials (Q4W-Q16W, with an interval extension of 4 weeks) that was approved and is part of Vabysmo SmPC.

This treat -and-extend approach was proposed to be implemented after 3 consecutive monthly initiation doses. However, this is not in line with the approach used in pivotal studies as in both studies during first 24 weeks of treatment patients received in total 6 injections given every 4 weeks (Q4W). Treat -and-extend approach was being introduced later (i.e after 24 weeks of treatment).

In order to support this posology (and implantation of treat -and-extend after 3 consecutive monthly initiation), a post-hoc analysis of the data up to Week 24 was conducted to further explore what proportion of patients in the faricimab Q4W arm achieved disease stability starting from Week 8.

This analysis indicated that, after 3 consecutive monthly initiation doses, RVO patients on average do not gain additional meaningful benefit from continued monthly dosing, as shown by the small difference in the change from baseline in BCVA, CST, and proportion of patients gaining ≥ 15 letters in BCVA from baseline between Week 12 and Week 24. Further, it was noted that 79% and 71% of patients in BALATON and COMINO, respectively, achieved disease stability at Week 8. For those patients who achieved stability at Week 8, the mean change in BCVA from Week 12 to Week 24 was less than < 2 letters, which is not considered clinically significant.

Real-world evidence (RWE) from anti-VEGF treatment in patients with macular oedema secondary to RVO also supports the recommended faricimab posology of 3 or more consecutive monthly doses followed by adjustable dosing intervals (i.e., treat-and extend), which may result in less than 6 monthly injections. The RWE shows that the mean (SD) number of injections received in the first 6 months of treatment since diagnosis was 4.2 (1.5) injections in patients with BRVO and 4.3 (1.4) injections in patients with CRVO. More injections were received in the first three months of treatment (Months 0-3 mean [SD]: 2.7 [0.8] in BRVO and CRVO) compared to the following three months (Months 4-6 mean [SD]: 1.6 [1.0] in BRVO and CRVO.

Finally, the MAH highlighted that, the pivotal studies for aflibercept and ranibizumab had similar designs (monthly dosing for 6 months, followed by a move to a different dosing regimen), but have posologies that allow an individualised approach to treatment after 3 consecutive monthly doses. Therefore, taking into consideration the totality of the data, the proposed recommendation i.e. an individualised approach to treatment after 3 consecutive monthly doses can also be accepted by the CHMP.

As outlined in section 4.2 of the SmPC, the recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly); 3 or more consecutive, monthly injections may be needed.
Thereafter, treatment is individualised using a treat -and-extend approach. Based on the physician's judgement of the patient's anatomic and/or visual outcomes, the dosing interval may be extended, in increments of up to 4 weeks.

The data from the second part of both studies showed that the BCVA gains' and central subfield thickness (CST) reductions achieved at Week 24 were maintained through Week 72, during which time all patients were on the 6 mg faricimab personalised treatment interval (PTI) dosing regimen.
The primary analysis of the Phase III studies in RVO (BALATON and COMINO) indicate that the 6 mg faricimab Q4W dose had a comparable safety profile to the 2 mg aflibercept Q4W dose and was generally well tolerated and demonstrated non-inferiority to aflibercept on the primary endpoint. Age-adjusted change in BCVA was similar across the ranges of faricimab exposure and therefore no age-based dose adjustment is needed.

Treatment intervals shorter than 4 weeks and longer than 4 months between injections have not been studied and this is highlighted in section 4.2 of the SmPC.

2.4.2. Main study(ies)

Clinical evidence supporting the efficacy, safety, and favourable benefit-risk assessment of faricimab is mainly based on the primary analysis results of two pivotal Phase III studies:

- Study GR41984 (hereafter referred to as BALATON) in patients with macular oedema due to branch retinal vein occlusion (BRVO)
- Study GR41986 (hereafter referred to as COMINO) in patients with macular oedema due to central retinal vein occlusion or hemi-retinal vein occlusion (C/HRVO).

Title of the pivotal studies

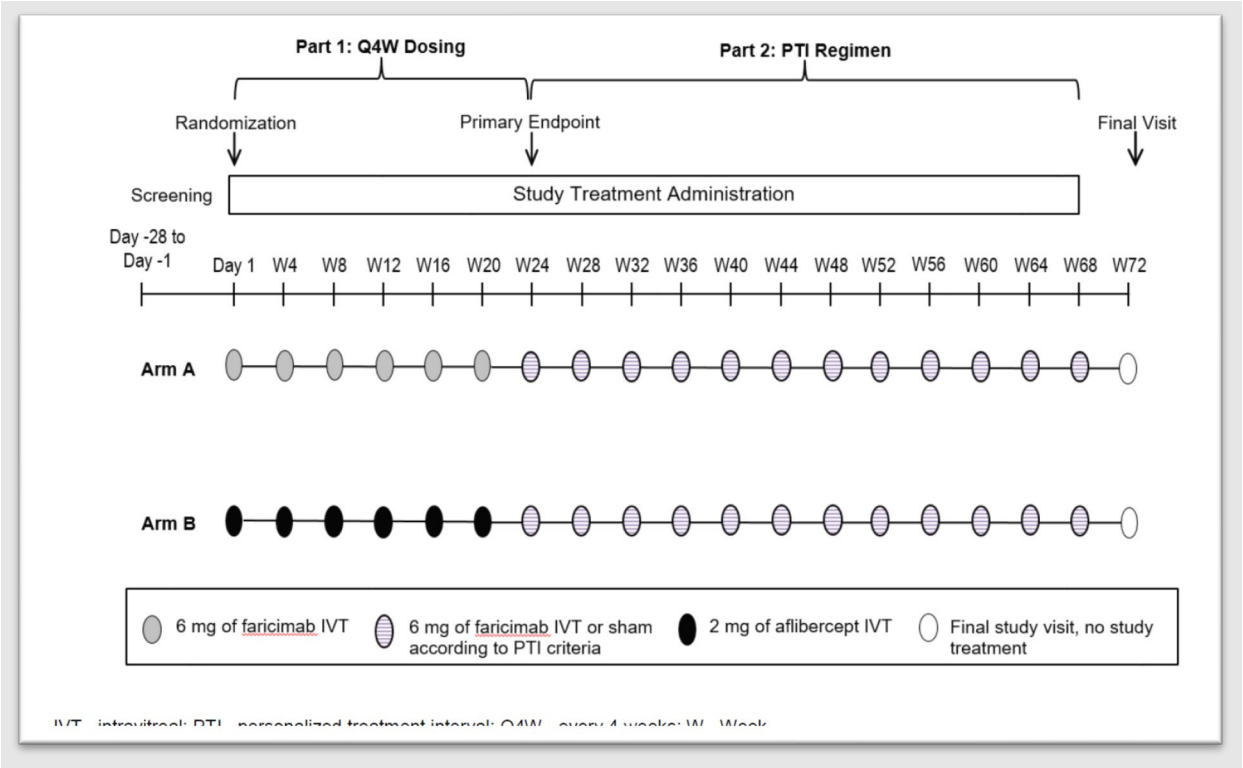
- Phase III, Multicentre, Randomised, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients with Macular Oedema Secondary to **Branch Retinal Vein Occlusion (BALATON study).**

- A Phase III, Multicentre, Randomised, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab in Patients with Macular Oedema Secondary to **Central Retinal or Hemi-retinal Vein Occlusion (COMINO study).**

Methods

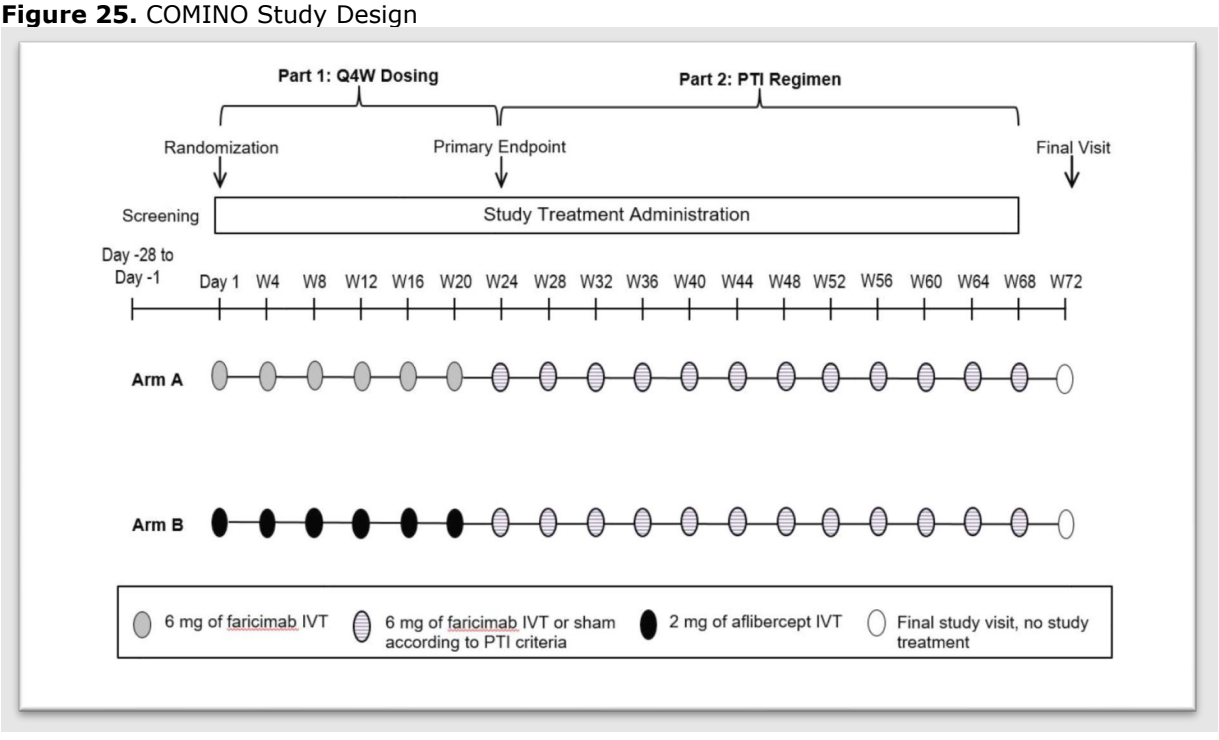
BALATON (Study GR41984) is a Phase III, multicentre, randomised, double-masked, active comparator−controlled, parallel-group, 2-part study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24, followed by a period of study without active control to evaluate faricimab administered according to a personalised treatment interval (PTI) dosing regimen in patients with macular oedema due to BRVO where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment and faricimab treatment interval in Part 2.

Figure 24. BALATON Study Design



COMINO (Study GR41986) is a Phase III, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until week 24, followed by a period of study without active control to evaluate faricimab administered according to a personalised treatment interval (PTI) dosing regimen in patients with macular oedema due to CRVO or HRVO where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment and faricimab treatment interval in Part 2.

Figure 25. COMINO Study Design



The design of both studies was similar and therefore they are discussed together. Any differences are clearly highlighted.

Both studies were comprised of two parts:

- **Part 1 (Day 1 through Week 24)** compared faricimab every 4 weeks (Q4W) versus aflibercept Q4W.
- **Part 2 (Week 24 through Week 72)** evaluated faricimab administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on PTI dosing criteria.

In Part 1 (Q4W dosing), patients were randomized in a 1:1 ratio to one of two treatment arms, with treatment defined as follows:

- **Arm A (treatment arm):** Patients randomly assigned to Arm A received 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections).
- **Arm B (comparator arm):** Patients randomly assigned to Arm B received 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections).

Randomization was stratified by the following baseline factors as assessed on Day 1:

BALATON study	**COMINO study**
Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≥ 55 letters vs. ≤ 54 letters)	Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≤34 letters, 35-54 letters, and≥ 55 letters)

• Region: United States and Canada, Asia, and the rest of the world

In Part 2 (PTI regimen), patients in both Arms A and B received 6 mg faricimab intravitreal injections according to a PTI dosing regimen from Week 24 through Week 68.

All patients should complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure was administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment was administered.

Only one eye was assigned as the study eye. If both eyes were considered eligible, the eye with the worse 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.

There was a minimum of two investigators per site to fulfil the masking requirements of the study. At least one investigator was designated as the assessor physician who was masked to each patient's treatment assignment and who evaluated ocular assessments.
At least one other investigator was unmasked and performed study treatments.

The study consisted of a screening period of up to 28 days (Days −28 to −1) and an approximately 68-week treatment period, followed by the final study visit at Week 72. A unique screening number was assigned to each screened patient through a web-based response system (IxRS).

The CHMP noted that comparative data are available only for the first 24 weeks, as in part 2 of the studies all patients were receiving faricimab in variable intervals. Furthermore, in both studies patients were stratified depending on the baseline BCVA score (with different cuts off depending on the study) and based on the region (United States and Canada, Asia, and the rest of the world).

Study participants

BALATON study investigating Branch Retinal Vein Occlusion	**COMINO study investigating Central Retinal or Hemiretinal Vein Occlusion**
Inclusion Criteria	
General Inclusion Criteria • Signed Informed Consent Form • Age ≥ 18 years at time of signing Informed Consent Form	
Ocular Inclusion Criteria for Study Eye	
Foveal centre–involved macular oedema **due to BRVO** diagnosed no longer than **4 months** prior to the screening visit and confirmed by central reading centre (CRC) based on spectral-domain optical coherence tomography (SD-OCT) (or swept-source optical coherence tomography [SS-OCT]) images. BRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in one quadrant or less of the retina drained by the affected vein.	Foveal centre–involved macular oedema **due to CRVO or HRVO** diagnosed no longer than 4 months prior to the screening visit and confirmed by central reading centre (CRC) based on spectral-domain optical coherence tomography (SD-OCT) (or swept-source optical coherence tomography [SS-OCT]) images. CRVO or HRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in the entire retina (CRVO) or two quadrants of the retina (HRVO)
• BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity (VA) chart at a starting test distance of 4 meters (see the BCVA manual for additional details) on Day 1 • Central subfield thickness (CST) ≥325 µm, as measured on Spectralis SD-OCT, or ≥315 µm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (SSOCT acceptable after confirmation with CRC)	
Key Exclusion Criteria	
General Exclusion Criteria Patients who met any of the following exclusion criteria were excluded from study entry. • Uncontrolled blood pressure, defined as systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg while a patient is at rest on Day 1 • If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1. • Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1	

Ocular Exclusion Criteria for Study Eye

- History of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed more than 4 months before screening
- History of retinal detachment or macular hole (Stage 3 or 4)
- Any prior or current treatment for macular edema due to RVO, including anti−VEGF intravitreal injections for macular oedema due to RVO
- Macular laser (focal/grid) in the study eye at any time prior to Day 1
- Any intravitreal treatment for any other retinal diseases that can lead to macular oedema complication
- Any prior or current treatment for macular edema; macular neovascularization, including diabetic macular edema and neovascular age-related macular degeneration; and vitreomacular-interface abnormalities, including, but not restricted to, intravitreal treatment with anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection

Ocular Exclusion Criteria for Fellow (Non-Study) Eye

- Patients who met the following ocular exclusion criterion for the fellow (non-study) eye at both screening and Day 1 were excluded from study entry:
- Non-functioning fellow eye, defined as either one of the following:
- – BCVA 20/320 or worse
- – No physical presence of fellow eye (i.e., monocular)

The CHMP noted that the inclusion criteria (broadly agreed during the SA) were similar between both pivotal studies with an exception: the BALATON study enrolled patients with macular oedema due to BRVO whereas the COMINO study enrolled patients with macular oedema due to CRVO or HRVO. In both studies patients had to be diagnosed no longer than 4 months prior to the screening visit and the diagnosis had to be confirmed by the central reading centre.

The MAH clarified that although BALATON (GR41984) and COMINO (GR41986) studies enrolled patients who were diagnosed within 4 months of the screening visit this is generally reflective of what happens in clinical practice. It was also indicated that in patients with RVO the treatment is usually started shortly after diagnosis.
The key criteria also included the threshold requirement for BCVA 73 letters or less (minimum of 19 letters) at screening to ensure that patients had room to improve by at least 15 letters, while also allowing the inclusion of patients presenting with ischemic RVO (who tend to present baseline BCVA <20/200 and have a more guarded prognosis). Further, as indicated by the MAH, patients with BCVA less than 19 are more likely to have disease-induced irreversible retinal damage and therefore unable to respond to therapy. A similar approach was used in studies investigating other anti−VEGF for the treatment of RVO.

In relation to the exclusion criteria, the study included **only patients without prior treatment for macular oedema** due to RVO, including anti−VEGF intravitreal injections, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection and laser therapy. Therefore, the pivotal study data can only provide supporting evidence for faricimab being used as a first line therapy. The efficacy of this product in patients who failed other treatment options is not available and this limitation of the data is highlighted accordingly in the SmPC (e.g. section 4.4).
History of retinal detachment, or macular hole was also an exclusion criterion and blood pressure was required to be controlled at enrolment.

Treatments
The investigational medicinal product (IMP) for this study was faricimab. Aflibercept was used as an active comparator in study in Part 1; therefore, aflibercept was also considered an IMP for this study when administered to the study eye. The sham is a procedure that mimics an intravitreal injection to preserve the study masking and involved the blunt end of an empty syringe, without a needle, being pressed against an anaesthetised eye.

Part 1
In Part 1 of the study, patients randomly assigned to Arm A received 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20, for a total of 6 injections; and patients randomly assigned to Arm B received 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20, for a total of 6 injections.

Part 2
In Part 2 of the study, patients in both Arm A and Arm B in Part 1 were receiving 6 mg faricimab intravitreal injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. At faricimab dosing visits, treatment intervals were maintained or adjusted (i.e. increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values.

Faricimab Interval Determination
The algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA at faricimab dosing visits compared with the reference CST and reference BCVA, is outlined as follows and in the Figure below. The faricimab dosing interval can be extended, maintained, or reduced as follows.

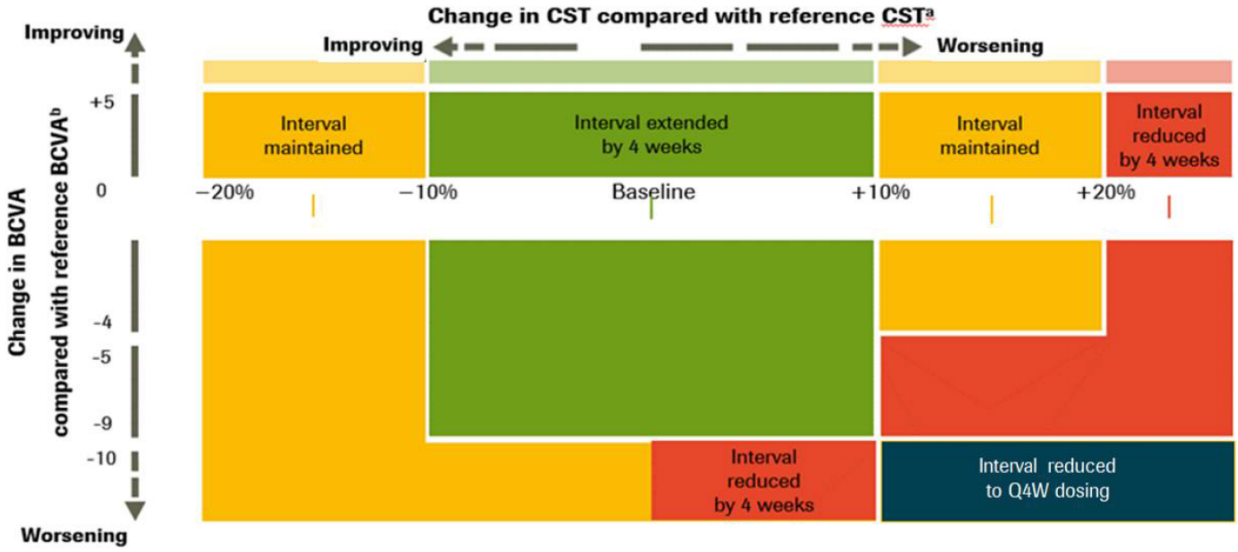
Interval extended by 4 weeks
– If the CST value is increased or decreased by ≤10% without an associated ≥10-letter BCVA decrease.

Interval maintained if any of the following criteria are met:
– If the CST value is decreased by > 10%
– If the CST value is decreased ≤10% with an associated ≥ 10-letter BCVA decrease
– If the CST value is increased between >10% and < 20% without an associated ≥5-letter BCVA decrease

Interval reduced by 4 weeks if any of the following criteria are met:
- If the CST value is increased between > 10% and ≤ 20% with an associated≥ 5-to < 10-letter BCVA decrease.
- If the CST value is increased by > 20% without an associated ≥ 10-letter BCVA decrease.
- If the CST value is increased by ≤ 10% with an associated BCVA decrease of ≥ 10-letters.

Interval reduced to Q4W:
If the CST value is increased by > 10% with an associated ≥ 10-letter BCVA Decrease.

Figure 26. Algorithm for IxRS-Determined Faricimab Personalized Treatment Dosing Intervals



BCVA = best-corrected visual acuity; CST = central subfield thickness; IxRS = interactive web-based response system; Q4W = every 4 weeks.

[a] Initial reference CST = CST value when the initial CST threshold criteria are met, but no earlier than Week 20. Reference CST is adjusted if CST decreases by > 10% from the previous reference CST for two consecutive faricimab dosing visits and the values obtained are within 30 μm. The CST value obtained at the latter visit will serve as the new reference CST, starting immediately at that visit.

[b] Reference BCVA = mean of the three best BCVA scores obtained at any prior dosing visit.

Patients will therefore receive **between 3 and 12 injections** during the period from Week 24 through Week 68.

Both treatment Arms A and B maintained Q4W study visits for the 72-week study duration. To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, the sham procedure was administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment was administered.

All faricimab and aflibercept administrations were performed at the site.

Prior and Concomitant Therapy

Permitted Therapy

Patients who use maintenance therapies should continue their use. Of note, the following are common therapies that are permitted:

- Treatment for onset of **ocular hypertension or glaucoma** in the study eye during a patient's study participation, as clinically indicated.

- Treatment of onset of **cataract or posterior capsular opacification** in either eye during a patient's study participation, as clinically indicated.

  Short-term use of topical ocular corticosteroids after cataract surgery, yttrium-aluminum garnet capsulotomy, peripheral iridotomy, argon/selective laser trabeculoplasty, or ocular allergic conditions in study eye or fellow eye.

Complete, sector, or local panretinal photocoagulation in the study eye or fellow eye could be allowed if needed for the treatment of ischemic RVO or new peripheral neovascularization.

Vitrectomy could be performed at the discretion of the masked investigator in the event that study eye develops sight-threatening vitreous haemorrhage or retinal detachment.

- Fellow (non-study) eye could be treated with anti-VEGF therapy licensed for ocular use, if diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved by the country regulatory agency and at the discretion of the masked investigator.

- At the discretion of the investigator, patients could continue to receive medications and standard treatments administered for other conditions.

Prohibited Therapy

The following medications and treatments are prohibited from use during a patient's study treatment participation. Patients may be discontinued from study treatment and/or the study to receive these therapies:

- Systemic anti-VEGF therapy
- Systemic drugs known to cause macular edema (fingolimod, tamoxifen)
  IVT anti-VEGF agents (other than study-assigned aflibercept or faricimab) in study eye
- IVT, periocular (subtenon), steroid implants (i.e., Ozurdex, Iluvien), or chronic topical ocular corticosteroids in study eye
- Treatment with verteporfin (Visudyne) in study eye.

The CHMP noted that, in both pivotal studies, patients were randomly assigned to 6 mg of faricimab intravitreal injections in Arm A or 2 mg aflibercept intravitreal injections in Arm B. During first 24 weeks of treatment (in Part 1 of the study) patients in both treatment arms received in total 6 injections given every 4 weeks (Q4W). Furthermore, in Part 2 all patients were receiving 6 mg of faricimab intravitreal injections therefore no comparative data are available beyond week 24. This is a limitation of this study.

In Part 2 the treatment intervals could be maintained or adjusted (increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values.

In the SmPC (in section 4.2 and 5.1) only limited information is included in this regard. The SmPC only states that the treatment intervals are to be adjusted based on anatomic and/or visual outcomes but CST and BCVA value which should be used for adjustment were not specified. The MAH was requested to justify why more detailed recommendations are not included in the SmPC**.** It was clarified that, regarding physician judgement of visual and/or anatomical changes to determine the best treatment interval, the SmPC language is consistent with the treatment guidance in the posology of the currently approved Vabysmo indications as well as for anti-VEGF products across retina disease indications. This justification was considered acceptable by the CHMP.

Comparator

Both pivotal studies were active-controlled. The lack of a placebo arm is agreed given the existing therapeutic alternatives. The MAH selected aflibercept as a comparator in the studies, which was acceptable. Aflibercept, given at the dose of 2 mg, is approved for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO). The monthly regimen for the comparator in Part 1 of the study was discussed and agreed during the SA.

Prior and Concomitant Therapy

In relation to the exclusion criteria the study included only patients without prior treatment for macular oedema due to RVO, including anti−VEGF intravitreal injections, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection and laser therapy. In this context, the data generated in the pivotal studies can support the use of the product as first line therapy in patients' macular oedema due to RVO. On the other hand, it is not clear if the results could be extrapolated to patients relapsing after other therapies. Information highlighting that there no data in patients who failed previous therapy has therefore been included in section 4.4 of the SmPC. This lack of data should be considered accordingly by the physician when treating such patients In both studies, in the study eye the

treatment with other therapies for macular oedema due to RVO were not allowed as well as systemic anti-VEGF therapy and systemic drugs known to cause macular oedema. Of note, fellow (non-study) eye could be treated with anti-VEGF therapy licensed for ocular use.

Objectives

Part 1
Primary Efficacy Objective
To evaluate the efficacy of 6 mg faricimab intravitreal injections Q4W compared with 2 mg aflibercept intravitreal injections Q4W on BCVA outcome.
In the study there were also secondary efficacy objectives (corresponding to secondary efficacy endpoints).

Safety Objective
To evaluate the safety and tolerability of faricimab

Pharmacokinetic Objectives
To characterise the faricimab PK profile

Immunogenicity Objectives
To evaluate the antibody immune response to faricimab

Outcomes/endpoints

Primary endpoint Change from baseline in BCVA **at** Week 24.

Secondary endpoints
- Change from baseline in BCVA at specified time points through Week 24
- Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 24
- Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline through
- Week 24
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, or ≥ 5 letters in BCVA from baseline through Week 24
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better (BCVA ≥ 69 letters) through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse (BCVA ≤ 38 letters) through Week 24
- Change from baseline in CST (ILM-BM) through Week 24
- Change from baseline in NEI VFQ-25 composite score through Week 24
- Proportion of patients with absence of macular edema, defined as CST of < 325 µm through Week 24
- Proportion of patients with absence of intraretinal fluid through Week 24
- Proportion of patients with absence of subretinal fluid through Week 24
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid through Week 24 manual ETDRS

Part 2 (Week 24 through Week 72
- Change from baseline in BCVA averaged over Week 64/68/72 and over time through Week 72
- Change from Week 24 in BCVA averaged over Week 64/68/72 and over time through Week 72
- Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline averaged over Week 64/68/72 and overtime through Week 72
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, or ≥ 5 letters in BCVA from baseline averaged over Week 64/68/72 and over time through Week 72

- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA over Week 64/68/72 and over time through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better (BCVA ≥ 69 letters) over Week 64/68/72 and over time through Week 72
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68
- Change from baseline in central subfield thickness (CST) averaged over Week 64/68/72 and over time through Week 72
- Change from baseline in NEI VFQ-25 composite score through Week 72
- Proportion of patients with absence of macular edema, defined as CST of< 325 µm, averaged over Week 64/68/72 and over time through Week 72
- Proportion of patients with absence of intraretinal fluid over time through Week 72
- Proportion of patients with absence of subretinal fluid over time through Week 72
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time through Week 72

The CHMP noted that the primary endpoint in the study was the change from baseline in best corrected visual acuity (BCVA) at week 24. The timing of the primary endpoint was agreed during the SA and was the same as used in pivotal studies supporting the authorisation of other anti-VEGFs (i.e. aflibercept and ranibizumab) and is considered acceptable. In relation to the selected primary outcome measure (i.e. change from baseline in BCVA) this is also considered acceptable.

Both studies had a non-inferiority design. For the primary analysis, if the lower bound of the 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.

There were a number of secondary endpoints again investigating the effect on best corrected visual acuity (BCVA) including the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline, patients achieving ≥ 84, 69 letters or ≤ 38 letters, all assessed through and at week 24. Other aspects investigated in the study included changes from baseline in central subfield thickness (CST), proportion of patients with absence of macular oedema, with absence of intraretinal fluid or with absence of subretinal fluid.

The secondary endpoints were assessed through week 24 (Part 1 of the study) or through Week 64/68/72 (averaged) or over time through Week 72 (Part 2 of the study).

Definitions

Best corrected visual acuity (BCVA)

Best-corrected visual acuity (BCVA) was assessed on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart, at a starting test distance of 4 meters.

The refraction BCVA assessment had to be conducted before pupil dilation. The refraction and BCVA were measured by trained and certified personnel at the study sites. Both refraction and BCVA were assessed at every study visit, however, only study eye refraction on Day 1, Week 24, and Week 68 visits was entered on the refraction-specific electronic Case Report Form (eCRF).

Sample Size

BALATON study

Determination of sample size was based on patients enrolled in the global enrolment phase. Global enrolment phase of approximately 570 patients was planned. Patients were randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison is between the active comparator (aflibercept Q4W) and the faricimab Q4W arm at Week 24.

A sample size of approximately 285 patients in each arm provided > 90% power to show NI of faricimab to aflibercept in the change in BCVA at Week 24 in ITT population, using a NI margin of 4 letters, and under the following assumptions:

• No difference in the mean change from baseline in BCVA between the two treatment arms
• Standard deviation (SD) of **13** letters for the change from baseline in BCVA at Week 24
• Two-sample t-tests
• 2.5% one-sided type I error rate
• 10% dropout rate

Furthermore, a sample size of approximately 285 patients per arm provided greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

COMINO study
Determination of sample size was based on patients enrolled in the global enrolment phase. Global enrollment phase of approximately 750 patients was planned. Patients were randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison is between the active comparator (aflibercept Q4W) and the faricimab Q4W arm at Week 24.

A sample size of approximately 375 patients in each arm provided > 90% power to show NI of faricimab to aflibercept in the change in BCVA at Week 24 in ITT population, using a NI margin of 4 letters, and under the following assumptions:
• No difference in the mean change from baseline in BCVA between the two treatment arms
• Standard deviation (SD) of **15** letters for the change from baseline in BCVA at Week 24
• Two-sample t-tests
• 2.5% one-sided type I error rate
• 10% dropout rate

Furthermore, a sample size of approximately 375 patients per arm provided greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

The CHMP considered the sample size justification for each study as acceptable.

Randomisation
All patients received a screening number assigned through the IxRS and were randomised in a 1:1 ratio to one of two study treatment arms (faricimab Q4W or aflibercept Q4W). A stratified block randomisation scheme was used and was stratified by the following baseline factors as assessed on Day 1:

BALATON study	**COMINO study**
Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≥ 55 letters vs. ≤ 54 letters)	Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≤34 letters, 35-54 letters, and≥ 55 letters)

• Region (United States and Canada, Asia, and the rest of the world)

Blinding (masking)
This was a double-masked study (up to Week 24). A minimum of two investigators per site were needed to fulfil the masking requirements of this study, and both investigators were required to be present at each scheduled study visit.

BALATON
There had to be a minimum of two investigators per site to fulfil the masking requirements of this study and both investigators are required to be present at each scheduled study visit.

Masked Roles

Principal Investigator

The Principal Investigator was a retina specialist (or the equivalent in ex-U.S. countries) and had to be in a masked role to oversee conduct of the whole trial. The Principal Investigator had to be masked to patients' treatment assignment and could assume any other masked role for which he or she qualifies, except for BCVA examiner tasks.

Assessor Physician/Masked Investigator

At least one investigator who was a retina specialist (or the equivalent in ex-U.S. countries) was designated as the assessor physician/masked investigator. The investigator(s) was masked to patient treatment assignments and evaluated all pre-dose assessments, as well as all assessments performed at screening, Day 7, and at the final or early termination visit. The assessor physician/masked investigator also evaluated the causality of all adverse events reported by the treatment administrator/unmasked investigator. If qualified, this role could take on any other masked role tasks except tasks performed by the BCVA examiner.

Photographer(s) and OCT Technician(s)

If qualified, the photographers and OCT technicians can share any other masked role tasks except tasks performed by the BCVA examiner.

Study Coordinator(s)

If qualified, the study coordinator(s) can share any other masked role tasks except tasks performed by the BCVA examiner.

BCVA Examiner

The BCVA examiner will be masked to both the assigned treatment arm and designation of the study eye. **The BCVA examiner may have access only to a patient's refraction data from previous visits**. Patients' medical charts and visual acuity scores from patients' previous visits are not accessible to the BCVA examiner. The BCVA examiner is not allowed to perform any other task involving direct patient care.

Unmasked Roles

Treatment Administrator/Unmasked Investigator

At least one investigator will be designated as the treatment administrator and will be unmasked to the patients' treatment assignment. The treatment administrator/unmasked investigator will be a retina specialist (or the equivalent in ex- U.S. countries). In addition, ophthalmologists who have completed a minimum of 2 full years of ophthalmology residency (or equivalent in ex-U.S. countries) may be permitted to perform the role of the treatment administrator/unmasked investigator following Sponsor approval.

The treatment administrator/unmasked investigator(s) performing the study treatment administration (faricimab, aflibercept, or **sham**) will also perform the post-dose administration safety assessments (finger-counting, hand-motion and/or light-perception tests [if applicable] and post-dose IOP measurement) and will treat adverse events that occur during or shortly after the study treatment administration. The person in this role, however, will not evaluate the causality of adverse events, which is the responsibility of the assessor physician/masked investigator(s). The treatment administrator/unmasked investigator will also perform post-dose IOP measurements, as well as optional aqueous humour and vitreous humour sample collection. In addition, the qualifying treatment administrator/unmasked investigator can assist with and perform the screening and Day 1 visit assessments. The treatment administrator/unmasked investigator must not be involved in any other aspect of the study and must preserve masking of treatment assignment.

Unmasked Assistants and Pharmacist

If desired, sites may have designated qualified unmasked assistants who can, for example, assemble study treatment supplies, prepare sterile field, prepare the patient's study eye for treatment, discard all injection materials (i.e., syringes and needles) immediately following study treatment, and place

vials in the kit box. The qualified unmasked assistants can be assigned to measure post-dose IOP. If the site uses a pharmacy, the unmasked role is also assigned to the pharmacist who can take on IMP/NIMP-related tasks as applicable per the site delegation log. In addition, qualifying unmasked assistants can assist with and perform the screening and Day 1 visit assessments.

Number of Unmasked Personnel per Site
Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There should be no more than **six unmasked personnel** (e.g., treatment administering physician[s] and assisting technician[s] if applicable) at an investigative site at one time. In certain circumstances, the total number of unmasked personnel might be increased after discussion with and approval by the Medical Monitor. If the site is using a pharmacist, this person may be in an unmasked role in addition to the unmasked staff at the site.
Any other study assisting personnel not listed above will be in the masked roles.

Role Switching
Once personnel assigned to the designated unmasked role start performing that role, they cannot switch to a masked role during the study. Switching from a masked role to an unmasked role may be possible and must be documented in the site delegation log.

Masking of Vendors, Sponsor's Agents, a CRC personnel, study vendors, the Sponsor, and its agents will also **be masked to treatment assignment**, with the exception of individuals who require access to patient treatment assignments to fulfil their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, drug accountability clinical research associates, the images coordinator, iDCC and iDMC members, and an internal unmasking statistician (this person is from the Sponsor's unmasking group and will follow the Sponsor's standard operation procedures to audit the implementation of the randomization scheme and the dosing interval assignment by the IxRS vendor periodically during the conduct of the study; this person will not be involved in other study-related activities).

To maintain the masked design of the study, blood samples, optional aqueous humor samples, and optional vitreous humor samples obtained at the timepoints specified in the schedule of activities (see Appendix 1) will be obtained from consenting patients in any treatment arm. The laboratories responsible for performing sample analyses will be unmasked to patients' treatment assignment to identify appropriate samples to be analyzed. Unmasking for analysis of the relevant biosamples during the conduct of the study will be performed by personnel outside of the study team and according to the Sponsor’s internal standard procedures to ensure the integrity of the data. The number of Roche representative(s) and delegates who are unmasked will be kept to the minimum required to address the objective of the biosample analysis.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the masking of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unmasked to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analysed for faricimab PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analysed.
for all patients. Post-baseline immunogenicity samples from patients assigned to the comparator arm will not be analysed for ADAs except by request.

Patient Masking
Patients will be masked to treatment assignment during the study and until study closeout, or until the Sponsor indicates that the study can be unmasked.

Single-Patient Emergency Unmasking
If unmasking is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the masked investigator will be able to break the treatment code by contacting the IxRS.

Single-Patient Non-Emergency Unmasking
If the masked investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.

The masked investigator should document and provide an explanation for any nonemergency unmasking.

If the Medical Monitor agrees to patient unmasking, the masked investigator will be able to break the treatment code by contacting the IxRS.

The CHMP noted that the MAH described accordingly in the study protocols roles (masked and unmasked) at the study site. In summary, as indicated:

- A minimum of two investigators (one masked and one unmasked) per site were needed to fulfil the masking requirements of this study and both investigators are required to be present at each scheduled study visit.
- The role of unmasked investigator was to administer the study treatment (faricimab, aflibercept, or sham) to perform the post-dose administration safety assessments and to treat adverse events that occur during or shortly after the study treatment administration.
- The masked investigator was to evaluate all pre-dose assessments, as well as all assessments performed at screening, Day 7 and at the final or early termination visit. Further the masked investigator was to perform the causality assessment of AEs reported during the study.
- In the study at each trial site there was a BCVA Examiner who was masked to both the assigned treatment arm and designation of the study eye.

The roles of additional personnel were also described. As stated in the protocol, there should be no more than six unmasked personnel at each trial site.

Statistical methods
The statistical methods were similar in both studies. They are briefly described as follows; differences are highlighted.

Statistical Hypothesis
The primary efficacy endpoint was the change from baseline in BCVA at Week 24. The following hypotheses were tested:

- Non-inferiority (NI) of faricimab Q4W compared with aflibercept Q4W at Week 24 in the intent to treat (ITT population) population (at a one-sided 0.02485 significance level).
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a two-sided 0.0497 significance level)

The CHMP noted that the hypotheses on the primary endpoint were tested in the order shown above, proceeding sequentially starting from the non-inferiority test and only testing the superiority after achieving statistical significance on the non-inferiority test. It was also pointed out by the MAH that **there was no impact on the type I error rate for the superiority test following the NI test; therefore, in the MAH's view, a claim of superiority after NI could be made without multiplicity adjustment.**

Of note, in the SAP for each study the MAH mentioned: "*a nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary analysis, it is estimated that three safety interim*

data reviews will have been conducted by the iDMC; therefore, efficacy analyses would be performed with a family-wise significance level of 0.0497. The actual adjustment will depend on the actual number of IDMC interim safety reviews. This type I error adjustment is not expected to impact sample size or power".

The CHMP noted that, although the MAH would use the same confidence interval that concluded non-inferiority, for a switch to superiority (and therefore no type I error penalty incurred), the MAHs pre-specified analyses imposed a type I error, but its basis was not fully understood. However, this matter was not further pursued.

Analysis Populations

The following populations are defined:

Population	Definition
ITT	All patients who were randomized in the study. For analyses based on this patient population, patients were grouped according to the treatment assigned at randomization. *Note: Patients who were wrongly randomized to one study (BALATON or COMINO), discontinued without treatment, and were then randomized to the other study (BALATON or COMINO, respectively) are included in the latter study only.*
Per-Protocol	All patients randomized in the study who received at least one dose of study treatment and who did not have a major protocol violation that impacted the efficacy evaluation. [a] Prior to study unmasking, protocol deviations were reviewed and a determination of the definition of the population for per protocol (PP) analysis was made.
Safety-Evaluable	All patients who received at least one injection of active study drug (faricimab or aflibercept) in the study eye. [a]
Pharmacokinetic-Evaluable	Safety-evaluable patients with at least one plasma sample, and if sufficient dosing information (dose and dosing time) was available. [a]
Faricimab Pharmacokinetic-Evaluable	Pharmacokinetic-Evaluable patients from faricimab treatment group (as defined for Pharmacokinetic-Evaluable population)
Immunogenicity Analysis	The immunogenicity prevalence set consisted of all patients randomized to or received faricimab with at least one determinant anti-drug antibody (ADA against faricimab) assessment. Patients were grouped according to treatment received as described for the Safety-Evaluable population or if no treatment was received prior to study discontinuation, according to treatment assigned. The immunogenicity incidence set consisted of all patients who received faricimab with at least one determinant ADA assessment after the initiation of faricimab treatment. [a]

a Patients were grouped according to actual treatment received through Week 20. If by error, a patient received a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group was as randomized.

Efficacy Analysis
The primary and secondary efficacy analyses were based on the ITT population, unless otherwise specified, with patients grouped according to the treatment assigned at randomisation. Additional analysis based on the PP population was also conducted for the primary endpoint.
Unless otherwise noted, analyses of efficacy outcome measures were stratified by baseline BCVA ETDRS letter score, as assessed on Day 1, and region (United States and Canada, Asia, and the rest of the world).
The stratification factor as recorded in IxRS was used.

Continuous outcomes were analysed using a mixed model for repeated measures (MMRM). Binary secondary endpoints were analysed using stratified estimation for binomial proportions.

The CHMP noted that the primary analysis was based on using all time points through an MMRM analysis. The results of the sensitivity analysis (which used multiple imputation assuming MNAR, and were justified accordingly) supports the primary analysis results.

Invalid BCVA (BCVA values that are confirmed to be inaccurate, due to the BCVA test being performed incorrectly) were excluded from the analyses.

Non-standard BCVA data (such as assessed by ETDRS BCVA testing with prior visit refraction, BCVA test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor) were included in the analyses (1 patient in each treatment arm).
Supplementary per protocol analysis was performed with non-standard BCVA data excluded.

Primary Efficacy Analysis
The primary efficacy endpoint is the change from baseline in BCVA at Week 24. BCVA is assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters. The primary estimand is defined as follows:

Population

BALATON study	**COMINO study**
Adult patients with macular edema due to BRVO, as defined by the inclusion and exclusion criteria (ITT population)	Adult patients with macular edema due to CRVO or HRVO, as defined by the inclusion and exclusion criteria (ITT population)

- Variable: Change from baseline in BCVA at Week 24
- Treatments (as randomized):

– Experimental: 6 mg faricimab intravitreal injection Q4W
– Control: 2 mg aflibercept intravitreal injection Q4W

Intercurrent events prior to Week 24:
– Discontinuation of study treatment due to AEs or lack of efficacy
– Use of any prohibited systemic treatment or prohibited therapy in the study eye

Handling of intercurrent events
A treatment policy strategy was applied to all intercurrent events.
The primary comparison was between the active comparator (aflibercept Q4W) and faricimab Q4W at Week 24. The primary analysis was performed using a MMRM. The model included the change from baseline at Weeks 4-24 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.

All observed measurements were included in the analysis regardless of whether or not a patient had an intercurrent event.

Missing data were implicitly imputed by the MMRM model, assuming a missing at random mechanism.
The CHMP noted that the MAH proposed an MMRM analysis (see above) and a treatment policy estimand. The preferred estimand is one that is more akin to a PP analysis for a non-inferiority objective, in addition to other estimand approaches as sensitivity analyses. The CHMP had highlighted that the treatment policy estimand may not be of sufficiently sensitivity to departures in non-inferiority in this regard (this can be noted in the results where the 95% CI for the PP are wider). The MAH justified using a treatment policy strategy as the primary estimand.

Secondary Efficacy Analysis
Continuous outcomes were analysed using a MMRM unless otherwise specified. Binary secondary endpoints were analysed using stratified estimation for binomial proportions using Cochran Mantel-Haenszel (CMH) weights. The estimates and CIs are provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment arm and for the difference in means or proportions between the aflibercept Q4W arm and the faricimab Q4W arm. All CIs are two-sided and at the 95.03% level.

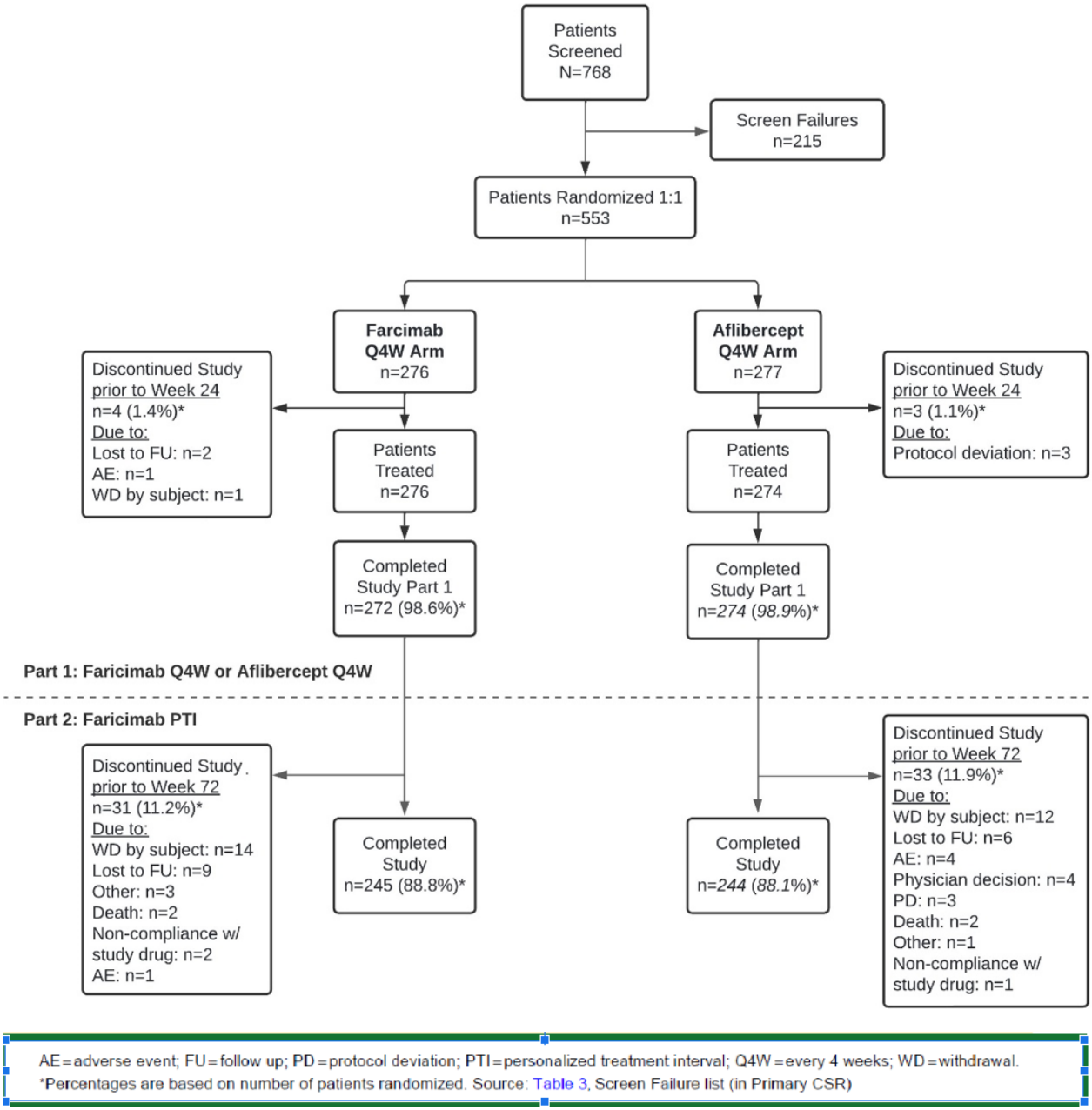
PRO data were also collected through the use of the NEI VFQ-25 to assess the treatment benefit of faricimab.

Results

BALATON study

This Primary CSR provides results up to the primary analysis (Week 24) for the global enrolment phase with a clinical cutoff date (CCOD) of 6 July 2022.
A total of 553 patients with BRVO were randomized 1:1 into the study using a stratified permuted-block randomization scheme: 276 to the faricimab Q4W arm and 277 to the aflibercept Q4W arm in 149 sites in 22 countries.
As specified in the protocol, two randomization stratification factors were used (baseline BCVA ETDRS letter score and region) to balance these characteristics across the treatment arms.

Figure 27. Participant flow-Balaton study (Part 1 and Part 2)



AE = adverse event; FU = follow up; PD = protocol deviation; PTI = personalized treatment interval; Q4W = every 4 weeks; WD = withdrawal.
*Percentages are based on number of patients randomized. Source: Table 3, Screen Failure list (in Primary CSR)

Table 12. Summary of Patient Disposition and Reason for Discontinuation prior to Week 24, ITT Population

Status / Primary Reason for Discontinuation	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=277)	All Patients (N=553)
Number of Patients Randomized	276 (100.0%)	277 (100.0%)	553 (100.0%)
Number of Patients Treated	276 (100.0%)	274 (98.9%)	550 (99.5%)
Discontinued Study Treatment in Study Eye prior to Week 24*			
Total	9 (3.3%)	3 (1.1%)	12 (2.2%)
Lost To Follow-up	5 (1.8%)	2 (0.7%)	7 (1.3%)
Withdrawal by Subject	2 (0.7%)	1 (0.4%)	3 (0.5%)
Adverse Event	1 (0.4%)	0	1 (0.2%)
Death	1 (0.4%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Non-Compliance With Study Drug	0	0	0
Other	0	0	0
Physician decision	0	0	0
Pregnancy	0	0	0
Protocol Deviation	0	0	0
Study Terminated By Sponsor	0	0	0
Discontinued Study prior to Week 24**			
Total	4 (1.4%)	3 (1.1%)	7 (1.3%)
Protocol Deviation	0	3 (1.1%)	3 (0.5%)
Lost To Follow-up	2 (0.7%)	0	2 (0.4%)
Adverse Event	1 (0.4%)	0	1 (0.2%)
Withdrawal by Subject	1 (0.4%)	0	1 (0.2%)
Death	0	0	0
Lack of Efficacy	0	0	0
Non-Compliance With Study Drug	0	0	0
Other	0	0	0
Physician decision	0	0	0
Pregnancy	0	0	0
Study Terminated By Sponsor	0	0	0

* Percentages are based on number of patients treated.
**Percentages are based on number of patients randomized.
Includes discontinuation occurring prior to day 154 (first day of week 24 analysis visit window).

At Week 24, overall, in the ITT population, 12 patients (2.2%) discontinued study treatment with a comparable proportion between treatment arms (3.3% of patients in the faricimab Q4W arm and 1.1% of patients in the aflibercept Q4W arm). The reasons for study treatment discontinuation were lost to follow-up (1.8% in the faricimab Q4W arm and 0.7% in the aflibercept Q4W arm), withdrawal by subject (0.7% in the faricimab Q4W arm and 0.4% in the aflibercept Q4W arm), adverse event (0.4% in the faricimab Q4W arm) and death (0.4% in the faricimab Q4W arm).

Seven patients (1.3%) withdrew from the study with a comparable proportion between treatment arms (1.4% in the faricimab Q4W arm and 1.1% in the aflibercept Q4W arm).

One patient in the faricimab Q4W arm died on Day 162. The patient's treatment discontinuation date was derived as the last treatment day (Day 132), which was before the start of the Week 24 window (Day 154).

Table 13. Summary of Patient Disposition and Reason for Discontinuation through Week 72, ITT Population

Protocol: GR41984

Status / Primary Reason for Discontinuation	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=277)	All Patients (N=553)
Number of Patients Randomized	276 (100.0%)	277 (100.0%)	553 (100.0%)
Number of Patients Treated	276 (100.0%)	274 (98.9%)	550 (99.5%)
Discontinued Study Treatment in Study Eye prior to Week 72*			
Total	32 (11.6%)	28 (10.2%)	60 (10.9%)
Withdrawal by Subject	14 (5.1%)	11 (4.0%)	25 (4.5%)
Lost To Follow-up	10 (3.6%)	6 (2.2%)	16 (2.9%)
Adverse Event	1 (0.4%)	4 (1.5%)	5 (0.9%)
Death	2 (0.7%)	2 (0.7%)	4 (0.7%)
Physician decision	0	4 (1.5%)	4 (0.7%)
Non-Compliance With Study Drug	2 (0.7%)	1 (0.4%)	3 (0.5%)
Lack of Efficacy	2 (0.7%)	0	2 (0.4%)
Other	1 (0.4%)	0	1 (0.2%)
Pregnancy	0	0	0
Protocol Deviation	0	0	0
Study Terminated By Sponsor	0	0	0
Discontinued Study prior to Week 72**			
Total	31 (11.2%)	33 (11.9%)	64 (11.6%)
Withdrawal by Subject	14 (5.1%)	12 (4.3%)	26 (4.7%)
Lost To Follow-up	9 (3.3%)	6 (2.2%)	15 (2.7%)
Adverse Event	1 (0.4%)	4 (1.4%)	5 (0.9%)
Death	2 (0.7%)	2 (0.7%)	4 (0.7%)
Other	3 (1.1%)	1 (0.4%)	4 (0.7%)
Physician decision	0	4 (1.4%)	4 (0.7%)
Non-Compliance With Study Drug	2 (0.7%)	1 (0.4%)	3 (0.5%)
Protocol Deviation	0	3 (1.1%)	3 (0.5%)
Lack of Efficacy	0	0	0
Pregnancy	0	0	0
Study Terminated By Sponsor	0	0	0

*Percentages are based on number of patients treated.
**Percentages are based on number of patients randomized.
Includes discontinuation occurring through the end of study.

COMINO study

This Primary CSR provides results up to the primary analysis (Week 24) for the global enrolment phase with a clinical cutoff date (CCOD) of 9 August 2022.

A total of 729 patients with C/HRVO were randomized 1:1 into the study using a stratified permuted-block randomization scheme: 366 to the faricimab Q4W arm and 363 to the aflibercept Q4W arm in 192 sites in 22 countries. One patient was wrongly randomized to the COMINO study (GR41986), immediately discontinued and was then subsequently randomized to the BALATON study (GR41984). This subject's data are only included in the BALATON CSR, resulting in a total of 553 and 729 patients included in BALATON and COMINO, respectively.

As specified in the protocol, two randomization stratification factors were used (baseline BCVA ETDRS letter score and region) to balance these characteristics across the treatment arms. Overall, 6 patients were mis-stratified by the incorrect BCVA letter score category (34 letters or worse, 35-54 letters, or 55 letters or better). Since the number of patients mis-stratified was low and balanced across treatment arms, no specific measures were needed to be considered in the statistical analysis.

Three patients (1 patient in the faricimab Q4W arm and 2 patients in the aflibercept Q4W arm) were randomized but did not receive any treatment. The reasons for these patients not receiving treatment were: 'other' (BCVA score of 85 letters on repeat testing at Day 1) for the patient in the faricimab Q4W arm, and physician decision (subject randomized by error) and protocol deviation (study eye: increase of > 10 letters in BCVA ETDRS score between screening and Day 1) for the 2 patients in the aflibercept Q4W arm.

Patients Who Discontinued from Study Treatment or Study

Overall, in the ITT population, 26 patients (3.6%) discontinued study treatment with a comparable proportion between treatment arms (3.0% in the faricimab Q4W arm and 4.2% in the aflibercept Q4W arm). The most common reason for study treatment discontinuation was withdrawal by subject;). One

patient withdrew from study treatment for a reason categorized as 'Other', which was non-compliance with study drug.

Sixteen patients (2.2%) withdrew from the study with a comparable proportion between treatment arms (1.6% in the faricimab Q4W arm and 2.8% in the aflibercept Q4W arm).

Figure 28. Patient Disposition-Comino study (Part 1 and Part 2)

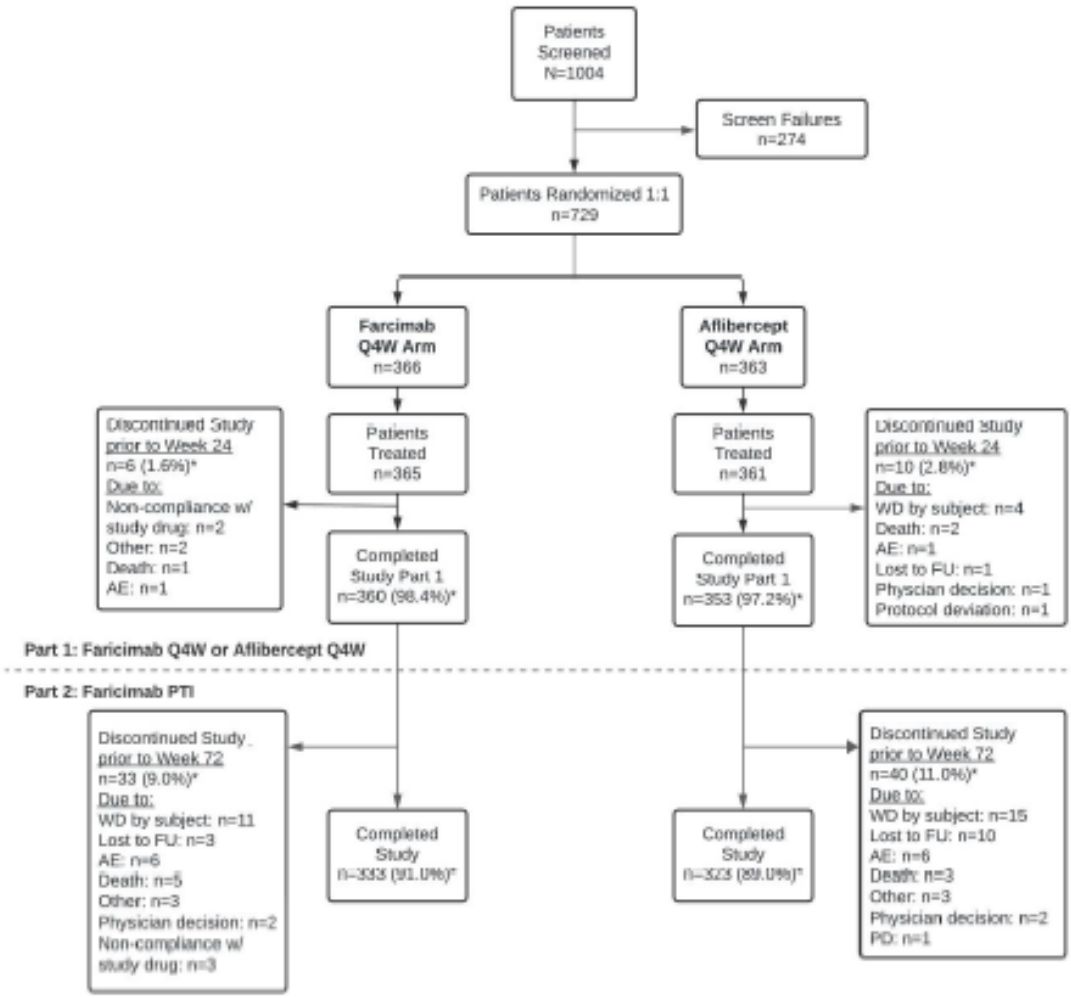


Table 14. Summary of Patient Disposition and Reason for Discontinuation through Week 72, ITT Population

Patient Disposition and Reason for Discontinuation through Week 72, Intent-to-Treat Population
Protocol: GR41986

Status / Primary Reason for Discontinuation	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=366)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=363)	All Patients (N=729)
Number of Patients Randomized	366 (100.0%)	363 (100.0%)	729 (100.0%)
Number of Patients Treated	365 (99.7%)	361 (99.4%)	726 (99.6%)
Discontinued Study Treatment in Study Eye prior to Week 72*			
Total	36 (9.9%)	42 (11.6%)	78 (10.7%)
Withdrawal by Subject	11 (3.0%)	15 (4.2%)	26 (3.6%)
Adverse Event	8 (2.2%)	10 (2.8%)	18 (2.5%)
Lost To Follow-up	3 (0.8%)	10 (2.8%)	13 (1.8%)
Death	4 (1.1%)	3 (0.8%)	7 (1.0%)
Physician decision	4 (1.1%)	3 (0.8%)	7 (1.0%)
Non-Compliance With Study Drug	4 (1.1%)	0	4 (0.6%)
Other	2 (0.5%)	1 (0.3%)	3 (0.4%)
Lack of Efficacy	0	0	0
Pregnancy	0	0	0
Protocol Deviation	0	0	0
Study Terminated By Sponsor	0	0	0
Discontinued Study prior to Week 72**			
Total	33 (9.0%)	40 (11.0%)	73 (10.0%)
Withdrawal by Subject	11 (3.0%)	15 (4.1%)	26 (3.6%)
Lost To Follow-up	3 (0.8%)	10 (2.8%)	13 (1.8%)
Adverse Event	6 (1.6%)	6 (1.7%)	12 (1.6%)
Death	5 (1.4%)	3 (0.8%)	8 (1.1%)
Other	3 (0.8%)	3 (0.8%)	6 (0.8%)
Physician decision	2 (0.5%)	2 (0.6%)	4 (0.5%)
Non-Compliance With Study Drug	3 (0.8%)	0	3 (0.4%)
Protocol Deviation	0	1 (0.3%)	1 (0.1%)
Lack of Efficacy	0	0	0
Pregnancy	0	0	0
Study Terminated By Sponsor	0	0	0

*Percentages are based on number of patients treated.
**Percentages are based on number of patients randomized.
Includes discontinuation occurring through the end of study.

The CHMP noted that in the Balaton study a total of 553 patients with BRVO were randomised 1:1 into the study: 276 to the faricimab Q4W arm and 277 to the aflibercept Q4W. The majority of patients completed 24 weeks treatment period i.e. 543 out of 553 subjects. 12 patients in total discontinued the study treatment prior to 24 and the main reason for discontinuation was lost for follow up and due to an adverse event. One patient in the faricimab arm died prior to week 24. It was also pointed out that the population of patients enrolled in the Comino study was slightly bigger as compared to the Balaton study. The Comino study enrolled 729 patients with C/HRVO who were randomized 1:1 into two treatment arms: 366 to the faricimab Q4W arm and 363 to the aflibercept Q4W arm. Again, most patients (713 out of 729) completed 24 weeks treatment period. 26 patients (3.6%) discontinued study treatment prior to week 24. The main reason for discontinuation was withdrawal by subject. 3 patients died while on study. Discontinuation rate was also small in Part 2 of the study (after week 24 through week 72). 60 (10.9%) and 78 (10.7%) patients discontinued study treatment in study eye prior to Week 72 in the Balaton and Comino study, respectively.

Recruitment

Balaton study

The first patient was enrolled on 2 March 2021 and the last patient was randomized on 20 January 2022. Patients were recruited from 149 sites in 22 countries.

With day 120 responses the MAH provided the Final CSR which included results from analyses through Week 72, corresponding to the end of the enrollment phase with a last patient last visit (LPLV) of 12 June 2023.

COMINO study

The first patient was enrolled on 2 March 2021 and the last patient was randomized on 17 February 2022. Patients were recruited from 192 sites in 22 countries.

With day 120 responses the MAH provided the updated CSR which included results from analyses through Week 72, corresponding to the end of the global enrollment phase with an LPLV of 12 July 2023.

Conduct of the study

Protocol Deviations

BALATON study

In the ITT population, 532 major protocol deviations were reported in 287 patients (51.9%): 146 patients (52.9%) in the faricimab Q4W to faricimab PTI arm and 141 patients (50.9%) in the aflibercept Q4W to faricimab PTI Q4W arm. Approximately 16.7% (89/532) of the major protocol deviations in the ITT population through Week 72 were related to COVID-19.

The majority of the major protocol deviations were procedural, with 'missed visits' (missed any of the Week 4, 8, 12, 16, 20, 24, 60, 64, 68 or 72 visits; 26.6% overall) and 'study eye: major issues with images' (defined as any major issue that can prevent the assessment of any of optical coherence tomography [OCT], color fundus photographs [CFP] or fluorescein angiography [FA] images per the schedule of assessments; 12.7% overall) being the most common major protocol deviations.

The incidence of 'missed visits' was 24.6% in the faricimab Q4W to faricimab PTI arm and 28.5% in the aflibercept Q4W to faricimab PTI arm.

The incidence of 'study eye: major issues with images' was 14.5% in the faricimab Q4W to faricimab PTI arm and 10.8% in the aflibercept Q4W to faricimab PTI arm.

The incidence of 'other significant procedural deviation issues' was 6.9% and 5.4% in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arm, respectively. This subcategory covers a variety of protocol deviations that were considered major, for safety or efficacy reasons, but were not covered by the pre-defined subcategories.

Some examples of the nature of the protocol deviations included in this subcategory are: treatment administration performed by a role in the delegation log, but not by a retina specialist as per protocol that occurred at one site; last visit (Week 72) performed out of window; images not taken at the last visit (Week 72); split visits where key assessments were not repeated, among others.

During the study through Week 72, 9 patients (1.6%) had optional samples (plasma, aqueous humor samples, and/or Research Biosample Repository) collected without a signed optional ICF samples. These unconsented samples were destroyed and not analyzed or reported in any analysis.

Table 15. Summary of Major Protocol Deviations through Week 72, ITT Population- Balaton study

Category Description	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=277)	All Patients (N=553)
Total number of patients with at least one major protocol deviation	146 (52.9%)	141 (50.9%)	287 (51.9%)
Total number of major protocol deviations	274	258	532
PROCEDURAL			
Total number of patients with at least one major protocol deviation	131 (47.5%)	123 (44.4%)	254 (45.9%)
Total number of major protocol deviations	233	211	444
SE: Major issues with images	40 (14.5%)	30 (10.8%)	70 (12.7%)
Week 24 missed	15 (5.4%)	27 (9.7%)	42 (7.6%)
Week 60 missed	17 (6.2%)	22 (7.9%)	39 (7.1%)
Other significant procedural deviation issues	19 (6.9%)	15 (5.4%)	34 (6.1%)
Week 20 missed	15 (5.4%)	17 (6.1%)	32 (5.8%)
Week 64 missed	12 (4.3%)	20 (7.2%)	32 (5.8%)
Week 68 missed	17 (6.2%)	10 (3.6%)	27 (4.9%)
Week 72 missed	14 (5.1%)	9 (3.2%)	23 (4.2%)
Week 16 missed	11 (4.0%)	11 (4.0%)	22 (4.0%)
ICF update not signed by patient in timely manner	8 (2.9%)	8 (2.9%)	16 (2.9%)
Week 12 missed	10 (3.6%)	5 (1.8%)	15 (2.7%)
Week 8 missed	7 (2.5%)	5 (1.8%)	12 (2.2%)
Optional samples collected without signed optional ICF	5 (1.8%)	4 (1.4%)	9 (1.6%)
ICF not signed by patient in timely manner	4 (1.4%)	4 (1.4%)	8 (1.4%)
SAE/AESI not reported in timely manner	4 (1.4%)	4 (1.4%)	8 (1.4%)
Week 4 missed	5 (1.8%)	2 (0.7%)	7 (1.3%)
Non-study staff performed assessment(s) at scheduled study visit	3 (1.1%)	2 (0.7%)	5 (0.9%)
Incorrect BCVA entered in IxRS leading to incorrect stratification	2 (0.7%)	2 (0.7%)	4 (0.7%)
Week 12 injection missed	1 (0.4%)	2 (0.7%)	3 (0.5%)
Incorrect IXRS data entry impacting treatment assignment	1 (0.4%)	1 (0.4%)	2 (0.4%)
Pt. treatment assignment inadvertently unmasked	1 (0.4%)	1 (0.4%)	2 (0.4%)
Investigator acting in dual role (masked/unmasked)	0	1 (0.4%)	1 (0.2%)
Pt. randomized without CRC confirmation of eligibility	1 (0.4%)	0	1 (0.2%)
Study treatment not administered because visit was beyond maximum visit window	0	1 (0.4%)	1 (0.2%)
Unmasked MD performed masked MD task	1 (0.4%)	0	1 (0.2%)
Week 16 injection missed	0	1 (0.4%)	1 (0.2%)
Week 20 injection missed	1 (0.4%)	0	1 (0.2%)
Week 64 injection missed	0	1 (0.4%)	1 (0.2%)
MEDICATION			
Total number of patients with at least one major protocol deviation	21 (7.6%)	26 (9.4%)	47 (8.5%)
Total number of major protocol deviations	34	39	73
Time window between 2 consecutive doses is < 21 days	12 (4.3%)	12 (4.3%)	24 (4.3%)

Category Description	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=276)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=277)	All Patients (N=553)
MEDICATION (cont.)			
SE: Study kit administered with temperature excursion error	7 (2.5%)	4 (1.4%)	11 (2.0%)
Received prohibited meds while on study treatment	2 (0.7%)	8 (2.9%)	10 (1.8%)
SE: medication error	1 (0.4%)	2 (0.7%)	3 (0.5%)
SE: intercepted medication error	0	1 (0.4%)	1 (0.2%)
EXCLUSION CRITERIA			
Total number of patients with at least one major protocol deviation	3 (1.1%)	8 (2.9%)	11 (2.0%)
Total number of major protocol deviations	3	8	11
SE: Increase of >= 10 letters in BCVA ETDRS score between screening and Day 1	1 (0.4%)	2 (0.7%)	3 (0.5%)
SE: Diagnosis of DR, DME, nAMD, GA, myopic choroidal neovascularization as assessed by investigator	0	2 (0.7%)	2 (0.4%)
Active cancer within 12 months prior to Day 1	0	1 (0.4%)	1 (0.2%)
Any systemic corticosteroid use within 1 month of the screening visit	1 (0.4%)	0	1 (0.2%)
SE: Prior or current treatment for macular edema; macular neovascularization, including DME and nAMD, etc	0	1 (0.4%)	1 (0.2%)
SE: Prior/current treatment for macular edema due to RVO, including anti-VEGF IVT for macular edema due to RVO	0	1 (0.4%)	1 (0.2%)
Stroke or myocardial infarction within 6 months prior to Day 1	0	1 (0.4%)	1 (0.2%)
Uncontrolled blood pressure on Day 1	1 (0.4%)	0	1 (0.2%)
INCLUSION CRITERIA			
Total number of patients with at least one major protocol deviation	4 (1.4%)	0	4 (0.7%)
Total number of major protocol deviations	4	0	4
SE: BCVA of 73 to 19 letters, inclusive on Day 1	3 (1.1%)	0	3 (0.5%)
SE: Foveal center-involved macular edema due to BRVO, diagnosed no longer than 4 months prior to the screening visit	1 (0.4%)	0	1 (0.2%)

AESI = Adverse Event of Special Interest; BCVA = Best-Corrected Visual Acuity; BRVO = Branch Retinal Vein Occlusion; CRC = Central Reading Center; CST = Central Subfield Thickness; DM = Diabetes Mellitus; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IXRS = Interactive voice or web Response System; MD = Doctor of Medicine; nAMD = neovascular Age-related Macular Degeneration; Pt = patient; SAE = Serious Adverse Event; SE = Study Eye; VA = Visual Acuity; VEGF = Vascular Endothelial Growth Factor.
Regular clinic staff refers to those who are not listed on the delegation log for this study. Missed injections refer to the cases when patients attended the visit but did not receive the injections due to reasons other than dose hold, such as unmasked physician was not available to complete treatment.
Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.
For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.

COMINO study

In the ITT population, 814 major protocol deviations were reported in 385 patients (52.8%): 186 patients (50.8%) in the faricimab Q4W to faricimab PTI arm and 199 patients (54.8%) in the aflibercept Q4W to faricimab PTI Q4W arm. Approximately 13.7% (112/814) of the major protocol deviations in the ITT population through Week 72 were related to COVID-19.
The majority of the major protocol deviations were procedural, with 'missed visits' (missed any of the Week 4, 8, 12, 16, 20, 24, 60, 64, 68 or 72 visits; 28.4% overall) and 'study eye: major issues with images (defined as any major issue that can prevent the assessment of any of optical coherence tomography [OCT], color fundus photographs [CFP] or fluorescein angiography [FA] images per the schedule of assessments; 13.6% overall,) being the most common major protocol deviations.
The incidence of 'missed visits' was 25.7% in the faricimab Q4W to faricimab PTI arm and 31.1% in the aflibercept Q4W to faricimab PTI arm.

The incidence of 'study eye: major issues with images' was 13.7% in the faricimab Q4W arm and 13.5% in the aflibercept Q4W arm (Table below).

The incidence of 'other significant procedural deviation issues' was 7.4% and 8.3% in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arm, respectively. This subcategory covers a variety of protocol deviations that were considered major, for safety or efficacy reasons, but were not covered by the pre-defined subcategories. Some examples of the nature of the protocol deviations included in this subcategory are: treatment administration performed by a role in the delegation log, but not by a retina specialist as per protocol that occurred at one site; last visit (Week 72) performed out of window; images not taken at the last visit (Week 72); split visits where key assessments were not repeated, among others.

During the study through Week 72, 30 patients (4.1%) had optional samples (plasma, aqueous humor, and/or Research Biosample Repository) collected without a signed optional ICF samples. These unconsented samples were destroyed and not analyzed or reported in any analysis.

Table 16. Summary of Major Protocol Deviations through Week 72, ITT Population

Category Description	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=366)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=363)	All Patients (N=729)
Total number of patients with at least one major protocol deviation	186 (50.8%)	199 (54.8%)	385 (52.8%)
Total number of major protocol deviations	383	431	814
PROCEDURAL			
Total number of patients with at least one major protocol deviation	172 (47.0%)	179 (49.3%)	351 (48.1%)
Total number of major protocol deviations	324	358	682
SE: Major issues with images	50 (13.7%)	49 (13.5%)	99 (13.6%)
Other significant procedural deviation issues	27 (7.4%)	30 (8.3%)	57 (7.8%)
Week 60 missed	18 (4.9%)	27 (7.4%)	45 (6.2%)
Week 20 missed	18 (4.9%)	23 (6.3%)	41 (5.6%)
Week 24 missed	19 (5.2%)	22 (6.1%)	41 (5.6%)
Week 68 missed	18 (4.9%)	20 (5.5%)	38 (5.2%)
Week 16 missed	17 (4.6%)	18 (5.0%)	35 (4.8%)
Week 12 missed	16 (4.4%)	17 (4.7%)	33 (4.5%)
Week 64 missed	13 (3.6%)	20 (5.5%)	33 (4.5%)
Optional samples collected without signed optional ICF	16 (4.4%)	14 (3.9%)	30 (4.1%)
SAE/AESI not reported in timely manner	14 (3.8%)	12 (3.3%)	26 (3.6%)
Week 72 missed	13 (3.6%)	12 (3.3%)	25 (3.4%)
ICF update not signed by patient in timely manner	13 (3.6%)	8 (2.2%)	21 (2.9%)
Week 8 missed	5 (1.4%)	12 (3.3%)	17 (2.3%)
Week 4 missed	9 (2.5%)	7 (1.9%)	16 (2.2%)
Non-study staff performed assessment(s) at scheduled study visit	1 (0.3%)	6 (1.7%)	7 (1.0%)
Incorrect BCVA entered in IxRS leading to incorrect stratification	4 (1.1%)	2 (0.6%)	6 (0.8%)
ICF not signed by patient in timely manner	3 (0.8%)	2 (0.6%)	5 (0.7%)
Masked MD performed unmasked MD task	1 (0.3%)	3 (0.8%)	4 (0.5%)
SE: ETDRS BCVA assessment not done or testing stopped too early Study eye	1 (0.3%)	3 (0.8%)	4 (0.5%)
Unmasked MD performed masked MD task	2 (0.5%)	2 (0.6%)	4 (0.5%)
Week 16 injection missed	2 (0.5%)	0	2 (0.3%)
Week 60 injection missed	2 (0.5%)	0	2 (0.3%)
Week 64 injection missed	1 (0.3%)	1 (0.3%)	2 (0.3%)
Incorrect IXRS data entry impacting treatment assignment	0	1 (0.3%)	1 (0.1%)
Investigator acting in dual role (masked/unmasked)	1 (0.3%)	0	1 (0.1%)
Pt. randomized without CRC confirmation of eligibility	0	1 (0.3%)	1 (0.1%)
Pt. treatment assignment inadvertently unmasked	1 (0.3%)	0	1 (0.1%)
Week 12 injection missed	0	1 (0.3%)	1 (0.1%)
Week 20 injection missed	1 (0.3%)	0	1 (0.1%)
Week 8 injection missed	1 (0.3%)	0	1 (0.1%)

Category Description	Faricimab 6 mg Q4W to Faricimab 6 mg PTI (N=366)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI (N=363)	All Patients (N=729)
MEDICATION			
Total number of patients with at least one major protocol deviation	36 (9.8%)	41 (11.3%)	77 (10.6%)
Total number of major protocol deviations	53	63	116
Time window between 2 consecutive doses is < 21 days	18 (4.9%)	22 (6.1%)	40 (5.5%)
SE: Study kit administered with temperature excursion error	4 (1.1%)	11 (3.0%)	15 (2.1%)
Received prohibited meds while on study treatment	8 (2.2%)	6 (1.7%)	14 (1.9%)
Non adherence to study treatment dose interruption	3 (0.8%)	2 (0.6%)	5 (0.7%)
Received prohibited concomitant medication or treatment to Study eye	2 (0.5%)	2 (0.6%)	4 (0.5%)
SE: medication error	1 (0.3%)	1 (0.3%)	2 (0.3%)
SE: intercepted medication error	1 (0.3%)	0	1 (0.1%)
EXCLUSION CRITERIA			
Total number of patients with at least one major protocol deviation	5 (1.4%)	8 (2.2%)	13 (1.8%)
Total number of major protocol deviations	5	8	13
SE: Increase of >= 10 letters in BCVA ETDRS score between screening and Day 1	2 (0.5%)	3 (0.8%)	5 (0.7%)
Uncontrolled blood pressure on Day 1	1 (0.3%)	3 (0.8%)	4 (0.5%)
Systemic treatment for suspected/ active systemic infection on Day 1	2 (0.5%)	0	2 (0.3%)
SE: Any other intraocular surgery	0	1 (0.3%)	1 (0.1%)
Stroke or myocardial infarction within 6 months prior to Day 1	0	1 (0.3%)	1 (0.1%)
INCLUSION CRITERIA			
Total number of patients with at least one major protocol deviation	1 (0.3%)	2 (0.6%)	3 (0.4%)
Total number of major protocol deviations	1	2	3
SE: Foveal center-involved macular edema due to BRVO, diagnosed no longer than 4 months prior to the screening visit	1 (0.3%)	1 (0.3%)	2 (0.3%)
SE: CST>=325 µm (Spectralis) or >=315 µm (Cirrus or Topcon) at screening	0	1 (0.3%)	1 (0.1%)

AESI = Adverse Event of Special Interest; BCVA = Best-Corrected Visual Acuity; BRVO = Branch Retinal Vein Occlusion; CRC = Central Reading Center; CST = Central Subfield Thickness; DM = Diabetes Mellitus; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = Informed Consent Form; IVT = Intravitreal; IXRS = Interactive voice or web Response System; MD = Doctor of Medicine; nAMD = neovascular Age-related Macular Degeneration; Pt = patient; SAE = Serious Adverse Event; SE = Study Eye; VA = Visual Acuity; VEGF = Vascular Endothelial Growth Factor.
Regular clinic staff refers to those who are not listed on the delegation log for this study. Missed injections refer to the cases when patients attended the visit but did not receive the injections due to reasons other than dose hold, such as unmasked physician was not available to complete treatment.
Major issues with images include: images not acquired according to study protocol, images not acquired at an attended study visit, images not submitted to/rejected by reading center, imaging performed by non-study certified personnel.
Percentages are based on N in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.
For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.

The MAH was subsequently requested to clarify the criteria used to decide the impact of major protocol deviations on the efficacy results (for determination of the per protocol population) in both BALATON and COMINO studies.

The list of major protocol deviations which could have an impact on the efficacy results is summarised in the Table 17 below.

In summary, major protocol deviations (that potentially introduced bias to BCVA assessments) pertained to specific inclusion/exclusion criteria that could impact the treatment effect, major protocol deviations for the receipt of prohibited therapy, or missed study treatment at specific timepoints. They were all considered as having the potential to impact the primary endpoint (change from baseline in BCVA) and therefore excluded from the per protocol analysis.

Table 17. Criteria Used to Assess Major Protocol Deviations that Impact Efficacy at Week 24 Major PD That Do Not Impact Efficacy Major PD That Impact Efficacy

Major PD That Do Not Impact Efficacy	Major PD That Impact Efficacy
1. Systemic treatment for suspected or active systemic infection on Day 1. [This could impact patient safety, not efficacy.]	14. BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters on Day 1.
2. Any systemic corticosteroid use (e.g., oral or injectable) within 1 month of the screening visit. [This could impact patient safety, not efficacy.]	15. Any other intraocular surgery (e.g., pars plana vitrectomy, scleral buckle, glaucoma surgery corneal transplant, or radiotherapy) in the study eye.
3. Uncontrolled blood pressure defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg while a patient is at rest on Day 1. [This could impact patient safety, not efficacy.]	16. Any prior or current treatment for macular edema due to RVO, including anti-VEGF IVT for macular edema due to RVO in the study eye.
4. Stroke or myocardial infarction within 6 months prior to Day 1. [This could impact patient safety, not efficacy.]	17. Diagnosis of DR moderate non-proliferative or worse, proliferative DR, DME, nAMD, geographic atrophy, myopic choroidal neovascularization as assessed by the investigator in the study eye.
5. ICF and ICF update not signed by patient in a timely manner.	18. Increase of ≥10 letters in BCVA ETDRS score between screening and Day 1 in the study eye.
6. Optional samples collected without signed optional ICF.	19. Patient randomized without central reading center confirmation of eligibility.
7. Incorrect BCVA total score reported to IxRS which caused incorrect stratification at randomization. [Very low percentage of patients were mis-stratified and their BCVA values used in the analyses were correct, hence this was not considered to impact efficacy [a].]	20. Medication error in study eye.
8. Intercepted medication error in the study eye. [The medication error was intercepted and did not cause a true medication error.]	21. Received prohibited concomitant medication or treatment to study eye.
9. Non-adherence to study treatment dose interruption. [Failing to comply with the study treatment interruption criteria could potentially have an impact on patient safety but would not directly impact efficacy.]	22. Received prohibited medications while on study treatment.
10. SAE/AESI not reported in a timely manner. [This could impact patient safety, not efficacy.]	23. Missing any dose/visit out of the 3 initial doses/visits, missing 2 consecutive doses/visits, or missing Week 20 dose/visit. [Greatest BCVA gains are seen during the initial 3 months. Maximum suppression of Ang-2 and VEGF levels in the aqueous for 8 weeks post injection of faricimab drives the 2 consecutive dose criteria. Week 20 is the visit prior to the primary endpoint at Week 24 hence missing dose is considered to impact efficacy.]

Major PD That Do Not Impact Efficacy	Major PD That Impact Efficacy
11. Major issues with images in study eye. [This would only impact the secondary endpoints of e.g., change in CST over time and other secondary anatomical endpoints, and not the primary endpoint for efficacy, i.e., BCVA.] 12. Study treatment not administered because visit was beyond maximum visit window. [If missed doses/visits, a separate major protocol deviation was reported.] 13. Time window between 2 consecutive doses is <21 days.	24. Patient treatment assignment is inadvertently unmasked to masked roles and/or patient.

Ang-2=angiopoietin-2 (protein); AESI=adverse events of special interest; BCVA=best-corrected visual acuity; CST=central subfield thickness; DME=diabetic macular edema; DR=diabetic retinopathy; ETDRS=Early Treatment Diabetic Retinopathy Study; ICF=informed consent form; IVT=intravitreal; IxRS=interactive web-based response system; nAMD=neovascular age-related macular degeneration; PD=protocol deviation; RVO=retinal vein occlusion; SAE=serious adverse event; VEGF=vascular endothelial growth factor

[a] 0.9% of patients (11/1282) across BALATON and COMINO were mis-stratified and their BCVA values used in the analyses were correct.

Baseline data

BALATON study

In the ITT population, baseline demographics were comparable between the treatment arms (Table 18). The overall mean age at randomization was **64.1 years** (**64.3 years** in the faricimab Q4W arm and **63.8 years** in the aflibercept Q4W arm) with half of patients (50.1%) in the < 65 years of age category. Half the patients (50.6%) were female. The majority of patients were white (62.2%), and of Not Hispanic or Latino ethnicity (81.0%). Patients were from the following regions: 'Rest of World', mostly consisting of European and South American countries (46.5%), Asia (30.7%), and US/Canada (22.8%).

Table 18. Baseline Demographics, ITT Population- BALATON study

Protocol: GR41984
Clinical Cutoff Date: 06JUL2022

	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=277)	All Patients (N=553)
Region			
n	276	277	553
Rest of the World	129 (46.7%)	128 (46.2%)	257 (46.5%)
Asia	85 (30.8%)	85 (30.7%)	170 (30.7%)
US and Canada	62 (22.5%)	64 (23.1%)	126 (22.8%)
Age (years)			
n	276	277	553
Mean (SD)	64.3 (10.7)	63.8 (10.6)	64.1 (10.7)
Median	65.0	64.0	64.0
Min - Max	35 - 93	28 - 88	28 - 93
Age group (years)			
n	276	277	553
<65	133 (48.2%)	144 (52.0%)	277 (50.1%)
>=65	143 (51.8%)	133 (48.0%)	276 (49.9%)
<65	133 (48.2%)	144 (52.0%)	277 (50.1%)
>=65 - <75	100 (36.2%)	93 (33.6%)	193 (34.9%)
>=75 - <85	33 (12.0%)	36 (13.0%)	69 (12.5%)
>=85	10 (3.6%)	4 (1.4%)	14 (2.5%)
Sex			
n	276	277	553
Female	133 (48.2%)	147 (53.1%)	280 (50.6%)
Male	143 (51.8%)	130 (46.9%)	273 (49.4%)
Ethnicity			
n	276	277	553
Not Hispanic or Latino	224 (81.2%)	224 (80.9%)	448 (81.0%)
Hispanic or Latino	47 (17.0%)	51 (18.4%)	98 (17.7%)
Unknown	4 (1.4%)	1 (0.4%)	5 (0.9%)
Not Reported	1 (0.4%)	1 (0.4%)	2 (0.4%)
Race			
n	276	277	553
American Indian or Alaska Native	3 (1.1%)	0	3 (0.5%)
Black or African American	6 (2.2%)	7 (2.5%)	13 (2.4%)
Native Hawaiian or other Pacific Islander	1 (0.4%)	0	1 (0.2%)
White	172 (62.3%)	172 (62.1%)	344 (62.2%)
Unknown	4 (1.4%)	4 (1.4%)	8 (1.4%)
Asian	90 (32.6%)	94 (33.9%)	184 (33.3%)
Chinese	41 (45.6%)	44 (46.8%)	85 (46.2%)
Taiwanese	0	0	0
Asian Indian	1 (1.1%)	2 (2.1%)	3 (1.6%)
Korean	29 (32.2%)	21 (22.3%)	50 (27.2%)
Malaysian	0	0	0
Vietnamese	0	0	0
Japanese	14 (15.6%)	22 (23.4%)	36 (19.6%)
Filipino	0	1 (1.1%)	1 (0.5%)
Other Asian	5 (5.6%)	4 (4.3%)	9 (4.9%)

Age is at randomization.
Asian origin percentages are based on the overall Asian denominator.
Ethnicity= not reported if it cannot collected due to local regulations.

COMINO study

In the ITT population, baseline demographics were comparable between treatment arms (Table 19). The overall mean age at randomization was 65.1 years (65.6 years in the faricimab Q4W arm and 64.7 years in the aflibercept Q4W arm) with the majority of patients (56.1%) in the ≥ 65 years of age category. The majority (53.9%) of patients were male, white (68.0%), and of Not Hispanic or Latino ethnicity (78.1%). Patients were from the following regions: 'Rest of World', mostly consisting of European and South American countries (51.3%), Asia (22.9%), and US/Canada (25.8%).

Table 19. Baseline Demographics, ITT Population-COMINO study

Protocol: GR41986
Clinical Cutoff Date: 09AUG2022

	Faricimab 6 mg Q4W (N=366)	Aflibercept 2 mg Q4W (N=363)	All Patients (N=729)
Region			
n	366	363	729
Rest of the World	187 (51.1%)	187 (51.5%)	374 (51.3%)
US and Canada	95 (26.0%)	93 (25.6%)	188 (25.8%)
Asia	84 (23.0%)	83 (22.9%)	167 (22.9%)
Age (years)			
n	366	363	729
Mean (SD)	65.6 (13.1)	64.7 (13.3)	65.1 (13.2)
Median	67.0	66.0	66.0
Min - Max	22 - 100	27 - 95	22 - 100
Age group (years)			
n	366	363	729
<65	162 (44.3%)	158 (43.5%)	320 (43.9%)
>=65	204 (55.7%)	205 (56.5%)	409 (56.1%)
<65	162 (44.3%)	158 (43.5%)	320 (43.9%)
>=65 - <75	113 (30.9%)	119 (32.8%)	232 (31.8%)
>=75 - <85	71 (19.4%)	74 (20.4%)	145 (19.9%)
>=85	20 (5.5%)	12 (3.3%)	32 (4.4%)
Sex			
n	366	363	729
Male	193 (52.7%)	200 (55.1%)	393 (53.9%)
Female	173 (47.3%)	163 (44.9%)	336 (46.1%)
Ethnicity			
n	366	363	729
Not Hispanic or Latino	286 (78.1%)	283 (78.0%)	569 (78.1%)
Hispanic or Latino	66 (18.0%)	73 (20.1%)	139 (19.1%)
Unknown	10 (2.7%)	3 (0.8%)	13 (1.8%)
Not Reported	4 (1.1%)	4 (1.1%)	8 (1.1%)
Race			
n	366	363	729
American Indian or Alaska Native	2 (0.5%)	3 (0.8%)	5 (0.7%)
Black or African American	10 (2.7%)	13 (3.6%)	23 (3.2%)
Native Hawaiian or other Pacific Islander	0	1 (0.3%)	1 (0.1%)
White	243 (66.4%)	253 (69.7%)	496 (68.0%)
Multiple	1 (0.3%)	0	1 (0.1%)
Unknown	21 (5.7%)	5 (1.4%)	26 (3.6%)
Asian	89 (24.3%)	88 (24.2%)	177 (24.3%)
Chinese	36 (40.4%)	33 (37.5%)	69 (39.0%)
Taiwanese	0	0	0
Asian Indian	1 (1.1%)	0	1 (0.6%)
Korean	21 (23.6%)	22 (25.0%)	43 (24.3%)
Malaysian	0	0	0
Vietnamese	1 (1.1%)	0	1 (0.6%)
Japanese	24 (27.0%)	27 (30.7%)	51 (28.8%)
Filipino	0	3 (3.4%)	3 (1.7%)
Other Asian	6 (6.7%)	3 (3.4%)	9 (5.1%)

Age is at randomization.
Asian origin percentages are based on the overall Asian denominator.
Ethnicity= not reported if it cannot collected due to local regulations.

The CHMP noted that slightly older patients were enrolled to the **Comino study:** the overall mean age at randomisation was 65.1 years (65.6 years in the faricimab Q4W arm and 64.7 years in the aflibercept Q4W arm) whereas in the **Balaton study**, the mean age of enrolled patients was 64.1 years (64.3 years in the faricimab Q4W arm and 63.8 years in the aflibercept Q4W arm).

The youngest age at enrolment across studies was 22, the oldest 100. Similar percentage of patients in both studies were male or female. The majority of patients were white and of Not Hispanic or Latino ethnicity.

In relation to age and gender, the CHMP agreed that the study populations can be considered as representative of the general population of patients with RVO. The majority of patients in both studies were in the > 65 years of age category, which is expected as the prevalence of RVO is strongly associated with increasing age. RVO is rarely seen in individuals younger than 50, but it is occurring more frequently in the older age group.

The prevalence did not differ significantly between sexes. In relation to ethnicity, white and of not Hispanic or Latino ethnicity is overrepresented in the studies. However, as clarified by the MAH, the

population pharmacokinetic (PopPK) analysis has shown no effect of race on the pharmacokinetics (PK, ocular and systemic) of faricimab; therefore the CHMP concluded that no differences in efficacy are excepted.

Baseline Disease Characteristics

BALATON study

Ocular
In the ITT population, baseline ocular characteristics were comparable between treatment arms (Table 20). Mean baseline BCVA in all patients was 57.6 letters: 57.5 and 57.6 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Mean baseline CST in all patients was 558.2 microns: 558.3 and 558.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively.

Table 20. Ocular Baseline Characteristics in the Study Eye, ITT Population-BALATON study

	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=277)	All Patients (N=553)
Study Eye			
n	276	277	553
Left	140 (50.7%)	127 (45.8%)	267 (48.3%)
Right	136 (49.3%)	150 (54.2%)	286 (51.7%)
Bilateral Eligibility			
n	0	0	0
Eye with worse BCVA selected	0	0	0
Eye with better BCVA selected	0	0	0
No difference in BCVA between eyes	0	0	0
Months since RVO diagnosis in the Study Eye			
n	271	275	546
Mean (SD)	1.26 (1.88)	1.65 (7.27)	1.46 (5.32)
Median	0.82	0.89	0.85
Min - Max	0.2 - 27.7	0.1 - 120.6	0.1 - 120.6
Unknown	5	2	7
BCVA (letters)			
n	276	277	553
Mean (SD)	57.50 (13.04)	57.64 (12.15)	57.57 (12.59)
Median	60.00	60.00	60.00
Min - Max	19.0 - 76.0	21.0 - 73.0	19.0 - 76.0
Missing/Invalid	0	0	0
BCVA (letters) categories			
n	276	277	553
<= 54 (20/80 or worse)	89 (32.2%)	90 (32.5%)	179 (32.4%)
>= 55 (20/80 or better)	187 (67.8%)	187 (67.5%)	374 (67.6%)
CST (ILM-BM) (microns)			
n	275	275	550
Mean (SD)	558.32 (177.03)	558.12 (180.26)	558.22 (178.49)
Median	518.00	506.00	511.50
Min - Max	281.0 - 1154.0	290.0 - 1208.0	281.0 - 1208.0
Missing/Ungradable	1	2	3
Macular Ischemic Non-Perfusion			
n	276	277	553
Yes	49 (17.8%)	48 (17.3%)	97 (17.5%)
No	70 (25.4%)	66 (23.8%)	136 (24.6%)
Missing/Ungradable	157 (56.9%)	163 (58.8%)	320 (57.9%)

	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=277)	All Patients (N=553)
Intraocular pressure (mmHg)			
n	276	277	553
Mean (SD)	14.57 (2.88)	14.48 (2.94)	14.52 (2.91)
Median	14.00	14.00	14.00
Min - Max	7.0 - 21.0	7.0 - 22.0	7.0 - 22.0
Lens Status			
n	276	276	552
Phakic	236 (85.5%)	239 (86.3%)	475 (85.9%)
Pseudophakic	40 (14.5%)	36 (13.0%)	76 (13.7%)
Aphakic	0	1 (0.4%)	1 (0.2%)
Other	0	0	0

BCVA=Best Corrected Visual Acuity; CRC = Central Reading Center; CST=Central Subfield Thickness; ILM = Internal Limiting Membrane.
Baseline is the last available value taken on or prior to randomization.
Invalid BCVA values are excluded from analysis. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by the CRC. Absence of
macular ischemic non perfusion is defined as an area of ischemic non perfusion within the macula of 0 to 0.1 mm2

Non-Ocular
In the ITT population, baseline non-ocular characteristics were comparable between treatment arms.

Prior Disease

Ocular Medical History
In the ITT population, the proportion of patients with at least one targeted prior ocular medical condition in the study eye was comparable between treatment arms (30.8% in the faricimab Q4W arm and 29.6% in the aflibercept Q4W arm).

General Medical History
In the ITT population, the majority of patients had at least one prior non-ocular condition(67.1%), and the proportions were comparable between treatment arms (65.6% in the faricimab Q4W arm and 68.6% in the aflibercept Q4W arm**.** The most common conditions were systemic hypertension (54.3% and 60.3%), Type 2 diabetes (17.8% and 16.6%), and diabetes mellitus uncomplicated (10.1% and 7.2%) in the faricimab Q4W and aflibercept Q4W
arms, respectively.

COMINO study

Baseline Disease Characteristics
Ocular
In the ITT population, baseline ocular characteristics were comparable between treatment arms (Table 21). Mean baseline BCVA in all patients was 50.5 letters: 50.3 and 50.7 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Mean baseline CST was 711.6 microns: 702.2 and 721.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Overall, 82.5% of patients had CRVO and 17.5% had HRVO, with the proportion of patients with CRVO or HRVO being comparable between treatment arms.
Baseline ocular characteristics in the study eye in the PP population were comparable with the ITT population and comparable between treatment arms.

Table 21 Ocular Baseline Characteristics in the Study Eye, ITT Population - Comino study

Protocol: GR41986
Clinical Cutoff Date: 09AUG2022

	Faricimab 6 mg Q4W (N=366)	Aflibercept 2 mg Q4W (N=363)	All Patients (N=729)
Study Eye			
n	366	363	729
Left	180 (49.2%)	181 (49.9%)	361 (49.5%)
Right	186 (50.8%)	182 (50.1%)	368 (50.5%)
Bilateral Eligibility			
n	0	0	0
Eye with worse BCVA selected	0	0	0
Eye with better BCVA selected	0	0	0
No difference in BCVA between eyes	0	0	0
Months since RVO diagnosis in the Study Eye			
n	360	352	712
Mean (SD)	1.57 (6.39)	1.10 (0.95)	1.34 (4.60)
Median	0.89	0.79	0.82
Min - Max	0.1 - 120.3	0.1 - 8.9	0.1 - 120.3
Unknown	6	11	17
BCVA (letters)			
n	366	363	729
Mean (SD)	50.25 (16.25)	50.71 (16.34)	50.48 (16.29)
Median	54.00	54.00	54.00
Min - Max	19.0 - 87.0	19.0 - 73.0	19.0 - 87.0
Missing/Invalid	0	0	0
BCVA (letters) categories			
n	366	363	729
<= 34 letters (20/200 or worse)	79 (21.6%)	80 (22.0%)	159 (21.8%)
>34 (better than 20/200) - <55 (worse than 20/80)	106 (29.0%)	105 (28.9%)	211 (28.9%)
>= 55 letters (20/80 or better)	181 (49.5%)	178 (49.0%)	359 (49.2%)
CST (ILM-BM) (microns)			
n	359	359	718
Mean (SD)	702.21 (244.00)	721.07 (242.86)	711.64 (243.44)
Median	668.00	701.00	684.00
Min - Max	266.0 - 1500.0	281.0 - 1419.0	266.0 - 1500.0
Missing/Ungradable	7	4	11
Macular Ischemic Non-Perfusion			
n	366	363	729
Yes	38 (10.4%)	37 (10.2%)	75 (10.3%)
No	194 (53.0%)	177 (48.8%)	371 (50.9%)
Missing/Ungradable	134 (36.6%)	149 (41.0%)	283 (38.8%)
Intraocular pressure (mmHg)			
n	366	363	729
Mean (SD)	14.89 (3.06)	14.97 (3.17)	14.93 (3.11)
Median	15.00	15.00	15.00
Min - Max	7.0 - 25.0	7.0 - 26.0	7.0 - 26.0
Lens Status			
n	366	363	729
Phakic	308 (84.2%)	314 (86.5%)	622 (85.3%)
Pseudophakic	57 (15.6%)	48 (13.2%)	105 (14.4%)
Aphakic	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	0	0	0
Retinal Vein Occlusion Subtype			
n	365	359	724
Central Retinal Vein Occlusion	303 (83.0%)	294 (81.9%)	597 (82.5%)
Hemiretinal Vein Occlusion	62 (17.0%)	65 (18.1%)	127 (17.5%)

BCVA=Best Corrected Visual Acuity; CRC = Central Reading Center; CST=Central Subfield Thickness; ILM = Internal Limiting Membrane.
Baseline is the last available value taken on or prior to randomization.
Invalid BCVA values are excluded from analysis. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by the CRC.
Absence of macular ischemic non perfusion is defined as an area of ischemic non perfusion within the macula of 0 to 0.1 mm2

Non-Ocular
In the ITT population, baseline non-ocular characteristics were comparable between treatment arms except for body mass index (BMI) categories. The proportion of patients in the BMI category of≥ 30 kg/m2 was lower in the faricimab Q4W arm (24.0% [88/366]) compared to the aflibercept Q4W arm (32.8% [119/363]).
Prior Disease

Ocular Medical History
In the ITT population, the proportion of patients with at least one targeted prior ocular medical condition in the study eye was comparable between treatment arms (42.6% in the faricimab Q4W arm and 39.9% in the aflibercept Q4W arm)

General Medical History
In the ITT population, the majority of patients had at least one targeted prior non-ocular condition (65.0%), and the proportions were comparable between treatment arms (64.5% in the faricimab Q4W arm and 65.6% in the aflibercept Q4W arm; the most common conditions were systemic hypertension (54.6%% and 56.2%), type 2 Diabetes (20.2% and 21.8%%) and diabetes mellitus uncomplicated (9.3% and 11.3%) in the faricimab Q4W and aflibercept Q4W arm, respectively.

In summary, the CHMP noted that both studies enrolled patients with a relatively short history from RVO diagnosis (i.e. less than 4 months as per the inclusion criteria). The mean time since diagnosis was 1.46 months in the Balaton study and 1.34 months in the Comino study). Single patients had a longer history, which represents the protocol deviation.

Both studies were aimed to enrol patients with BCVA of 73 to 19 letters at screening and with objective sign of macular oedema with central subfield thickness (CST) ≥325 µm, as measured on Spectralis SD-OCT. As indicated by the MAH patients with BCVA less than 19 are more likely to have disease-induced irreversible retinal damage and therefore unable to respond to the therapy. The MAH also clarified that a similar range was used in trials supporting the authorization of other anti-VGFs.

In the BALATON study the mean baseline BCVA in all patients was 57.6 letters (range 19 to 76): 57.5 and 57.6 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Mean baseline CST in all patients was 558.2 microns: 558.3 and 558.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively.

In the COMINO study more severe populations, with respect to the lower BCVA at enrolment and higher mean baseline CST, were enrolled. In this study mean baseline BCVA in all patients was 50.5 letters (range 19 to 87): 50.3 and 50.7 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Mean baseline CST was 711.6 microns: 702.2 and 721.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively.

Some patients (around 17% in the BALATON study and 10% in the COMINO study) had confirmed macular ischemic non-perfusion. The mean intraocular pressure was similar across studies (14 mmHg) but the maximum values reported were higher in the Comino study (up to 26 mmHg). Patients with macular ischemic non-perfusion is an important subgroup for which the efficacy result needs to be discussed.

The COMINO study enrolled patients with central retinal or hemi-retinal vein occlusion. The majority of patients (82%) enrolled had central retinal vein occlusion.

PRIOR AND CONCOMITANT THERAPY

BALATON study

Prior Medication

Prior Targeted Ocular Therapies/Treatments

In the ITT population, the proportion of patients that had received at least one targeted prior ocular therapy or treatment in the study eye was lower in the faricimab Q4W arm (2.9%) compared to the aflibercept Q4W arm (5.8%).

The reported treatments were 'other' prior ocular therapy (2.2% and 4.7%), other laser photocoagulation (0.7% and 0.4%), dietary supplement (0 and 0.4%), panretinal photocoagulation laser (PRP; 0 and 0.4%), and topical steroids (0 and 0.4%) in the faricimab Q4W and aflibercept Q4W arms, respectively. The "other" category comprised therapy used to treat prior concomitant anterior segment ocular conditions, which included dry eye syndrome, glaucoma and ocular hypertension.

Prior Surgeries and Procedures

Ocular

The proportion of patients with at least one prior ocular surgery/procedure in the study eye was comparable between treatment arms (17.4% in the faricimab Q4W arm and 16.6% in the aflibercept Q4W arm). Cataract surgery was the most common previous surgery/procedure in the ITT population (14.5% in the faricimab Q4W arm and 11.9% in the aflibercept Q4W arm).

Concomitant Medications

Concomitant Therapies and Treatments

Ocular

In the safety-evaluable population, the proportion of patients who had at least one concomitant treatment in the study eye was lower in the faricimab Q4W arm (13.8%) compared to the aflibercept Q4W arm (20.1%).

Overall, the most commonly reported concomitant treatments were in the category ophthalmologicals (13.0% in the faricimab Q4W arm and 20.1% in the aflibercept Q4W arm), in which topical ocular hypotensive medications such as latanoprost (1.8% and 1.8%), and dorzolamide hydrochloride/timolol maleate (1.8% and 1.8%) and ocular surface lubricants such as sodium hyaluronate (1.1% and 2.9%) were the most common treatments in the faricimab Q4W and aflibercept Q4W arms, respectively.

Concomitant Ocular Surgeries and Procedures

In the ITT population, 3 patients (1.1% in) the faricimab Q4W arm and no patients in the aflibercept Q4W arm and concurrent ocular surgery/procedure in the study eye. The concurrent ocular surgeries and procedures in the faricimab Q4W arm were panretinal photocoagulation (0.7%) and cataract surgery (0.4%).

COMINO study

Prior Medication

Prior Targeted Ocular Therapies/Treatments

In the ITT population, the proportion of patients that had received at least one targeted prior ocular therapy or treatment in the study eye was comparable between treatment arms (5.7% in the faricimab and 5.0% in the aflibercept Q4W arms; The reported treatments were 'other' prior ocular therapy (4.9% and 4.1%), other laser photocoagulation (0.5% and 0), dietary supplement (0.3% and 0.3%), panretinal photocoagulation laser (PRP; 0 and 0.3%), and topical steroids (0 and 0.3%) in the faricimab Q4W and aflibercept Q4W arms, respectively.

The "other" category comprised therapy used to treat prior concomitant anterior segment ocular conditions, which included dry eye syndrome, glaucoma and ocular hypertension.

Prior Surgeries and Procedures

Ocular
The proportion of patients with at least one prior ocular surgery/procedure in the study eye was comparable between treatment arms (17.5% in the faricimab Q4W arm and 15.2% in aflibercept Q4W arm. Cataract surgery was the most common previous surgery/procedure in the ITT population (15.0% in the faricimab Q4W arm and 11.6% in the aflibercept Q4W arm).

Concomitant Medications

Concomitant Therapies and Treatments

Ocular
In the safety-evaluable population, the proportion of patients who had at least one concomitant treatment in the study eye was comparable between treatment arms (24.7% in the faricimab Q4W arm and 25.2% in the aflibercept Q4W arm). Overall, the most commonly reported concomitant treatments were in the category ophthalmologicals (24.4% in the faricimab Q4W arm and 24.7% in the aflibercept Q4W arm), in which topical ophthalmic ocular hypotensive medications latanoprost (4.1% and 5.0%) and dorzolamide hydrochloride/timolol maleate combination (4.9% and 2.8%) eye drops were the most common treatments in the faricimab Q4W and aflibercept Q4W arms, respectively.

Concomitant Ocular Surgeries and Procedures
In the ITT population, 5 patients (1.4%) in the faricimab Q4W arm and 12 patients (3.3%) in the aflibercept Q4W arm had a concurrent ocular surgery/procedure in the study eye.
The most common concurrent ocular surgery and procedure was laser retinopexy (0.5% in the faricimab Q4W arm and 0.6% in the aflibercept Q4W arm)

The CHMP noted that, as per the exclusion criteria, any prior or current treatment/procedures for macular oedema due to RVO, and other types of macular oedema, were prohibited. Other therapies with no significant impact were allowed; however, the proportion of patients that had received at least one prior ocular therapy or treatment in the study eye was low in both studies (less than 6% in any treatment arm).
In addition, while in the study treatment for ocular hypertension or glaucoma, cataract or posterior capsular opacification and short-term use of topical ocular corticosteroids was allowed. The percentage of patients receiving concomitant therapies varied between studies and was most frequently reported in the Comino study (up to 25%) as compared to up to 17 % in the Balaton study. Ophthalmic ocular hypotensive medications were the most frequently used.

Numbers analysed

Table 22. Overview of Analysis Populations-Balaton study

Analysis Populations	Faricimab 6 mg Q4W to Faricimab 6 mg PTI	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI	All Patients
ITT Population (as Randomized)	276	277	553
Safety-Evaluable Population (as Treated)	276	274	550
Number of patients included for Part 2 safety analysis*	270	267	537
Per-Protocol Population (as Treated)	225	221	446
Pharmacokinetic-Evaluable Population (as Treated)	276	268	544
Immunogenicity-Analysis Population (as Treated)	276	275	551

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

Table 23. Overview of Analysis Populations- Comino study

Analysis Populations	Faricimab 6 mg Q4W to Faricimab 6 mg PTI	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI	All Patients
ITT Population (as Randomized)	366	363	729
Safety-Evaluable Population (as Treated)	365	361	726
Number of patients included for Part 2 safety analysis*	359	342	701
Per-Protocol Population (as Treated)	296	277	573
Pharmacokinetic-Evaluable Population (as Treated)	365	347	712
Immunogenicity-Analysis Population (as Treated)	366	363	729

ITT: Intent-to-Treat.
ITT Population: All patients who are randomized in the study.
Safety-Evaluable Population: All patients randomized in the study who received at least one injection of active study drug (faricimab or aflibercept) in the study eye.
Number of patients included for Part 2 safety analysis*: For the faricimab Q4W to faricimab PTI arm, all patients with Week 24 treatment or dose hold or if none follow-up beyond Day 168; For the aflibercept Q4W to faricimab PTI arm, all patients with a faricimab dose.
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.
Pharmacokinetic-Evaluable Population: All safety-evaluable patients randomized to faricimab arm or who received faricimab with at least one plasma sample, provided sufficient dosing information (dose and dosing time) is available.
Immunogenicity-Analysis Population: All patients with at least one determinant anti-drug antibody (ADA against faricimab) assessment.

Outcomes and estimation

BALATON study

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in BCVA at Week 24, with a positive number of letters indicating an improvement. BCVA is assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters.

At Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was **16.9** and **17.5** letters in the faricimab Q4W and aflibercept Q4W arms, respectively (Table 24); the difference was **−0.6 letters (95% CI: −2.2, 1.1).**

In the ITT population, patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W, as the lower bound of the 95% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than − 4 letters. Superiority for the primary endpoint was not met; patients treated with faricimab Q4W did not have a superior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W.

Table 24. Primary endpoint results - BALATON study

Week 24		
n	254	247
Adjusted Mean (SE)	16.9 (0.60)	17.5 (0.60)
95% CI for Adjusted Mean	(15.7, 18.1)	(16.3, 18.6)
Difference (vs. Aflibercept) in Adjusted Means (SE)	-0.6 (0.84)	
95% CI for Difference in Adjusted Means	(-2.2, 1.1)	
P-value (for superiority test)	0.4978	

Units: letters. 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 BCVA (continuous), baseline BCVA (<=54 letters vs. >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. 95% CI is a rounding of 95.03% CI.

Sensitivity and Supplementary Analysis of Primary Endpoint-Balaton study and Comino study

The primary analysis used a treatment policy strategy for all intercurrent events and was performed based on all observed data, with missing data imputed implicitly by the MMRM under the missing at random (MAR) assumption.

The following sensitivity/supplemental analyses were performed to assess the robustness of the main analysis, applying different handling strategies for analysis populations, intercurrent events, and missing data:

- **Multiple imputation:** the analysis was conducted following the same intercurrent events and handling of intercurrent events as the primary analysis. Missing BCVA assessments at Week 24 due to any reason were imputed via multiple imputation assuming MNAR and imputed using the worse outcomes. The analyses were performed using an analysis of covariance (ANCOVA) model with adjustment for the following covariates: treatment group, baseline BCVA (continuous), as well as randomization stratification factors.

  The use of MI imputing worse outcomes was considered reasonable by the CHMP. The MAH also explained that the form of the multiple imputation (MI) model was non-parametric using approximate Bayesian bootstrap method to impute missing change from baseline in BCVA at Week 24. From all the non-missing change from baseline in BCVA at Week 24, the 20th percentile was used to identify the worst (lowest) 20% values. The missing change from baseline in BCVA at Week 24 was imputed by randomly drawing samples without replacement from the worst 20% non-missing change from baseline in BCVA at Week 24.

- **Analysis based on the PP population:** the analysis was conducted following the same intercurrent events, handling of intercurrent events, handling of missing data and analysis method as the primary analysis, with the exception that the analysis will be based on the PP population.

  Analysis distinguishing COVID and non-COVID intercurrent events: the analysis was conducted following the same handling of missing data and analysis method as the primary analysis, with the exception that COVID-19 related intercurrent events and non-COVID-19 related intercurrent events were handled using a **hypothetical strategy and treatment policy strategy**, respectively.

  The rationale for applying the hypothetical strategy for COVID-19 related intercurrent events was to discard potentially confounding impacts of the pandemic and estimate the treatment effect in the absence of COVID-19, assuming COVID-19 will not be present or will not have the same

impact in the future. The rate of non-COVID-19 related intercurrent events was low and generally balanced across the treatment arms.

- **Hypothetical strategy for all intercurrent events**: the analysis was conducted following the same intercurrent events, handling of missing data and analysis method as the primary analysis, with the exception that all intercurrent events were handled using a hypothetical strategy, where all values were censored after the occurrence of the intercurrent events.

The CHMP noted that, for COVID related intercurrent events, a hypothetical approach was considered: data were censored at the time the IE occurred. A supplemental analysis applying a treatment policy strategy for non-COVID related intercurrent events and a hypothetical strategy for COVID related intercurrent events was also performed, and the results were consistent with the main analysis for the primary endpoint. This approach is agreeable.

BALATON study

The results of the sensitivity analyses (using multiple imputation) support the results of the primary analysis.

Table 25. Change from Baseline in BCVA in the Study Eye at Week 24- Balaton study

	Faricimab 6 mg Q4W Adjusted Mean (95% CI)	Afilbercept 2 mg Q4W Adjusted Mean (95% CI)	Difference in Adjusted Means (95% CI)
Mean (SE) Baseline BCVA [a]	57.5 (0.78)	57.6 (0.73)	—
Main Analysis – MMRM Method			
ITT population	16.9 (15.7, 18.1)	17.5 (16.3, 18.6)	–0.6 (–2.2, 1.1) [b]
Sensitivity Analysis – Multiple Imputation: ANCOVA Method			
ITT population	15.7 (14.3, 17.1)	15.7 (14.3, 17.2)	–0.1 (–1.9, 1.7)
Supplementary Analyses			
PP analysis – MMRM method; PP population	17.1 (15.8, 18.3)	17.4 (16.2, 18.6)	–0.3 (–2.1, 1.4)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	17.0 (15.8, 18.2)	17.5 (16.3, 18.7)	–0.5 (–2.1, 1.2)
Analysis of hypothetical strategy for all intercurrent events – MMRM method; ITT population	16.9 (15.7, 18.1)	17.5 (16.3, 18.7)	–0.6 (–2.3, 1.0)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MI=multiple imputation; MMRM=mixed model for repeated measures; MNAR=missing not at random; PP=per protocol; Q4W=every four weeks.

Notes: ITT population: faricimab Q4W=276; aflibercept Q4W=277. PP population: faricimab Q4W=241; aflibercept Q4W=243.

For the primary analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (≤ 54 letters vs. ≥ 55 letters), and region (United States and Canada, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI was a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA at Week 24 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (≤ 54 letters vs. ≥ 55 letters), and region (United States and Canada, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing primary endpoint BCVA assessments were imputed using MI assuming MNAR and imputed using the worse outcomes. Invalid BCVA values are excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the primary analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

For the analysis using a hypothetical strategy for all intercurrent events, the analysis was conducted following the same analysis method as the primary analysis except a hypothetical strategy was applied to the intercurrent events.

[a] The mean baseline BCVA values presented in this row are non-adjusted.

[b] For the primary analysis, if the lower bound of the 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.

Intercurrent Events for the Primary Estimand

Through Week 24, 2 patients (0.7%) in the faricimab Q4W arm and 2 patients (0.7%) in the aflibercept Q4W arm experienced at least one intercurrent event (Table 26). Of these, one patient in the faricimab Q4W arm experienced 'discontinuation of study treatment due to adverse events or lack of efficacy'. Of note, this patient did not discontinue study treatment due to lack of efficacy. One patient in the faricimab Q4W arm and two patients in the aflibercept Q4W arm received prohibited systemic treatment or prohibited therapy in the study eye.

Table 26. Summary of Intercurrent Events through Week 24, ITT Population-Balaton study

	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=277)
Patients with at least one type of intercurrent event*	2 (0.7%)	2 (0.7%)
Patients who discontinued study treatment due to adverse events (AEs) or lack of efficacy**	1 (0.4%)	0
Patients who received any prohibited systemic treatment or prohibited therapy in the study eye***	1 (0.4%)	2 (0.7%)

VEGF = Vascular Endothelial Growth Factor.
Percentages are based on N in the column headings.
*Includes events occurred on or prior to Week 24 treatment or if none on or prior to Day 181.
** Lack of Efficacy was determined by investigator judgment, with the terms lack of efficacy, progressive disease, disease relapse, or symptomatic deterioration qualifying as lack of efficacy.
***Prohibited therapy is concurrent use of any systemic anti-VEGF agents or any protocol defined prohibited study eye therapy.

COMINO study

Primary Efficacy Endpoint-Comino study

The primary efficacy endpoint is the change from baseline in BCVA at Week 24 (Table 27), with a positive number of letters indicating an improvement. Faricimab demonstrated non-inferiority to aflibercept on the primary endpoint, defined as the change from baseline in BCVA at Week 24 as measured on the ETDRS letter chart in patients with C/HRVO.

At Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.4 letters (95% CI: -2.5, 1.6). In this population, patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W, as the lower bound of the 95% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than -4 letters. Superiority for the primary endpoint was not met; patients treated with faricimab Q4W did not have a superior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W.

Sensitivity and Supplementary Analysis of Primary Endpoint (the same approach as in Balaton study, discussed above).

The CHMP noted that the results of the sensitivity analysis (using multiple imputation) support the results of the primary analysis.

Table 27. Change from Baseline in BCVA in the Study Eye at Week 24-Comino study

	Faricimab 6 mg Q4W Adjusted Mean (95% CI)	Aflibercept 2 mg Q4W Adjusted Mean (95% CI)	Difference in Adjusted Means (95% CI)
Mean (SE) Baseline BCVA [a]	50.2 (0.85)	50.7 (0.86)	—
Main Analysis – MMRM Method			
ITT population	16.9 (15.4, 18.3)	17.3 (15.9, 18.8)	–0.4 (–2.5, 1.6) [b]
Sensitivity Analysis – Multiple Imputation: ANCOVA Method			
ITT population	16.5 (14.6, 18.3)	16.6 (14.7, 18.4)	–0.1 (–2.2, 2.0)
Supplementary Analyses			
PP analysis – MMRM method; PP population	17.3 (15.8, 18.8)	18.4 (16.9, 19.9)	–1.1 (–3.2, 0.9)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	16.9 (15.5, 18.4)	17.4 (15.9, 18.8)	–0.4 (–2.5, 1.6)
Analysis of Hypothetical Strategy for All Intercurrent Events – MMRM method; ITT population	16.8 (15.4, 18.3)	17.3 (15.9, 18.8)	-0.5 (-2.5, 1.6)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MI=multiple imputation; MMRM=mixed model for repeated measures; MNAR=missing not at random; PP=per protocol; Q4W=every 4 weeks.

Notes: ITT population: faricimab Q4W=366; aflibercept Q4W=363. PP population: faricimab Q4W=328; aflibercept Q4W=311.

For the primary analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (≤34 letters, 35–54 letters, and ≥55 letters) and region (United States and Canada, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA at Week 24 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (≤34 letters, 35–54 letters, and ≥55 letters), and region (United States and Canada, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing primary endpoint BCVA assessments were imputed using MI assuming MNAR and imputed using the worse outcomes. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the primary analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

Intercurrent Events for the Primary Estimand
Through Week 24, 3 patients (0.8%) in the faricimab Q4W arm and 7 patients (1.9%) in the aflibercept Q4W arm experienced at least one intercurrent event (Table 28). Of these, three patients in the faricimab Q4W arm and 4 patients in the aflibercept Q4W arm experienced 'discontinuation of study treatment due to adverse events or lack of efficacy'. Of note, none of these patients discontinued study treatment due to lack of efficacy. The remaining 3 patients in the aflibercept Q4W arm received prohibited systemic treatment or prohibited therapy in the study eye.

Table 28. Summary of Intercurrent Events through Week 24, ITT Population-Comino study

	Faricimab 6 mg Q4W (N=366)	Aflibercept 2 mg Q4W (N=363)
Patients with at least one type of intercurrent event*	3 (0.8%)	7 (1.9%)
Patients who discontinued study treatment due to adverse events (AEs) or lack of efficacy**	3 (0.8%)	4 (1.1%)
Patients who received any prohibited systemic treatment or prohibited therapy in the study eye***	0	3 (0.8%)

VEGF = Vascular Endothelial Growth Factor.
Percentages are based on N in the column headings.
*Includes events occurred on or prior to Week 24 treatment or if none on or prior to Day 181.
** Lack of Efficacy was determined by investigator judgment, with the terms lack of efficacy, progressive disease, disease relapse, or symptomatic deterioration qualifying as lack of efficacy.
***Prohibited therapy is concurrent use of any systemic anti-VEGF agents or any protocol defined prohibited study eye therapy.

Secondary endpoint

BALATON study

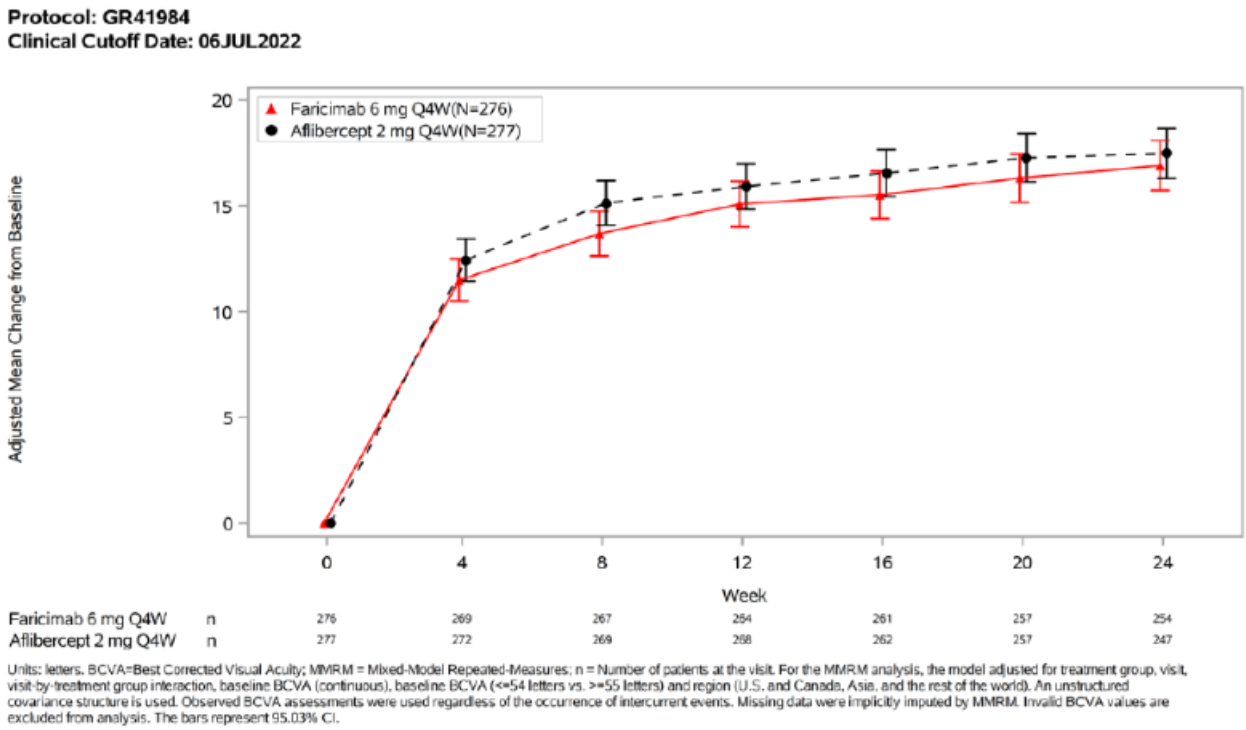
Secondary Efficacy Endpoints- Part 1 of the study

Binary secondary endpoints were analysed using the CMH method using missing data imputed using last observation carried forward (LOCF).
Nominal superiority p-values are included for secondary endpoints for reference purposes only. No formal superiority test was performed for secondary endpoints.

Additional BCVA Outcomes

Change from Baseline in BCVA over Time
The change from baseline in BCVA through Week 24 was comparable between the faricimab Q4W and aflibercept Q4W arms.

Figure 29. Change from Baseline in BCVA in the Study Eye through Week 24: MMRM Method, Primary Estimand, ITT Population- Balaton study



EMA note: please also refer to section 2.4.2 (Main studies) of this AR (justification for MMRM assumptions).

Proportion of Patients Gaining ≥ 15, ≥ 10, ≥ 5, or > 0 Letters in BCVA from Baseline at Week 24

A similar proportion of patients treated with faricimab Q4W gained ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 56.1% and 60.4% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was −4.3% (95% CI: −12.3%, 3.8%).

Similar results were also seen across the two treatment arms for patients gaining ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at Week 24.

Table 29. Proportion of Patients Gaining Letters by Category in BCVA from Baseline in the Study Eye at Week 24: CMH Method, ITT Population- BALATON study

		Faricimab 6 mg Q4W (N = 276)	Aflibercept 2 mg Q4W (N = 277)	Difference in CMH Weighted % Faricimab vs. Aflibercept
Gaining Letters by Category				
Main Analysis: Gaining ≥ 15 Letters in BCVA from BL	CMH weighted estimate	56.1%	60.4%	–4.3%
	(95% CI)	(50.4%, 61.9%)	(54.7%, 66.0%)	(–12.3%, 3.8%)
Supplementary Analysis: Gaining ≥ 15 Letters in BCVA from BL	CMH weighted estimate	52.5%	54.6%	–2.1%
	(95% CI)	(46.7%, 58.3%)	(48.9%, 60.3%)	(–10.2%, 6.1%)
Main Analysis: Gaining ≥ 10 Letters in BCVA from BL	CMH weighted estimate	77.5%	77.3%	0.2%
	(95% CI)	(72.6%, 82.4%)	(72.4%, 82.2%)	(–6.7%, 7.1%)
Main Analysis: Gaining ≥ 5 Letters in BCVA from BL	CMH weighted estimate	90.9%	89.6%	1.4%
	(95% CI)	(87.6%, 94.3%)	(86.0%, 93.1%)	(–3.5%, 6.3%)
Main Analysis: Gaining >0 Letters in BCVA from BL	CMH weighted estimate	97.1%	95.7%	1.4%
	(95% CI)	(95.2%, 99.1%)	(93.3%, 98.0%)	(–1.6%, 4.5%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; Q4W = every four weeks.

Notes: The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤ 54 letters vs. ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and estimates below 0% or above 100% were imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization. Invalid BCVA were excluded.

For the main analysis, all observed values were used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Proportion was calculated after LOCF imputation. N in the header is the number of patients randomized (used as the denominator when calculating proportion).

For the supplementary analysis, a composite variable strategy was applied where patients with any intercurrent event were assumed to be failures. Missing assessments at Week 24 were imputed using LOCF with the exception that for patients missing all three assessments at Week 16, Week 20, Week 24, who were imputed as failures.

Proportion of Patients Gaining ≥ 15, ≥ 10, ≥ 5, or > 0 Letters in BCVA from Baseline over Time

A similar proportion of patients treated with faricimab Q4W gained ≥ 15 letters from baseline through Week 24 compared with patients treated with aflibercept Q4W. Similar results were also seen across the two treatment arms for patients gaining ≥ 10, ≥ 5, or >0 letters in BCVA from baseline over time.

Proportion of Patients Avoiding a Loss of ≥ 15, ≥ 10, or ≥ 5 Letters in BCVA from Baseline at Week 24

A similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 99.6% and 98.6% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who avoided a loss of ≥ 15 letters from baseline between the faricimab Q4W arm, when compared to the aflibercept Q4W arm at Week 24, was 1.0% (95% CI: −0.5%, 2.6%). Similar results were also seen across the two treatment arms for patients avoiding a loss of ≥ 10 or ≥ 5 letters in BCVA from baseline at Week 24.

Table 30. Proportion of Patients Avoiding Loss of Letters by Category in BCVA from Baseline in the Study Eye at Week 24: CMH Method, ITT Population- Balaton study

		Faricimab 6 mg Q4W (N = 276)	Aflibercept 2 mg Q4W (N =277)	Difference in CMH Weighted % Faricimab vs. Aflibercept
Avoiding Loss of Letters by Category				
Main Analysis: Avoiding a Loss of ≥ 15 Letters in BCVA from BL	CMH weighted estimate (95% CI)	99.6% (98.9%, 100.0%)	98.6% (97.2%, 99.9%)	1.1% (–0.5%, 2.6%)
Supplementary Analysis: Avoiding a Loss of ≥ 15 Letters in BCVA from BL	CMH weighted estimate (95% CI)	91.7% (88.4%, 94.9%)	88.1% (84.3%, 91.8%)	3.6% (–1.4%, 8.6%)
Main Analysis: Avoiding a Loss of ≥ 10 Letters in BCVA from BL	CMH weighted estimate (95% CI)	99.6% (98.9%, 100.0%)	98.2% (96.7%, 99.7%)	1.4% (–0.3%, 3.1%)
Main Analysis: Avoiding a Loss of ≥ 5 Letters in BCVA from BL	CMH weighted estimate (95% CI)	98.6% (97.2%, 100.0%)	97.5% (95.7%, 99.3%)	1.1% (–1.2%, 3.4%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; Q4W = every four weeks

Notes: The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤ 54 letters vs. ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and 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. Invalid BCVA were excluded.

For the main analysis, all observed values were used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Proportion was calculated after LOCF imputation. N in the header is the number of patients randomized (used as the denominator when calculating proportion).

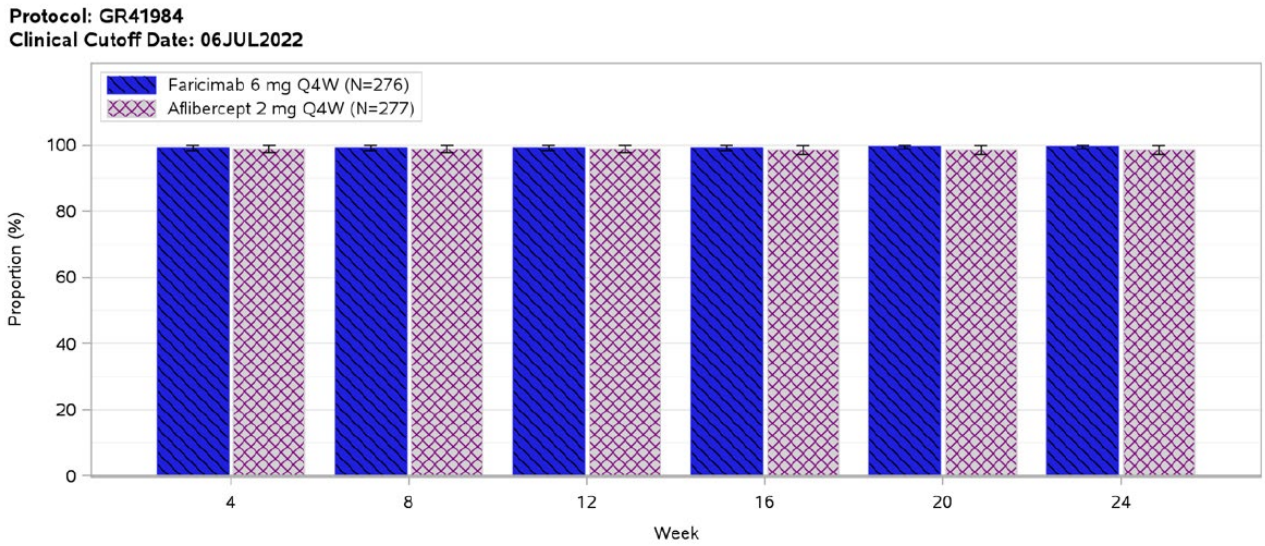
For the supplementary analysis, a composite variable strategy was applied where patients with any intercurrent event were assumed to be failures. Missing assessments at Week 24 were imputed using LOCF with the exception that for patients missing all three assessments at Weeks 16, 20, and 24, who were imputed as failures.

Proportion of Patients Avoiding a Loss of ≥ 15, ≥ 10, or ≥ 5 Letters in BCVA from Baseline over Time

A similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline through Week 24 compared with patients treated with aflibercept Q4W.

Similar results were also seen across the two treatment arms for patients avoiding a loss of ≥ 10 or ≥ 5 letters in BCVA from baseline over time.

Figure 30. Proportion of Patients Avoiding a Loss of ≥ 15 Letters in BCVA from Baseline in the Study Eye over Time through Week 24: CMH Method, ITT Population- BALATON study



BCVA = Best-corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward; The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95% confidence interval for the CMH weighted estimates.

Proportion of Patients Achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA over Time

At baseline, no patients had vision ≥ 84 letters in either treatment arm.

At Week 24, 22.9% and 23.8% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, achieved a BCVA equivalent of 20/20 or better (BCVA ≥ 84 letters).

Over time, a comparable proportion of patients treated with faricimab Q4W achieved a BCVA Snellen equivalent of 20/20 or better from baseline through Week 24 compared with patients treated with aflibercept Q4W.

Proportion of Patients with BCVA Snellen Equivalent of 20/40 or Better (BCVA ≥ 69 letters) over Time

At baseline, 20.3% of patients in the faricimab Q4W arm and 17.0% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better (BCVA ≥ 69 letters).

At Week 24, 73.7% of patients in the faricimab Q4W arm and 76.5% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better. Over time, a comparable proportion of patients treated with faricimab Q4W achieved BCVA Snellen equivalent of 20/40 or better compared with patients treated with aflibercept Q4W.

Proportion of Patients with BCVA Snellen Equivalent of 20/200 or Worse (BCVA ≤ 38 letters) over Time

At baseline, 10.9% and 9.7% of patients in the faricimab Q4W and aflibercept Q4W arms had 20/200 or worse (BCVA ≤ 38 letters) vision, respectively.

Beginning at Week 4, the proportion of patients with 20/200 or worse vision across both treatment arms stayed ≤ 4% at all timepoints through Week 24.

Anatomic Outcome Measures using SD-OCT

Change from Baseline in CST (ILM-BM) at Week 24

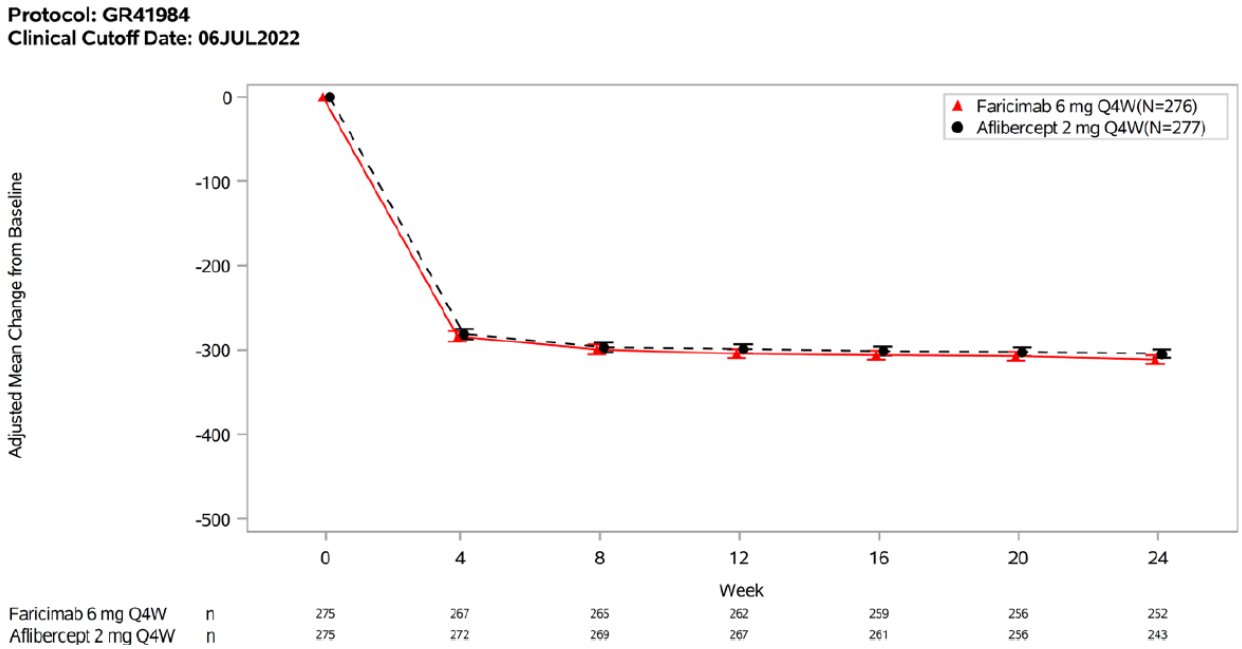
At baseline, the mean CST was 558. 3µm and 558.1 µm in the faricimab Q4W and aflibercept Q4W arms, respectively.

Patients treated with faricimab Q4W had comparable reductions in CST from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, the adjusted mean change from baseline in CST was −311.4 µm and −304.4 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −7.0 µm (95% CI: −14.1, 0).

Change from Baseline in CST (ILM-BM) over Time

Patients treated with faricimab Q4W consistently had comparable reductions in mean change from baseline in CST through Week 24 compared with the aflibercept Q4W arm.

Figure 31. Change from Baseline in CST (ILM-BM) in the Study Eye over Time through Week 24: MMRM Method, ITT Population- BALATON study



Units: microns. CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. The bars represent 95.03% CI. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by CRC.

Proportion of Patients with Absence of Macular Edema (CST < 325 µm) at Week 24

At baseline, 2.5% and 3.6% of patients in the faricimab Q4W and aflibercept Q4W arms had an absence of macular oedema in the central 1 mm, respectively.

A comparable proportion of patients treated with faricimab Q4W had an absence of macular oedema in the central 1 mm at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 95.3% and 93.9% of patients had an absence of macular oedema in the faricimab Q4W and aflibercept Q4W arms, respectively.

The difference in the adjusted proportion of patients who had an absence of macular oedema between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was 1.4% (95% CI: −2.3%, 5.0%).

Proportion of Patients with Absence of Macular Oedema (CST < 325 µm) over Time

Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of macular edema in the central 1 mm through Week 24 compared with patients treated with aflibercept Q4W.

Proportion of Patients with Absence of Intraretinal Fluid over Time
At baseline, 1.1% and 2.9% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had an absence of intraretinal fluid in the central 1 mm subfield.
Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of intraretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 72.5% and 66.0% of patients had an absence of intraretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who had an absence of intraretinal fluid between the faricimab Q4W arm, when compared to the aflibercept Q4W arm at Week 24, was 6.4% (95% CI: −1.2%, 14.0%).

Proportion of Patients with Absence of Subretinal Fluid over Time
At baseline, 33.3% and 33.2% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had an absence of subretinal fluid in the central 1 mm subfield.

Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of subretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 91.3% and 90.3% of patients had an absence of subretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who had an absence of subretinal fluid between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was 1.0% (95% CI: −3.7%, 5.8%).

Proportion of Patients with Absence of both Intraretinal Fluid and Subretinal Fluid over Time
At baseline, two patients (0.7%) in the faricimab Q4W arm and one patient (0.4%) in the aflibercept Q4W arm had an absence of both intraretinal fluid and subretinal fluid in the central 1 mm subfield.
Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of both intraretinal fluid and subretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 66.3% and 61.0% of patients had an absence of both intraretinal fluid and subretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively.
The difference in the adjusted proportion of patients who had an absence of both intraretinal fluid and subretinal fluid between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was 5.3% (95% CI: −2.7%, 13.3%).

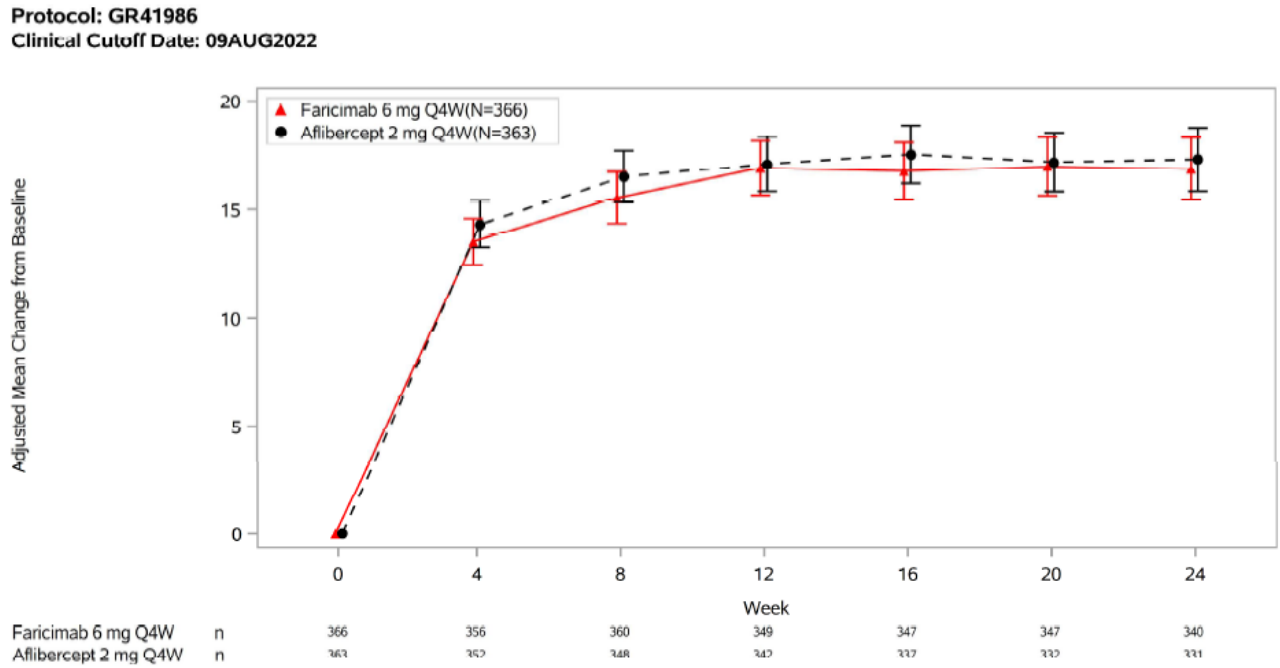
Patient-Reported Vision-Related Functioning and Quality of Life using NEI VFQ-25

Change from Baseline in NEI VFQ-25 Composite Score over Time
At baseline, the mean NEI VFQ-25 composite scores were 80.7 and 80.2 points out of a maximum score of 100 for the faricimab Q4W and aflibercept QW4 arms, respectively.
Patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W.
At Week 24, the adjusted mean change from baseline in NEI VFQ-25 composite score was 5.6 and 5.9 points in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted mean change from baseline in NEI VFQ-25 composite score between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was −0.4 points (95% CI: −1.9, 1.1).

COMINO study
Secondary Efficacy Endpoints
Binary secondary endpoints were analysed using the CMH method using missing data imputed using last observation carried forward (LOCF). Nominal superiority p-values are included for secondary endpoints for reference purposes only. No formal superiority test was performed for secondary endpoints.

Additional BCVA Outcomes
Change from Baseline in BCVA over Time
The change from baseline in BCVA through Week 24 was comparable between the faricimab Q4W and aflibercept Q4W arms.

Figure 32. Change from Baseline in BCVA in the Study Eye through Week 24: MMRM Method, Primary Estimand, ITT Population-Comino study



Proportion of Patients Gaining ≥ 15, ≥ 10, ≥ 5, or > 0 Letters in BCVA from Baseline at Week 24

A similar proportion of patients treated with faricimab Q4W gained ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 56.6% and 58.1% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was -1.5% (95% CI: -8.4%, 5.3%).

Similar results were also seen across the two treatment arms for patients gaining ≥ 10, ≥ 5, or >0 letters in BCVA from baseline at Week 24.

Table 31. Proportion of Patients Gaining Letters by Category in BCVA from Baseline in the Study Eye at Week 24: CMH Method, ITT Population-Comino study

		Faricimab 6 mg Q4W (N = 366)	Aflibercept 2 mg Q4W (N = 363)	Difference in CMH Weighted % Faricimab vs. Aflibercept
Gaining Letters by Category				
Main Analysis: Gaining ≥ 15 Letters in BCVA from BL	CMH weighted estimate	56.6%	58.1%	–1.5%
	(95% CI)	(51.7%, 61.5%)	(53.3%, 62.9%)	(–8.4%, 5.3%)
Supplementary Analysis: Gaining ≥ 15 Letters in BCVA from BL	CMH weighted estimate	54.1%	55.1%	–1.0%
	(95% CI)	(49.2%, 59.0%)	(50.2%, 59.9%)	(–7.9%, 6.0%)
Main Analysis: Gaining ≥ 10 Letters in BCVA from BL	CMH weighted estimate	72.2%	73.3%	–1.1%
	(95% CI)	(67.7%, 76.6%)	(68.8%, 77.7%)	(–7.4%, 5.2%)
Main Analysis Gaining ≥ 5 Letters in BCVA from BL	CMH weighted estimate	85.3%	84.6%	0.7%
	(95% CI)	(81.8%, 88.8%)	(80.9%, 88.2%)	(–4.3%, 5.8%)
Main Analysis: Gaining > 0 Letters in BCVA from BL	CMH weighted estimate	91.6%	89.8%	1.8%
	(95% CI)	(88.8%, 94.3%)	(86.7%, 92.9%)	(–2.4%, 5.9%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; Q4W = every four weeks.

Notes: The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤ 34 letters, 34–54 letters, and ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and estimates below 0% or above 100% were imputed as 0% or 100% respectively. Baseline is defined as the last available measurement obtained on or prior to randomization. Invalid BCVA were excluded.

For the main analysis, all observed values were used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Proportion was calculated after LOCF imputation. N in the header is the number of patients randomized (used as the denominator when calculating proportion).

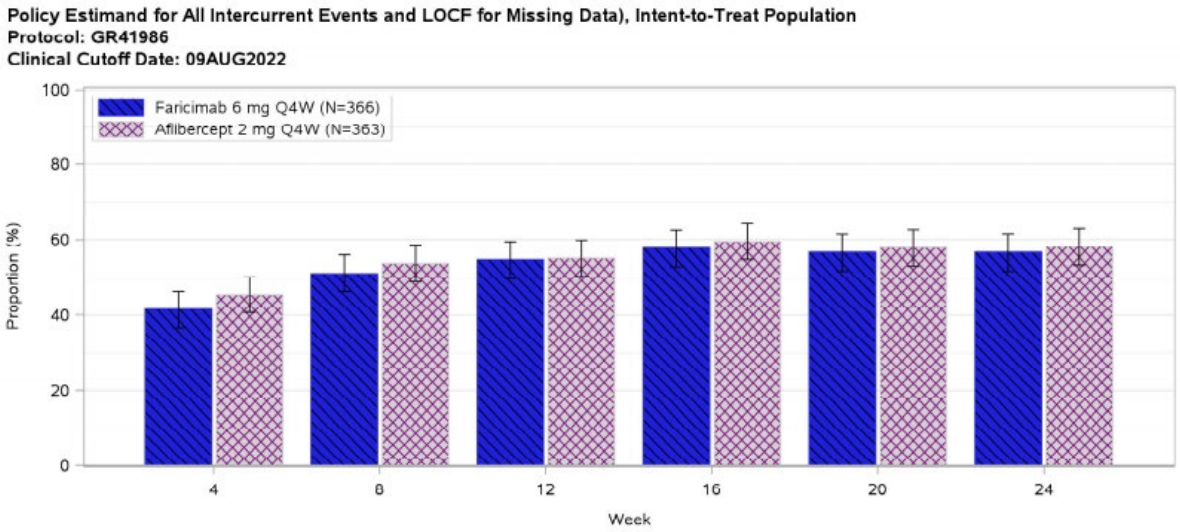
For the supplementary analysis, a composite variable strategy was applied where patients with any intercurrent event were assumed to be failures. Missing assessments at Week 24 were imputed using LOCF with the exception that for patients missing all three assessments at Week 16, Week 20, Week 24, who were imputed as failures.

Proportion of Patients Gaining ≥ 15, ≥ 10, ≥ 5, or > 0 Letters in BCVA from Baseline over Time

A similar proportion of patients treated with faricimab Q4W gained ≥ 15 letters from baseline through Week 24 compared with patients treated with aflibercept Q4W.

Similar results were also seen across the two treatment arms for patients gaining ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline over time.

Figure 33. Proportion of Patients Gaining ≥ 15 Letters from Baseline in BCVA in the Study Eye over Time through Week 24: CMH Method, Primary Estimand, ITT Population - COMINO study



BCVA = Best-corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward; The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95% confidence interval for the CMH weighted estimates.

Proportion of Patients Avoiding a Loss of ≥ 15, ≥ 10, ≥ 5 Letters in BCVA from Baseline at Week 24.

A similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 96.2% and 96.7% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who avoided a loss of ≥ 15 letters from baseline between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was -0.5% (95% CI: -3.2%, 2.2%).

Similar results were also seen across the two treatment arms for patients avoiding a loss of ≥ 10 or ≥ 5 letters in BCVA from baseline at Week 24.

Table 32. Proportion of Patients Avoiding Loss of Letters by Category in BCVA from Baseline in the Study Eye at Week 24: CMH Method, ITT Population-Comino study

		Faricimab 6 mg Q4W (N = 366)	Aflibercept 2 mg Q4W (N =363)	Difference in CMH Weighted % Faricimab vs. Aflibercept
Avoiding Loss of Letters by Category				
Main Analysis: Avoiding a Loss of ≥ 15 Letters in BCVA from BL	CMH weighted estimate (95% CI)	96.2% (94.3%, 98.1%)	96.7% (94.9%, 98.5%)	–0.5% (–3.2%, 2.2%)
Supplementary Analysis: Avoiding a Loss of ≥ 15 Letters in BCVA from BL	CMH weighted estimate (95% CI)	90.4% (87.5%, 93.4%)	89.0% (85.8%, 92.2%)	1.5% (–2.9%, 5.8%)
Main Analysis: Avoiding a Loss of ≥ 10 Letters in BCVA from BL	CMH weighted estimate (95% CI)	95.1% (92.9%, 97.3%)	95.9% (93.8%, 97.9%)	–0.8% (–3.7%, 2.2%)
Main Analysis: Avoiding a Loss of ≥ 5 Letters in BCVA from BL	CMH weighted estimate (95% CI)	94.0% (91.6%, 96.4%)	93.7% (91.2%, 96.1%)	0.4% (–3.1%, 3.8%)

BCVA = best-corrected visual acuity; BL = baseline; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; Q4W = every four weeks.

Notes: The weighted estimate was based on CMH weights stratified by baseline BCVA score (≤ 34 letters, 35–54 letters, and ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). 95% CI is a rounding of 95.03% CI and 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. Invalid BCVA were excluded.

For the main analysis, all observed values were used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Proportion was calculated after LOCF imputation. N in the header is the number of patients randomized (used as the denominator when calculating proportion).

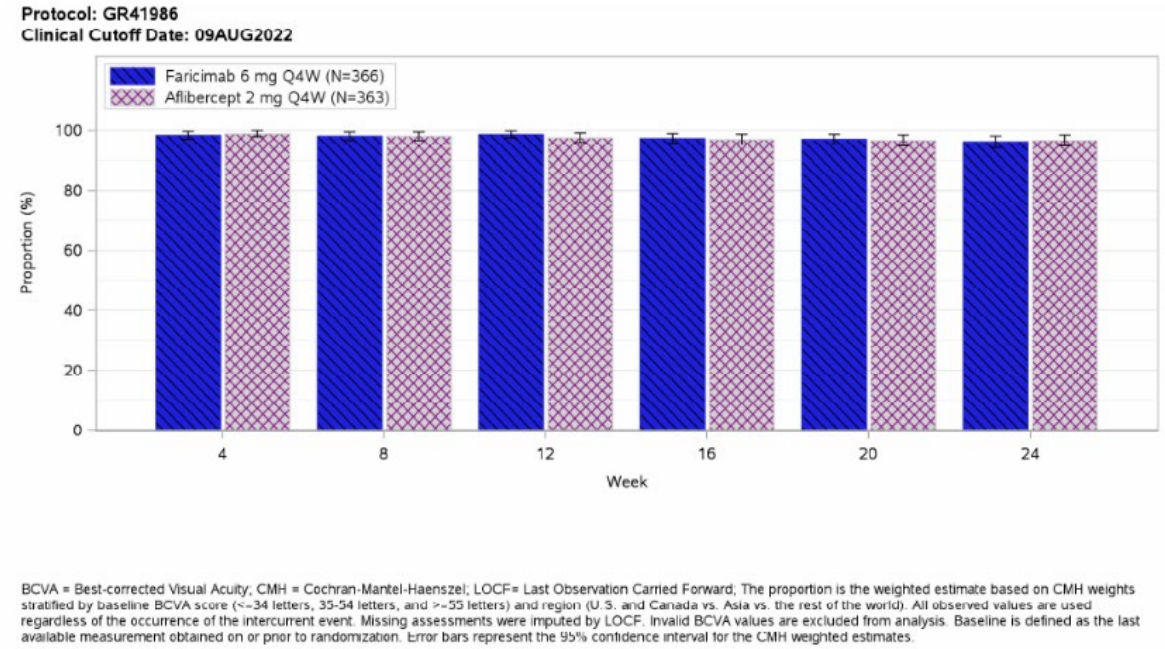
For the supplementary analysis, a composite variable strategy was applied where patients with any intercurrent event were assumed to be failures. Missing assessments at Week 24 were imputed using LOCF with the exception that for patients missing all three assessments at Weeks 16, 20, and 24, who were be imputed as failures.

Proportion of Patients Avoiding a Loss of ≥ 15, ≥ 10, or ≥ 5 Letters in BCVA from Baseline over Time

A similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline through Week 24 compared with patients treated with aflibercept Q4W.

Similar results were also seen across the two treatment arms for patients avoiding a loss of ≥ 10, or ≥5 letters in BCVA from baseline over time.

Figure 34. Proportion of Patients Avoiding a Loss of ≥ 15 Letters in BCVA from Baseline in the Study Eye over Time through Week 24: CMH Method, ITT Population - COMINO study



BCVA = Best-corrected Visual Acuity; CMH = Cochran-Mantel-Haenszel; LOCF= Last Observation Carried Forward; The proportion is the weighted estimate based on CMH weights stratified by baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada vs. Asia vs. the rest of the world). All observed values are used regardless of the occurrence of the intercurrent event. Missing assessments were imputed by LOCF. Invalid BCVA values are excluded from analysis. Baseline is defined as the last available measurement obtained on or prior to randomization. Error bars represent the 95% confidence interval for the CMH weighted estimates.

Proportion of Patients Achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA over Time
At baseline, there was one patient with vision of 87 letters that was randomized in error but did not receive any treatment and discontinued the study early. There were no other patients with vision ≥ 84 letters at baseline in either treatment arm.
At Week 24, 14.5% and 15.2% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, achieved a BCVA Snellen equivalent of 20/20 or better (BCVA ≥ 84 letters). Over time, a comparable proportion of patients treated with faricimab Q4W achieved a BCVA Snellen equivalent of 20/20 or better from baseline through Week 24 compared with patients treated with aflibercept Q4W.

Proportion of Patients with BCVA Snellen Equivalent of 20/40 or Better (BCVA ≥ 69 letters) over Time
At baseline, 11.7% of patients in the faricimab Q4W arm and 13.5% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better (BCVA ≥ 69 letters).
At Week 24, 55.7% of patients in the faricimab Q4W arm and 59.0% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better. Over time, a comparable proportion of patients treated with faricimab Q4W achieved BCVA Snellen equivalent of 20/40 or better compared with patients treated with aflibercept Q4W.

Proportion of Patients with BCVA Snellen Equivalent of 20/200 or Worse (BCVA ≤ 38 letters) over Time
At baseline, 27.0% and 26.7% of patients in the faricimab Q4W and aflibercept Q4W arms had 20/200 or worse (BCVA ≤ 38 letters) vision, respectively.
Beginning at Week 4, the proportion of patients with 20/200 or worse vision across both treatment arms stayed ≤ 11% at all timepoints through Week 24.

Anatomic Outcome Measures using SD-OCT

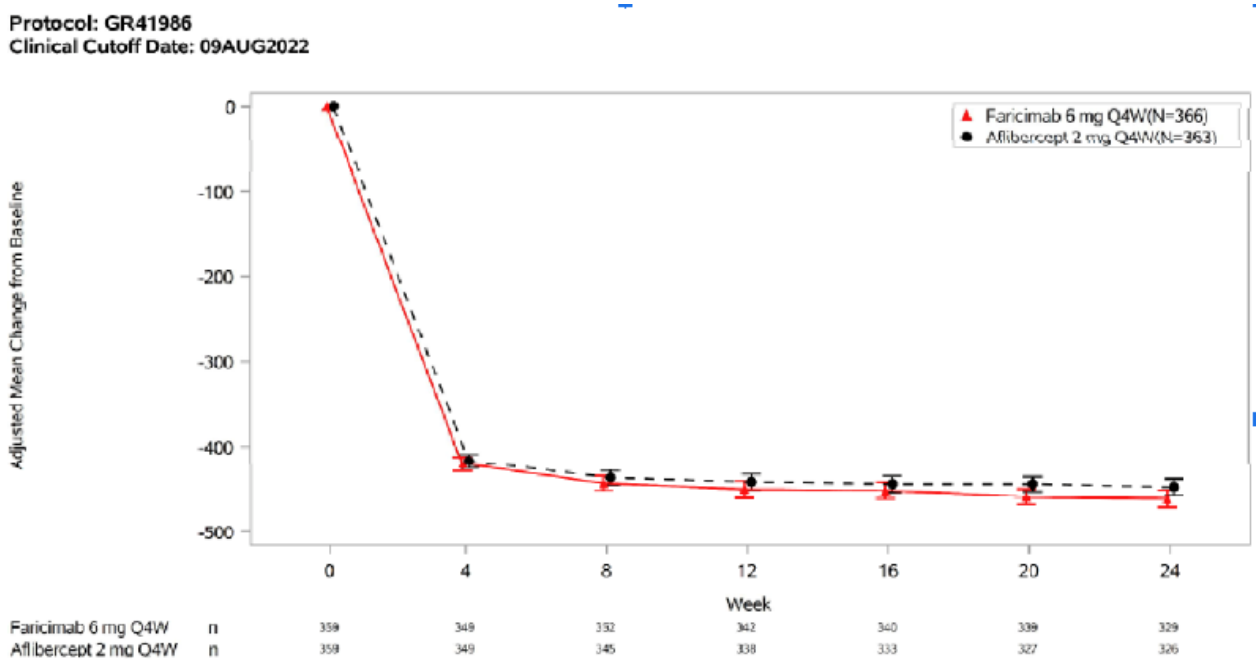
Change from Baseline in CST (ILM-BM) at Week 24
At baseline, the mean CST was 702.2 µm and 721.1 µm in the faricimab Q4W and aflibercept Q4W arms, respectively.

Patients treated with faricimab Q4W had comparable reductions in CST from baseline at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, the adjusted mean change from baseline in CST was −461.6 µm and −448.8 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −12.8 µm (95% CI: −26.7, 1.0).

Change from Baseline in CST (ILM-BM) over Time

Patients treated with faricimab Q4W consistently had comparable reductions in mean change from baseline in CST through Week 24 compared with the aflibercept Q4W arm.

Figure 35. Change from Baseline in CST (ILM-BM) in the Study Eye over Time through Week 24: MMRM Method, ITT Population - COMINO study



Units: microns. CRC = Central Reading Center; CST = Central Subfield Thickness; ILM = Internal Limiting Membrane; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. The bars represent 95.03% CI. CST is defined as the distance between ILM and Bruch's membrane (BM) as assessed by CRC.

Proportion of Patients with Absence of Macular Edema (CST <325 µm) at Week 24

At baseline, 4.1% and 2.5% of patients in the faricimab Q4W and aflibercept Q4W arms had an absence of macular edema in the central 1 mm, respectively.

A comparable proportion of patients treated with faricimab Q4W had an absence of macular oedema in the central 1 mm at Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 93.7% and 92.0% of patients had an absence of macular oedema in the faricimab Q4W and aflibercept Q4W arms, respectively.

The difference in the adjusted proportion of patients who had an absence of macular oedema between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was 1.7% (95% CI: -2.0%, 5.4%).

Proportion of Patients with Absence of Macular Edema (CST -325 µm) over Time

Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of macular oedema in the central 1 mm through Week 24 compared with patients treated with aflibercept Q4W.

Proportion of Patients with Absence of Intraretinal Fluid over Time

At baseline, 3.3% and 1.9% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had an absence of intraretinal fluid in the central 1 mm subfield.

Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of intraretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 76.2% and 70.8% of patients had an absence of intraretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively). The difference in the adjusted proportion of patients who had an absence of intraretinal fluid between the faricimab Q4W arm when compared to the aflibercept Q4W arm was 5.4% (95% CI: -0.9%, 11.7%) at Week 24.

Proportion of Patients with Absence of Subretinal Fluid over Time
At baseline, 24.3% and 19.0% of patients in the faricimab Q4W and aflibercept Q4W arms, respectively, had an absence of subretinal fluid in the central 1 mm subfield.
Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of subretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 96.4% and 93.4% of patients had an absence of subretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who had an absence of subretinal fluid between the faricimab Q4W arm when compared to the aflibercept Q4W arm was 3.1% (95% CI: -0.1%, 6.2%) at Week 24.

Proportion of Patients with Absence of both Intraretinal Fluid and Subretinal Fluid over Time
At baseline, 7 patients (1.9%) and 3 patients (0.8%) in the faricimab Q4W and aflibercept Q4W arms, respectively, had an absence of both intraretinal fluid and subretinal fluid in the central 1 mm subfield.
Over time, a comparable proportion of patients treated with faricimab Q4W had an absence of both intraretinal fluid and subretinal fluid from baseline through Week 24 compared with patients treated with aflibercept Q4W. At Week 24, 75.1% and 68.6% of patients had an absence of both intraretinal fluid and subretinal fluid in the faricimab Q4W and aflibercept Q4W arms, respectively.
The difference in the adjusted proportion of patients who had an absence of both intraretinal fluid and subretinal fluid between the faricimab Q4W arm when compared to the aflibercept Q4W arm at Week 24 was 6.5% (95% CI: 0.1%, 13.0%).

Patient-Reported Vision-Related Functioning and Quality of Life using NEI VFQ-25

Change from Baseline in NEI VFQ-25 Composite Score over Time
At baseline, the mean NEI VFQ-25 composite scores were 76.6 and 76.9 points out of a maximum score of 100 for the faricimab Q4W and aflibercept Q4W arms, respectively.
Patients treated with faricimab Q4W had comparable mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W.
At Week 24, the adjusted mean changes from baseline in NEI VFQ-25 composite score was 6.9 and 8.1 points in the faricimab Q4W and aflibercept Q4W arms, respectively.
The difference in the adjusted mean change from baseline in NEI VFQ-25 composite score between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24, was −1.2 points (95% CI: −2.7, 0.3).

Secondary Efficacy Endpoints- Part 2 -BALATON and COMINO study

Change from Baseline in BCVA after week 24
The adjusted mean change from baseline in BCVA through Week 24 was comparable between the faricimab and aflibercept arms in both BALATON and COMINO studies. In the **BALATON study**, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 18.1 and 18.8 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

Table 33. Change from Baseline in BCVA in the Study Eye at Week 64/68/72-BALATON study

	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Adjusted Mean (95% CI)	Afilbercept 2 mg Q4W to Faricimab 6 mg PTI Adjusted Mean (95% CI)
Mean (SE) Baseline BCVA [a]	57.5 (0.78)	57.7 (0.73)
Main Analysis – MMRM Method		
ITT population	18.1 (16.9, 19.4)	18.8 (17.5, 20.0)
Sensitivity Analysis – Multiple Imputation: ANCOVA Method		
ITT population	16.5 (15.0, 18.0)	17.1 (15.5, 18.6)
Supplementary Analyses		
PP analysis – MMRM method; PP population	18.3 (17.0, 19.7)	19.4 (18.0, 20.7)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	18.2 (16.9, 19.5)	18.9 (17.6, 20.2)
Analysis of Hypothetical Strategy for All Intercurrent Events – MMRM method; ITT population	18.2 (16.9, 19.5)	18.8 (17.5, 20.1)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MMRM=mixed model for repeated measures; PP=per protocol; PTI = personalized treatment interval; Q4W=every 4 weeks; SE = standard error.

Notes:
ITT population: faricimab Q4W to faricimab PTI=276; aflibercept Q4W to faricimab PTI=277. PP population: faricimab Q4W to faricimab PTI=225; aflibercept Q4W to faricimab PTI=221.

For the main analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (≤ 54 letters and ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA averaged over Weeks 64, 68 and 72 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (≤ 54 letters and ≥ 55 letters), and region (United States and Canada, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing post-baseline BCVA assessments were imputed using multiple imputation (MI) assuming missing not at random (MNAR) and imputed using the worse outcomes. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

For the analysis using a hypothetical strategy for all intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a hypothetical strategy was applied to the intercurrent events.

[a] The mean baseline BCVA values presented in this row are non-adjusted.

In **the COMINO study**, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.1 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

Table 34. Change from Baseline in BCVA in the Study Eye at Week 64/68/72

	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Adjusted Mean (95% CI)	Afilbercept 2 mg Q4W to Faricimab 6 mg PTI Adjusted Mean (95% CI)
Mean (SE) Baseline BCVA [a]	50.2 (0.85)	50.7 (0.86)
Main Analysis – MMRM Method		
ITT population	16.9 (15.2, 18.6)	17.1 (15.4, 18.8)
Sensitivity Analysis – Multiple Imputation: ANCOVA Method		
ITT population	16.3 (14.1, 18.6)	16.3 (14.2, 18.5)
Supplementary Analyses		
PP analysis – MMRM method; PP population	18.5 (16.8, 20.3)	18.6 (16.8, 20.4)
Analysis of distinguishing COVID and non-COVID intercurrent events – MMRM method; ITT population	16.9 (15.2, 18.6)	17.0 (15.3, 18.8)
Analysis of Hypothetical Strategy for All Intercurrent Events – MMRM method; ITT population	16.9 (15.2, 18.6)	17.0 (15.2, 18.7)

ANCOVA=analysis of covariance; BCVA=best corrected visual acuity; COVID=coronavirus disease; ITT=intent-to-treat; MMRM=mixed model for repeated measures; PP=per protocol; PTI = personalized treatment interval; Q4W=every 4 weeks; SE = standard error.

Notes:

ITT population: faricimab Q4W to faricimab PTI=366; aflibercept Q4W to faricimab PTI=363. PP population: faricimab Q4W to faricimab PTI=296; aflibercept Q4W to faricimab PTI=277.

For the main analysis, an MMRM analysis was performed; the model was adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (≤54letters and ≥55 letters) and region (United States and Canada, Asia, and the rest of the world). An unstructured covariance structure was used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

For the sensitivity analysis using MI, an ANCOVA analysis was performed; the model used the non-missing change from baseline in BCVA averaged over Weeks 64, 68 and 72 as the response variable adjusted for the treatment group, baseline BCVA (continuous), baseline BCVA score (≤54 letters and ≥55 letters), and region (United States and Canada, Asia, and the rest of the world). Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing post-baseline endpoint BCVA assessments were imputed using multiple imputation (MI) assuming missing not at random (MNAR) and imputed using the worse outcomes. Invalid BCVA values were excluded from analysis. 95% CI is a rounding of 95.03% CI.

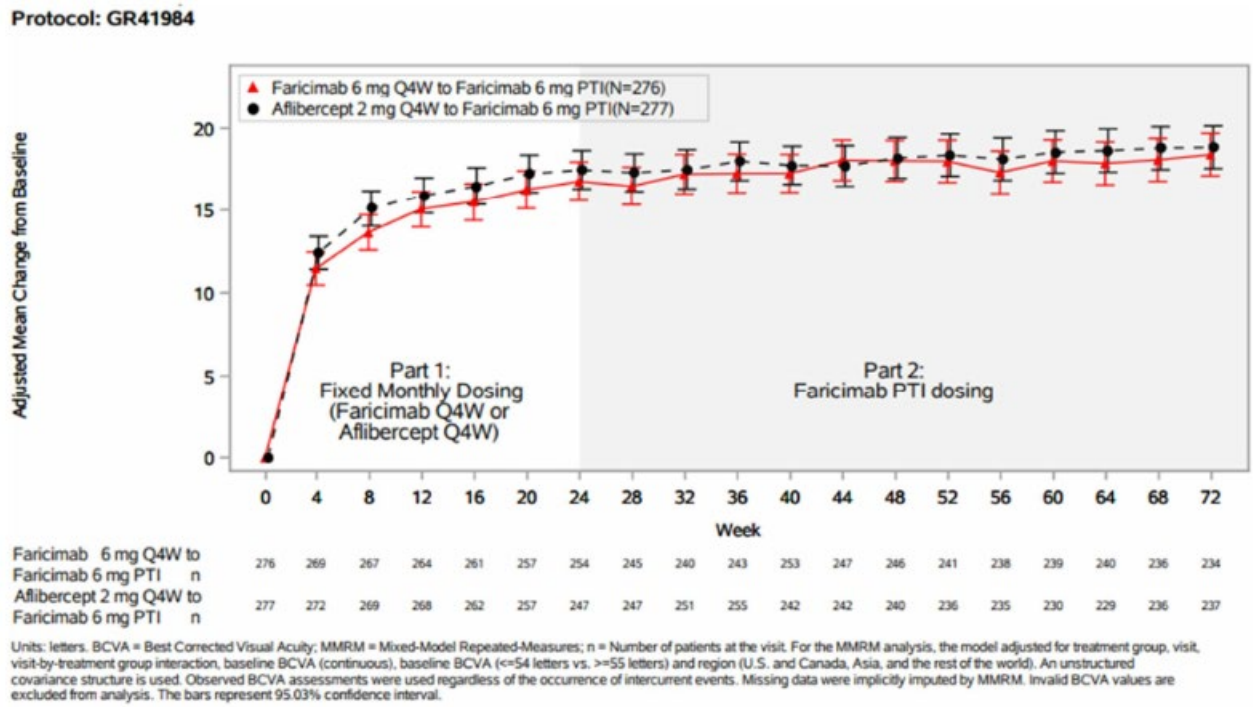
For the analysis distinguishing COVID and non-COVID intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a treatment policy strategy and hypothetical strategy were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively.

For the analysis using a hypothetical strategy for all intercurrent events, the analysis was conducted following the same analysis method as the main analysis except a hypothetical strategy was applied to the intercurrent events.

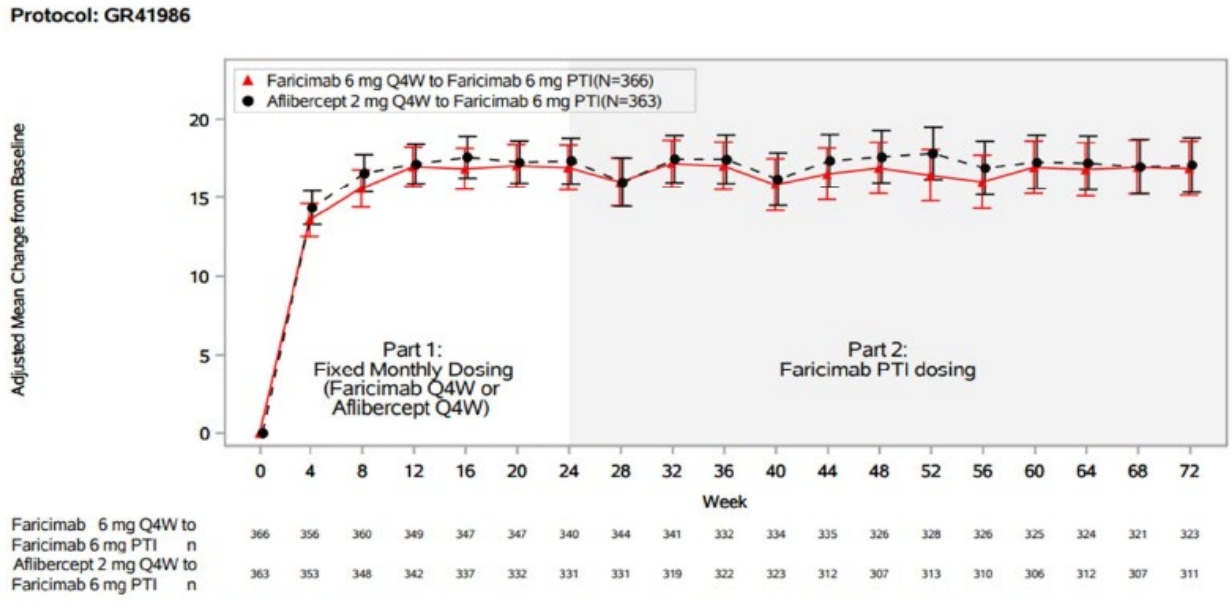
[a] The mean baseline BCVA values presented in this row are non-adjusted.

The BCVA gains achieved at Week 24 were maintained through Week 72 in both studies, during which time patients were on the faricimab adjustable T&E type regimen.

Figure 36. BALATON and COMINO: Change from Baseline in BCVA in the Study Eye over Time through Week 72



Units: letters. BCVA = Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=54 letters vs. >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% confidence interval.



Units: letters. BCVA = Best Corrected Visual Acuity; MMRM = Mixed-Model Repeated-Measures; n = Number of patients at the visit. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=34 letters, 35-54 letters, and >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). An unstructured covariance structure is used. Observed BCVA assessments were used regardless of the occurrence of intercurrent events. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% confidence interval.

Proportion of Patients Gaining ≥15 letters in BCVA from Baseline

The proportion of patients who gained ≥15 letters in BCVA score from baseline at Week 64/68/72 was 61.5% and 65.8% in BALATON and 57.6% and 59.5% in COMINO in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. The proportion of patients gaining ≥ 15 letters was maintained from Week 24 through Week 72, during which time patients were on the faricimab adjustable T&E type regimen.

Proportion of Patients Avoiding a Loss of ≥ 15 Letters in BCVA from Baseline
The proportion of patients who avoided a loss of ≥15 letters in BCVA score from baseline at Week 64/68/72 was 98.9% and 98.2% in BALATON and 93.7% and 95.6% in COMINO in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.The proportion of patients avoiding a loss of ≥ 15 letters was maintained from Week 24 through Week 72, during which time patients were on the faricimab adjustable T&E type regimen

Proportion of Patients with BCVA Snellen Equivalent of 20/40 or Better (BCVA-ETDRS ≥ 69 Letters) at Week 64/68/72

In the BALATON study, at baseline, 20.3% of patients in the faricimab Q4W arm and 17.0% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better (≥ 69 letters); at Week 24, 73.7% and 76.5% of patients, respectively, had a BCVA Snellen equivalent of 20/40 or better; at Week 64/68/72, 78.0% and 80.4% of patients, respectively, had BCVA Snellen equivalent of 20/40 or better.
In COMINO, at baseline, 11.7% of patients in the faricimab Q4W arm and 13.5% of patients in the aflibercept Q4W arm had a BCVA Snellen equivalent of 20/40 or better; at Week 24, 55.7% and 59.0% of patients, respectively, had a BCVA Snellen equivalent of 20/40 or better; at Week 64/68/72, 55.7% and 56.8% of patients, respectively, had BCVA Snellen equivalent of 20/40 or better.

Faricimab PTI Treatment Intervals in Study Part 2

Proportion of Patients on a Q4W, Q8W, Q12W, or Q16W Treatment Interval at Week 68

At Week 68 (the last treatment interval decision time point in the study), approximately, 60% of patients in BALATON and 48% of patients in COMINO were on a dosing interval of Q12W or Q16W

Table 35 Proportion of Patients on a Q4W, Q8W, Q12W, and Q16W Treatment Interval at Week 68: Descriptive Summary, ITT Population

	BALATON		COMINO	
Faricimab Interval	Faricimab Q4W to Faricimab PTI (N=276)	Aflibercept Q4W to Faricimab PTI (N=277)	Faricimab Q4W to Faricimab PTI (N=366)	Aflibercept Q4W to Faricimab PTI (N=363)
Q4W	56 (22.6%)	61 (25.0%)	114 (34.5%)	102 (32.4%)
Q8W	33 (13.3%)	44 (18.0%)	66 (20.0%)	55 (17.5%)
Q12W	29 (11.7%)	23 (9.4%)	28 (8.5%)	35 (11.1%)
Q16W	130 (52.4%)	116 (47.5%)	122 (37.0%)	123 (39.0%)

ITT=intent-to-treat; PTI=personalized treatment interval; Q4W=every 4 weeks.
Source: BALATON Final CSR, Report 1126074, Table 14 and COMINO Update CSR, Report 1126075, Table 14.

Between Week 24 and Week 68, 81.5% and 74.0% of patients achieved a faricimab Q12W or Q16W dosing interval in BALATON and COMINO, respectively. Of these patients, 72.1% and 61.6% completed at least one cycle of Q12W and maintained Q16W or Q12W dosing interval without an interval reduction below Q12W through Week 68 in BALATON and COMINO, respectively. The proportion of patients who only received Q4W dosing through Week 68 in BALATON and COMINO was low (1.2% and 2.5%, respectively.

Anatomic Outcome Measures using SD-OCT

Change from Baseline in CST over Time
In both BALATON and COMINO, patients in the faricimab and aflibercept arms had comparable reductions in CST from baseline at Week 24. Greater reductions in CST were observed in COMINO compared with BALATON, which is as expected due to the higher mean CST baseline value for COMINO compared with BALATON (baseline CST for BALATON: 559.3 µm and 559.1 µm vs COMINO: 701.1 µm

and 721.6 µm in the faricimab and aflibercept arms, respectively. The reductions in CST were maintained through Week 72.
In the BALATON study, at Week 24, the adjusted mean changes from baseline in CST were -311.4 µm and - 304.4 µm in the faricimab and aflibercept arms, respectively; at Week 64/68/72, those reductions were maintained (-310.9 µm and -307.0 µm in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.
In the COMINO study, at Week 24, the adjusted mean changes from baseline in CST were - 461.6 µm and - 448.8 µm in the faricimab and aflibercept arms, respectively; at Week 64/68/72, those reductions were maintained (- 465.9 µm and - 460.6 µm in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

Proportion of Patients with Absence of both Intraretinal Fluid and Subretinal Fluid over Time through Week 72

In the BALATON study, at baseline, 2 patients (0.7%) in the faricimab arm and 1 patient (0.4%) in the aflibercept arm had an absence of both intraretinal fluid and subretinal fluid in the central 1 mm subfield. The proportion of patients with an absence of both intraretinal fluid and subretinal fluid at Week 24 was comparable between the faricimab and aflibercept arms (67.4% and 64.3%, respectively). The proportion of patients with an absence of both intraretinal fluid and subretinal fluid was generally maintained from Week 24 through Week 72 (70.7% and 71.1% in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively).
In the COMINO study, at baseline, 7 patients (1.9%) in the faricimab arm and 3 patients (0.8%) in the aflibercept arm had an absence of both intraretinal fluid and subretinal fluid in the central 1 mm subfield. The proportion of patients with an absence of both intraretinal fluid and subretinal fluid at Week 24 was comparable between the faricimab and aflibercept arms (76.0% and 68.6%, respectively). The proportion of patients with an absence of both intraretinal fluid and subretinal fluid was generally maintained from Week 24 through Week 72 (77.0% and 71.6% in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively).

Patient-Reported Vision-Related Functioning and Quality of Life using NEI VFQ-25
Change from Baseline in NEI VFQ-25 Composite Score over Time through Week 72

In both BALATON and COMINO studies, patients in the faricimab arm had comparable adjusted mean changes from baseline at Week 24 in the National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) composite score compared with patients in the aflibercept arm, which were maintained in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, through Week 72.

In the BALATON study, at Week 24, the adjusted mean changes from baseline in the NEI VFQ-25 composite score were 5.6 and 5.9 points in the faricimab and aflibercept arms, respectively; at Week 72, the adjusted mean changes from baseline in the NEI VFQ-25 composite score were 6.0 and 7.8 points in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.
In the COMINO study, at Week 24, the adjusted mean change from baseline in the NEI VFQ-25 composite score were 7.0 and 8.2 points in the faricimab and aflibercept arms, respectively; at Week 72, the adjusted mean changes from baseline in the NEI VFQ-25 composite score were 7.8 and 8.5 points in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.
In summary, in both pivotal studies the primary endpoint was the change from baseline in BCVA at Week 24 as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters. In addition, in both pivotal studies investigating patients with branch retinal vein occlusion (Balaton study) and patients with central or hemi-retinal vein occlusion (Comino study), **the primary endpoint was met as the patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W**, as the lower bound of the 95% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than − 4 letters.

In the **BALATON study**, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.5 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was **−0.6 letters (95% CI: −2.2, 1.1).**

In the **COMINO study**, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was **-0.4 letters (95% CI: -2.5, 1.6).**

Of note, in the primary analysis a treatment policy strategy was applied to all intercurrent events and missing data were implicitly imputed by the MMRM model, assuming a missing at random mechanism. The results of the sensitivity analysis (which used multiple imputation assuming MNAR) supports the primary analysis results.

In both pivotal studies, the results of the primary analysis were also supported by supplementary analyses performed by the MAH such as the analysis based on the PP population, analysis distinguishing COVID and non-COVID intercurrent events and analysis using hypothetical strategy for all intercurrent events.

In both studies there were a number of secondary endpoints which could be grouped into three categories. In first category the effect on best corrected visual acuity (BCVA) was investigated in second category the MAH investigation anatomic outcome measures SD-OCT whereas in third category patient-reported outcome. Of note, secondary endpoints were not included in the multiplicity adjustment strategy.

In relation to effect on **additional BCVA outcomes** including the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline, patients achieving ≥ 84, 69 letters or ≤ 38 letters, all assessed at week 24, in both pivotal studies the results were comparable between the treatment groups.
The graph of change from baseline in visual acuity vs. time shows that, in both group, visual acuity sharply improves by Month 4, and gradually continues to improve thereafter.

In the **BALATON study**, at Week 24, **56.1% and 60.4%** of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was −4.3% (95% CI: −12.3%, 3.8%).

In the **COMINO study**, at week 24, **56.6% and 58.1%** of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was -1.5% (95% CI: -8.4%, 5.3%).

Also, a similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. In the **Balaton study**, at Week 24, **99.6% and 98.6%** of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. In the **Comino study**, at Week 24, **96.2% and 96.7%** of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively.

In relation the effect on **anatomic outcome measures** macular oedema was reduced significantly in both treatment groups, which was also reflected by an increase in the proportion of patients with absence of macular oedema or absence of intraretinal subretinal fluid**.** Of note, at baseline macular oedema was more significant in patients with central or hemi-retinal vein occlusion, or in those with branch retinal vein occlusion and improvements seen in patients with central or hemi-retinal vein occlusion was higher.

In the BALATON study At Week 24, the adjusted mean change from baseline in CST was **−311.4 µm** and **−304.4** µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −7.0 µm (95% CI: −14.1, 0).

In the COMINO study, at Week 24, the adjusted mean change from baseline in CST was **−461.6 µm** and **−448.8 µm** in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −12.8 µm (95% CI: −26.7, 1.0).

In relation to the **patients reported outcomes**, in both studies patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W.

The comparative data are available for 24 weeks. In Part 2 of the study, patients in both Arm A and Arm B in Part 1 were receiving 6 mg faricimab intravitreal injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. Based on the visual and/or anatomical changes the best treatment interval was determined.

As indicated by the MAH, the majority of patients in Part 2 of studies were treated using Q12W or Q16W dosing interval. Between Week 24 and Week 68, 81.5% and 74.0% of patients achieved a faricimab Q12W or Q16W dosing interval in BALATON and COMINO, respectively. The proportion of patients who only received Q4W dosing through Week 68 in BALATON and COMINO was low (1.2% and 2.5%, respectively.

Of note, despite the lower frequency of the treatment, the efficacy was maintained.

In the **BALATON study**, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 18.1 and 18.8 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

In **the COMINO study**, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.1 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

The proportion of patients who gained ≥15 letters in BCVA score from baseline at Week 64/68/72 was 61.5% and 65.8% in BALATON and 57.6% and 59.5% in COMINO in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

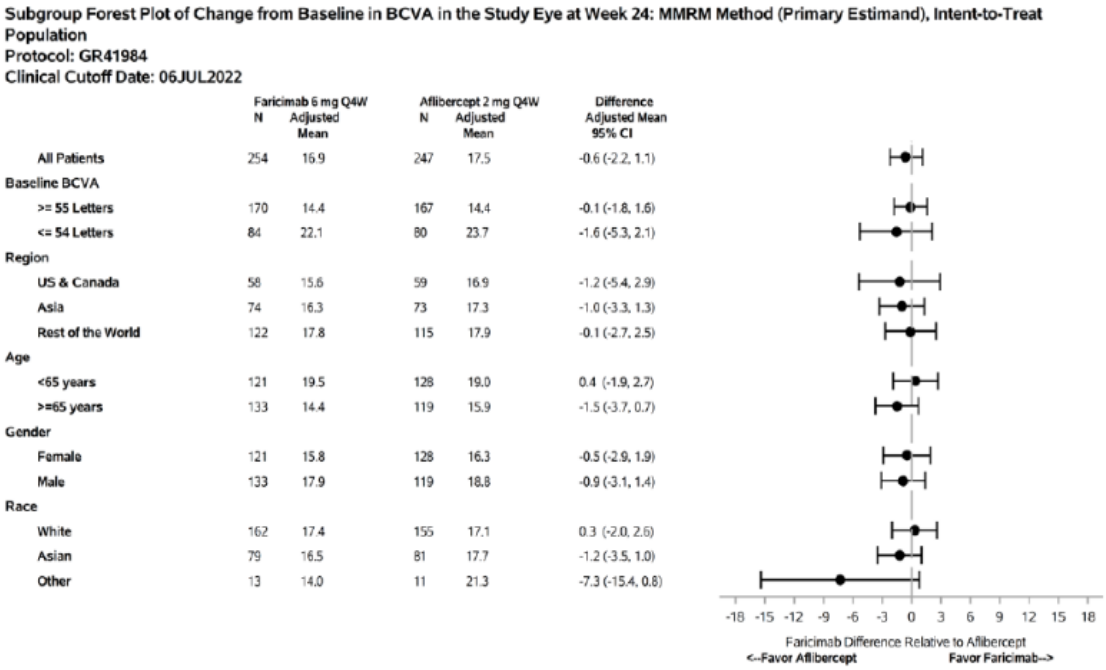
The proportion of patients who avoided a loss of ≥15 letters in BCVA score from baseline at Week 64/68/72 was 98.9% and 98.2% in BALATON and 93.7% and 95.6% in COMINO in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

Taking into consideration the efficacy data reported in Part 2 of the studies, the personalized treatment interval (PTI) treatment regimen is considered acceptable by the CHMP. The maximum treatment interval has been specified accordingly in the SmPC, in line with the approach taken for other indications**.**

Ancillary analyses

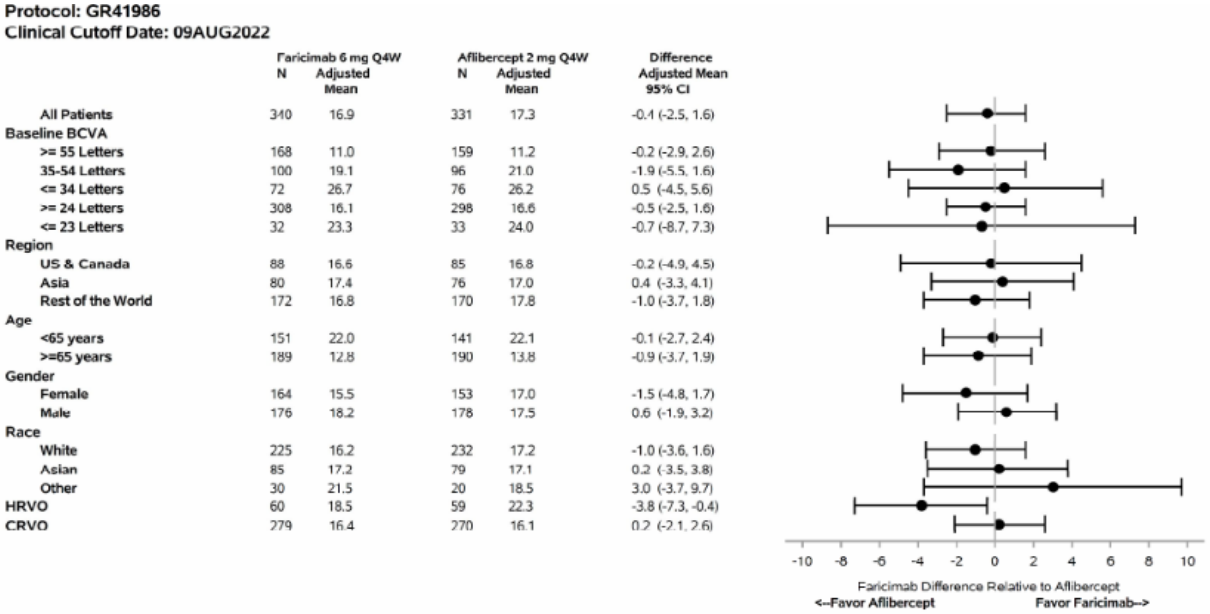
In both pivotal studies, the primary endpoint of the adjusted mean change from baseline in BCVA at Week 24 was analysed across subgroups including (<65 years and ≥ 65 years) Region (United States and Canada, Asia, and the rest of the world), Gender (female and male), Race (White, Asian, and other).
In addition, the primary endpoint was analysed depending on baseline BCVA in the BALATON study in the subgroups of ≤ 54 letters and ≥ 55 letters and low vision of ≤ 23 letters and ≥ 24 letters, whereas in the COMINO study in the subgroups ≤34 letters, 35-54 letters, and ≥55 letters and low vision of ≤ 23 letters and ≥24 letters. Furthermore, in the COMINO study the results were analysed depending on the RVO Subtype (CRVO and HRVO. The results of these analyses are presented below.

Figure 37. Subgroup Forest Plot of Change from Baseline in BCVA in the Study Eye at Week 24 for Faricimab Q4W vs. Aflibercept Q4W: MMRM Method, Primary Estimand, ITT Population



Units: letters. BCVA=Best Corrected Visual Acuity;Q4W=Every 4 weeks; MMRM = Mixed-Model Repeated-Measure. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=54 letters vs. >=55 letters) 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. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% CI.

Figure 38. Subgroup Forest Plot of Change from Baseline in BCVA in the Study Eye at Week 24 for Faricimab Q4W vs. Aflibercept Q4W: MMRM Method, Primary Estimand, ITT Population



Units: letters. BCVA=Best Corrected Visual Acuity;Q4W=Every 4 weeks; MMRM = Mixed-Model Repeated-Measure. For the MMRM analysis, the model adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (<=34 letters, 35-54 letters, and >=55 letters) 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. Missing data were implicitly imputed by MMRM. Invalid BCVA values are excluded from analysis. The bars represent 95.03% CI.

In the BALATON study there were no major differences in treatment effects in the subgroups investigated, although wider confidence intervals were seen in subgroups with smaller number of participants. The CHMP noted that the number of patients included in "Other" race category was particularly small.

The lower treatment effect was seen in patients with HRVO as compared to those with CRVO. The MAH discussed this matter further, as requested. Patients with HRVO comprised 18% of the total patient population in the COMINO study, with 62 patients randomized to the faricimab arm and 65 patients randomized to aflibercept arm, respectively. The MAH considered that although the efficacy results in this group of patients were slightly less favourable in the faricimab Q4W arm as compared the aflibercept Q4W arm, in both groups clinically relevant improvement was reported. In the HRVO subgroup, BCVA gains at Week 24 were 18.5 (95% CI: 16.0, 20.9) ETDRS letters in the faricimab Q4W arm and 22.3 (95% CI: 19.9, 24.7) ETDRS letters in the aflibercept Q4W arm, respectively. Furthermore, having presented the treatment by subgroup interaction, the MAH concluded that no physiological plausibility for a different response to faricimab treatment between patients with CRVO and HRVO could be identified. Therefore, the CHMP agreed this could be a chance finding.
The MAH also analysed the efficacy results in patients with ischemic non-perfusion and compared the results between the treatment groups. It was subsequently clarified that only approximately 3/4 of patients across the two studies had standard FFA imaging used to evaluate peripheral nonperfusion. Secondary, only 48% of the acquired standard FFA images were gradable for the presence of ischemic disease by the reading center in the BALATON and COMINO studies. Therefore, the conclusion on the efficacy in patients with ischemic non-perfusion RVO as determined by FFA imaging could not be made. Instead, the MAH presented the efficacy results in the group of patients with the most severe visual impairment (i.e. 20/200; 38 letters or worse) as these patients are more likely to have ischemic RVO. The CHMP noted that the additional analysis conducted in this group of patients showed comparable BCVA gains in the faricimab Q4W and aflibercept Q4W arms at Week 24.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present RVO application for EoI. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment in the later sections of this assessment report.

Table 36. Summary of efficacy for trial BALATON (GR41984)

Title: A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab in patients with macular edema secondary to branch retinal vein occlusion		
Study identifier	GR41984, BALATON ClinicalTrials.gov Identifier: NCT04740905 EudraCT: 2020-000440-63	
Design	Multicenter, randomized, active comparator (aflibercept) controlled, double masked, parallel-group, 2-part, 72-week study to evaluate the efficacy, safety, durability, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24 (Part 1), followed by a period of study without active control to evaluate faricimab administered according to a personalized treatment interval (PTI) dosing regimen in treatment-naïve patients with macular edema due to branch retinal vein occlusion (BRVO) (Part 2), where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment in Part 1 and faricimab treatment interval in Part 2.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	72 weeks 28 days (screening visit to Day -1) Not applicable

Hypothesis	The primary efficacy endpoint was the change from baseline in best corrected visual acuity (BCVA) at Week 24. The following hypotheses were tested: • Non-inferiority (NI) of faricimab Q4W compared with aflibercept Q4W at Week 24 in the intent to treat (ITT) population • Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population		
Treatments groups	<u>Day 1 to Week 20:</u> Faricimab Q4W <u>Week 24 to Week 68:</u> Faricimab PTI		6 mg faricimab intravitreal injection on Day 1 then Q4W up to Week 20 (6 injections in total), followed by a faricimab PTI regimen (adjustable dosing administered in 4-, 8-, 12- or 16-week intervals) to Week 68; n=276 patients randomized.
	<u>Day 1 to Week 20:</u> Aflibercept Q4W <u>Week 24 to Week 68:</u>		2 mg aflibercept intravitreal injection on Day 1, then Q4W up to Week 20 (6 injections in total), followed by a faricimab PTI regimen (adjustable dosing administered in 4-, 8-, 12- or 16-week intervals) to Week 68; n=277 patients randomized.
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 24	Change from baseline (CfBL) in BCVA at Week 24 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 24	Proportion of patients gaining ≥15 letters in BCVA from baseline at Week 24
	Secondary endpoint:	Prop. of pts avoiding loss of ≥15 letters in BCVA from BSL at Week 24	Proportion of patients avoiding loss of ≥15 letters in BCVA from baseline at Week 24
	Secondary endpoint:	CfBL in CST at Week 24	Change from baseline in central subfield thickness (CST) at Week 24
Database lock	Database lock has not yet occurred; study is ongoing. The summary is based on a data cut with a clinical cut-off date of 6 July 2022 for the primary analysis of efficacy data through Week 24.		
<u>Results and Analysis</u>			
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 had either completed the study through Week 24 or had discontinued from the study prior to Week 24, whichever was later.		
Descriptive statistics and estimate	Treatment group	Faricimab Q4W	Aflibercept Q4W
	Number of subjects	N = 276	N = 277

variability	Primary Endpoint: CfBL in BCVA at Week 24 Adjusted Mean (95.03% CI)	16.9 (15.7, 18.1)	17.5 (16.3, 18.6)
	Secondary endpoint: Prop. of pts gaining ≥15 letters in BCVA from BSL at Week 24 CMH Weighted Estimate (95.03% CI)	56.1% (50.4%, 61.9%)	60.4% (54.7%, 66.0%)
	Secondary endpoint: Prop. of pts avoiding loss of ≥15 letters in BCVA from BSL at Week 24 CMH Weighted Estimate (95.03% CI)	99.6% (98.9%, 100.0%)	98.6% (97.2%, 99.9%)
	Secondary endpoint: CfBL in CST at Week 24 Adjusted Mean (95.03% CI)	−311.4 (−316.4, −306.4)	−304.4 (−309.3, −299.4)
Effect estimate per comparison	Primary Endpoint: CfBL in BCVA at Week 24	Comparison groups (MMRM)	Faricimab Q4W vs. Aflibercept Q4W
		Difference in Adjusted Means (95.03%) NI margin: -4 letters	−0.6 (−2.2, 1.1)
Notes	Non-inferiority of faricimab Q4W to aflibercept Q4W was demonstrated. Results from the primary endpoint analysis were consistent between the ITT population and per protocol population (all patients randomized in the study who received at least one dose of study treatment and who did not have a major protocol violation that impacted the efficacy evaluation). Findings from all sensitivity and supplementary analyses using different intercurrent event and missing data handling strategies were consistent and support the main analysis results. Superiority for the primary endpoint was not met.		

Table 37. Summary of efficacy for trial COMINO (GR41986)

Title: A phase III, multicenter, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of faricimab in patients with macular edema secondary to central retinal or hemiretinal vein occlusion			
Study identifier	GR41986, COMINO ClinicalTrials.gov Identifier: NCT04740931 EudraCT: 2020-000441-13		
Design	Multicenter, randomized, active comparator (aflibercept) controlled, double masked, parallel-group, 2-part, 72-week study to evaluate the efficacy, safety, durability, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24 (Part 1), followed by a period of study without active control to evaluate faricimab administered according to a personalized treatment interval (PTI) dosing regimen in treatment naïve patients with macular edema due to central retinal or hemiretinal vein occlusion (C/HRVO) (Part 2), where investigators and patients are masked to treatment assignment in Part 1 and to both original treatment assignment in Part 1 and faricimab treatment interval in Part 2.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 weeks 28 days (screening visit to Day -1) Not applicable
Hypothesis	The primary efficacy endpoint was the change from baseline in best corrected visual acuity (BCVA) at Week 24. The following hypotheses were tested: • Non-inferiority (NI) of faricimab Q4W compared with aflibercept Q4W at Week 24 in the intent to treat (ITT population) population • Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population		
Treatments groups	Day 1 to Week 20: Faricimab Q4W Week 24 to Week 68: Faricimab PTI		6 mg faricimab intravitreal injection on Day 1 then Q4W up to Week 20 (6 injections in total), followed by a faricimab PTI regimen (adjustable dosing administered in 4-, 8-, 12- or 16-week intervals) to Week 68; n=366 patients randomized.
	Day 1 to Week 20: Aflibercept Q4W Week 24 to Week 68: Faricimab PTI		2 mg aflibercept intravitreal injection on Day 1, then Q4W up to Week 20 (6 injections in total), followed by a faricimab PTI regimen (adjustable dosing administered in 4-, 8-, 12- or 16-week intervals) to Week 68; n=363 patients randomized.
Endpoints and definitions	Primary endpoint	CfBL in BCVA at Week 24	Change from baseline (CfBL) in BCVA at Week 24 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 24	Proportion of patients gaining ≥15 letters in BCVA from baseline at Week 24

	Secondary endpoint:	Prop. of pts avoiding loss of ≥15 letters in BCVA from BSL at Week 24	Proportion of patients avoiding loss of ≥15 letters in BCVA from baseline at Week 24
	Secondary endpoint:	CfBL in CST at Week 24	Change from baseline in central subfield thickness (CST) at Week 24
Database lock	Database lock has not yet occurred; study is ongoing. The summary is based on a datacut with a clinical cut-off date of 9 August 2022 for the primary analysis of efficacy data through Week 24.		
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 24 or had discontinued from the study prior to Week 24, whichever was later.		
Descriptive statistics and estimate variability	Treatment group	Faricimab Q4W	Aflibercept Q4W
	Number of subjects	N = 366	N = 363
	Primary Endpoint: CfBL in BCVA at Week 24 Adjusted Mean (95.03% CI)	16.9 (15.4, 18.3)	17.3 (15.9, 18.8)
	Secondary endpoint: Prop. of pts gaining ≥15 letters in BCVA from BSL at Week 24 CMH Weighted Estimate (95.03% CI)	56.6% (51.7%, 61.5%)	58.1% (53.3%, 62.9%)
	Secondary endpoint: Prop. of pts avoiding loss of ≥15 letters in BCVA from BSL at Week 24 CMH Weighted Estimate (95.03% CI)	96.2% (94.3%, 98.1%)	96.7% (94.9%, 98.5%)
	Secondary endpoint: CfBL in CST at Week 24 Adjusted Mean (95.03% CI)	-461.6 (-471.4, -451.9)	-448.8 (-458.6, -439.0)

Effect estimate per comparison	Primary Endpoint: CfBL in BCVA at Week 24	Comparison groups (MMRM)	Faricimab Q4W vs. Aflibercept Q4W
		Difference in Adjusted Means (95.03%) NI margin: -4 letters	-0.4 (-2.5, 1.6)
Notes	Non-inferiority of faricimab Q4W to aflibercept Q4W was demonstrated. Results from the primary endpoint analysis were consistent between the ITT population and per protocol population (all patients randomized in the study who received at least one dose of study treatment and who did not have a major protocol violation that impacted the efficacy evaluation). Findings from all sensitivity and supplementary analyses using different intercurrent event and missing data handling strategies were consistent and support the main analysis results. Superiority for the primary endpoint was not met.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

Real World Data Results Supplementing the Recommended RVO Dosing Regimen
Large observational studies of treatment patterns and outcomes of macular oedema secondary to RVO in routine clinical practice are scarce. A non-interventional retrospective observational study is being conducted to assess real-world anti-VEGF treatment patterns and visual acuity (VA) outcomes over time in patients with macular oedema secondary to BRVO or CRVO. The analysis uses data from Vestrum Health, a database of electronic health records from private retina specialist clinics in the United States. We report findings from the treatment pattern analysis that describe the average number of anti-VEGF injections received in the first 6 months of treatment for macular oedema secondary to BRVO or CRVO separately.

Data from **2014-2021** were extracted from the Vestrum Health database, which include de-identified electronic health record **data from private retina specialist clinics in the United States**. The Vestrum Health database is a collection of data from multiple different electronic health record systems, totalling up to > 360 physicians and > 65 practices across all regions in the United States. Data from some physicians begin in 2013 with complete coverage for all specialists beginning by 2015. The electronic health record represents the entire patient's file as maintained by the treating physician and practice with the exception of diagnostic images. Records are continuous regardless of the physician in the practice treating the patient, but only to the extent the patient is treated in the same practice. Data recorded within the electronic health record include diagnoses, procedures, drugs administered, payer, and outcomes such as visual acuity.

Eyes with a diagnosis of macular oedema secondary to BRVO or CRVO from January 1, 2014 to November 30, 2021, were identified. The analytic cohort included eyes that received ≥ 1 anti-VEGF injection after the index diagnosis, and patients were required to be aged ≥ 18 years at the index anti-VEGF treatment date. Eyes were required to have a VA reading at baseline (index anti-VEGF treatment); be treatment-naive to anti-VEGF, intravitreal steroids, and grid/focal laser therapy at the index treatment date; and have a minimum of 3 months of follow-up from the index anti-VEGF treatment.

Eyes diagnosed with the following conditions on or before index diagnosis were excluded: moderate non-proliferative diabetic retinopathy or worse, proliferative diabetic retinopathy, diabetic macular oedema, neovascular age-related macular degeneration, geographic atrophy, myopic choroidal neovascularization, cystoid macular oedema, and retinal neovascularisation.
RVO is defined in the Vestrum database using International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9, ICD-10). ICD-9 codes are used for eyes with initial diagnosis between January 01, 2014 – September 30, 2015 (BRVO: 362.36, CRVO: 362.35). ICD-10 codes are used for eyes with initial diagnosis from October 1, 2015 onwards (BRVO: H34.83xx, CRVO: H34.81xx, where x denotes a wildcard used in the query of ICD-10 codes). BRVO with macular edema or CRVO with macular edema can be identified using ICD-10 codes H34.83x0 or H34.81x0, respectively. Macular edema is defined using a combination of ICD codes (362.83, and H35.81), along with free text searches of Vestrum's "Exam Findings" field. An eye would be considered to have macular edema if either of these were present at a visit. Some examples of exam findings are: "Macular Edema OD", "Findings consistent with macular edema", "Retinal thickening consistent with macular edema". Macular edema secondary
to RVO is defined as the first instance of macular edema (defined above) on or after the initial diagnosis of RVO. The eye must also still have an associated RVO ICD code at this time. The first instance of this occurring is identified as the index diagnosis of macular edema secondary to RVO in a patient's eye.

Anti-VEGF treatments (e.g., ranibizumab, aflibercept) were identified using Healthcare Common Procedure Coding System (HCPCS) codes (J2778, C9233, J0178, Q2046, C9291, J9035, C9257, J0179, Q9977, and J3590) along with the Current Procedural Terminology (CPT) code for intravitreal injection (67028). Intravitreal injections of anti- VEGFs with an unclassified drug HCPCS code J3490 are also included when the entries identify the anti-VEGF drug administered.

Demographic and baseline clinical characteristics were descriptively analyzed (Table 38). The mean (SD) of anti-VEGF injections received in the first six months of treatment were described (Table 39). The number of injections during a time interval were reported as the sum of all eligible anti-VEGF injections, regardless of the drug type, during that period.

Results
The analytic sample included 22,365 eyes with macular oedema secondary to BRVO and 18,064 eyes with macular edema secondary to CRVO. For BRVO with macular oedema, mean age was 70.6 years and 55.1% were female. For CRVO with macular oedema, mean age was 71.9 years and 49.6% were female. The mean (SD) time from index diagnosis to index treatment was 31.6 (141.1) days for BRVO and 19.5 (98.4) days for CRVO with macular oedema.

Table 38. Patient Demographic and Clinical Characteristics

Characteristics	BRVO with macular edema Mean (SD) or n (%)	CRVO with macular edema Mean (SD) or n (%)
n, eyes	22,365	18,064
Age, years	70.6 (12.2)	71.9 (13.2)
Sex		
Female	12,321 (55.1%)	8,942 (49.5%)
Male	10,044 (44.9%)	9,122 (50.5%)
Region		
Midwest	2,682 (12.0%)	2,362 (13.1%)
Northeast	6,422 (28.7%)	5,205 (28.8%)
Southeast	6,257 (28.0%)	5,117 (28.3%)
Southwest	2,203 (9.9%)	1,676 (9.3%)
West	4,801 (21.5%)	3,704 (20.5%)
Time From Index Diagnosis to Index Treatment, days	31.6 (141.1)	19.5 (98.4)
Visual Acuity (VA) at Index Treatment	53.4 (22.5)	36.5 (27.7)
Lens Status		
Phakic	13,530 (60.5%)	10,366 (57.4%)
Pseudophakic	7,509 (33.6%)	6,529 (36.1%)
Missing	1,326 (5.9%)	1,169 (6.5%)
Hypertension, n (%)	14,037 (62.8%)	11,664 (64.6%)
History of smoking, n (%)	6,633 (29.7%)	5,493 (30.4%)

Within the first 6 months of treatment, eyes with BRVO and CRVO with macular oedema received a mean (SD) of 4.2 (1.5) and 4.3 (1.4) injections, respectively. More injections were received in the first three months of treatment compared to months 4-6. Both BRVO and CRVO with macular oedema eyes received a mean (SD) of 2.7 (0.8) injections in months 0-3, and 1.6 (1.0) injections in months 4-6.

Table 39. Mean Number of Anti-VEGF Injections Received

	BRVO with macular edema			CRVO with macular edema		
Time period	Months 0-6	Months 0-3	Months 4-6	Months 0-6	Months 0-3	Months 4-6
n	19,714	22,365	19,714	15,841	18,064	15,841
Mean (SD)	4.2 (1.5)	2.7 (0.8)	1.6 (1.0)	4.3 (1.4)	2.7 (0.8)	1.6 (1.0)

The average number of anti-VEGF injections were summarized for previously treatment naive BRVO and CRVO with macular oedema eyes that received treatment in routine clinical practice. The number of injections received by eyes with macular oedema secondary to BRVO or CRVO were similar. On

average, eyes received approximately 4 injections in the first 6 months of treatment, which are fewer than the 6 initial monthly injections studied in all of the pivotal RVO anti-VEGF trials. The lower number of anti- VEGF treatments received in real-world practice compared to pivotal trials may potentially be due to the burden of frequent injections, as suggested by prior studies (Ang et al. 2020; Callizo et al. 2019), or differences in treatment regimens due to treatment response or disease control. Results also show that injection frequency was highest in the first three months of treatment, where eyes received almost monthly injections. However, the number of injections declined in months 4-6, where eyes for BRVO or CRVO with macular oedema received an average of 1.6 injections over a three-month period. These results suggest that 6 initial monthly doses of intravitreal injections may not be possible or necessary for some patients and that a more flexible and personalized dosing regimen in the first six months of treatment may be needed.

The CHMP acknowledged the MAH's effort to collect real world data results supporting the proposed dose regimen and noted the main outcome of the analysis: on average, eyes received approximately 4 injections in the first 6 months of treatment, which are fewer than the 6 initial monthly injections studied in all of the pivotal RVO anti-VEGF trials. However, importantly, the CHMP highlighted that the type of anti-VEGF treatments considered is not specified and no efficacy results associated with this less frequently dosing was provided.

2.4.3. Discussion on clinical efficacy

Dose finding studies

No dose finding studies were performed for the treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (RVO). The CHMP noted that the proposed posology is similar to that used in patients with diabetic macular oedema (DME). As indicated by the MAH, the dose of 6 mg was selected for RVO patients based on similarities in pathophysiology of macular oedema and vision loss in patients with DME and RVO and similar faricimab PK and PD characteristics in DME and RVO.

As detailed in section 4.2 of the SmPC, the recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly); 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualised using a treat -and-extend approach. Based on the physician's judgement of the patient's anatomic and/or visual outcomes, the dosing interval may be extended in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate.

The treat -and-extend approach was proposed to be implemented after 3 consecutive monthly initiation doses. However, this is not in line with the approach implemented in pivotal studies as in both studies during the first 24 weeks of treatment patients received a total 6 injections given every 4 weeks (Q4W). Treat -and-extend approach was introduced later (i.e. after 6 injections/24 weeks of treatment). Therefore, it was requested to justify the proposed dose regimen.

In order to support the proposed posology (i.e. implantation of treat -and-extend after 3 consecutive monthly initiation), a post-hoc analysis of the data up to Week 24 was conducted.

This analysis indicated that, after 3 consecutive monthly initiation doses, RVO patients on average do not gain additional meaningful benefit from continued monthly dosing, as shown by the small difference in the change from baseline in BCVA, CST, and proportion of patients gaining ≥ 15 letters in BCVA from baseline between Week 12 and Week 24. Further, it was noted that 79% and 71% of patients in BALATON and COMINO, respectively, achieved disease stability at Week 8. For those patients who achieved stability at Week 8, the mean change in BCVA from Week 12 to Week 24 was less than < 2 letters, which is not considered clinically significant.

Finally, the MAH highlighted that, the pivotal studies for aflibercept and ranibizumab had similar designs (monthly dosing for 6 months, followed by a move to a different dosing regimen), but have

posologies that allow an individualised approach to treatment after 3 consecutive monthly doses. Therefore, taking into consideration the totality of the data, the proposed recommendation for an individualised approach to treatment after 3 consecutive monthly doses was accepted by the CHMP.

The data from the second part of both studies showed that the BCVA gains and central subfield thickness (CST) reductions achieved at Week 24 were maintained through Week 72, during which time all patients were on the 6 mg faricimab personalised treatment interval (PTI) dosing regimen.

Design and conduct of clinical studies

Clinical evidence supporting the efficacy, safety, and favourable benefit-risk assessment of faricimab is mainly based on the primary analysis results of two pivotal Phase III studies:

- Study GR41984 (hereafter referred to as **BALATON**) in patients with macular oedema due to branch retinal vein occlusion (BRVO)
- Study GR41986 (hereafter referred to as **COMINO**) in patients with macular oedema due to central retinal vein occlusion or hemi-retinal vein occlusion (C/HRVO).

The design of both pivotal studies was similar. Both studies consisted of two treatment periods. Part 1 (Day 1 through week 24) which compared faricimab every 4 weeks (Q4W) Arm A) versus aflibercept Q4W (Arm B) and Part 2 (week 24 through week 72) which was evaluating faricimab administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on PTI dosing criteria. Of note the comparative data are available only for the first 24 weeks only as in part 2 all patients were receiving faricimab.

In the studies patients were stratified depending on the baseline BCVA score (with different cuts off depending on the study) and based on the region (United States and Canada, Asia, and the rest of the world).

Study population

The inclusion criteria (broadly agreed during the SA) were similar between both pivotal studies with an exception that the BALATON study enrolled patients with macular oedema due to BRVO whereas the COMINO study enrolled patients with macular oedema due to CRVO or HRVO. In both studies patients had to be diagnosed no longer than 4 months prior to the screening visit and the diagnosis had to be confirmed by the central reading centre. The MAH clarified that although BALATON (GR41984) and COMINO (GR41986) studies enrolled patients who were diagnosed within 4 months of the screening visit, this is generally reflective of what happens in clinical practice. It was also indicated by the MAH that in patients with RVO the treatment is usually started shortly after diagnosis.

The key criteria also include the threshold requirement for BCVA 73 letters or less (minimum of 19 letters) at screening to ensure that patients had room to improve by at least 15 letters, while also allowing the inclusion of patients presenting with ischemic RVO (who tend to present baseline BCVA <20/200 and have a more guarded prognosis). Further, as indicated by the MAH patients with BCVA less than 19 are more likely to have disease-induced irreversible retinal damage and are therefore unable to respond to therapy. A similar approach was used in studies investigating other anti−VEGF investigated for the treatment of RVO.

In relation to the exclusion criteria the study included **only patients without prior treatment for macular oedema** due to RVO, including anti−VEGF intravitreal injections, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection and laser therapy. Therefore, the pivotal study data could only provide supporting evidence for faricimab being used as a first line therapy. The efficacy of this product in patients who failed other treatment options is not available and this limitation of the data set is highlighted in section 4.4 of the SmPC**.**

In both pivotal studies, patients were randomly assigned to 6 mg of faricimab intravitreal injections in Arm A or 2 mg aflibercept intravitreal injections in Arm B. During the first 24 weeks of treatment (in

Part 1 of the study) patients in both treatment arms received in total 6 injections given every 4 weeks (Q4W).
In Part 2 all patients received 6 mg of faricimab intravitreal injections; therefore, no comparative data are available beyond week 24.

In part 2 the treatment intervals could be maintained or adjusted (increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values. The study protocols provided a detailed instruction on how the dose should be adjusted. On the other hand, in the SmPC (in section 4.2 and 5.1) only limited information was included in this regard. The SmPC only states that the treatment intervals are to be adjusted based on anatomic and/or visual outcomes change but CST and BCVA value which should be used for this adjustment is not specified. However, as the same approach was used for other approved indication this was considered acceptable by the CHMP.

Furthermore, also in SmPC section 4.2 it is highlighted that treatment intervals shorter than 4 weeks and longer than 4 months between injections have not been studied. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion but there is no requirement for monthly monitoring between injections.

Comparator
Both pivotal studies were-active controlled up to Week 24. The lack of a placebo arm is agreed given the existing therapeutic alternatives. The MAH selected aflibercept as a comparator in the studies, which is acceptable. Aflibercept given at the dose of 2 mg is approved for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO). The monthly regimen for the comparator in Part 1 of the study was discussed and agreed during the SA.

Prior and Concomitant Therapy
In relation to the exclusion criteria only patients without prior treatment for macular oedema due to RVO were included. In this context, as discussed, the data generated in the pivotal studies can support the use of the product as first line therapy in patients' macular oedema due to RVO.

Study endpoints
The primary endpoint in the study was the change from baseline in best corrected visual acuity (BCVA) at week 24. The timing of the primary endpoint was agreed during the SA and was the same as used in the pivotal studies supporting the authorisation of other anti-VEGFs (i.e. aflibercept and ranibizumab) and was considered acceptable by the CHMP. In relation to the selected primary outcome measure (i.e. change from baseline in BCVA) this is also considered acceptable.
Both studies had a non-inferiority design. For the primary analysis, if the lower bound of the 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.
There were a number of secondary endpoints again investigating the effect on best corrected visual acuity (BCVA) including the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline, patients achieving ≥ 84, 69 letters or ≤ 38 letters. Other aspects investigated in the study included changes from baseline in central subfield thickness (CST), proportion of patients with absence of macular oedema, with absence of intraretinal fluid or with absence of subretinal fluid.Both studies were double-masked. The MAH described accordingly in the study protocols procedures and roles (masked and unmasked) at the study site.

Efficacy data and additional analyses
In the Balaton study a total of 553 patients with BRVO were randomised 1:1 into the study: 276 to the faricimab Q4W arm and 277 to the aflibercept Q4W. The majority of patients completed the 24 weeks treatment period (i.e. 543 out of 553 subjects). 12 patients in total discontinued the study treatment prior to week 24 and the main reason for discontinuation was lost for follow up and due to an adverse event. One patient in the faricimab arm died prior to week 24.

The population of patients enrolled to in Comino study was slightly bigger as compared to the Balaton study. The Comino study enrolled 729 patients with C/HRVO who were randomized 1:1 into two treatment arms: 366 to the faricimab Q4W arm and 363 to the aflibercept Q4W arm. Again, most patients (713 out of 729) completed the 24 weeks treatment period. 26 patients (3.6%) discontinued the study treatment prior to week 24. The main reason for discontinuation was withdrawal by the subject. 3 patients died while on the study.

The CHMP noted that the discontinuation rate was also small in Part 2 of the study (after week 24 through week 72). 60 (10.9%) and 78 (10.7%) patients discontinued the study treatment prior to Week 72 in the BALATON and COMINO study, respectively.

Baseline characteristics

In the **BALATON study**, the mean age of enrolled patients was 64.1 years (64.3 years in the faricimab Q4W arm and 63.8 years in the aflibercept Q4W arm). Slightly older patients were enrolled to the **COMINO study**, where the overall mean age at randomisation was 65.1 years (65.6 years in the faricimab Q4W arm and 64.7 years in the aflibercept Q4W arm).

The youngest age at enrolment across studies was 22, the oldest 100. Similar percentages of patients in both studies were male or female. The majority of patients were white and of Not Hispanic or Latino ethnicity.

In relation to age and gender, the study populations can be considered as representative of the general population of patients with RVO. The majority of patients in both studies were in the > 65 years of age category, which is expected as the prevalence of RVO is strongly associated with increasing age. RVO is rarely seen in individuals younger than 50, but it is occurring more frequently in the older age group.

The prevalence of this disease is known to not differ significantly between sexes, which is reflected in the study population. In relation to ethnicity, the CHMP noted that white and Not Hispanic or Latino ethnicity is overrepresented in the studies. However, as clarified by the MAH, the population pharmacokinetic (PopPK) analysis has shown no effect of race on the pharmacokinetics (PK, ocular and systemic) of faricimab, and therefore no differences in the efficacy isexpected.

Both studies enrolled patients with a relatively short history from RVO diagnosis (i.e. less than 4 months as per the inclusion criteria). The mean time since diagnosis was 1.46 months in the BALATON study and 1.34 months in the COMINO study.

Both studies were aimed to enrol patients with BCVA of 73 to 19 letters at screening and with objective sign of macular oedema with central subfield thickness (CST) ≥325 µm, as measured on Spectralis SD-OCT.

In the BALATON study the mean baseline BCVA in all patients was 57.6 letters (range 19 to 76): 57.5 and 57.6 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. Mean baseline CST in all patients was 558.2 microns: 558.3 and 558.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively.

The COMINO study, enrolled a more severe populations with respect to the lower BCVA at enrolment, higher mean baseline CST. In this study the mean baseline BCVA in all patients was 50.5 letters (range 19 to 87): 50.3 and 50.7 in the faricimab Q4W arm and aflibercept Q4W arm, respectively. The mean baseline CST was 711.6 microns: 702.2 and 721.1 in the faricimab Q4W arm and aflibercept Q4W arm, respectively.

Some patients (around 17% in the BALATON study and 10% in the COMINO study, respectively) had confirmed macular ischemic non-perfusion. The mean intraocular pressure was similar across studies (14 mmHg) but the maximum values reported were higher in the COMINO study (up to 26 mmHg).

The COMINO study enrolled patients with Central Retinal or Hemi-retinal Vein Occlusion. The majority of patients (82%) enrolled had CRVO.

Primary endpoint results

In both pivotal studies the primary endpoint was the change from baseline in BCVA at Week 24, as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters.

In both pivotal studies investigating patients with branch retinal vein occlusion (Balaton study) and patients with central or hemi-retinal vein occlusion (COMINO study), the primary endpoint was met as the patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W, as the lower bound of the 95% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than − 4 letters.

In the BALATON study, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.5 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was −0.6 letters (95% CI: −2.2, 1.1). In the COMINO study, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.4 letters (95% CI: -2.5, 1.6).

The CHMP noted that, in the primary analysis a treatment policy strategy was applied to all intercurrent events and missing data were implicitly imputed by the MMRM model, assuming a missing at random mechanism. The results of the sensitivity analysis (which used multiple imputation assuming MNAR, and were justified accordingly) supported the primary analysis results.

In both pivotal studies, the results of the primary analysis were also supported by supplementary analyses performed by the MAH, such as the analysis based on the PP population, analysis distinguishing COVID and non-COVID intercurrent events and analysis using hypothetical strategy for all intercurrent events.

Secondary endpoints

Part 1

In both studies there were a number of secondary endpoints which could be grouped into three categories. In the first category the effect on best corrected visual acuity (BCVA) was investigated; in the second category the MAH investigated anatomic outcome measures SD-OCT whereas in the third category patient-reported outcomes were looked at. Of note for the CHMP, secondary endpoints were not included in the multiplicity adjustment strategy.

In relation to effect on additional BCVA outcomes including the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline, patients achieving ≥ 84, 69 letters or ≤ 38 letters, all assessed at week 24, in both pivotal studies the results were comparable between the treatment groups.

The graph of change from baseline in visual acuity vs. time shows that, in both groups, visual acuity sharply improves by Month 4, and gradually continues to improve thereafter.

In the BALATON study, at Week 24, 56.1% and 60.4% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was −4.3% (95% CI: −12.3%, 3.8%). In the COMINO study, at week 24, 56.6% and 58.1% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was -1.5% (95% CI: -8.4%, 5.3%).

Also, a similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. In the BALATON study, at Week 24, 99.6% and 98.6% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. In the COMINO study, at Week 24, 96.2% and 96.7% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively.

In relation to the effect on anatomic outcome measures macular oedema was reduced significantly in both treatment groups, which was also reflected by an increase in the proportion of patients with absence of macular oedema or absence of intraretinal subretinal fluid. Of note, at baseline macular oedema was more significant in patients with central or hemi-retinal vein occlusion, or in those with branch retinal vein occlusion and improvements seen in patients with central or hemi-retinal vein occlusion were higher.

In the BALATON study At Week 24, the adjusted mean change from baseline in CST was −311.4 µm and −304.4 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −7.0 µm (95% CI: −14.1, 0).
In the COMINO study, at Week 24, the adjusted mean change from baseline in CST was −461.6 µm and −448.8 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −12.8 µm (95% CI: −26.7, 1.0).

In relation to the patients' reported outcomes, in both studies patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score at Week 24 compared with patients treated with aflibercept Q4W.

Part 2
The comparative data are available for 24 weeks. In Part 2 of the study, patients in both Arm A and Arm B in Part 1 were receiving 6 mg faricimab intravitreal injections administered according to a PTI dosing regimen in intervals between Q4W and Q16W. Based on the visual and/or anatomical changes the best treatment interval was determined.

As indicated by the MAH, the majority of patients in Part 2 of the studies were treated using Q12W or Q16W dosing interval. Between Week 24 and Week 68, 81.5% and 74.0% of patients achieved a faricimab Q12W or Q16W dosing interval in BALATON and COMINO studies, respectively. The proportion of patients who only received Q4W dosing through Week 68 in BALATON and COMINO was low (1.2% and 2.5%, respectively;

The CHMP noted that, despite the lower frequency of the treatment in Part 2 of the study, the efficacy was maintained.

In the BALATON study, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 18.1 and 18.8 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. In the COMINO study, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.1 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

The proportion of patients who gained ≥15 letters in BCVA score from baseline at Week 64/68/72 was 61.5% and 65.8% in the BALATON study and 57.6% and 59.5% in the COMINO study in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

The proportion of patients who avoided a loss of ≥15 letters in BCVA score from baseline at Week 64/68/72 was 98.9% and 98.2% in the BALATON study and 93.7% and 95.6% in the COMINO study in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

Taking into consideration the efficacy data reported in Part 2 of the studies, the PTI treatment regimen is considered acceptable by the CHMP.

Subgroup analysis
In the BALATON study there was no major differences in treatment effects according to subgroups investigated, although wider confidence intervals were seen in subgroups with smaller number of participants. The CHMP noted that the number of patients included in "Other" race category was particularly small.

The lower treatment effect was seen in patients with HRVO as compared to those with CRVO. However, there is no physiological plausibility for a different response to faricimab treatment between patients with CRVO and HRVO and therefore the CHMP agreed this could be a chance finding.

The MAH was requested to discuss the efficacy results in patients with ischemic non-perfusion and compare the results between the treatment groups. It was clarified that only approximately 3/4 of patients across the two studies had standard fundus fluorescein angiography (FFA) imaging used to evaluate peripheral nonperfusion. Secondary, only 48% of the acquired standard FFA images were gradable for the presence of ischemic disease by the reading center in the BALATON and COMINO studies. Therefore, a conclusion on the efficacy in patients with ischemic non-perfusion RVO as determined by FFA imaging can't be made.

Instead, the MAH presented the efficacy results in the group of patients with the most severe visual impairment i.e. 20/200 (38 letters or worse) as these patients are more likely to have ischemic RVO. The additional analysis conducted in this group showed comparable BCVA gains in the faricimab Q4W and aflibercept Q4W arms at Week 24.

Immunogenicity
The incidence of immunogenicity to faricimab is based on patients with treatment emergent-ADAs in both BALATON (18/259 patients; 6.9%) and COMINO (30/338 patients; 8.9%) was low. The median onset time of ADA response was 24 weeks. Based on all available data to date, no meaningful impact of ADA was observed on efficacy.

2.4.4. Conclusions on the clinical efficacy

In summary, from an efficacy perspective, the CHMP concluded that this EoI is approvable.

2.5. Clinical safety

Introduction

Vabysmo was first authorised in the US on 28 January 2022 and in the EU on 15 September 2022. At the time of filing submission Vabysmo had been approved in a total of 53 countries for the treatment of patients with DME and nAMD. In Europe, Vabysmo was authorised for the treatment of neovascular age related macular degeneration (nAMD) and diabetic macular oedema (DME) on 15 September 2022, based on the efficacy and safety results of four Phase III pivotal trials - TENAYA (GR40306) and LUCERNE (GR40844) for nAMD and YOSEMITE (GR40349) and RHINE (GR40398) for DME, respectively.

Summary of known safety profile

The most **frequently** reported adverse reactions were cataract (13%), conjunctival haemorrhage (8%), vitreous detachment (5%), IOP increased (4%), vitreous floaters (4%), eye pain (3%) and retinal pigment epithelial tear (nAMD only) (3%).

The most **serious adverse reactions** were uveitis (0.6%), endophthalmitis (0.5%), vitritis (0.3%), retinal tear (0.2%), rhegmatogenous retinal detachment (0.1%) and traumatic cataract (< 0.1%) (see section 4.4).

From the known safety profile from the currently approved faricimab indications, the important identified risks in faricimab risk management plan (RMP) include **infectious endophthalmitis** and **intraocular inflammation.** Important potential risks are **arterial thromboembolic events and Central Nervous System haemorrhagic events**. In the Periodic Safety Update Single Assessments (PSUSA) for faricimab (solution for intravitreal injection) PSURs covering the period from 28th July 2022 to 27th January 2023 the most common adverse events reported were from the Soc Eye disorders, which is already known and adequately addressed in the SmPC. A safety signal of Retinal Arterial Occlusive Event was closed during the reporting period without CDS change, which is endorsed.

Also in the PSUSA covering the period from 28th January 2023 to 27th July 2023 the most common adverse events reported were from the SOC Eye disorders. During the late-breaking interval of this PSUR, the MAH validated a signal for retinal vasculitis and was requested to discuss it in the next PSUR (covering the period from 28th July 2023 to 27th January 2024), under assessment at the time of authoring this CHMP AR (PRAC recommendation: 5 September 2024).As of 27th July 2023, the total estimated cumulative patient exposure to faricimab from clinical trials (5,150 patients) and marketing experience (249,956 patients) is 255,106 patients.

RVO indication
RVO is one of the most common retinal vascular disorders and its prevalence is strongly associated with increasing age. Additional risk factors are hypertension, diabetes, hyperlipidemia, high BMI, cardiovascular disease and cigarette smoking. RVO is associated with varying degrees of visual loss, depending on the location of the obstruction, which determines the three main subtypes of BRVO (branch retinal vein occlusion), HRVO (hemiretinal vein occlusion) and CRVO (central retinal vein occlusion).

RVO has been reported as the second leading cause of blindness in patients with retinal vascular disease, following diabetic retinopathy. Macular oedema is a frequent cause of visual acuity loss in RVO, but vision loss can also occur from macular ischemia and/or complications of retinal or iris neovascularisation. If left untreated, RVO-induced chronic macular oedema can lead to permanent vision loss**.**

Safety in this application was assessed through descriptive summaries of ocular and non-ocular adverse events, including SAEs and adverse events of special interest, deaths, and ocular assessments (IOP, slit lamp examination, and indirect ophthalmoscopy). Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities were reported as AEs and evaluated as part of the AE assessments.

The following Standard MedDRA Queries (SMQs) are used to present unadjudicated non-ocular ATEs and cerebrovascular haemorrhagic AEs:
• Unadjudicated ATEs include non-ocular events from the following narrow SMQ: Myocardial infarction; Ischaemic central nervous system vascular conditions; Other ischaemic heart disease; Embolic and thrombotic events, arterial.
• Cerebrovascular haemorrhagic events include non-ocular events from the following narrow SMQs: Conditions associated with central nervous system haemorrhages and cerebrovascular accidents; Haemorrhagic central nervous system vascular conditions.
The safety analyses are based on the safety-evaluable population. The AE data in this initial submission are presented before the Week 24 visit whereas the summaries by visit including labs, vital signs, and other ocular assessments (IOP, slitlamp examination, and indirect ophthalmoscopy) are presented through Week 24.

The safety profile of faricimab in patients with RVO, is based on data from the two pivotal, nearly identically designed Phase III studies, multicentre, randomised, double-masked, 2-part studies in patients with RVO, as also detailed in the efficacy section of this AR:

- **Study GR41984 (BALATON)** in patients with macular oedema due to **branch** retinal vein occlusion (BRVO).
- **Study GR41986 (COMINO)** in patients with macular oedema due to **central** retinal vein occlusion or **hemiretinal** vein occlusion (C/HRVO).

As summarised in Table 40 below, this safety analysis from the two individual studies and pooled Phase III safety data (BALATON and COMINO), is presented by:

- Data through the day before the Week 24 visit,
- Data from Week 24 through the clinical cutoff date (CCOD) of 6 July 2022 for BALATON and 9 August 2022 for COMINO. These data are from Part 2 of the RVO studies, which are evaluating a 6 mg faricimab PTI dosing regimen for all patients in the faricimab Q4W and aflibercept Q4W arms from Part 1.

Table 40. Summary table of the safety analysis from the two individual studies and pooled Phase III safety data (BALATON and COMINO)

Protocol Name/No.	Countries	Study Design	Patient Subset	Criteria for Evaluation	Dose, Duration	No. of Patients	Study Status
Pivotal Studies							
BALATON (GR41984) **COMINO** (GR41986)	Global	Phase III, Two-Part, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, Parallel-Group Study	Patients with RVO: BRVO (BALATON) or C/HRVO (COMINO)	Efficacy, Safety, PK and PD	Part 1 (Q4W Dosing): Arm A: 6 mg faricimab intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Arm B: 2 mg aflibercept intravitreal injections Q4W from Day 1 through Week 20 (6 injections) Part 2 (PTI Regimen)*: Patients in both Arms A and B received 6 mg faricimab intravitreal injections to a PTI dosing regimen from Week 24 through Week 68	**Total Randomized** =1282 BALATON = 553 COMINO = 729 **Pooled Safety-Evaluable** = 1276 BALATON = 550 COMINO = 726	BALATON: Ongoing (CCOD 6 Jul 2022) COMINO: Ongoing (CCOD 9 Aug 2022) Primary analysis at Week 24[b]

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CCOD = clinical cutoff date; CRVO = central retinal vein occlusion; HRVO = hemiretinal vein occlusion; PD = pharmacodynamic; PK = pharmacokinetic; PTI = personalized treatment interval; Q4W = every 4 weeks; Q16W = every 16 weeks

* 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 Q16W or a minimum of Q4W based on the relative change of the CST and BCVA compared with the patient's reference CST and reference BCVA.

[b] Includes adverse events with onset prior to Week 24 treatment or dose hold or, if no Week 24 treatment or dose hold, prior to Day 168.

In **Part 1** (Q4W dosing) of the studies, 570 and 750 patients (in BALATON and COMINO, respectively) were planned to be randomised in a 1:1 ratio to one of two treatment arms (**faricimab 6mg** or aflibercept 2mg) as follows:

- **Faricimab** Q4W arm (n = 285 [BALATON]; n=375 [COMINO]): Patients randomly assigned to Arm A received faricimab 6 mg intravitreal injections Q4W from Day 1 through **Week 20** (6 injections).
- **Aflibercep**t Q4W arm (comparator arm, n= 285 [BALATON]; n=375 [COMINO]): patients randomly assigned to Arm B received aflibercept 2 mg intravitreal injections Q4W from Day 1 through Week 20 (6 injections).

In **Part 2**, patients received faricimab 6mg according to a personalised treatment interval (PTI) dosing schedule from Week 24 and had scheduled study **visits Q4W** through the end of the study (Week 72).

All patients should complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure is administered during study visits when (according to the PTI dosing regimen) no faricimab treatment is administered.

The primary analysis for BALATON and COMINO at Week 24 had been completed at the time of the initial submission for this EoI, and all safety data up to the clinical cutoff date (CCOD) based on the last patient last visit (LPLV) date for Week 24 for each study were reported herein. Patients randomized during the global enrolment phase of the studies are included.
At the time of the primary analysis, the Phase III RVO trials were ongoing. Safety data available from Week 24 to the CCOD was also assessed (i.e. the subset of patients with follow-up data beyond Week 24 up to the CCOD for the primary analysis (6 July 2022 for BALATON and 9 August 2022 for COMINO).

Updated safety data were also submitted to include the full safety data set with the MAH's responses to the Request for Supplementary Information (RSI) and are discussed under the relevant sections below.

In summary, the safety of faricimab was assessed in the two randomised, multi-centre, double-masked, 72-week long studies in patients with macular oedema secondary to BRVO (BALATON) or CRVO/HRVO (COMINO). Active comparator-controlled data are available through month 6, then as per the study design, in Part 2, all patients at Week 24 received either intravitreal faricimab 6 mg or sham treatment based on the T&E type regimen.

After 6 initial monthly doses, patients initially randomized to the aflibercept 2 mg arm were switched to the faricimab Q16W adjustable dosing arm, and could have received faricimab 6 mg according to a standardized treat-and-extend approach, where the dosing interval could be increased in 4-week increments or decreased by 4, 8 or 12-weeks based on anatomic and/or visual outcomes, using data obtained only at study drug dosing visits.

Study Populations
BALATON enrolled patients with macular oedema due to BRVO, whereas COMINO enrolled patients with macular oedema due to CRVO or HRVO. In both BALATON and COMINO studies, patients with BRVO or C/HRVO, respectively, had to be diagnosed no longer than 4 months prior to the screening visit and confirmed by the central reading centre based on spectral-domain optical coherence tomography (SD-OCT) or swept-source optical coherence tomography (SS-OCT) images.

Pooling and Safety Data Presentation
Safety data from BALATON and COMINO were pooled for the assessment of safety as both studies have a nearly identical study design, the same treatment regimens, same collection of safety data and no substantial difference in the overall safety profile of faricimab was expected in the BRVO and C/HRVO populations.

The analysis of pooled data up to Week 24 was based on the pooled safety-evaluable population (defined as all patients in either of the Phase III studies who received at least one injection of active study drug [faricimab or aflibercept], grouped according to the actual treatment received through Week 20) using the same analysis methodology as described in the individual studies SAP. The analysis of pooled data from Week 24 to CCOD was based on the pooled Part 2 safety-evaluable population, defined as all patients from either of the Phase III studies who have follow-up on or after the day of the Week 24 treatment (faricimab or sham) or Week 24 dose hold (or day 168 if neither treatment nor dose hold date are available), for patients who received faricimab in Part 1 of the studies receive at least one dose of faricimab, for patients who received aflibercept in Part 1 of the studies. For these analyses, patients are grouped according to the actual treatment received in Part 1 of the studies.

The safety data submitted with the responses to the RSI are presented by 3 groups:
- The 'pooled Part 2 dataset' (from Week 24 through the end of the studies, when all patients were on faricimab; BALATON and COMINO pooled),

- The 'Entire Study' group by treatment arms (from baseline through the end of the studies; BALATON and COMINO pooled), and
- The 'All Faricimab' group (from receiving the first administration of faricimab through the end of the studies; BALATON and COMINO pooled).

Overall extent of exposure

Overall, treatment exposure in all treatment arms was balanced between the individual Phase III studies. The majority of the randomised patients received at least one dose of study treatment in each treatment arm of the pooled dataset before the Week 24 visit. The median duration of exposure was the same between both treatment arms (20.1 weeks) in the individual studies and pooled dataset (Table 41 below). In the pooled dataset the mean and median number of study drug administrations was the same in the faricimab Q4W and aflibercept Q4W arms (mean= 5.8, median= 6.0).

Table 41. Summary of Study Treatment Exposure in the Study Eye through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Patients)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Treatment duration (weeks)						
n	276	274	365	361	641	635
Mean (SD)	19.7 (2.63)	20.0 (1.46)	19.9 (2.06)	19.7 (2.25)	19.8 (2.33)	19.8 (1.95)
Median	20.1	20.1	20.1	20.1	20.1	20.1
Min-max	0 - 21	8 - 21	0 - 22	0 - 22	0 - 22	0 - 22
Number of study drug administrations						
n	276	274	365	361	641	635
Mean (SD)	5.8 (0.72)	5.8 (0.46)	5.7 (0.68)	5.7 (0.72)	5.8 (0.69)	5.8 (0.62)
Median	6.0	6.0	6.0	6.0	6.0	6.0
Min-max	1 - 6	3 - 6	1 - 6	1 - 6	1 - 6	1 - 6
Dose interruption						
Number of doses interrupted	3	5	21	14	24	19
At least one interrupted dose	3 (1.1%)	5 (1.8%)	15 (4.1%)	11 (3.0%)	18 (2.8%)	16 (2.5%)
Intraocular inflammation	0	1 (0.4%)	2 (0.5%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
BCVA decrease	0	0	3 (0.8%)	0	3 (0.5%)	0
Elevated intraocular pressure	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
Rhegmatogenous retinal break	0	0	1 (0.3%)	0	1 (0.2%)	0
Rhegmatogenous retinal detachment or macular hole	0	0	0	0	0	0
Active or suspected infection	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
Cataract surgery in the study eye	1 (0.4%)	0	0	0	1 (0.2%)	0
Vitrectomy	0	0	1 (0.3%)	0	1 (0.2%)	0
Intraocular surgery in study eye	1 (0.4%)	0	0	0	1 (0.2%)	0
On-study prohibited medications	0	0	0	0	0	0
Other	2 (0.7%)	5 (1.8%)	11 (3.0%)	8 (2.2%)	13 (2.0%)	13 (2.0%)
Interruptions per patient						
n	3	5	15	11	18	16
1	3 (1.1%)	5 (1.8%)	10 (2.7%)	9 (2.5%)	13 (2.0%)	14 (2.2%)
2	0	0	4 (1.1%)	1 (0.3%)	4 (0.6%)	1 (0.2%)
3	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)

Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day. Includes study treatment received and dose hold on or prior to Week 24 treatment or dose hold or if none prior to Day 168. Percentages are based on N in the column headings. The number of study drug administered may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies. Active/suspected infection are ocular.

Before the Week 24 visit, 2.0% and 1.7% of patients received at least one anti-VEGF treatment administration in the fellow eye in the faricimab Q4W and aflibercept Q4W arms, respectively, with the most common anti-VEGFs being aflibercept and ranibizumab (Table 42 below). The majority were prescribed to treat fellow eye RVO.

Table 42. Summary of Anti-VEGF Administration in the Fellow Eye through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Patients)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Anti-VEGF administration in the fellow eye*						
At least one dose of anti-VEGF	5 (1.8%)	4 (1.5%)	8 (2.2%)	7 (1.9%)	13 (2.0%)	11 (1.7%)
Lucentis (ranibizumab)	2 (0.7%)	0	1 (0.3%)	2 (0.6%)	3 (0.5%)	2 (0.3%)
Macugen (pegaptanib sodium)	0	0	0	0	0	0
Eylea (aflibercept)	3 (1.1%)	4 (1.5%)	7 (1.9%)	5 (1.4%)	10 (1.6%)	9 (1.4%)
Avastin (Bevacizumab)	1 (0.4%)	0	0	0	1 (0.2%)	0
Other	0	0	0	0	0	0
Number of anti-VEGF doses						
1	0	0	1 (0.3%)	3 (0.8%)	1 (0.2%)	3 (0.5%)
2	3 (1.1%)	1 (0.4%)	3 (0.8%)	2 (0.6%)	6 (0.9%)	3 (0.5%)
3	1 (0.4%)	2 (0.7%)	3 (0.8%)	0	4 (0.6%)	2 (0.3%)
4	1 (0.4%)	1 (0.4%)	0	2 (0.6%)	1 (0.2%)	3 (0.5%)
5	0	0	1 (0.3%)	0	1 (0.2%)	0

VEGF = Vascular Endothelial Growth Factor.
Percentages are based on N in the column headings. Includes treatment received on or prior to Week 24 treatment or dose hold or if none prior to Day 168.
Patients with multiple administrations of the same drug are counted once. Patients with multiple administrations of different drugs are counted once for each drug.
*Anti-VEGF treatments prior to baseline are excluded.

At the time of the primary analysis, the Phase III trials were ongoing. Therefore, cumulative exposure data available as of the CCOD was also assessed (i.e., the subset of patients with follow-up data beyond Week 24). From Week 24, an additional 16.1 weeks (median) of treatment duration for 615 patients (out of 629 patients) in the faricimab Q4W to faricimab PTI arm and 12.3 weeks (median) of treatment duration for 586 patients (out of 586 patients) in the aflibercept Q4W to faricimab PTI arm were observed up to the CCOD.
From Week 24 to the CCOD, the additional mean number of study drug administrations were 2.6 in the faricimab Q4W faricimab PTI arm and 2.5 in the aflibercept Q4W faricimab PTI arm, and the median number of study drug administrations was 2.0 in both arms. From Week 24 to the CCOD, 1.9% and 1.0% of patients received at least one anti-VEGF administration in the fellow eye in the faricimab and aflibercept arms, respectively, with the most common anti-VEGFs being aflibercept and ranibizumab.
The updated safety discussion in this AR is mainly focused on the pooled Part 2 dataset (Week 24 through Week 72).

Extent of Exposure
The majority of randomized patients received at least one dose of study treatment (i.e., faricimab or aflibercept) during the entire study and most patients continued the study to receive faricimab adjustable T&E type regimen in Part 2.

Pooled Part 2 Dataset
In the pooled Part 2 dataset, the median duration of exposure to faricimab was longer in the faricimab Q4W to faricimab PTI arm than the aflibercept Q4W to faricimab PTI arm (**44.1 weeks** and **40.1 weeks** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively;) because the exposure is counted from Week 24 for the faricimab Q4W to faricimab PTI arm in contrast to the aflibercept Q4W to faricimab PTI arm where the exposure is counted from the first faricimab dose on or after Week 24. While the faricimab PTI dosing regimen started at Week 24, most patients received sham injections and not faricimab at Week 24 with 7% [19/270] and 11% [39/359] of patients in the faricimab Q4W to faricimab PTI arms and 9% [24/267] and 12% [40/342] of patients in the aflibercept Q4W to faricimab PTI arms receiving a faricimab dose in the BALATON and COMINO studies, respectively.

In the **pooled Part 2 dataset,** the mean (median) number of faricimab administrations was similar in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (5.3 [4.0] and 5.2 [4.0], respectively). In the separate studies, the mean (median) number of faricimab injections administered in Part 2 was generally comparable: BALATON: 4.8 (4.0) and 4.9 (4.0) vs. COMINO: 5.6 (5.0) and 5.5 (4.0) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI

arm, respectively. In the pooled Part 2 dataset, **1,238 patients** received at least one dose of faricimab (629 patients in the faricimab Q4W to faricimab PTI arm and 609 patients in the aflibercept Q4W to faricimab PTI arm.

Entire Study
In the **entire study** dataset, the median duration of exposure was 68.1 weeks in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (and the same duration in each study); the mean (median) number of study treatment administrations (i.e., faricimab or aflibercept) in the pooled dataset was the same in each treatment arm (10.8 [10.0]; the mean (median) number of study treatment administrations was comparable between the BALATON and COMINO studies: 10.3 (9.0) and 11.2 (10.0) vs. 10.6 (10.0) and 10.9 (10.0) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively .

All Faricimab
In the All Faricimab dataset, the median duration of exposure to faricimab was 44.1 weeks (same duration in each study); **the mean (median) number of faricimab administrations in the pooled dataset was 8.1** (9.0) and was comparable between the studies (7.7 [9.0] in BALATON and 8.4 [9.0] in COMINO.

The CHMP noted an integrated safety analysis based on pooling of the week 24 data from the two phase III, clinical studies BALATON and COMINO and considered this approach as acceptable: both studies are very similar with almost identical study design and include the same treatment regimens and collection of safety data.

Further limited data beyond week 24 until the CCOD in Part 2 of both studies was also initially provided.
The overall extent of exposure to faricimab and the comparator aflibercept to week 24 was balanced across both phase III studies.
As previously highlighted, both clinical studies were ongoing at the time of initial submission of this application, therefore the full safety data set was subsequently submitted during the procedure with the responses to the RSI. Throughout the study period, exposure across treatment arms was similar in both BALATON and COMINO studies.

A total of 1,282 patients (553 in BALATON and 729 in COMINO) were enrolled in the two studies, with **1,276 patients** treated with at least one dose through **week 24** (641 with faricimab). Patient ages ranged from 28 to 93 with a mean [SD] of 64 [10.7] years, and 22 to 100 with a mean [SD] of 65 [13.2] years in BALATON and COMINO, respectively.

In the **pooled Part 2** dataset, **1,238 patients** received at least one dose of faricimab (629 patients in the faricimab Q4W to faricimab PTI arm and 609 patients in the aflibercept Q4W to faricimab PTI arm.

In the **pooled Part 2** dataset, the mean (median) number of **faricimab** administrations was similar in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (5.3 [4.0] and 5.2 [4.0], respectively). In the separate studies, the mean (median) number of faricimab injections administered in Part 2 was generally comparable: BALATON: 4.8 (4.0) and 4.9 (4.0) vs. COMINO: 5.6 (5.0) and 5.5 (4.0) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

While focus is on the pooled Part 2 dataset (Week 24 through Week 72), of note the faricimab Q4W to faricimab PTI arm in the **Entire Study** group has the longest, continuous faricimab treatment duration of any of the safety groups and therefore it is reasonable that this data be used to support the consistency of safety profile in RVO with that in the DME (100 Weeks) and nAMD (112 Weeks), using exposure-adjusted AE rates from the faricimab arms in the other Phase III trials.

In the **Entire Study** dataset, the median duration of exposure was **68.1 weeks** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (and the same duration in each study).

In the **All Faricimab** dataset, the median duration of exposure to faricimab was 44.1 weeks (same duration in each study).

Demographics
In the pooled dataset, the overall mean age at randomization was 64.7 years with approximately half of the patients (53.4%) in the ≥ 65-year age category, and 3.6% in the ≥ 85-year age category. Approximately half of patients were female (48.0%) and from the 'Rest of the world countries' (49.2%; mostly consisting of European and South American countries). The majority of the patients were White (65.5%), and not of Hispanic or Latino ethnicity (79.3%).
The CHMP also noted that, for both phase III studies, the baseline demographic characteristics were broadly similar across both treatment arms in the pooled populations. However, limited numbers of patients > 85 years were included in both RVO studies. Safety in this population, particularly, in the RVO indication, is of interest due to limitations of (safety) data, reflected accordingly in SmPC (section 4.2, under "Special populations", Section 4.4 under "Systemic effects" and "Populations with limited data'', and PL section 2 - "What you need to know before you receive Vabysmo") also in relation to nAMD, as also outlined below.

Populations with limited data
The MAH highlighed that there is only limited experience in the treatment of nAMD patients ≥ 85 years, DME patients with type I diabetes, patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), high blood pressure (≥ 140/90 mmHg) and vascular disease, sustained dosing intervals shorter than every 8 weeks (Q8W), or nAMD, DME, and RVO patients with active systemic infections. Furthermore, there is limited safety information on sustained dosing intervals of 8 weeks or less and these may be associated with a higher risk of ocular and systemic adverse reactions, including serious adverse reactions. There is also no experience of treatment with faricimab in diabetic or RVO patients with uncontrolled hypertension. As mentioned in the SmPC (section 4.4), this lack of information should be considered accordingly by the physician when treating such patients.

Baseline Ocular Characteristics
In the ITT population, mean baseline BCVA and mean baseline CST in the study eye were comparable between faricimab Q4W and aflibercept Q4W arms in both BALATON and COMINO studies. As expected from the RVO phenotype, patients in the BALATON study had a higher baseline BCVA and lower CST values compared to patients in the COMINO study. Mean (SD) time since diagnosis RVO in the study eye was 1.39 (4.92) months, while the median (min-max) was 0.84 months (0.1-120.6).

Baseline Non-ocular Characteristics
In the pooled ITT population, non-ocular baseline characteristics were comparable across the two treatment arms, with no significant differences observed between the individual study populations.

Adverse events

Table 43. Overview of Safety through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety- Evaluable Patients)

	GR41984(BALATON) (N=550)		GR41986(COMINO) (N=726)		Pooled(BALATON and COMINO) (N=1276)	
	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one AE	125 (45.3%)	128 (46.7%)	174 (47.7%)	200 (55.4%)	299 (46.6%)	328 (51.7%)
Total number of AEs	227	290	403	465	630	755
Total number of patients with at least one SAE	12 (4.3%)	17 (6.2%)	32 (8.8%)	33 (9.1%)	44 (6.9%)	50 (7.9%)
Total number of SAEs	13	24	40	58	53	82
Total number of deaths	1 (0.4%)	0	1 (0.3%)	2 (0.6%)	2 (0.3%)	2 (0.3%)
Total number of patients withdrawn from study due to an AE	2 (0.7%)	1 (0.4%)	2 (0.5%)	4 (1.1%)	4 (0.6%)	5 (0.8%)
Total number of patients withdrawn from study treatment due to an AE	1 (0.4%)	1 (0.4%)	3 (0.8%)	3 (0.8%)	4 (0.6%)	4 (0.6%)
Total number of patients with at least one AESI	1 (0.4%)	2 (0.7%)	9 (2.5%)	14 (3.9%)	10 (1.6%)	16 (2.5%)
Ocular events: study eye total number of patients with at least one						
AE	45 (16.3%)	56 (20.4%)	84 (23.0%)	100 (27.7%)	129 (20.1%)	156 (24.6%)
SAE	3 (1.1%)	2 (0.7%)	9 (2.5%)	12 (3.3%)	12 (1.9%)	14 (2.2%)
AE leading to withdrawal from study treatment	0	0	3 (0.8%)	2 (0.6%)	3 (0.5%)	2 (0.3%)
Treatment related AEs	1 (0.4%)	2 (0.7%)	14 (3.8%)	8 (2.2%)	15 (2.3%)	10 (1.6%)
Treatment related SAEs	0	0	3 (0.8%)	2 (0.6%)	3 (0.5%)	2 (0.3%)
AE of Special Interest	1 (0.4%)	2 (0.7%)	8 (2.2%)	12 (3.3%)	9 (1.4%)	14 (2.2%)
Drop in VA score >=30	1 (0.4%)	2 (0.7%)	6 (1.6%)	6 (1.7%)	7 (1.1%)	8 (1.3%)
Associated with severe IOI	0	0	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	2 (0.5%)	6 (1.7%)	2 (0.3%)	6 (0.9%)
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	26 (9.4%)	20 (7.3%)	28 (7.7%)	34 (9.4%)	54 (8.4%)	54 (8.5%)
SAE	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
AE of Special Interest	0	0	1 (0.3%)	2 (0.6%)	1 (0.2%)	2 (0.3%)
Drop in VA score >=30	0	0	1 (0.3%)	2 (0.6%)	1 (0.2%)	2 (0.3%)
Associated with severe IOI	0	0	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0	0	0
Non-ocular events total number of patients with at least one						
AE	90 (32.6%)	97 (35.4%)	121 (33.2%)	134 (37.1%)	211 (32.9%)	231 (36.4%)
SAE	9 (3.3%)	16 (5.8%)	22 (6.0%)	23 (6.4%)	31 (4.8%)	39 (6.1%)
AE leading to withdrawal from study treatment	1 (0.4%)	1 (0.4%)	0	1 (0.3%)	1 (0.2%)	2 (0.3%)
AE of Special Interest	0	0	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0	0	0
Adjudicated APTC events	3 (1.1%)	4 (1.5%)	4 (1.1%)	5 (1.4%)	7 (1.1%)	9 (1.4%)
Non-fatal MI	1 (0.4%)	2 (0.7%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	4 (0.6%)
Non-fatal Stroke	2 (0.7%)	2 (0.7%)	3 (0.8%)	2 (0.6%)	5 (0.8%)	4 (0.6%)
Death	0	0	0	1 (0.3%)	0	1 (0.2%)

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; AE= adverse events; SAE=Serious Adverse Event; MI = myocardial infarctions; 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 25.0.
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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

The safety data in **Part 1** indicates that faricimab has a comparable safety profile to aflibercept at Week 24. The safety data in **Part 2** indicate that faricimab continues to be generally well tolerated.

As noted in the RVO initial clinical overview (CO), a slightly higher incidence of ocular AEs (including ocular SAEs) in both treatment arms continued to be reported in Part 2 in COMINO (C/HRVO) compared with BALATON (BRVO) which is consistent with historical RVO pivotal trials.

Key pooled safety results (BALATON and COMINO, n = 1,238 patients) from **Part 2** are presented in the table below.

Table 44. Safety Summary for Study Part 2, Safety-Evaluable Population

	Pooled(BALATON and COMINO)	
	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=629)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=609)
Total number of patients with at least one AE	419 (66.6%)	394 (64.7%)
Total number of AEs	1339	1198
Total number of patients with at least one SAE	84 (13.4%)	77 (12.6%)
Total number of SAEs	121	116
Total number of deaths	5 (0.8%)	3 (0.5%)
Total number of patients withdrawn from study due to an AE	9 (1.4%)	9 (1.5%)
Total number of patients withdrawn from study treatment due to an AE	8 (1.3%)	10 (1.6%)
Total number of patients with at least one AESI	23 (3.7%)	10 (1.6%)
Ocular events: study eye total number of patients with at least one		
AE	206 (32.8%)	199 (32.7%)
SAE	30 (4.8%)	15 (2.5%)
AE leading to withdrawal from study treatment	5 (0.8%)	4 (0.7%)
Treatment related AEs	21 (3.3%)	19 (3.1%)
Treatment related SAEs	4 (0.6%)	0
AE of Special Interest	22 (3.5%)	10 (1.6%)
Drop in VA score >=30	16 (2.5%)	8 (1.3%)
Associated with severe IOI	0	1 (0.2%)
Intervention req. to prevent permanent vision loss	6 (1.0%)	1 (0.2%)
Suspected transmission of infectious agent by study drug	0	0
Non-ocular events total number of patients with at least one		
AE	327 (52.0%)	300 (49.3%)
SAE	55 (8.7%)	64 (10.5%)
AE leading to withdrawal from study treatment	3 (0.5%)	6 (1.0%)
AE of Special Interest	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0
Adjudicated APTC events	10 (1.6%)	14 (2.3%)
Non-fatal MI	4 (0.6%)	4 (0.7%)
Non-fatal Stroke	3 (0.5%)	8 (1.3%)
Death	3 (0.5%)	3 (0.5%)

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; AE= adverse events; SAE=Serious Adverse Event; MI = myocardial infarctions; 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 26.0.

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. Part 2, for faricimab Q4W to faricimab PTI arm, includes AEs with onset on or after the Week 24 treatment or dose hold or if none onset on or after Day 168 through Week 72, or for the aflibercept Q4W to faricimab PTI arm, includes AEs with an onset on or after the date of the first faricimab dose through Week.

Adverse events-pooled phase III RVO studies

Before the Week 24 Visit

In the pooled RVO safety data, the incidence of ocular AEs in the study eye was comparable across the treatment arms (20.1% and 24.6% in the faricimab Q4W and aflibercept Q4W arms, respectively).

The most common ocular AEs in the study eye (≥2% incidence in either pooled treatment arm: faricimab Q4W arm and aflibercept Q4W arm, respectively) by PT were conjunctival haemorrhage (2.8% and 3.8%), intraocular pressure increased (1.4% and 3.1%), vitreous detachment (2.3% and 1.7%), and dry eye (1.6% and 2.4%).

Ocular AEs in the study eye occurring in ≥1% in any treatment arm are summarized in Table 45 below.

There were no clinically meaningful differences in incidence of ocular AEs in the study eye across the treatment arms. Where minor numerical differences in the incidence of ocular AEs were noted in the faricimab Q4W arm between the BALATON and COMINO, the type and nature of the events were similar (for example, vitreous detachment, IOP increased, ocular hypertension).

The **per 1000 injection rate** of ocular AEs in the study eye was 51.23 and 61.24 events per 1000 injections in the faricimab Q4W and aflibercept Q4W arms, respectively.

The overall exposure-adjusted incidence rates for ocular AEs per 100 patient years (PY) in the study eye were 63.60 and 76.31, in the faricimab Q4W and aflibercept Q4W arms respectively.

In the **BALATON** study through Week 24 the incidence of ocular AEs in the study eye was comparable between the treatment arms (16.3% and 20.4% in the faricimab Q4W and aflibercept Q4W arms, respectively) The most common ocular AEs (≥ 2% in any treatment arm) were conjunctival haemorrhage, dry eye, vitreous floaters and IOP increased. The incidence of ocular AEs suspected by the investigator to be related to the study treatment was low (1 patient [0.4%] and 2 patients [0.7%] in the faricimab Q4W and aflibercept Q4W arms, respectively. The per 1000 injection rate of ocular AEs in the study eye was 37.08 and 50.66 events in the faricimab Q4W and aflibercept Q4W arms, respectively. The rate of ocular AEs per 100 patient years was 46.15 and 63.92 in the faricimab Q4W and aflibercept Q4W arms, respectively. The majority of ocular events in the study eye were mild 4 patients (1.4%) and 8 patients (2.9%) experienced events of moderate severity in the faricimab Q4W and aflibercept Q4W arms, respectively. No patients experienced severe events in the faricimab Q4W arm, and 1 patient experienced a severe event of vitreous haemorrhage in the aflibercept Q4W arm.

In the **COMINO** study, the incidence of ocular AEs in the study eye was comparable between the treatment arms (23.0% and 27.7% in the faricimab Q4W and aflibercept Q4W arms, respectively).

The most common ocular AEs (> 2% in any treatment arm) were conjunctival haemorrhage, IOP increased and vitreous detachment.

The incidence of ocular AEs suspected by the investigator to be related to the study treatment was low and numerically higher in the faricimab Q4W arm compared with the aflibercept Q4W arm (14 patients [3.8%] and 8 patients [2.2%] in the faricimab Q4W and aflibercept Q4W arms, respectively). The overall most common ocular AE related to study treatment was IOP increased (1 patient [0.3%] and 4 patients [1.1%] in the faricimab Q4W and aflibercept Q4W arms, respectively). In the faricimab Q4W arm, the most frequent related AE was vitritis (3 patients [0.8%], all events were non-serious and mild in severity), which were linked to a small number of IOI events).

The per 1000 injection rate of ocular AEs in the study eye was comparable across treatment arms (61.96 and 69.45 events in the faricimab Q4W and aflibercept Q4W arms, respectively).

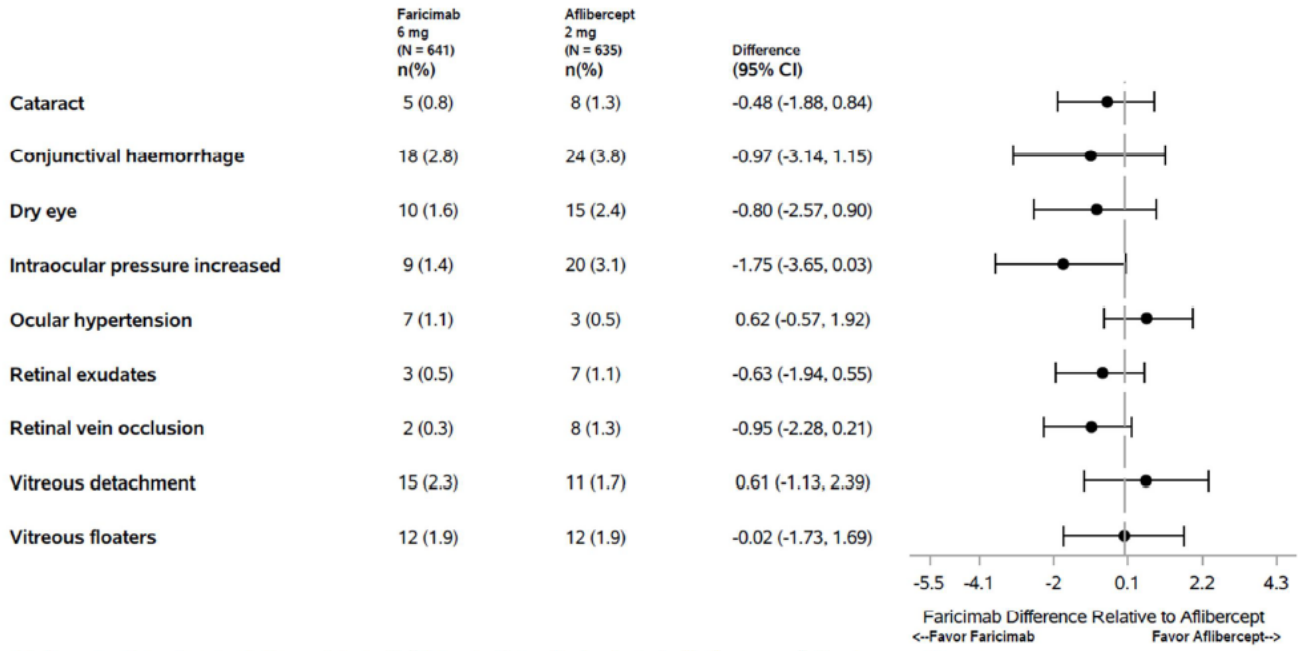
The rate of ocular AEs per 100 patient years was comparable between the treatment arms (76.78 and 85.72 in the faricimab Q4W and aflibercept Q4W arms, respectively.

Table 45. Common Ocular Adverse Events (1% in Any Treatment Arm) in the Study Eye through Week 24 from the Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	45 (16.3%)	56 (20.4%)	84 (23.0%)	100 (27.7%)	129 (20.1%)	156 (24.6%)
Total number of events	59	81	130	143	189	224
Conjunctival haemorrhage	8 (2.9%)	10 (3.6%)	10 (2.7%)	14 (3.9%)	18 (2.8%)	24 (3.8%)
Intraocular pressure increased	1 (0.4%)	7 (2.6%)	8 (2.2%)	13 (3.6%)	9 (1.4%)	20 (3.1%)
Vitreous detachment	4 (1.4%)	2 (0.7%)	11 (3.0%)	9 (2.5%)	15 (2.3%)	11 (1.7%)
Dry eye	5 (1.8%)	9 (3.3%)	5 (1.4%)	6 (1.7%)	10 (1.6%)	15 (2.4%)
Vitreous floaters	6 (2.2%)	6 (2.2%)	6 (1.6%)	6 (1.7%)	12 (1.9%)	12 (1.9%)
Cataract	3 (1.1%)	1 (0.4%)	2 (0.5%)	7 (1.9%)	5 (0.8%)	8 (1.3%)
Eye pain	0	4 (1.5%)	6 (1.6%)	2 (0.6%)	6 (0.9%)	6 (0.9%)
Epiretinal membrane	2 (0.7%)	3 (1.1%)	3 (0.8%)	2 (0.6%)	5 (0.8%)	5 (0.8%)
Ocular hypertension	0	1 (0.4%)	7 (1.9%)	2 (0.6%)	7 (1.1%)	3 (0.5%)
Retinal exudates	2 (0.7%)	3 (1.1%)	1 (0.3%)	4 (1.1%)	3 (0.5%)	7 (1.1%)
Retinal vein occlusion	1 (0.4%)	3 (1.1%)	1 (0.3%)	5 (1.4%)	2 (0.3%)	8 (1.3%)
Cystoid macular oedema	0	1 (0.4%)	3 (0.8%)	5 (1.4%)	3 (0.5%)	6 (0.9%)
Pain	5 (1.8%)	0	1 (0.3%)	1 (0.3%)	6 (0.9%)	1 (0.2%)
Retinal tear	0	0	2 (0.5%)	4 (1.1%)	2 (0.3%)	4 (0.6%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; AE = Adverse Event;
Investigator text for AEs encoded using MedDRA version 25.0. Retinal Vein Occlusion (RVO) refers to unexpected worsening of RVO. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Figure 39. Common Ocular Adverse Events (1% in Any Treatment Arm) in the Study Eye through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)



AE= Adverse Events; Investigator text for AEs encoded using MedDRA version 25.0. n = Number of patients with at least one applicable adverse event. Percentages are based on N in the column headings. Includes events with onset prior to Week 24 treatment or dose hold or if none prior to Day 168. Newcombe with continuity correction method is used for the difference and 95% CI.

Ocular Adverse Events Related to Treatment: before the week 24 visit Ocular AEs Suspected by the Investigator to be Related to Faricimab
The incidence of ocular AEs suspected by the investigator to be related to faricimab was low (2.3% in the faricimab Q4W arm). There were more ocular AEs that were suspected by the investigator to be related to faricimab occurring in COMINO (1 patient in BALATON vs. 14 patients in COMINO).

In the faricimab Q4W arm, the most common (>2 patients) ocular AEs suspected by the investigator to be related to study treatment in the study eye were **vitritis** (3 patients [0.5%]) and **intraocular pressure increased, cataract, uveitis,** and **vitreous floaters** (2 patients [0.3%] each).

Ocular AEs Suspected by the Investigator to be Related to Aflibercept
The incidence of ocular AEs suspected by the investigator to be related to aflibercept was low (1.6% in the aflibercept Q4W arm). There were more ocular AEs that were suspected by the investigator to be related to aflibercept occurring in COMINO (2 patients in BALATON vs. 8 patients in COMINO. In the aflibercept Q4W arm, the most common (>2 patients) ocular AE suspected by the investigator to be related to study treatment in the study eye was **intraocular pressure increased** (4 patients [0.6%]).

Part 2: Week 24 through CCOD
At the time of the primary analysis, the Phase III RVO trials were ongoing. Safety data available from Week 24 to the CCOD were also assessed (i.e., the subset of patients with follow-up data beyond Week 24 up to the CCOD for the primary analysis).

As per the RVO study designs, all patients at Week 24 received either intravitreal faricimab 6 mg or sham treatment based on the PTI dosing regimen. Therefore, safety data from Week 24 through CCOD are discussed for patients in the faricimab Q4W arm, and patients in the aflibercept Q4W arm in Part 1 of the studies who switched to faricimab PTI in Part 2.

For the aflibercept Q4W to faricimab PTI arm (i.e., patients switching from aflibercept to faricimab after Week 20), AEs are listed from the first faricimab dose on or after Week 24 to CCOD.
For the patients who received aflibercept 2 mg Q4W in Part 1, any ocular events occurring after Week 24 and prior to receiving the first faricimab injection are listed. Most ocular AEs that occurred in this period were non-serious and mild to moderate.

In Part 2, **20.7%** of patients and **17.1%** of patients experienced at least one ocular AE in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.
In the aflibercept Q4W to faricimab PTI arm, the types of ocular adverse events were generally consistent with the events seen in the aflibercept Q4W arm before the Week 24 visit.

Similarly, the types of events observed in the faricimab Q4W to faricimab PTI arm from Week 24 to the CCOD were consistent with those in the faricimab Q4W arm before the Week 24 visit.

The most **common ocular AEs** in the study eye (> 2% incidence in any treatment arm: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arm, respectively,) by PT were **macular oedema** (2.2% and 2.6%) and **intraocular pressure increased** (2.1% and 1.9%).

The **incidence** of ocular AEs in both arms from Week 24 to CCOD was consistent with the incidence of ocular AEs before Week 24. The incidence of ocular AEs suspected by the investigator to be related to faricimab in the **faricimab Q4W to faricimab PTI arm** remained low (9 patients **[1.4%]**)**.** The most common (2 patients) ocular AEs suspected by the investigator to be related to study treatment in the study eye were **intraocular pressure increased** and **epiretinal membrane** (2 patients each).The incidence of ocular AEs suspected by the investigator to be related to faricimab in **the aflibercept Q4W to faricimab PTI arm** remained low (9 patients **[1.5%]**).The most common (2 patients) ocular

AEs suspected by the investigator to be related to study treatment in the study eye were **intraocular pressure increased** (3 patients) and **vitreous floaters** (2 patients).

The number of **ocular AEs per 1000 injections** in the study eye was **120.61 in** the faricimab Q4W to faricimab PTI arm and **108.00** in the aflibercept Q4W to faricimab PTI arm. However, the number of injections from Week 24 is lower as patients are receiving sham in Part 2, resulting in a higher rate per 1000 injections from Week 24 to CCOD. The exposure-adjusted incidence rates of **ocular AEs per 100 PY** were comparable between the faricimab Q4W to faricimab PTI arm and the aflibercept Q4W to faricimab PTI arm (**75.49** and **82.85,** respectively).

Ocular AEs Pooled Part 2 dataset
The most common ocular AEs by PT occurring in the study eye (≥ 2% in any treatment arm of the **pooled Part 2** dataset: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) were **intraocular pressure** (IOP) increased (4.8% and 3.8%), **cataract** (3.7% and 4.1%), **macular oedema** (MO; 3.2% and 3.1%; majority reported as verbatim worsening), **conjunctival haemorrhage** (3.3% and 2.8%), **RVO** (3.2% and 2.6%; majority reported as verbatim worsening of RVO), **vitreous detachment** (2.1% and 3.8%), **cystoid macular oedema** (CMO; 3.3% and 2%; majority reported as verbatim worsening), **epiretinal membrane** (1% and 3%), and **vitreous floaters** (0.2% and 2.6%). The majority of the events of MO, CMO, and RVO were reported as verbatim worsening of disease. These were mostly reported as non-serious and resolved by the end of the study. The total incidence of **worsening of disease** in the **pooled Part 2** dataset was approximately **10%** (approximately 3% for MO, CMO and RVO each.

The majority of the reported **epiretinal membrane** (ERM) **events** were reported as non-serious and mild in severity. The presence of RVO is a risk factor for the formation of epiretinal membrane. The overall rates of epiretinal membrane events were low, with the majority reported as non-serious and mild in severity. Epiretinal membrane prevalence increases in the presence of RVO, with the Blue Mountains Eye Study finding a prevalence rate of 16.1% in those with RVO, compared with 6.2% in idiopathic cases (Mitchell et al. 1997). The MAH was therefore requested to discuss this topic further and consider the need to reflect information relating to this issue in the PI.

In it's response, the MAH acknowledged that the incidence of ERM events was higher in the Phase III RVO studies than what previously reported from DME and nAMD Phase III trials. However, in the absence of any evidence of a causal association between faricimab and ERM events, updates to SmPC (i.e. section 4.4 and 4.8) for the RVO indication were not considered warranted. Evidence supporting this view is summarised below.

Of note, unlike the Phase III DME trials, the presence of ERM at baseline was **not** an exclusion criteria for the RVO trials.

ERMs are commonly found in older people and can be associated with ocular pathology, although most cases occur in the absence of ocular disease and are considered idiopathic (Kanukollu and Agarwal 2023). However, ERMs can also be associated with diabetic eye disease and RVO, where there is an upregulation of pro-inflammatory cytokines resulting in a proliferation of fibrocellular tissue on the retinal surface leading to ERM formation (Romano et al. 2018; Lee et al. 2020).

The Blue Mountains Eye Study showed that a higher prevalence of ERM was observed among individuals with RVO (16.1%) compared to those with no ocular disease (6.2% idiopathic cases; Mitchell et al. 1997). Furthermore, ERM prevalence was also higher in those who had cataract surgery (16.8%) followed by diabetic retinopathy (11%). Overall, the prevalence of ERMs vary widely, with reports ranging from 2.2% to 18.5% (Ng et al. 2011).

Individuals with ERM are generally asymptomatic, and treatment (which involves a surgical intervention of peeling the ERM away from the overlying retina) is only required if there is progression

resulting in a significant distortion of vision. In the Blue Mountains Eye Study, progression of ERM occurred in ~29% of individuals (Fraser-Bell et al. 2003).

As above stated, and also summarised in the Week 72 Addendum to the CO, the overall rates of ERM events reported from the RVO Phase III studies were low with the majority reported as non-serious, mild in severity, and all having confounding factors related to underlying disease, concurrent events, or ocular procedures.

There was one event in the faricimab arm in the COMINO study reported as severe and that required surgical intervention. However, this case was confounded by the fact that the patient had a prior event of intraocular inflammation (uveitis) and worsening of macular oedema, which would have increased the risk of ERM development.

In summary, in the MAH's view, ERM formation and progression is known to be associated with the underlying RVO disease. On review of all applicable data, the MAH considered that an update to the EU SmPC to include information on epiretinal membrane events in patients treated with faricimab in the RVO indication was not warranted.

The MAH considers that an update to the EU SmPC to include information on epiretinal membrane events in patients treated with faricimab in the RVO indication is not warranted given the lack of evidence of any causal association with the occurrence of ERM events and treatment with faricimab.
The CHMP accepted the MAH's conclusion. However, **ERM events should continue to be closely monitored and presented in future PSURs.**

All the **vitreous floaters** events were reported as non-serious, and most were considered mild in severity. The rate of vitreous floaters per 100 patient years (PY) in the pooled Part 2 dataset of the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, was consistent with that in Part 1.

The exposure-adjusted incidence rate of ocular AEs per 100 PY was consistent with Part 1 for both arms (**65.23** and **71.53** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively, 63.60 and 76.31 in the pooled faricimab and aflibercept arms in Part 1, respectively.

In the **Entire Study** dataset, the incidence of **ocular AEs** in the faricimab Q4W to faricimab PTI arm representing the longer-term safety data for faricimab was 43.2%. The majority of RVO disease worsening events (i.e., worsening of RVO, MO and CMO) were reported as non-serious, mild, and resolved by the end of the study.
The exposure-adjusted incidence rates of ocular AEs per 100 PY in the faricimab Q4W to faricimab PTI arm was 65.96. This rate was consistent with the other faricimab Phase III studies (DME: 56.88 and nAMD: 68.90; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS).

The **rates of ocular AEs per 1000 injections** in the faricimab Q4W to faricimab PTI arm was **82.18.** This rate was consistent with the other pooled faricimab treatment arms in the Phase III studies (DME: **81.68** and nAMD: **131.73;** DME Yr2 2.7.4 SCS). The ADRs that were reported with a frequency of ≥1% in the BRVO and C/HRVO in the All Faricimab group at **Week 72** were **conjunctival hemorrhage, cataract, vitreous detachment, vitreous floaters, eye pain, and IOP increased**.

Table 46. ADR Ocular Adverse Events in the Study Eye for All Faricimab Exposure through the Entire Study (Week 112 nAMD, Week 100 DME, Week 72 RVO), Safety-Evaluable Population

	nAMD	DME	BRVO	C/HRVO	Combined Indications
MedDRA Preferred Term	All Faricimab Patients (N=664)	All Faricimab Patients (N=1262)	All Faricimab Patients (N=543)	All Faricimab Patients (N=707)	All Faricimab Patients (N=3176)
Total number of patients with at least one adverse event	240 (36.1%)	421 (33.4%)	107 (19.7%)	154 (21.8%)	922 (29.0%)
Total number of events	489	694	161	262	1606
Cataract	58 (8.7%)	187 (14.8%)	21 (3.9%)	32 (4.5%)	298 (9.4%)
Conjunctival haemorrhage	59 (8.9%)	96 (7.6%)	27 (5.0%)	27 (3.8%)	209 (6.6%)
Vitreous detachment	34 (5.1%)	59 (4.7%)	20 (3.7%)	31 (4.4%)	144 (4.5%)
Intraocular pressure increased	27 (4.1%)	53 (4.2%)	21 (3.9%)	36 (5.1%)	137 (4.3%)
Vitreous floaters	30 (4.5%)	49 (3.9%)	16 (2.9%)	14 (2.0%)	109 (3.4%)
Eye pain	25 (3.8%)	32 (2.5%)	7 (1.3%)	13 (1.8%)	77 (2.4%)
Lacrimation increased	6 (0.9%)	15 (1.2%)	3 (0.6%)	5 (0.7%)	29 (0.9%)
Eye pruritus	8 (1.2%)	10 (0.8%)	2 (0.4%)	5 (0.7%)	25 (0.8%)
Corneal abrasion	12 (1.8%)	10 (0.8%)	2 (0.4%)	0	24 (0.8%)
Vision blurred	8 (1.2%)	8 (0.6%)	3 (0.6%)	4 (0.6%)	23 (0.7%)
Visual acuity reduced	4 (0.6%)	9 (0.7%)	5 (0.9%)	5 (0.7%)	23 (0.7%)
Ocular hyperaemia	8 (1.2%)	8 (0.6%)	0	6 (0.8%)	22 (0.7%)
Eye irritation	12 (1.8%)	7 (0.6%)	1 (0.2%)	1 (0.1%)	21 (0.7%)
Iritis	8 (1.2%)	5 (0.4%)	2 (0.4%)	6 (0.8%)	21 (0.7%)
Ocular discomfort	8 (1.2%)	9 (0.7%)	1 (0.2%)	1 (0.1%)	19 (0.6%)
Retinal pigment epithelial tear	19 (2.9%)	0	0	0	19 (0.6%)
Iridocyclitis	2 (0.3%)	5 (0.4%)	2 (0.4%)	8 (1.1%)	17 (0.5%)
Vitreous haemorrhage	3 (0.5%)	6 (0.5%)	2 (0.4%)	5 (0.7%)	16 (0.5%)
Uveitis	4 (0.6%)	7 (0.6%)	0	3 (0.4%)	14 (0.4%)
Vitritis	4 (0.6%)	2 (0.2%)	1 (0.2%)	7 (1.0%)	14 (0.4%)
Sensation of foreign body	2 (0.3%)	7 (0.6%)	0	2 (0.3%)	11 (0.3%)
Endophthalmitis	3 (0.5%)	6 (0.5%)	0	1 (0.1%)	10 (0.3%)
Retinal tear	1 (0.2%)	3 (0.2%)	2 (0.4%)	4 (0.6%)	10 (0.3%)
Conjunctival hyperaemia	2 (0.3%)	3 (0.2%)	0	2 (0.3%)	7 (0.2%)
Procedural pain	3 (0.5%)	1 (<0.1%)	0	0	4 (0.1%)
Rhegmatogenous retinal detachment	1 (0.2%)	1 (<0.1%)	1 (0.2%)	1 (0.1%)	4 (0.1%)
Visual acuity reduced transiently	0	1 (<0.1%)	0	1 (0.1%)	2 (<0.1%)
Cataract traumatic	1 (0.2%)	0	0	0	1 (<0.1%)

MedDRA = Medical Dictionary for Regulatory Activities. Investigator text for AEs encoded using MedDRA version 24.1 for nAMD, MedDRA version 24.0 for DME and MedDRA version 26.0 for RVO(BRVO and C/HRVO). 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 an onset on or after the date of the first faricimab dose through end of study.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all six studies.

ADR terms: Uveitis, Iritis, Vitritis, Iridocyclitis, 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 haemorrhage, Vitreous floaters, Eye pruritus, Eye irritation, Ocular discomfort, Eye pain, Sensation of foreign body, Corneal abrasion, Cataract, Visual acuity reduced, Conjunctival hyperaemia, Vitreous detachment, Cataract traumatic, Procedural pain.

The most common pooled **serious ADRs** in the RVO indications (≥2 patients) by PT were **uveitis** (3 patients in the faricimab Q4W to faricimab PTI arm for C/HRVO), **cataract** (1 patient each in the aflibercept Q4W to faricimab PTI arm for BRVO and C/HRVO, respectively), **rhegmatogenous retinal detachment** (1 patient each in the faricimab Q4W to faricimab PTI arm for BRVO and C/HRVO, respectively), and **vitreous haemorrhage** (2 patients in the faricimab Q4W to faricimab PTI arm for C/HRVO). The majority of the serious ADRs resolved, resolved with sequelae, or were resolving by Week 72 for BRVO and C/HRVO events, with the exception of **cataract** and **vitritis**).

Cataract was a sight-threatening ADR that caused a decrease of ≥30 letters in VA score lasting more than 1 hour in ≥ 2 patients in the All Faricimab group; no sight-threatening ADRs that required surgical or medical intervention to prevent permanent loss of sight occurred in ≥2 patients in the faricimab Q4W arm.

There was one pooled **sight-threatening ADR (endophthalmitis), which was associated with severe IOI.**

Having considered available data, the CHMP agreed that, in relation to ocular AEs, the overall rates observed across the pooled phase III studies were generally balanced between faricimab and aflibercept to week 24.The CHMP also noted that the most commonly reported ocular AEs, overall in

any treatment arm were conjunctival haemorrhage, IOP increased and vitreous detachment. The ocular safety profile observed to week 24 was generally in line with the established safety profile. In addition it was likewise noted that most of these AEs were mild to moderate in severity.

Ocular AEs from the pooled part 2 dataset
The most common ocular AEs by PT occurring in the study eye (≥ 2% in any treatment arm of the **pooled Part 2** dataset: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) were **intraocular pressure** (IOP) increased (4.8% and 3.8%), **cataract** (3.7% and 4.1%), **macular oedema** (MO; 3.2% and 3.1%; majority reported as verbatim worsening), **conjunctival haemorrhage** (3.3% and 2.8%), **RVO** (3.2% and 2.6%; majority reported as verbatim worsening of RVO), **vitreous detachment** (2.1% and 3.8%), **cystoid macular oedema** (CMO; 3.3% and 2%; majority reported as verbatim worsening), **epiretinal membrane** (1% and 3%), and **vitreous floaters** (0.2% and 2.6%).

The CHMP agreed that the most common ocular AEs in the study eye reported above are consistent with the disease under study, the RVO Week 24 data, and the known faricimab safety profile in other indications (DME and nAMD).

The exposure-adjusted incidence **rate of ocular AEs** per 100 PY was generally consistent with Part 1 for both arms (**65.23** and **71.53** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and **63.60** and **76.31** in the pooled faricimab and aflibercept arms in Part 1, respectively.

In the **entire study** dataset, the incidence of **ocular AEs** in the faricimab Q4W to faricimab PTI arm representing the longer-term safety data for faricimab was **43.2%.** The majority of RVO disease worsening events (i.e., worsening of RVO, MO and CMO) were reported as non-serious, mild, and resolved by the end of the study.

In the **entire study** dataset, the exposure-adjusted incidence **rates of ocular AEs** per 100 PY in the faricimab Q4W to faricimab PTI arm was **65.96.** This rate was consistent with the other faricimab Phase III studies(DME: **56.88** and nAMD: **68.90**; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS).
The rates of ocular AEs per 1000 injections in the faricimab Q4W to faricimab PTI arm was **82.18.** This rate was consistent with the other pooled faricimab treatment arms in the Phase III studies (DME: 81.68 and nAMD: 131.73).

Serious Ocular AEs in the Study Eye from the Pooled Phase III RVO Studies

Before the Week 24 Visit
The incidence of **serious ocular AEs** in the study eye occurred in the faricimab Q4W and aflibercept Q4W arms was comparable (1.9% and 2.2%, respectively). The overall incidence was low, and there were no differences observed at the individual PT level between the treatment arms.

The **most common serious ocular AE** in the study eye (2 patients in the faricimab Q4W arm or aflibercept Q4W arm) by PT were:

- retinal ischaemia (3 patients [0.5%] and 2 patients [0.3%]),
- CMO (verbatim: worsening of CMO, 2 patients [0.3%] and 2 patients [0.3%]),
- RVO (verbatim: worsening of CRVO, 2 patients [0.3%] and 2 patients [0.3%]),
- RAO (2 patients [0.3%] and 1 patient [0.2%]),
- uveitis (2 patients [0.3%] and 0 patients).

Most of these serious ocular AEs in the study eye occurred in the **COMINO** study.

By Week 24, **the majority of serious ocular AEs** had resolved or were resolving in both treatment arms.

The **serious ocular AEs** in the study eye that were **not resolved,** were macular ischaemia, RAO and RVO (verbatim: progression of CRVO) in 1 patient each in the **faricimab** Q4W arm and RVO (verbatim: progression of CRVO and progression of BRVO to CRVO) and retinal ischaemia in 2 patients each and RAO and vitreous haemorrhage in 1 patient each in the **aflibercept** Q4W arm (Table 47).

By Week 24, 3 patients (0.5%) and 2 patients (0.3%) in the faricimab Q4W arm and aflibercept Q4W arm, respectively, experienced at least one serious ocular AE suspected by the investigator to be related to faricimab. The serious ocular AEs suspected by the investigator to be related to faricimab were **uveitis** (2 patients [0.3%]), and **CMO, RAO**, and **retinal ischaemia** (1 patient [0.2%] each). All of these serious ocular AEs suspected by the investigator to be related to faricimab were either resolved or resolving by Week 24.

The **serious ocular AEs** suspected by the investigator to be related to aflibercept were intraocular pressure increased and retinal tear (1 patient 0.2%] each); both were resolved by Week 24.

The **rates of serious ocular AEs** per 1000 injections were comparable between the faricimab Q4W and aflibercept Q4W arms (**4.34** and **3.83**, respectively).

The exposure-adjusted incidence rates for serious ocular AEs per 100 PY in the study eye were similar between the faricimab Q4W and aflibercept Q4W arms (**5.38** and **4.77**, respectively)

Table 47. Serious Ocular Adverse Events in the Study Eye through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	GR41984(BALATON) (N=550)		GR41986(COMINO) (N=726)		Pooled(BALATON and COMINO) (N=1276)	
MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	3 (1.1%)	2 (0.7%)	9 (2.5%)	12 (3.3%)	12 (1.9%)	14 (2.2%)
Total number of events	3	2	13	12	16	14
Retinal ischaemia	2 (0.7%)	0	1 (0.3%)	2 (0.6%)	3 (0.5%)	2 (0.3%)
Cystoid macular oedema	0	0	2 (0.5%)	2 (0.6%)	2 (0.3%)	2 (0.3%)
Retinal vein occlusion	1 (0.4%)	1 (0.4%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
Retinal artery occlusion	0	0	2 (0.5%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Uveitis	0	0	2 (0.5%)	0	2 (0.3%)	0
Vitreous haemorrhage	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Eye injury	0	0	1 (0.3%)	0	1 (0.2%)	0
Intraocular pressure increased	0	0	0	1 (0.3%)	0	1 (0.2%)
Macular ischaemia	0	0	1 (0.3%)	0	1 (0.2%)	0
Macular oedema	0	0	0	1 (0.3%)	0	1 (0.2%)
Non-infectious endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Retinal artery embolism	0	0	0	1 (0.3%)	0	1 (0.2%)
Retinal tear	0	0	0	1 (0.3%)	0	1 (0.2%)
Rhegmatogenous retinal detachment	0	0	1 (0.3%)	0	1 (0.2%)	0
Visual acuity reduced	0	0	1 (0.3%)	0	1 (0.2%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities;
Investigator text for AEs encoded using MedDRA version 25.0. Retinal Vein Occlusion (RVO) refers to unexpected worsening of RVO. Relatedness are per principal investigator's assessments. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Table 48. Comparison of Ocular AEs and Ocular SAEs in RVO Pivotal Trials at Week 2

Study Drug	Pivotal Trial (FPI) RVO Subtype	Treatments[1] (Q4W)	Proportion of Patients with ≥1 Ocular AEs	Proportion of Patients with ≥1 Ocular SAEs (N)	
faricimab	BALATON (2021) BRVO	fari. 6 mg (n=276) aflib. 2 mg (n=274)	16.3% 20.4%	1.1% (3) 0.7% (2)	Primary CSR, Table 15, Table 16
	COMINO (2021) CRVO[4]	fari. 6 mg (n=365) aflib. 2 mg (n=361)	23.0% 27.7%	2.5% (9) 3.3% (12)	Primary CSR, Table 15, Table 16

BALATON study

The **per 1000 injection rate** of **serious ocular AEs** in the study eye was low and comparable across the treatment arms (1.89 and 1.25 in the faricimab Q4W and aflibercept Q4W arms, respectively).

The **rate** of serious ocular AEs per 100 patient years was also low and comparable in both treatment arms (2.35 and 1.58 in the faricimab Q4W and aflibercept Q4W arms).

The **incidence** of serious ocular AEs in the study eye was low, with 3 patients (1.1%) in the faricimab Q4W arm (RVO [verbatim: worsening of RVO; 1 patient] and retinal ischemia [2 patients]), and 2 patients (0.7%) in the aflibercept Q4W arms (RVO [1 patient] and vitreous haemorrhage [1 patient] (Table 49). By Week 24, the 3 serious ocular AEs in the faricimab Q4W arm had resolved, while the 2 serious ocular AEs in the aflibercept Q4W arm (vitreous haemorrhage and RVO) had not resolved. There were **no serious ocular AEs** suspected by the investigator to be related to study treatment in either arm and no serious ocular AEs that resulted in study treatment interruption or withdrawal.

Table 49. BALATON Study - Serious Ocular Adverse Events in the Study Eye through Week 24, Safety-Evaluable Population

MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)
Total number of patients with at least one adverse event	3 (1.1%)	2 (0.7%)
Total number of events	3	2
Retinal vein occlusion	1 (0.4%)	1 (0.4%)
Retinal ischaemia	2 (0.7%)	0
Vitreous haemorrhage	0	1 (0.4%)

MedDRA = Medical Dictionary for Regulatory Activities; AE = Adverse Event;
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Serious Ocular AEs week 24 through CCOD

Serious Ocular AEs occurred in 20 patients [3.2%] and 7 patients [1.2%] in the faricimab Q4W to faricimab PTI arm and the aflibercept Q4W to faricimab PTI arm, respectively. The most **common serious ocular AEs** in the study eye (2 patients in any treatment arm; faricimab Q4W to faricimab

PTI arm and the aflibercept Q4W to faricimab PTI arm, respectively) by PT were **RVO** (5 patients [0.8%] and 1 patient [0.2%]), **CMO** (4 patients [0.6%] and 1 patient [0.2%]), **retinal ischaemia** (1 patient [0.2%] and 2 patients [0.3%]) and **macular oedema** (2 patients [0.3%] and 0 patients).

All of these events, except 1 event of RVO (verbatim: new onset BRVO in patient with CRVO) and 1 event of retinal ischaemia, were reported verbatim as worsening. All of the serious ocular AEs in the faricimab Q4W to faricimab PTI arm occurred in the **COMINO** Study.

The serious ocular AEs suspected by the investigator to be related to study treatment in the study eye were epiretinal membrane, vitritis, uveitis, and iritis all in 1 patient each in the faricimab Q4W to faricimab PTI arm. The events of **epiretinal membrane** and **vitritis** were not resolved by the CCOD, while the other events were either resolved or resolving. The number of **serious ocular AEs per 1000 injections** in the study eye was **13.25** in the faricimab Q4W to faricimab PTI arm and **4.78** in the aflibercept Q4W to faricimab PTI arm.

The **incidence** of serious ocular AEs in both arms from Week 24 to CCOD was consistent with the incidence of serious ocular AEs before Week 24. However, the number of injections from Week 24 is lower as patients are receiving sham in Part 2, resulting in a higher rate per 1000 injections from Week 24 to CCOD.

The exposure-adjusted incidence rate of **serious ocular AEs per 100 PY** in the study eye was **8.30** in the faricimab Q4W to faricimab PTI arm and **3.67** in the aflibercept Q4W to faricimab PTI arm.

Serious Ocular AEs Pooled Part 2 Dataset
In the pooled Part 2 dataset, the rates of **serious ocular AEs** were mainly driven by disease worsening of CMO, RVO, and MO events. Most of these serious ocular AEs in the study eye occurred in the **COMINO** study. All were assessed as not suspected to be related to study treatment. The majority were resolved or resolving by the end of the study (Week 72) with no additional treatment and no lasting impact on the patient's long-term vision.

The most **common serious ocular** AEs by PT occurring in the study eye (≥ 2 patients in any of the treatment arm of the pooled Part 2 dataset: the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) were **RVO** (5 patients [0.8%] and 3 patients [0.5%]; majority reported as verbatim worsening), **CMO** (5 patients [0.8%] and 1 patient [0.2%]; majority reported as verbatim worsening), **MO** (4 patients [0.6%] and 0; majority reported as verbatim worsening), **retinal ischaemia** (1 patient [0.2%] and 2 patients [0.3%]); **retinal neovascularization** (2 patients [0.3%] and 1 patient [0.2%]), **cataract** (0 patients and 2 patients [0.3%]), **macular ischaemia** (2 patients [0.3%] and 0 patients), and **retinal artery occlusion** (RAO, 0 patients and 2 patients [0.3%]).

The incidence of serious ocular AEs suspected by the investigator to be related to study treatment was low (4 patients in the faricimab Q4W to faricimab PTI arm in the COMINO study: epiretinal membrane, iridocyclitis, uveitis, and vitritis each in single patients.

The exposure-adjusted incidence **rate of serious ocular AEs** per 100 PY in Part 2 was consistent with Part 1 for both arms (**5.82** and **2.96** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and **5.38** and **4.77** in the pooled faricimab and aflibercept arms in Part 1, respectively.

Entire Study
In the entire study dataset, the incidence of **serious ocular AEs** in the faricimab Q4W to faricimab PTI arm was **6.4%.**The rates of ocular SAEs were mainly driven by the disease worsening of RVO (1.2%), CMO (1.1%), and MO (0.6%). The majority were resolved or resolving by the end of the study (Week 72) and had no lasting impact on the patient's long-term vision.
Having considered the number of patients by treatment interval at Week 68 in both BALATON and COMINO studies, the CHMP noted that the low number of patients treated at the Q8W and Q12W (and

Q4W for BALATON) dosing intervals means that data should be interpreted with caution, as the relative incidences of events will be accentuated due to the comparatively low sample size.

Ocular AEs
There was a higher incidence of ocular events in patients treated at the Q4W dosing interval compared to the Q16W dosing interval within each treatment arm. The higher incidence could be explained by a worse RVO disease status requiring more injections compared to the other dosing intervals throughout the study. The CHMP agreed that the incidence of events in patients treated at the Q8W and Q12W dosing intervals should be interpreted with caution due to the comparatively low sample size.

In the faricimab Q4W to faricimab PTI arm, 35.7% of patients and 26.2% of patients experienced at least one ocular AE in the Q4W and Q16W dosing intervals, respectively. In the aflibercept Q4W to faricimab PTI arm, 34.4% of patients and 22.4% of patients experienced at least one ocular AE in the Q4W and Q16W dosing intervals, respectively.

Ocular AEs in the study eye which contributed to the higher incidence of AEs in patients treated at the faricimab PTI Q4W dosing interval compared to faricimab Q16W in either treatment arm (2% difference between Q4W and Q16W interval in either treatment arms) were: intraocular pressure increased, conjunctival haemorrhage, cataract, macular oedema, retinal vein occlusion, retinal haemorrhage, cystoid macular oedema, retinal ischaemia, visual acuity reduced, and glaucoma. As expected, the rates of ocular AEs in the Q4W dosing regimen were mainly driven by disease worsening of cystoid macular oedema, retinal vein occlusion and disease complication (e.g., glaucoma, retinal haemorrhage, retinal ischaemia).

Ocular AEs in the study eye in Q8W and Q12W varied across treatment arms (30.3% of patients and 47.7% of patients for Q8W and 27.6% of patients and 43.5% of patients for Q12W in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) which was likely due to the small sample size.

In the faricimab Q4W to faricimab PTI arm, 48.2% of patients and 27.9% of patients experienced at least one ocular AE in the Q4W and Q16W dosing interval, respectively. In the aflibercept Q4W to faricimab PTI arm, 39.6% of patients and 29.3% of patients experienced at least one ocular AE in the Q4W and Q16W dosing interval, respectively.

Ocular AEs in the study eye which contributed to the higher incidence of AEs in patients treated at the faricimab PTI Q4W dosing interval compared to faricimab Q16W in either treatment arm (2% difference between Q4W and Q16W interval in either treatment arms)were: cataract, cystoid macular oedema, macular oedema, retinal vein occlusion, epiretinal membrane, glaucoma, vitreous floaters, retinal neovascularization, and iritis. As expected, the rates of ocular AEs in the Q4W dosing regimen were mainly driven by disease worsening of cystoid macular oedema, retinal vein occlusion, and macular oedema events and study disease complication (e.g., glaucoma, epiretinal membrane).

Three cases of iritis were reported in the faricimab Q4W to faricimab PTI arm in the Q4W dosing subgroup; however, no clear relationship could be established between time of injection and event onset. Notably, one case of iritis was reported in the Q16W dosing regimen subgroup.

Ocular AEs in the study eye in Q12W varied across treatment arms (21.4% of patients in the faricimab Q4W to faricimab PTI arm and 51.4% of patients in the aflibercept Q4W to faricimab PTI arm) which was likely due to the small sample size.

Non-ocular AEs
In the BALATON and COMINO studies, the incidence of non-ocular AEs in Part 2 were generally comparable across treatment intervals within each treatment arm. In the BALATON study, the observed numerically higher incidence of non-ocular AEs in the Q4W interval of the faricimab Q4W to

faricimab PTI arm compared to the other dosing intervals was not observed in the COMINO study and did not reveal any particular trend.

Having considered available data, the CHMP noted that, with regard to **Serious Ocular AEs**:
Part 1: from the pooled Phase III RVO Studies, the incidence of serious ocular AEs in the study eye occurred in the faricimab Q4W and aflibercept Q4W arms was comparable (1.9% and 2.2%, respectively)
The rates of serious ocular AEs per 1000 injections were generally comparable between the faricimab Q4W and aflibercept Q4W arms (4.34 and 3.83, respectively).
The exposure-adjusted incidence rates for serious ocular AEs per 100 PY in the study eye were similar between the faricimab Q4W and aflibercept Q4W arms (5.38 and 4.77, respectively).
The serious ocular AEs suspected by the investigator to be related to faricimab were **uveitis** (2 patients [0.3%]), and **CMO, RAO**, and **retinal ischaemia** (1 patient [0.2%] each). All of these serious ocular AEs suspected by the investigator to be related to faricimab were either resolved or resolving by Week 24.
Part 1 (Before the Week 24 Visit): in the **Balaton** study there were **no serious ocular AEs** suspected by the investigator to be related to study treatment in either arm and no serious ocular AEs that resulted in study treatment interruption or withdrawal.
Part 1 (Before the Week 24 Visit): study most of the serious ocular AEs in the study eye occurred in the **COMINO** study. The MAH was therefore requested to further discuss the numerically higher rate of exposure adjusted serious related ocular AEs in faricimab treatment group to week 24.
A summary of the MAH's response is presented below.
In Part 1 (before Week 24 visit) of COMINO study, the exposure-adjusted incidence rates (events per 100 patient years [PY]) of serious ocular AEs in COMINO were comparable between treatment arms (7.68 in the faricimab Q4W arm and 7.19 in the aflibercept Q4W arm. Similarly, the exposure-adjusted rates (events per 1000 injection) of serious ocular AEs were comparable between treatment arms (6.20 in the faricimab Q4W arm and 5.83 in the aflibercept Q4W arm).

The numerical difference between the rates is due to one more event in the faricimab Q4W arm compared to the aflibercept Q4W arm in COMINO (13 events vs. 12 events); also, no patterns were observed for any of the serious ocular AEs.

In Part 1 of the COMINO study, the incidence of related serious ocular AEs was low and comparable (3 patients [0.8%] in the faricimab Q4W arm and 2 patients [0.6%] in the aflibercept Q4W arm).

As acknowledged by the MAH, in the initial RVO Clinical Overview a numerically higher incidence of serious ocular AEs in both the faricimab and aflibercept treatment arms were reported in the COMINO study (C/HRVO) compared with the BALATON study (BRVO) in Part 1 (before the Week 24 visit).

CRVO is the most severe form of RVO and affects the entire retina (Bandello et al. 2010; Buehl et al. 2010). There are substantial differences between CRVO and BRVO concerning visual prognosis and risk of complications, with patients with CRVO at greater risk of secondary ocular complications.

As expected from the RVO phenotype:
- Patients with BRVO had a higher baseline BCVA and lower CST values compared to patients in COMINO.
- A lower rate of patients with BRVO compared with CRVO had prior targeted ocular medical history in the study eye (targeted means a patient had a pre-specified medical history.

condition/term in the eCRF):
- 85 patients (30.8%) in the faricimab Q4W arm and 82 patients (29.6%) in the aflibercept Q4W arm in the BALATON study.
- 156 patients (42.6%) in the faricimab Q4W arm and 145 patients (39.9%) in the aflibercept Q4W arm in the COMINO study.

Similar findings were observed in the historical pivotal RVO trials from baseline to Week 24, where a trend for a slightly higher incidence of serious ocular AEs in CRVO versus BRVO populations was generally observed across the ranibizumab and aflibercept RVO trials, as presented in Table 50 below.

Considering the more severe clinical picture of CRVO compared with BRVO and the precedent findings of RVO pivotal trials with other anti-VEGFs, in the MAH's view, it is not unexpected to observe a slightly higher rate of serious ocular AEs in patients with CRVO.

Table 50. Comparison of Ocular AEs and Ocular SAEs in RVO Pivotal Trials at Week 24

Study Drug	Pivotal Trial (FPI) RVO Subtype	Treatments[1] (Q4W)	Proportion of Patients with ≥ 1 Ocular AEs	Proportion of Patients with ≥ 1 Ocular SAEs (N)	Reference
ranibizumab	**BRAVO** (2007) BRVO[2]	ranib. 0.3 mg (n=134)	NR	**2.2% (3)**	FDA RVO Medical Review, p. 88
		ranib. 0.5 mg (n=130)	NR	**1.5% (2)**	
		sham (n=131)	NR	**0**	
	CRUISE (2007) CRVO	ranib. 0.3 mg (n=132)	NR	**3.0% (4)**	FDA RVO Medical Review, p. 88
		0.5 mg (n=129)	NR	**1.6% (2)**	
		sham (n=129)	NR	**0**	
aflibercept	**VIBRANT** (2012) BRVO[3]	aflib. 2 mg (n=91)	37.4%	**1.1% (1)**	Campochiaro et al. 2015, p. 542
		laser (n=90)	27.2%	**0**	
	COPERNICUS (2009) CRVO	aflib. 2 mg (n=114)	63.2%	**3.5% (4)**	Brown et al. 2013, Suppl. Table 1, Table 3
		sham (n=74)	66.2%	**13.5% (10)**	
	GALILEO (2009) CRVO	aflib. 2 mg (n=104)	54.8%	**2.9% (3)**	Holz et al. 2013, Table 6 (corrected)
		sham (n=68)	64.7%	**8.8% (6)**	
faricimab	**BALATON** (2021) BRVO	fari. 6 mg (n=276)	16.3%	**1.1% (3)**	Primary CSR, Table 15, Table 16
		aflib. 2 mg (n=274)	20.4%	**0.7% (2)**	
	COMINO (2021) CRVO[4]	fari. 6 mg (n=365)	23.0%	**2.5% (9)**	Primary CSR, Table 15, Table 16
		aflib. 2 mg (n=361)	27.7%	**3.3% (12)**	

AE = adverse event; aflib. = aflibercept; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CSR = Clinical Study Report; fari. = faricimab; FPI = first patient in; HRVO = hemiretinal vein occlusion; NR = not reported; Q4W = every 4 weeks; ranib. = ranibizumab; RVO = retinal vein occlusion; SAE = serious adverse event.

[1] All of the pivotal RVO trials had Q4W dosing from Day 0 or Day 1 to Week 20 (6 intravitreal injections in the study eye) with the primary analysis at Week 24.

[2] Included approximately 12-13% of patients with HRVO.

Having considered the MAH's clarification, the CHMP acknowledged that, bearing in mind the more severe clinical picture of CRVO compared with BRVO and the precedent findings of RVO pivotal trials with other anti-VEGFs, it is not unexpected to observe a slightly higher rate of serious ocular AEs in patients with CRVO. Therefore, the MAH was requested to reflect the available safety data in relation to this aspect in section 4.8 of the SmPC.

In its response to the above request, the MAH rather proposed to not adjust SmPC Section 4.8 in relation to the slightly higher rate of serious ocular adverse events (AEs) in patients with central retinal vein occlusion (CRVO), as it is well known by physicians that CRVO is the most severe form of RVO and affects the entire retina (Bandello et al. 2010; Buehl et al. 2010).

There are substantial differences between CRVO and branch retinal vein occlusion (BRVO) concerning visual prognosis and risk of complications, with patients with CRVO at greater risk of secondary ocular complications. Furthermore, reassuringly, the overall rate of serious ocular AEs and the rate of adverse drug reactions for RVO were still within the expected range for faricimab (Table 51 below).

In addition, general information about known risks related to the disease rather than the drug was not included in the Eylea or Lucentis label, nor are required per the EU SmPC guideline (2009).
Ultimately, the CHMP considered the MAH's justification as acceptable.

Table 51. Serious ocular AEs and ADRs across the faricimab trials

Faricimab Trial and Indication	Treatments	Proportion of Patients with Serious Ocular AEs	Proportion of Patients with ADRs
DME (YOSEMITE and RHINE)	Faricimab All Patients (n=1262)	4.8% (60)	31.1% (392)
nAMD (TENAYA and LUCERNE)	Faricimab All Patients (n=664)	4.4% (29)	36.1% (240)
RVO (BALATON and COMINO)	Faricimab All Patients (n=1250)	4.5% (56)	20.9% (261)

ADR=adverse drug reaction; AE=adverse event; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration; RVO=retinal vein occlusion

Note: The data presented in this table are for the entire duration of the global study for nAMD (Week 112), DME (Week 100), and RVO (Week 72).

Source: t_ae_pt_SOCUL_SER_SE_nAMD_HLSY2, t_ae_pt_SOCUL_SER_SE_DME_HLSY2, PR14107_t_ae_pt_SOCUL_AMD_ADR_SE, PR13349_t_ae_pt_SOCUL_DME_ADR_SE, t_ae_pt_SOCUL_SER_AFAR_SE_RVO_HLS72, PR15674_t_ae_pt_dme_amd_rvo72_ADR_NOII_SE

Part 2 Week 24 through CCOD Serious Ocular AEs*:* The number of **serious ocular AEs** per 1000 injections in the study eye was **13.25** in the faricimab Q4W to faricimab PTI arm and **4.78** in the aflibercept Q4W to faricimab PTI arm. The number of injections from Week 24 was lower as patients received **sham** in Part 2, resulting in a higher rate per 1000 injections from Week 24 to CCOD. The exposure-adjusted incidence rate of serious ocular AEs per 100 PY in the study eye was **8.30** in the faricimab Q4W to faricimab PTI arm and **3.67** in the aflibercept Q4W to faricimab PTI arm.

There was a notable difference in the number of serious ocular AEs in the faricimab Q4W to faricimab PTI arm in the aflibercept Q4W to faricimab PTI arm without the full data set these data were difficult to interpret.

As requested, the MAH clearly presented the full safety data set with the responses to the list of outstanding issues (LoOI), with a focus on the exposure adjusted data including a side-to-side comparison of those patients treated with faricimab in both parts versus those who had previously been treated with aflibercept in Part 1 of the studies. In addition, a breakdown was provided which clearly outlined the numbers of subjects who received 4 weekly vs 8 weekly vs 12 weekly vs 16 weekly injections in both arms and the corresponding serious ocular AEs for each group.

Overall, considering the limitations of the by treatment interval analysis, the CHMP noted that the safety profile of faricimab remained similar across all treatment interval subgroups, and the nature and type of non-ocular AEs and ocular AEs in the study eye reported in patients assigned to Q8W, Q12W, and Q16W dosing was also broadly similar. The higher incidence of certain adverse events observed with Q4W dosing could be explained by worse RVO disease status requiring more injections over the study, and higher number of injections compared to other faricimab dosing intervals.

Moderate IOI events included 1 serious uveitis, 1 serious vitritis, and 1 serious iritis by CCOD, the events of uveitis and iritis were recovered or recovering, respectively while the event of vitritis was noted as ongoing and, as requested, the MAH provided an update on this latter event.

In the **pooled Part 2 dataset**, the rates of **serious ocular AEs** were mainly driven by disease worsening of CMO, RVO, and MO events. The type of serious ocular AEs in Part 2 was consistent with Part 1. Most of these serious ocular AEs in the study eye occurred in the **COMINO** study. All were assessed as not suspected to be related to study treatment. The most **common** serious ocular AEs by PT occurring in the study eye (≥ 2 patients in any of the treatment arm of the pooled Part 2 dataset: the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) were **RVO** (5 patients [0.8%] and 3 patients [0.5%];**CMO** (5 patients [0.8%] and 1 patient [0.2%]; **MO** (4 patients [0.6%] and 0. The incidence of serious ocular AEs suspected by the investigator to be related to study treatment was low (4 patients in the faricimab Q4W to faricimab PTI arm in the COMINO study: epiretinal membrane, iridocyclitis, uveitis, and **vitritis** each in single patients.

The exposure-adjusted incidence **rate of serious ocular AEs** per 100 PY in Part 2 was consistent with Part 1 for both arms (**5.82** and **2.96** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and **5.38** and **4.77** in the pooled faricimab and aflibercept arms in Part 1, respectively.

In the **entire study** dataset, the incidence of **serious ocular** AEs in the faricimab Q4W to faricimab PTI arm was **6.4%.** The rates of ocular SAEs were mainly driven by the disease worsening of **RVO** (1.2%), **CMO** (1.1%), and **MO** (0.6%). The majority were resolved or resolving by the end of the study (Week 72) and had no lasting impact on the patient's long-term vision.

Ocular Adverse Events of Special Interest
Sight-Threatening AEs in the Study Eye

Before the Week 24 Visit
A comparable and low incidence of AESIs in the study eye occurred in the faricimab Q4W and aflibercept Q4W arms (9 patients [1.4%] and 14 patients [2.2%], respectively (Table 52). The majority of the ocular AESIs in the study eye occurred in the **COMINO** study, and most of these events resolved or were resolving by the CCOD.

The most common sight-threatening AEs in the study eye that caused a decrease of ≥30 letters in VA score lasting more than 1 hour (≥2 patients in any treatment arm: faricimab Q4W and aflibercept Q4W

arm, respectively) by PT were CMO (verbatim: worsening of CMO) and RVO (verbatim: worsening of RVO) (2 patients [0.3%] and 2 patients [0.3%] each. The sight-threatening AEs in the study eye that caused a decrease of ≥30 letters in VA score lasting more than 1 hour that were not resolved by Week 24 were macular ischaemia, RAO and RVO in 1 patient each in the faricimab Q4W arm, and RVO in 2 patients and vitreous haemorrhage and RAO in 1 patient each in the aflibercept Q4W arm.

The most common sight-threatening AEs in the study eye that required surgical or medical intervention to prevent permanent loss of sight (≥2 patients in any treatment arm: faricimab Q4W and aflibercept Q4W arm, respectively) was **retinal tear** (0 patients vs. 2 patients [0.3%]. There was 1 sight threatening AE in the study eye that required surgical or medical intervention to prevent permanent loss of sight that was not resolved by Week 24: **retinal ischaemia** in 1 patient in the aflibercept Q4W arm.
There were no patients who experienced sight-threatening AEs in the AESI category associated with 'severe intraocular inflammation' in either treatment arm. The per 1000 injection rate of ocular AESIs in the study eye was 2.44 and 3.83 in the faricimab Q4W and aflibercept Q4W arms, respectively.

The exposure-adjusted incidence rates of ocular AESIs per 100 PY were 3.03 and 4.77, in the faricimab Q4W and aflibercept Q4W arms respectively.

Table 52. Adverse Events of Special Interest in Study Eye through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
AE of Special Interest MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	1 (0.4%)	2 (0.7%)	8 (2.2%)	12 (3.3%)	9 (1.4%)	14 (2.2%)
Overall total number of events	1	2	8	12	9	14
CAUSES A DECREASE OF >=30 LETTERS IN VA SCORE LASTING MORE THAN 1 HOUR						
Total number of patients with at least one adverse event	1 (0.4%)	2 (0.7%)	6 (1.6%)	6 (1.7%)	7 (1.1%)	8 (1.3%)
Total number of events	1	2	6	6	7	8
Cystoid macular oedema	0	0	2 (0.5%)	2 (0.6%)	2 (0.3%)	2 (0.3%)
Retinal vein occlusion	1 (0.4%)	1 (0.4%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
Retinal artery occlusion	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
Endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Macular ischaemia	0	0	1 (0.3%)	0	1 (0.2%)	0
Macular oedema	0	0	0	1 (0.3%)	0	1 (0.2%)
Visual acuity reduced	0	0	1 (0.3%)	0	1 (0.2%)	0
Vitreous haemorrhage	0	1 (0.4%)	0	0	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	0	2 (0.5%)	6 (1.7%)	2 (0.3%)	6 (0.9%)
Total number of events	0	0	2	6	2	6
Retinal tear	0	0	0	2 (0.6%)	0	2 (0.3%)
Eye injury	0	0	1 (0.3%)	0	1 (0.2%)	0
Intraocular pressure increased	0	0	0	1 (0.3%)	0	1 (0.2%)
Non-infectious endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Retinal artery embolism	0	0	0	1 (0.3%)	0	1 (0.2%)
Retinal ischaemia	0	0	0	1 (0.3%)	0	1 (0.2%)
Rhegmatogenous retinal detachment	0	0	1 (0.3%)	0	1 (0.2%)	0

ALT = Alanine transaminase; AST = Aspartate transaminase; AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; VA = Visual Acuity.
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Ocular selected AEs: Intraocular Inflammation Events Before the Week 24 Visit
Intraocular inflammation was defined by the following PTs: anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, choroiditis, cyclitis, eye inflammation, iridocyclitis, iritis, keratic precipitates, keratouveitis, noninfective chorioretinitis, non-infectious endophthalmitis, ocular vasculitis, post procedural inflammation, retinal occlusive vasculitis, retinal vasculitis, haemorrhagic occlusive retinal vasculitis, uveitis, vitritis, and vitreal cells.

The incidence of IOI events in the study eye was low and comparable across all treatment arms (9 patients **[1.4%]** and 4 patients **[0.6%]** in the faricimab Q4W and aflibercept Q4W arms, respectively).

All the reported IOI events were in the **COMINO** study.

In the **BALATON** study, 1 patient in the faricimab Q4W arm had 1 event of 'vitreal cells' reported but the verbatim term was "non-inflammatory vitreous cells" and thus, not considered an IOI event. There

were no IOI events associated with retinal vasculitis or retinal occlusive disease in any treatment arms based on the reported preferred terms (PTs).

The most common IOI events in the study eye (≥2 patients in any treatment arm: faricimab Q4W and aflibercept Q4W arm, respectively) by PT were vitritis (3 patients [0.5%] and 0 patients), iritis (2 patients [0.3%] and 2 patients [0.3%]), and uveitis (2 patients [0.3%] and 1 patient [0.2%].

The majority of IOI events in the study eye were mild in severity in the faricimab Q4W and aflibercept Q4W arms, respectively (7 patients [1.1%] and 3 patients [0.5%]).

Moderate IOI events included **2 serious uveitis in the faricimab Q4W arm** and 1 serious non-infectious endophthalmitis in the faricimab Q4W and in the aflibercept Q4W arms, respectively (Table 53). By Week 24, 1 event of uveitis was recovering while the other events had recovered. There were no severe IOI events.

The IOI event rate per 1000 injections in the study eye was low and comparable (2.44 and 1.09 in the faricimab Q4W and aflibercept Q4W arms, respectively).

The exposure-adjusted incidence rates of IOI events per 100 PY were low and comparable between the faricimab Q4W and aflibercept Q4W arm (3.03 and 1.36, respectively).

There was 1 patient with a moderate IOI event of uveitis in the study eye in the faricimab Q4W arm associated with vision loss ≥15 letters which was recovering by Week 24. Sustained vision loss of ≥15 letters and ≥30 letters associated with an AE by Week 24 was measured as the change in BCVA at Week 24 minus the BCVA closest to and strictly before the first event onset.

For the **serious IOI events**, there was no clear relationship between injection day of study treatment and the timing of the events. However, the majority of the non-serious IOI events occurred after the first dose and no recurrence was observed by Week 24. The incidence of IOI events occurring in the fellow eye was low (1 patient [0.2%] each] in the faricimab Q4W and aflibercept Q4W arms) The IOI events in the fellow eye by PT were iridocyclitis in the faricimab Q4W arm and iritis in the aflibercept Q4W arm.

Table 53. Adverse Events of Intraocular Inflammation in the Study Eye through Week 24 from Individual and Pooled Phase III RVO studies (Pooled safety-Evaluable Population)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	1 (0.4%)	0	8 (2.2%)	4 (1.1%)	9 (1.4%)	4 (0.6%)
Total number of events	1	0	8	4	9	4
Iritis	0	0	2 (0.5%)	2 (0.6%)	2 (0.3%)	2 (0.3%)
Uveitis	0	0	2 (0.5%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Vitritis	0	0	3 (0.8%)	0	3 (0.5%)	0
Iridocyclitis	0	0	1 (0.3%)	0	1 (0.2%)	0
Non-infectious endophthalmitis	0	0	0	1 (0.3%)	0	1 (0.2%)
Vitreal cells	1 (0.4%)	0	0	0	1 (0.2%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities;
Intraocular Inflammation events include Anterior chamber cell, Anterior chamber flare, Anterior chamber inflammation, Chorioretinitis, Choroiditis, Cyclitis, Eye inflammation, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Noninfective chorioretinitis, Non-infectious Endophthalmitis, Ocular vasculitis, Post procedural inflammation, Retinal occlusive vasculitis, Retinal vasculitis, Haemorrhagic occlusive retinal vasculitis, Uveitis, Vitritis, and Vitreal cells.
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

AESIs week 24 through CCOD

The incidence of **AESIs** in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms was 16 patients **[2.5%]** and 4 patients **[0.7%],** respectively. All of the ocular

AESIs in the study eye occurred in **COMINO,** and the majority of these events resolved or were resolving by the CCOD.

IOI events week 24 through CCOD

IOI events in the study eye by PT were iritis (2 patients [0.3%]) and keratic precipitates, uveitis, and vitritis (1 patient [0.2%] each) all in the faricimab Q4W to faricimab PTI arm.

There were no IOI events reported in aflibercept Q4W to faricimab PTI arm. There was 1 event of IOI associated with sustained vision loss (15 letters). There were no IOI events associated retinal vasculitis or occlusive disease in any treatment arms. All the IOI events in the study eye were mild or moderate in severity across the treatment arms. Moderate IOI events included 1 serious uveitis, 1 serious vitritis, and 1 serious iritis by CCOD, the events of uveitis and iritis were recovered or recovering, respectively while the event of vitritis was ongoing. There were no additional IOI events reported in the fellow eye.

AESIs Pooled Part 2 Dataset

The majority of the **ocular AESIs** in the study eye occurred in the **COMINO** study, and the majority of these events were associated with study disease worsening and were resolved or resolving by the end of study:

- 16 patients **(2.5%)** and 8 patients **(1.3%)** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, experienced an ocular AESI causing a decrease of ≥ 30 letters in VA score lasting more than 1 hour. The majority were resolved or resolving by the end of the study.
- 6 patients **(1.0%)** and 1 patient **(0.2%)** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, experienced an ocular AESI that required surgical or medical intervention to prevent permanent loss of sight. **Four out of seven events were resolved by the end of the studies.**
- One patient in the aflibercept Q4W to faricimab PTI arm experienced an event in the AESI category of 'associated with severe IOI' (endophthalmitis). This event was resolved by the end of the study.

In the **pooled Part 2** dataset, the exposure-adjusted incidence **rate of AESIs per 100 PY** was consistent with Part 1 for both arms (**4.06** and **1.98** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and **3.03** and **4.77** in the pooled faricimab and aflibercept arms in Part 1, respectively.

Entire Study

In the entire study dataset, the incidence of AESIs in the faricimab Q4W to faricimab PTI arm was **4.7%.** The exposure-adjusted incidence **rates of AESIs per 100 PY** in the Faricimab Q4W to Faricimab PTI arm was **3.71**). This rate was consistent with other faricimab Phase III studies (DME: 3.05 and nAMD: 2.09; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS. The rates of **ocular AEs per 1000 injections** in the Faricimab Q4W to Faricimab PTI arm was **4.62** This rate was consistent with other faricimab Phase III studies (DME: 4.38 and nAMD: 3.99; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS.

IOI Events

Pooled Part 2 Dataset

In the pooled Part 2 dataset, the incidence of **IOI** events occurring in the study eye was low in both the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (**1.9%** and **1.3%,** respectively).

A higher incidence of **IOI** was reported in the **COMINO** study (**2.8%** and **1.5%** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively), which is in line with what has been observed in historical RVO pivotal trials. The MAH outlined that this is likely related to the greater severity of underlying **CRVO** disease compared with BRVO (Brown et al. 2010, Campochiaro et al. 2010). The majority were non-serious and mild and moderate in severity and had no impact on visual outcomes.

There was no clear relationship between injection day of study treatment and the timing of the events observed with the caveat that the number of IOI events reported was small. Additionally, IOI events associated with significant vision loss (≥ 15 letters or ≥ 30 letters) were infrequent (1 patient had a vision loss of ≥ 15 letters associated with a serious event of **vitritis** in the faricimab Q4W to faricimab PTI arm and 1 patient had a vision loss of ≥ 15 letters associated with a non-serious event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm). By **Week 72,** the majority of **IOI** events were resolved or resolving. **Four events** (vitritis, non-infectious endophthalmitis, iritis, and iridocyclitis [1 event each]) in the faricimab Q4W to faricimab PTI arm and 1 event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm were not resolved by Week 72. Two of these events occurred at the end of the study and therefore were still ongoing at the last study visit. One event of vitritis resulted in study discontinuation.

Entire Study
In the Entire Study dataset, the incidence of **IOI** in the faricimab Q4W to faricimab PTI arm was **3.0%.** The **IOI incidence** was higher in **CRVO,** but it is important to note that:

- The majority of the IOI events reported in COMINO were non-serious, mild or moderate in severity, and had no impact on visual outcomes.
- There was no clear relationship between injection day of study treatment and the timing of the events observed with the caveat that the number of IOI reported were small.
- In historical RVO pivotal trials IOI rates were also greater in the CRVO cohort. (Brown et al. 2011, Campochiaro et al. 2011).

Finally, **one site** reported **IOIs** in **7 patients** (2 and 1 patients in Part 1 on faricimab Q4W and aflibercept Q4W, respectively; and 1 and 3 patients in Part 2 on faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI, respectively). However, upon discussion with the medical monitor, the site could not confirm whether the cells were inflammatory in nature, and all events resolved.

The exposure-adjusted **incidence rate of IOIs per 100 PY** in the faricimab Q4W to faricimab PTI arm was **2.67.** This rate was consistent with other faricimab Phase III studies (DME: **1.13** and nAMD: **1.94;** DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS)
The CHMP noted that, based on the exposure-adjusted incidence rates of ocular AESIs per 100 PY which were 3.03 and 4.77, in the faricimab Q4W and aflibercept Q4W arms respectively, there were no major imbalances in ocular AESIs to **week 24**. There were no patients who experienced sight-threatening AEs in the AESI category associated with 'severe intraocular inflammation' in either treatment arm.

The per 1000 injection rate of ocular AESIs in the study eye was 2.44 and 3.83 in the faricimab Q4W and aflibercept Q4W arms, respectively. The IOI event rate per 1000 injections in the study eye was low and comparable (2.44 and 1.09 in the faricimab Q4W and aflibercept Q4W arms, respectively).
It was also critically noted that the incidence of IOI events was higher for the group treated with faricimab compared to aflibercept in the Comino study (8 patients [**2.2%**] and 4 patients [**1.1%**], respectively). It is further noted that in 6 patients the IOI event occurred shortly (i.e. ≤10 days) after the first injection of faricimab, whereas in only one patient the IOI occurred soon (i.e. ≤10 days) after the first injection of aflibercept. Notable differences across the rate of IOI in the COMINO study were observed. On this matter, the MAH further clarified that, considering the overall low incidence of IOI, the comparability with previous registrational studies, and the mild clinical presentation of the events in the faricimab Q4W arm, the current data does not support a significant difference between treatment arms in Part 1 of COMINO (the treatment difference was 1.1%; 95% CI: -0.93%, 3.26%).

Part 2 Week 24 through CCOD
Moderate IOI events included 1 serious uveitis, 1 serious vitritis, and 1 serious iritis by CCOD; the events of uveitis and iritis were recovered or recovering, respectively while the event of vitritis was ongoing. As requested, the MAH provided an update on this latter event. The MAH also discussed the

reasons for the noted imbalance in patients treated with faricimab Q4W (3.03) compared to aflibercept Q4W arm (1.36).
As highlighted in the Immunogenicity section, no conclusion concerning the potential impact of ADAs on clinical efficacy and safety from Week 24 could be made at the time of the initial report as post-Week ADA status for all patients was not available. The MAH was asked to present a complete discussion of the full safety data set with the responses to the LoOI, including a detailed discussion of possible differences in long-term immunogenicity and relevant AEs (including IOI events) reported for faricimab, relative to ADA status.

In its response, the MAH acknowledged that some uncertainty remains in relation to the long term safety and immunogenicity profile associated with faricimab in the RVO indication. Overall, a higher incidence of intraocular inflammation (IOI) events was observed in the ADA-positive subgroup in the COMINO study although IOI events were also reported in the ADA-negative subgroup. As outlined in the PI, cases of IOI events are known to be associated with faricimab treatment, warnings have been included (i.e. in section 4.4) and IOI events are also listed in SmPC section 4.8. Nevertheless, some uncertainty remains in relation to the long term immunogenicity data in the RVO indication: information currently available is considered limited by the CHMP and (as acknowledged in the SmPC) the clinical significance of anti-faricimab antibodies, with regard to safety, is unclear. In this context, as mentioned thereafter, the MAH should keep these issues as topics of special interest in the PSURs, especially IOI events and immunogenicity in the RVO population.
In the **BALATON** study, 1 patient in the faricimab Q4W arm had 1 event of 'vitreal cells' reported but the verbatim term was "non-inflammatory vitreous cells" and thus, not considered an IOI event.

All the reported IOI events were in the **COMINO** study. Moderate IOI events included **2 serious uveitis in the faricimab Q4W arm** and 1 serious non-infectious endophthalmitis in the faricimab Q4W and in the aflibercept Q4W arms, respectively. By Week 24, 1 event of uveitis was recovering while the other events had recovered. The MAH provided an update on the serious uveitis case which was documented as not recovered.

Pooled Part 2 Dataset
In the pooled Part 2 dataset, the incidence of **IOI** events occurring in the study eye was low in both the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (**1.9%** and **1.3%,** respectively).
A higher incidence of **IOI** was reported in **COMINO** (**2.8%** and **1.5%** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively), which is in line with what has been observed in historical RVO pivotal trials. The majority were non-serious and mild and moderate in severity and had no impact on visual outcomes.
By **Week 72,** the majority of **IOI** events were resolved or resolving. **Four events** (vitritis, non-infectious endophthalmitis, iritis, and iridocyclitis [1 event each]) in the faricimab Q4W to faricimab PTI arm and 1 event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm were **not resolved** by Week 72. Two of these events occurred at the end of the study; therefore, they were still ongoing at the last study visit. One event of vitritis resulted in study discontinuation.

Entire Study
In the entire study dataset, the incidence of **IOI** in the faricimab Q4W to faricimab PTI arm was **3.0%.** The **IOI incidence** was higher in **CRVO,** but it is important to note that:

- the majority of the IOI events reported in COMINO were non-serious, mild or moderate in severity, and had no impact on visual outcomes.
- There was no clear relationship between injection day of study treatment and the timing of the events observed with the caveat that the number of IOI reported were small.

There were no reported IOI events associated with retinal vasculitis or occlusive disease. The exposure-adjusted **incidence rate of IOIs per 100 PY** in the faricimab Q4W to faricimab PTI arm was **2.67.** The rates in the other faricimab Phase III studies were DME: **1.13** and nAMD: **1.94.**

The MAH was asked to discuss the specific long term monitoring of immunogenicity, in the RVO indication specifically. A comprehensive response was provided by the MAH, highlighting that the 72-week RVO data presented in the BALATON and COMINO CSRs in combination with the DME and nAMD LTE studies, and existing routine pharmacovigilance activities (i.e. adverse reaction reporting, Guided Questionnaires, signal detection and management activities), with all relevant safety data being reported in the PBRER, would be sufficient to provide long-term safety and immunogenicity data for faricimab to cover the RVO indication for the following reasons:

- The commonality between the pathophysiology and risk factors in DME and RVO supports that data from LTE studies in DME is relevant to the RVO population.
- Long-term RWD studies from anti-VEGF products have not identified a difference in safety profile between the DME and RVO population.
- Data obtained to date from the ongoing faricimab LTE studies in the DME and nAMD.

The CHMP considered acceptable both MAH's response and proposal : the MAH should keep this issue as a topic of special interest in future PSURs and continuously review the need to strengthen the current information on IOI events and immunogenicity in the RVO population, if necessary.

Non-Ocular Adverse Events from the Pooled Phase III RVO Studies
Before the Week 24 Visit

The incidence of non-ocular AEs was comparable across the two treatment arms (32.9% and 36.4% in the faricimab Q4W and aflibercept Q4W arms, respectively). The only event with a numerical ≥ 2% difference (in any treatment arm: faricimab Q4W and aflibercept Q4W arms, respectively) by PT was hypertension (4.7% and 2.7%) however, this is not considered clinically meaningful by the CHMP.

The most **common** (≥ 5% of patients) MedDRA system organ classes (SOCs) in which non-ocular AEs were reported in the faricimab and aflibercept Q4W arms were the following: Infections and infestations (12.9% and 14.5%, respectively), Musculoskeletal and connective tissue disorders (4.4% and 5.2%, respectively), Nervous system disorders (5.5% and 4.1%, respectively) Vascular disorders (5.1% and 3.9%, respectively).

The most **common non-ocular AEs** (≥2% incidence in any treatment arm: faricimab Q4W and aflibercept Q4W arm, respectively) by PT were COVID-19 (4.1% and 4.4%), **hypertension (4.7% and 2.7%),** back pain (7 patients [1.1%] and 18 patients [2.8%]), nasopharyngitis (1.7% and 2.0%), and upper respiratory tract infection (7 patients [1.1%] and 13 patients [2.0%]), with no appreciable difference between faricimab and aflibercept (Table 21). The small numerical difference in the hypertension AEs was mainly driven by patients in the **BALATON** study (17 patients [6.2%] and 7 patients 2.6%] patients in the faricimab Q4W and aflibercept Q4W arms, respectively), whose hypertension events were either reported as worsening of existing hypertension or had confounders. These events were all mild or moderate in severity, non-serious, and were not suspected by the investigator to be related to study treatment; most had resolved or were resolving by Week 24.

The majority of non-ocular AEs were mild or moderate in severity in the faricimab Q4W and aflibercept Q4W arms. Overall, 3.3% and 5.2% of patients experienced at least one severe non-ocular AE in the faricimab Q4W and aflibercept Q4W arm, respectively. The incidence of non-ocular AEs suspected by the investigator to be related to **faricimab** was low (4 patients [0.6%] in the faricimab Q4W arm). These AEs were cerebral infarction (2 patients [0.3%]), coronary artery disease and cerebrovascular accident (1 patient [0.2%] each). The incidence of non-ocular AEs suspected by the investigator to be related to
aflibercept was low (5 patients [0.8%] in the aflibercept Q4W arm). These AEs were coronary artery disease and acute myocardial infarction (2 patients [0.3%] each) and arteriosclerosis coronary artery, myocardial infarction, and myocardial ischaemia (1 patient [0.2%] each.

Non-Ocular Adverse Events of Special Interest

No cases of drug-induced liver injuries or suspected transmission of an infectious agent by the study drug were reported in the studies.

Table 54. Non-Ocular Adverse Events (≥2%) through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	35 (12.7%)	40 (14.6%)	41 (11.2%)	42 (11.6%)	76 (11.9%)	82 (12.9%)
Overall total number of events	40	44	43	47	83	91
Infections and infestations						
Total number of patients with at least one adverse event	20 (7.2%)	25 (9.1%)	24 (6.6%)	26 (7.2%)	44 (6.9%)	51 (8.0%)
Total number of events	20	27	25	28	45	55
COVID-19	10 (3.6%)	16 (5.8%)	16 (4.4%)	12 (3.3%)	26 (4.1%)	28 (4.4%)
Nasopharyngitis	6 (2.2%)	6 (2.2%)	5 (1.4%)	7 (1.9%)	11 (1.7%)	13 (2.0%)
Upper respiratory tract infection	4 (1.4%)	5 (1.8%)	3 (0.8%)	8 (2.2%)	7 (1.1%)	13 (2.0%)
Vascular disorders						
Total number of patients with at least one adverse event	17 (6.2%)	7 (2.6%)	13 (3.6%)	10 (2.8%)	30 (4.7%)	17 (2.7%)
Total number of events	18	7	13	10	31	17
Hypertension	17 (6.2%)	7 (2.6%)	13 (3.6%)	10 (2.8%)	30 (4.7%)	17 (2.7%)
Musculoskeletal and connective tissue disorders						
Total number of patients with at least one adverse event	2 (0.7%)	10 (3.6%)	5 (1.4%)	8 (2.2%)	7 (1.1%)	18 (2.8%)
Total number of events	2	10	5	9	7	19
Back pain	2 (0.7%)	10 (3.6%)	5 (1.4%)	8 (2.2%)	7 (1.1%)	18 (2.8%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities;
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Figure 40. Safety Plot of Non-Ocular AEs Reported in any Arm with an Incidence of ≥1% through Week 24 from Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

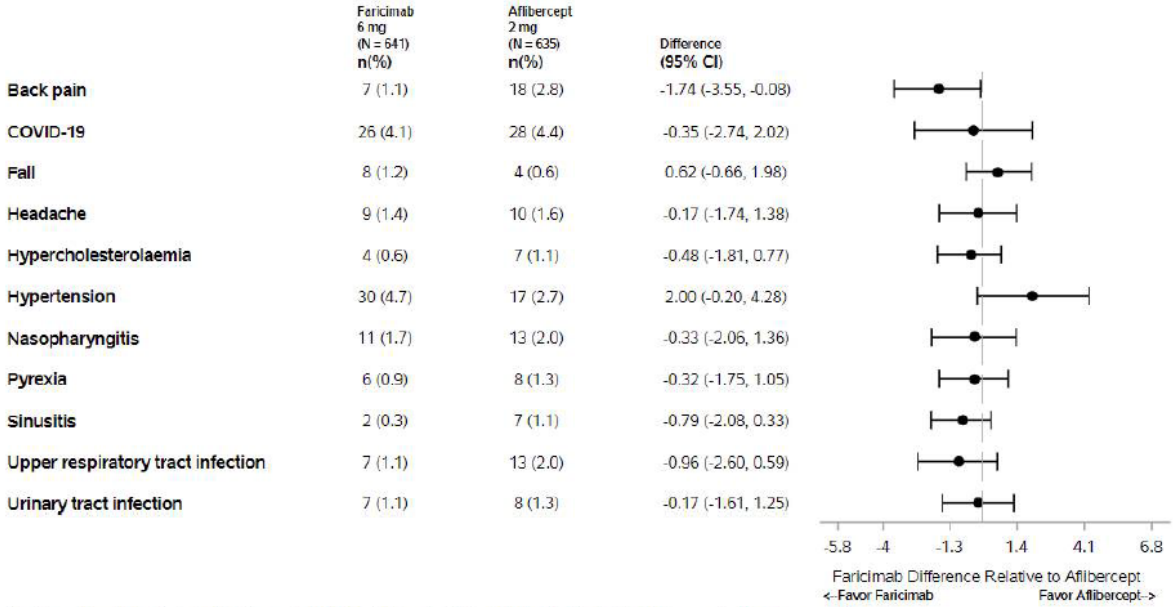


Table 55. Serious Non-Ocular Adverse Events (≥2 patients) through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	9 (3.3%)	16 (5.8%)	22 (6.0%)	23 (6.4%)	31 (4.8%)	39 (6.1%)
Total number of events	10	22	26	45	36	67
Cerebrovascular accident	1 (0.4%)	1 (0.4%)	2 (0.5%)	1 (0.3%)	3 (0.5%)	2 (0.3%)
Acute myocardial infarction	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.5%)
COVID-19	0	1 (0.4%)	3 (0.8%)	0	3 (0.5%)	1 (0.2%)
Myocardial infarction	1 (0.4%)	0	0	3 (0.8%)	1 (0.2%)	3 (0.5%)
Cerebral infarction	3 (1.1%)	0	0	0	3 (0.5%)	0
Coronary artery disease	0	2 (0.7%)	1 (0.3%)	0	1 (0.2%)	2 (0.3%)
Pneumonia	0	0	2 (0.5%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Inguinal hernia	0	0	2 (0.5%)	0	2 (0.3%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities;
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Table 56. Balaton Study: Most Common Serious Non-Ocular Adverse Events (≥ 1% in Any Treatment Arm) through Week 24, Safety-Evaluable Population

MedDRA Preferred Term	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)
Total number of patients with at least one adverse event	9 (3.3%)	16 (5.8%)
Total number of events	10	22
Cerebral infarction	3 (1.1%)	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities;
Investigator text for AEs encoded using MedDRA version 25.0. 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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Any non-ocular events: week 24 through CCOD

The incidence of **non-ocular AEs** was 31.3% and 21.0% in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively). The most common non ocular AEs (>2% incidence in any treatment arm: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arm, respectively) by PT were **COVID-19** (7.3% and 4.4%) and **hypertension** (2.5% and 1.5%). The event with a numerical >2% difference (in any treatment arm: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) by PT was COVID-19 (7.3% and 4.4%), however this was considered clinically meaningful. The majority of non-ocular AEs were mild or moderate in severity in both the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms.

The incidence of **serious non-ocular AEs** was comparable across the two treatment arms (4.8% and 6.1% in the faricimab Q4W and aflibercept Q4W arms, respectively. There were no serious non-ocular AEs with >1% incidence in any treatment arm.

Non-Ocular AEs Pooled Part 2 Dataset

In the pooled Part 2 dataset, the incidence of **non-ocular AEs** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms was **52%** and **49.3%,** respectively. The majority of non-ocular AEs were mild or moderate in severity.

Consistent with Part 1, the most common non-ocular AEs in **Part 2** (≥ 2% incidence in any treatment arm of the pooled Part 2 dataset: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) by PT were **COVID-19** (12.4% and 11.7%), **nasopharyngitis** (2.9% and 4.3%),

hypertension (4.3% and 2.6%), **upper respiratory tract infection** (2.2% and 2.8%), **back pain** (2.4% and 1.3%), and **influenza** (1.9% and 2.6%).

Update on hypertension
Hypertension is a major risk factor for **RVO** with a meta-odds ratio of 2.82 (95% CI: 2.12–3.75; Song et al. 2019). The overall rate of hypertension reported in the BALATON and COMINO studies was in line or lower than published data in this patient population.

All **hypertension** events were reported as non-serious and the majority were mild or moderate in severity (with the exception of one severe event) and either reported as worsening of hypertension or with risk factors (e.g., high blood pressure at screening and/or baseline, associated cardiovascular disorders, pre-existing systemic hypertension).

The MAH, requested to further discuss the issue of hypertension, confirmed that the number of patients with hypertension AEs in the faricimab Q4W arm in Part 1 slightly increased in the final analysis versus the primary analysis, due to continuous data cleaning and query resolution since the primary analysis (3 additional patients in the BALATON study and 2 additional patients in the COMINO study later reported in Part 1 using the final database).

BALATON Study: hypertension events in Part 1 (before Week 24 visit) and Part 2 (Week 24 to Week 72)
In **Part 1**, the incidence of hypertension events was higher in the faricimab Q4W arm (20 patients [7.2%]) compared to the aflibercept Q4W arm (7 patients [2.6%]) All events were reported as non-serious and none were assessed as related to the study treatment by the investigators or required a change in study treatment. In **Part 2**, the incidence of hypertension events were 14 patients (5.2%) in the faricimab Q4W to faricimab PTI arm and 8 patients (3.0%) in the aflibercept Q4W to faricimab PTI arm.

Overall, in the All Faricimab group **43 hypertension events** were reported in 40 patients receiving faricimab through Week 72. All of the events were reported as non-serious with the majority being of mild (n=25/43) or moderate (n=17/43) severity. None of the 43 events were assessed as related to the study treatment by the investigators or required a change in the study treatment.

In the absence of an imbalance of hypertension events in other population treated with faricimab (nAMD and DME), and considering that (1) majority of the cases reported in the faricimab RVO studies had risk factors associated with the events of hypertension, (2) the baseline medical history of patients with RVO, and (3) the rates of hypertension in published data for this population, the MAH considered the numerically higher rate of hypertension events in the faricimab Q4W arm as isolated findings in the BALATON study.

In the **pooled Part 2** dataset, the exposure-adjusted **incidence rate of non-ocular AEs** per 100 patient years was consistent with Part 1. (**145.10** and **141.68** in the pooled faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arms in Part 2, respectively; and **126.19** and **156.02** in the pooled faricimab and the aflibercept arms in **Part 1**, respectively.

In the pooled Part 2 dataset, the incidence of **serious non-ocular AEs** was low in both treatment arms. There were **no serious non-ocular AEs** with ≥ 1% incidence in any treatment arm of the pooled **Part 2** dataset.

Entire Study
In the entire study dataset, the incidence of **non-ocular AEs** in the faricimab Q4W to faricimab PTI arm was **63.2%.** The exposure-adjusted incidence **rate of non-ocular AEs per 100 PY** was **140.50** which was consistent with other faricimab Phase III studies (DME: **172.42** and nAMD: **139.29;** DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS).

In the **entire study** dataset, the incidence of **serious non-ocular AEs** in the faricimab Q4W to faricimab PTI arm was **12.6%.** The exposure-adjusted incidence rates of serious non-ocular AEs per 100 PY was **14.26** which was consistent with other faricimab Phase III studies (nAMD: 17.06 and DME: 27.83).

Adjudicated APTC-Defined Events
Before the Week 24 Visit
The incidence of externally adjudicated APTC-defined ATEs (adjudicated by an independent clinical coding committee at Cleveland Clinic, United States) was low and comparable across the two treatment arms (1.1% and 1.4% in the faricimab Q4W and aflibercept Q4W arms, respectively).

Death adjudicated APTC ATEs were reported in 1 patient (0.2%) in the aflibercept Q4W arm. The death adjudicated APTC ATE in the aflibercept Q4W arm was myocardial infarction, not suspected by the investigator to be related to the study treatment (please see Table 57, below).

Non-fatal myocardial infarction adjudicated APTC ATEs were reported in 2 patients (0.3%) and 4 patients (0.6%) in the faricimab Q4W and aflibercept Q4W arms, respectively.
The most common non-fatal myocardial infarction adjudicated APTC ATEs (2 patients in any treatment arm) by PT was acute myocardial infarction (3 patients [0.5%] in the aflibercept Q4W arm; Table below). Three of the non-fatal myocardial infarctions adjudicated APTC ATEs were suspected by the investigator to be related to study treatment: acute myocardial infarction (2 patients) and myocardial infarction (1 patient) in the aflibercept Q4W arm.

Non-fatal stroke adjudicated APTC ATEs were reported in 5 patients (0.8%) and 4 patients (0.6%) in the faricimab Q4W and aflibercept Q4W arms, respectively. The most common non-fatal stroke adjudicated APTC ATEs (2 patients in any treatment arm: faricimab Q4W and aflibercept Q4W arms, respectively) by PT were **cerebral infarction** (2 patients [0.3%] and 1 patient [0.2%]), **cerebrovascular accident** (1 patient [0.2%] and 2 patients [0.3%]) and **RAO** (2 patients [0.3%] and 1 patient [0.2 %])

Two of the non-fatal strokes adjudicated APTC ATEs were suspected by the investigator to be related to study treatment: cerebral infarction and cerebrovascular accident (1 patient each) in the faricimab Q4W arm.

The per 1000 injection rate of externally adjudicated APTC-defined ATEs in the study eye was **1.90** and **2.46** events per 1000 injections in the faricimab Q4W and aflibercept QW4 arms respectively.
The exposure-adjusted incidence rates of externally adjudicated APTC defined ATEs per 100 PY Week 24 were **2.36** and **3.07**, in the faricimab Q4W and aflibercept Q4W arms, respectively.

Table 57. Adjudicated APTC-Defined ATE Events through Week 24 from Individual and Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

Adjudicated APTC events MedDRA Preferred Term	GR41984 (BALATON) (N=550)		GR41986 (COMINO) (N=726)		Pooled (BALATON and COMINO) (N=1276)	
	Faricimab 6 mg Q4W (N=276)	Aflibercept 2 mg Q4W (N=274)	Faricimab 6 mg Q4W (N=365)	Aflibercept 2 mg Q4W (N=361)	Faricimab 6 mg Q4W (N=641)	Aflibercept 2 mg Q4W (N=635)
Total number of patients with at least one adverse event	3 (1.1%)	4 (1.5%)	4 (1.1%)	5 (1.4%)	7 (1.1%)	9 (1.4%)
Overall total number of events	3	4	4	5	7	9
NON-FATAL STROKE						
Total number of patients with at least one adverse event	2 (0.7%)	2 (0.7%)	3 (0.8%)	2 (0.6%)	5 (0.8%)	4 (0.6%)
Total number of events	2	2	3	2	5	4
Cerebral infarction	2 (0.7%)	1 (0.4%)	0	0	2 (0.3%)	1 (0.2%)
Cerebrovascular accident	0	1 (0.4%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.3%)
Retinal artery occlusion	0	0	2 (0.5%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
NON-FATAL MI						
Total number of patients with at least one adverse event	1 (0.4%)	2 (0.7%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	4 (0.6%)
Total number of events	1	2	1	2	2	4
Acute myocardial infarction	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.5%)
Myocardial infarction	1 (0.4%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
DEATH						
Total number of patients with at least one adverse event	0	0	0	1 (0.3%)	0	1 (0.2%)
Total number of events	0	0	0	1	0	1
Myocardial infarction	0	0	0	1 (0.3%)	0	1 (0.2%)

AE = Adverse Event; APTC = anti-Platelet Trialist's Collaboration; MI = myocardial infarctions; MedDRA = Medical Dictionary for Regulatory Activities;
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). If no events occurred for a certain category, the category are not presented. Investigator text for AEs encoded using MedDRA version 25.0.
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 prior to Week 24 treatment or dose hold or if none prior to Day 168.

Adjudicated APTC-defined ATEs: Week 24 through CCOD

There were 2 patients (0.3%) with a death adjudicated APTC-defined ATEs which occurred in the aflibercept Q4W to faricimab PTI arm. These events were coronary artery disease and death (verbatim: unexplained death), both of which not suspected by the investigator to be related to the study treatment.

One patient (0.2%) experienced a non-fatal MI adjudicated APTC-defined ATE in the faricimab Q4W to Faricimab PTI arm (myocardial infarction, not suspected by the investigator to be related to the study treatment).

One patient (0.2%) experienced a non-fatal stroke adjudicated APTC-defined ATE in the faricimab Q4W to faricimab PTI arm (RAO, not suspected by the investigator to be related to study treatment), and 2 patients (0.3%) patients with a non-fatal stroke in the aflibercept Q4W to faricimab PTI arm (cerebrovascular accident and RAO, both not suspected by the investigator to be related to the study treatment.

The per 1000 injection rate of externally adjudicated APTC-defined ATEs in the study eye from Week 24 to the CCOD was comparable between the two treatment arms (1.33 and 2.73 events per 1000 injections in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

In the **pooled Part 2** dataset, the incidence of externally adjudicated anti-platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic events (ATEs) was low across both treatment arms and remained as expected in this patient population. No clear pattern was identified between the injection day of study treatment and the timing of the APTC event, including for previously treated aflibercept Q4W patients who switched to faricimab PTI.

Three patients (0.5%) in each arm **had fatal adjudicated APTC-defined ATEs**. All these events were single events (aortic dissection, cardiac failure, coronary artery disease, death [verbatim: unexplained death], and myocardial infarction;). None were suspected by the investigator to be related to the study treatment.

Four patients (0.6%) in each arm **had non-fatal myocardial infarctions adjudicated APTC-defined ATEs.** These events were myocardial infarction (3 patients in the faricimab Q4W to faricimab PTI arm and 1 patient in the aflibercept Q4W to faricimab PTI arm), acute myocardial infarction (3 patients in the aflibercept Q4W to faricimab PTI arm), and stress cardiomyopathy (1 patient in the faricimab Q4W to faricimab PTI arm); none were suspected by the investigator to be related to study treatment. There were **3 patients** (0.5%) and **8 patients** (1.3%) that reported non-fatal stroke adjudicated APTC-defined ATEs in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. These will be discussed separately, below.
In the **Entire Study** dataset, the incidence of externally adjudicated APTC-defined ATEs in the faricimab Q4W to faricimab PTI arm was **2.8%.**

The **exposure-adjusted incidence rate of APTC-defined ATEs** per 100 PY was **2.20** which was consistent with other faricimab Phase III studies (DME: **2.79** and nAMD: **1.71**; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS). The rate of APTC-defined ATEs per 1000 injections was **2.74** which was consistent with other faricimab Phase III studies (DME: **6.66** and nAMD: **5.5**; DME Yr2 2.7.4 SCS, nAMD Wk112 2.7.4 SCS).

Arterial Thromboembolic Events and Cerebrovascular Haemorrhage Adverse Events by SMQ (Un-Adjudicated) Before the Week 24 Visit
The incidence of un-adjudicated ATE and cerebrovascular haemorrhage AEs was low and comparable across the two treatment arms (2.5% and 2.5% in the faricimab Q4W and aflibercept Q4W arms, respectively).

The most common events (2 patients in the faricimab Q4W and aflibercept Q4W arms, respectively) were cerebrovascular accident, (3 [0.5%] and 2 [0.3%]), coronary artery disease (1 [0.2%] and 4 [0.6%]), acute myocardial infarction (1 [0.2%] and 3 [0.5%]), cerebral infarction (3 [0.5%] and 1 [0.2%]), myocardial infarction (1 [0.2%] and 3 [0.5%]), carotid arteriosclerosis (3 [0.5%] and 0), carotid artery stenosis (0 and 3 [0.5%]).

The per 1000 injection rate of AEs of ATE and Cerebrovascular Haemorrhage AEs were 5.69 and 6.83 in the faricimab Q4W and aflibercept Q4W arms, respectively.

In the pooled Part 2 dataset, the incidence of non-ocular ATEs and cerebrovascular haemorrhagic AEs (non-adjudicated) was low in both treatment arms (**2.9%** and **3.0%** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) and remained as expected in this patient population. In the entire study, the incidence of non-ocular ATEs and cerebrovascular haemorrhagic AEs (non-adjudicated) in the faricimab Q4W to faricimab PTI arm was **5.1%.**

Discussion on Cerebral Vascular Events
In **Part 1** (before Week 24 visit) of the BALATON study, there were **3 patients** (1.1%) in the faricimab Q4W arm and **1 patient** (0.4%) in the aflibercept Q4W arm who experienced cerebral infarction events. The 3 cerebral infarction events in the faricimab Q4W arm were considered serious with 2 of these events suspected by the investigators to be related to study treatment (1 event resolved and 1 was unresolved by Week 72).

Part 1 Balaton Study: Narratives of cerebral infarction cases
Patient 1 was a 69-years-old Asian male who received Faricimab (6 mg IVT Q4W up to Week 20 followed by Faricimab PTI dosing of 6 mg IVT up to Week 68) experienced the event of **Cerebral infarction**. Prior to this event, the most recent dose of faricimab was administered on Study Day 85 **(Week 12).** The patient had received a total of **4 injections** of study treatment as of this Study Day. On Study **Day 97,** the patient suddenly fell and lost consciousness. He was diagnosed with severe cerebral infarction (diagnostic details reported as unknown), leading to hospitalisation. He received unspecified medications and underwent unspecified surgery. It was reported that it was impossible for the patient to continue the study due to hospitalisation in another hospital. The investigator was also unable to collect further information about concomitant medication or surgery/procedures due to his

consent withdrawal. The event of cerebral infarction remained unresolved at the time of clinical cut-off day. No information regarding the patient's discharge was provided. Due to this event, the study treatment was **permanently discontinued** with the last dose administered on Study **Day 85** (Week 12). The patient had received a total of 4 injections of study treatment. No other AE was experienced by the patient during the study. **The investigator considered cerebral infarction, to be related to study treatment.**

A further update on this serious event was provided by the MAH, stating that, for the above described patient, after the cerebral infarction event in **Part 1,** the study treatment was interrupted after Study Day 86 (Week 12). The study treatment was not administered between Weeks 16 and 24 and the next dose was administered on Study Day 198 **(Week 28).** This patient experienced **another cerebral infarction event** in Part 2 on Study Day 410 **(Week 58),** which was non-serious and considered by the investigator unrelated to the study treatment, and unresolved at the time of study completion.

Patient 2 was a 63-years-old Asian male in treatment arm A (Faricimab) received dosage regimen Faricimab (6 mg IVT Q4W up to Week 20 followed by Faricimab PTI dosing of 6 mg IVT up to Week 68). The study eye was the right eye. The Non-ocular concurrent conditions included hypertension, gout and renal failure. Prior to the **event of cerebral infarction**, the most recent dose of faricimab was administered on Study Day 141 (Week 20).

The patient had received a total of 6 injections of study treatment as of this Study Day. On Study Day 159, the patient experienced numbness and weakness of the left limb which was completely relieved within ten minutes and did not affect his ability of holding and walking. On Study Day 160, the patient again experienced numbness and weakness of the left limb which got worsened gradually. The patient experienced difficulty in walking and lifting of the upper limb was laborious. A cranial CT-scan did not show bleeding or infarction. On Study Day 162, the patient presented with ongoing numbness and weakness of the left limb. He was also noted with aggravation of hypertension (pre-existing condition) to moderate intensity (blood pressure 168/79 mmHg, unrelated). A MRI showed **pontine acute cerebral infarction**, multiple intracranial lacunar cerebral infarction with softening foci in few and leukoencephalopathy. Also, a brain atrophy, left maxillary sinus submucosal cyst, and bilateral otitis media.

The event of cerebral infarction was reported as resolving at the time of clinical cut-off. There was no change in study treatment due to the event of cerebral infarction. **The Investigator considered cerebral infarction, to be related to study treatment and concurrent illness** (hypertension and deep venous thrombosis). **At the time of clinical cut-off, the patient continued to receive study treatment.** Further updates on this serious event were received thereafter. Specifically, as this patient discontinued the study prior to Week 24 and withdrew consent, further information could not be collected. Thus, the cerebral infarction event remained unresolved at the time of treatment discontinuation.

Patient 3 was a 61-years-old Asian male in treatment arm A (who received dosage regimen faricimab of 6 mg IVT Q4W up to Week 20 followed by Faricimab PTI dosing of 6 mg IVT up to Week 68. The study eye was the right eye. Non-ocular concurrent conditions included hypertension and type 2 diabetes mellitus. At screening, the patient's BMI was 27.1 kg/m2.

On Study Day 1, the patient received his first study treatment with faricimab in the study eye.
Concomitant medication ongoing at Study Day 1 included herbal (unspecified) and herbal and traditional medicine (unspecified). The patient experienced (**Event 1**) **Cerebral infarction, (Event 2) Carotid arteriosclerosis** and (**Event 3**) **Carotid arteriosclerosis (Carotid plaque)**.
Prior to the events of cerebral infarction and carotid arteriosclerosis, the most recent dose of faricimab was administered on Study Day 86 (Week 12). The patient had received a total of 4 injections of study treatment as of this Study Day.

On Study Day 100, the patient developed right-side numbness and slurred speech for 15 hours.

An MRI showed a few bilateral acute and subacute **cerebral infarction** and lacunar infarction with white matter degeneration. On Study Day 110, the event of cerebral infarction was resolved, and the patient was discharged from the hospital. The events of hyperlipidemia, and carotid arteriosclerosis (both events) remained unresolved at the time of clinical cut-off. There was no change in the study treatment due to the events of cerebral infarction and carotid arteriosclerosis (both events).

The Investigator considered cerebral infarction and carotid arteriosclerosis both events **unrelated to the study treatment** and related to other causes (unspecified). At the time of clinical cut-off, the patient continued to receive study treatment. Further updates on this serious event were received thereafter. Specifically, at the time of the primary analysis, the cerebral infarction event was reported as resolving. There was no change in study treatment and on Study Day 511, the cerebral infarction event was considered resolved.

There was also one 49-year-old Asian female patient with a cerebral infarction event in the aflibercept Q4W arm occurring on Study Day 95, unresolved by the primary analysis. At the end of the study the event was considered severe, non-serious and not suspected by the investigator to be related to the study treatment.

Further updates on the serious events occurring in the faricimab Q4W arm through Week 72 are provided below.

In Part 2 (Week 24 through Week 72), there was 1 patient (0.4%) in each treatment arm (faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively) who experienced a cerebral infarction event. The one event in the aflibercept Q4W to faricimab PTI arm occurred on Study Day 417 (Week 59) and was considered serious, suspected by the investigator to be related to study treatment, and resolved by Week 72; the dose remained unchanged from the event.

For a 55-years-old Asian female in treatment arm B (Aflibercept) with dosage regimen of Aflibercept (2 mg IVT Q4W up to Week 20 followed by Faricimab PTI dosing of 6 mg IVT up to Week 68) (Study eye Right eye Event [PT]), following randomisation on Study Day 1.The patient was diagnosed with macular edema secondary to branch retinal vein occlusion(BRVO) of right eye on Study Day - 11.

No non-ocular medical/surgical history was reported. The patients non-ocular concurrent condition included systemic hypertension. At screening, the patients BMI was 23.7 kg/m2. At screening, the vitals showed blood pressure124/74 mmHg. On Study Day 1, the patient received her first study treatment with aflibercept in the study eye. Concomitant medication, ongoing at Study Day 1, included captopril.

On Study Day 138 (Week 20), the patient completed treatment with aflibercept. The patient had received a total of 6 injections of aflibercept. On Study Day 201 (Week 28), the patient received first study treatment with faricimab. The patient experienced the event of cerebral infarction.
Prior to the event of cerebral ischemia, the most recent and last dose of faricimab was administered on Study Day 394 (Week 56). The patient had received a total of 3 injections of faricimab as of this study Day.

On Study Day 417, a brain computed tomography (CT) scan showed left basal ganglia and coronary artery radiation infarction and she was diagnosed with severe cerebral infarction (initial intensity moderate, serious).

On Study Day 418, the patient was noted with worsening of hypertension (concurrent condition) to severe intensity (blood pressure not reported for this day; non-serious, unrelated). She also complained of right limb weakness for 18 hours. Subsequently, she was hospitalized due to cerebral infarction.

On Study Day 420, CT angiography of the head and neck showed cerebral arteriosclerosis, rough upper wall of left middle cerebral artery, carotid arteriosclerosis and tortuosity, embryonal posterior cerebral artery with vertebrobasilar dysplasia, and variation. It was reported that during hospitalization, she did not complain of obvious discomfort and her blood pressure was well controlled. On Study Day 426, she was discharged from the hospital (blood pressure upon discharge: 145/103 mmHg).

On Study Day 510, her blood pressure was 126/77 mmHg. On the same day (Study Day 510), the event of cerebral infarction was considered as resolved. The event of hypertension remained unresolved at the time of study completion.

On Study Day 510, the patient completed the study with the last dose of faricimab given on Study Day 394 (Week 56). The patient had received a total of 3 injections of faricimab.

The other cerebral infarction event in the faricimab Q4W to faricimab PTI arm in Part 2 is described above for another patient.

In the COMINO study, there was 1 patient (0.3%) who experienced a cerebral infarction event which occurred in the aflibercept Q4W to faricimab PTI arm in Part 2. The event was considered non-serious, not suspected by the investigator to be related to study treatment, and unresolved by Week 72.

There were no cerebral infarction events in Part 1 of the COMINO study.

The CHMP noted that all cerebral infarction events across treatment arms in the BALATON and COMINO studies above summarised were reported in Asian patients with a majority from China (5 out of 6 patients). However, other non-ocular non-fatal stroke adjudicated Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic event (ATEs) (ischemic stroke, cerebrovascular accident, and haematoma) were reported in the other racial subgroups (i.e., white, unknown and black or African American). Furthermore, the APTC rates reported in the entire study were consistent with the previous faricimab Phase III studies in nAMD and DME, and the rate of non-fatal strokes observed in Part 2 was consistent with Part 1. RVO is associated with cardiovascular risk factors which are also well-known risks for strokes (refer to Question 20 for further details). Additionally, the overall rate is in line with event rates for cerebrovascular accidents in patients with RVO reported in the literature.

The MAH also highlighted that stroke remains the leading cause of death in China, with an estimated 2.5 million incident strokes and 1.6 million deaths related to stroke occurring each year (Kim et al. 2015). A study estimated that the incidence rate of first-ever stroke in China (505.2 per 100 000 person-years for ages 40 years and older in 2020) was higher than that in Japan (317.0 per 100 000 person-years for ages 45 years and older in 2011), Singapore (229.6 per 100 000 population in 2017), and the European Union (Tu et al. 2023).

The non-ocular non-fatal stroke adjudicated APTC-defined ATEs in the entire pooled BALATON and COMINO studies were low across all racial subgroups (Table below).

Table 58. Non ocular non-fatal stroke adjudicated APTC-defined ATEs by study part and race though week 72 for pooled BALATON and COMINO studies, Safety-evaluable population

	Faricimab Q4W Part 1 (N=641)	Aflibercept Q4W Part 1 (N=635)	Faricimab Q4W to Faricimab PTI Part 2 (N=629)	Aflibercept Q4W to Faricimab PTI Part 2 (N=609)
Total	6 (0.9%)	4 (0.6%)	3 (0.5%)	8 (1.3%)
American Indian or Alaska native	0	0	0	0
Black or African American	0	0	0	1 (0.2%)
White	3 (0.5%)	3 (0.5%)	2 (0.3%)	4 (0.7%)
Unknown	0	0	0	1 (0.2%)
Asian	3 (0.5%)	1 (0.2%)	1 (0.2%)	2 (0.3%)

APTC = Anti-Platelet Trialists' Collaboration; ATE = arterial thromboembolic event; PTI = personalized treatment interval; Q4W = every 4 weeks

The MAH provided further details about the patient who suffered a second stroke. Based on available data, including Pop PK analysis, the CHMP concluded that no difference in safety profile across ethnic groups is anticipated. Nevertheless, the MAH should continue to closely monitor this topic, presenting focused updates in future PSURs, discuss / propose options to provide (further) longer-term safety data for the RVO indication. In addition, the MAH was recommended to strengthen current warnings in the PI related to the numbers of cases of APTC events (including cases of cerebral infarction considered causally related) reported in patients treated with faricimab (RVO indication). However, the MAH was rather of the view that information e.g. in SmPC section 4.4 and 4.8 (under "Systemic effects" and "Product-class-related adverse reactions," respectively) about Anti-Platelet Trialists' Collaboration (APTC) events reported in patients treated with faricimab was sufficient: APTC rates reported in RVO studies were low, the majority considered unrelated to faricimab and with other plausible (causal) explanations for the related events.

The CHMP also noted that **overall rates were consistent with those from the previous faricimab Phase III studies in diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) and the incidence of APTC events reported from the Phase III RVO trials with aflibercept** (VIBRANT and COPERNICUS; Brown et al. 2013, Campochiaro et al. 2015) and ranibizumab (BRAVO and CRUISE; FDA RVO Medical Review 2010). In summary, strengthening information in the PI for the RVO indication was not warranted for this potential risk in the RMP.

Through Week 72 of the pooled BALATON and COMINO studies, a total of 41 (3.2%) patients had an adjudicated APTC event (18 patients [2.8%] in the faricimab every 4 weeks [Q4W] to faricimab personalized treatment interval [PTI] arm and 23 patients [3.6%] in the aflibercept Q4W to faricimab PTI arm) of which 8 were considered related to study treatment. Of the 8 patients who had an adjudicated APTC event considered related to study treatment, 3 patients had events related to faricimab and 3 patients had events related to aflibercept in Part 1. The remaining two patients were in the aflibercept Q4W to faricimab PTI arm and had events related to faricimab in Part 2.

Over the entire RVO Phase III studies, the exposure-adjusted incidence rate of APTC-defined arterial thromboembolic events (ATEs) per 100 patient year (PY) was 2.20 in the faricimab Q4W to faricimab PTI arm, which was consistent with the pooled faricimab arms in the other faricimab Phase III studies (DME: 2.79 and nAMD: 1.71).

Since the faricimab Q4W to faricimab PTI arm in the Entire Study group has the longest, continuous faricimab treatment duration of any of the groups, the pooled data from this group were used for the best comparison to faricimab treatment in the other indications (DME and nAMD).

The table below is a summary of all the adjudicated APTC events considered related to study treatment by the investigator, along with the other risk factors associated with these events for each patient.

Table 59. Adjudicated APTC events related to study treatment in BALATON and COMINO over the entire study

Study	Patient ID	Event (PT)	Causality	Other risk factors
Part 1				
BALATON	214201	Cerebral Infarction	Related to Faricimab	Hypertension, Carotid arteriosclerosis, Deep Vein Thrombosis
BALATON	202103	Acute Myocardial Infarction	Related to Aflibercept	Ongoing systemic hypertension, Type V hyperlipidaemia, anaemia macrocytic
COMINO	313403	Retinal Artery Occlusion	Related to Faricimab	Local arterial vascular disease
COMINO	313404	Cerebrovascular Accident	Related to Faricimab	Medical history of transient ischaemic attack
COMINO	300602	Myocardial Infarction	Related to Aflibercept	Ongoing systemic hypertension
COMINO	303303	Acute Myocardial Infarction	Related to Aflibercept	Ongoing systemic hypertension, obesity, concurrent coronary artery disease

Part 2				
BALATON	214602	Cerebral Thrombosis	Related to Faricimab	Ongoing systemic hypertension
BALATON	214202	Cerebral Infarction	Related to Faricimab	Ongoing systemic hypertension

APTC =Anti-Platelet Trialists' Collaboration; PT =preferred term

Source: l_ae_APTC_SE_30AUG2023_41984, l_ae_APTC_SE_29AUG2023_41986, Final BALATON CSR Narrative, Report 1126074, p. 1395, Update COMINO CSR Narrative, Report 1126075, p. 1581

It is also well described that a long-term impairment of retinal microvasculature could lead directly to cerebral small-vessel disease and is characterized by lacunar infarcts and white matter lesions (Lindley et al. 2009; Li et al. 2016).

A retrospective cohort study in Taiwan analyzed data for patients with RVO and their risk of ischemic stroke, haemorrhagic stroke, and all-cause mortality from the National Health Insurance Research Database between January 2001 and December 2013 (Chen et al. 2018). Patients with RVO (22,919 patients) were compared with simple randomly sampled non-RVO group without matching the characteristics of the RVO group (114,595 patients) and propensity score (PS)-matched non-RVO comparison group (114,595 patients). The mean follow-up period for patients with RVO was 4.8 ± 3.5 years. The incidence of ischemic stroke (per 100 PY) was 4.31 in the RVO group and 3.17 in the non-RVO group (PS-matched).

Furthermore, considering the rapid plasma clearance (due to the specifically engineered Fc portion) which results in systemic plasma exposure approximately 6000-fold lower than in the vitreous humour, there is no evidence suggesting that faricimab increases the risk of systemic APTC events including ischemic stroke beyond what has been described above.

As incidence of APTC events is in line with the other faricimab Phase III studies and RVO trials with aflibercept and ranibizumab, in addition to evidence that the risk of APTC events increases with age, other comorbidities, and in the RVO population, the MAH, still, did not believe a label update was required. However, it proposed to continuously monitor APTC events (as part of routine signal detection) and include summary data in future PSURs.

The CHMP duly considered the MAH's position and information summarised below.

Through Week 72 of the pooled BALATON and COMINO studies, a total of 41 (3.2%) patients had an adjudicated APTC event (18 patients [2.8%] in the faricimab every 4 weeks [Q4W] to faricimab personalized treatment interval [PTI] arm and 23 patients [3.6%] in the aflibercept Q4W to faricimab PTI arm) of which 8 were considered related to study treatment. Of the **8 patients** who had an adjudicated APTC event considered **related to study treatment**, 3 patients had events related to faricimab and 3 patients had events related to aflibercept in Part 1. The remaining two patients were in the aflibercept Q4W to faricimab PTI arm and had events related to faricimab in Part 2.

Over the entire RVO Phase III studies, the exposure-adjusted incidence rate of APTC-defined arterial thromboembolic events (ATEs) per 100 patient year (PY) was 2.20 in the faricimab Q4W to faricimab PTI arm which was consistent with the pooled faricimab arms in the other faricimab Phase III studies (DME: 2.79 and nAMD: 1.71).

Additionally, it is known that in the general population, the incidence of APTC events increases with age and that patients with RVO are at an increased risk of cardiovascular events including stroke and myocardial infarction, as well as all-cause mortality compared to those without RVO.

The MAH outlined that the overall rates were consistent with those from the previous faricimab Phase III studies in diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) and the incidence of APTC events reported from the Phase III RVO trials with aflibercept.

Ultimately, on this basis, the CHMP reiterated the request to add RVO to the current warning in section 4.4 of the SmPC and any corresponding section of the PL. The MAH agreed.

Systemic effects

The CHMP also considered (and requested to reflect accordingly in the SmPC, and corresponding section of the PL) that systemic adverse events including arterial thromboembolic events were reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors and there is a theoretical risk that these may be related to VEGF inhibition. A low incidence rate of arterial thromboembolic events was observed in the faricimab clinical trials in patients with nAMD, and DME, and RVO. Given limited data on the safety of faricimab treatment in DME patients with high blood pressure (≥ 140/90 mmHg) and vascular disease, and in nAMD and RVO patients ≥ 85 years of age, the MAH should maintain APTC events under focused review in future PSUR. The MAH agreed.

Part 2

There were **3 patients** (0.5%) and **8 patients** (1.3%) that reported non-fatal stroke adjudicated APTC-defined ATEs in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively. These events were **RAO** (2 patients in both arms), **ischaemic stroke** (1 patient each in both arms), **cerebrovascular accident** (2 patients in the aflibercept Q4W to faricimab PTI arm), **cerebral hematoma**, **cerebral infarction,** and **cerebral thrombosis** (1 patient each in the aflibercept Q4W to faricimab PTI arm). The majority (81.8%, 9/11) were not suspected by the investigator to be related to study treatment and patients had risk factors for developing these events.

With regards to non-ocular events, the CHMP noted that, up to **week 24,** these AEs were generally reported at a similar rate across both treatment arms in the phase III clinical studies, except for **'hypertension'**, with a higher numerical frequency in the faricimab treatment arm of **BALATON** study. The MAH further clarified that, in the absence of an imbalance of hypertension events in other population treated with faricimab (nAMD and DME) and as majority of the cases reported in faricimab RVO studies had risk factors associated with hypertension, the baseline medical history of patients with RVO, and the rates of hypertension in published data for this population, the numerically higher rate of hypertension events in the faricimab Q4W arm was considered as isolated findings in the BALATON study. The CHMP agreed. Nevertheless, this topic should continue to be (routinely) monitored.

The Committee also noted that cases reporting **serious non-ocular events** were similar across faricimab and aflibercept treatment arms in **Part I** of both COMINO and BALATON phase III studies.

Overall, **to week 24**, the exposure-adjusted incidence rates of **externally adjudicated APTC** defined ATEs per 100 PY were 2.36 and 3.07, in faricimab Q4W and aflibercept Q4W arms, respectively. No major imbalances were observed in Part I of the clinical studies. The incidence of **un-adjudicated** ATE and cerebrovascular haemorrhage AEs was low and comparable across the two treatment arms (2.5% and 2.5% in the faricimab Q4W and aflibercept Q4W arms.

The per 1000 injection rate of AEs of ATE and cerebrovascular haemorrhage AEs were 5.69 and 6.83 in the faricimab Q4W and aflibercept Q4W arms, respectively. The MAH provided an overview and causality assessment of **all serious non ocular events** and satisfactory clarified the rationale for categorising them as adjudicated APTC ATEs versus un-adjudicated ATE.

Arterial thromboembolic events and central nervous system haemorrhagic events are known, important potential risks of faricimab. The MAH acknowledged that all cerebral infarction events across treatment arms in BALATON and COMINO studies of interest for this EoI were reported in Asian patients, with a majority from China (5 out of 6 patients). However, other non-ocular non-fatal stroke adjudicated Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic event (ATEs) (ischemic stroke, cerebrovascular accident, and haematoma) were reported in the other racial subgroups (i.e., White, unknown and black or African American). In addition, no differences in the faricimab safety profile across ethnicity are anticipated based on the conclusions from the PoP PK analysis.

The APTC rates reported in the entire study were consistent with the previous faricimab Phase III studies in nAMD and DME, and the rate of non-fatal strokes observed in Part 2 was consistent with Part 1. RVO is associated with cardiovascular risk factors which are also well-known risks for. Additionally, the overall rate is in line with event rates for cerebrovascular accidents in patients with RVO reported in the literature.

In summary, in Part 1 per the primary analysis, the exposure-adjusted incidence rates (events per 100 patient years) of externally adjudicated APTC events in the pooled BALATON and COMINO studies were comparable between treatment arms (2.36 in the faricimab Q4W arm and 3.07 in the aflibercept Q4W arm). In Part 2 from Week 24 to clinical cutoff date (CCOD) the exposure-adjusted incidence rates (events per 100 patient years) of externally adjudicated APTC ATEs in the pooled BALATON and COMINO studies were 0.83 in the faricimab Q4W to faricimab PTI arm and 2.10 in the aflibercept Q4W to faricimab PTI arm.

The MAH highlighted that although a numerical difference was observed in the exposure adjusted incidence rates of externally adjudicated APTC defined ATEs per 100 PY, the incidence of patient with these events was low (2 patients [0.3%] in the faricimab Q4W to faricimab PTI arm and 4 patients [0.7%] in the aflibercept Q4W to faricimab PTI arm).

In Part 2, from Week 24 to Week 72, the exposure-adjusted incidence rates (events per 100 patient years) of externally adjudicated APTC events in the pooled BALATON and COMINO studies were consistent with Part 1 (and reported as 1.76 in the faricimab Q4W to faricimab PTI arm and 2.96 in the aflibercept Q4W to faricimab PTI arm).

Over the entire study, the exposure-adjusted incidence rates (events per 100 patient years) of externally adjudicated APTC ATEs was 2.20 in the faricimab Q4W to faricimab PTI arm which was consistent in the pooled faricimab arms in the other Phase III studies (nAMD: 1.71 and DME: 2.79).
No new ADRs were identified using the criteria above for BRVO and C/HRVO, over and above those already identified during the nAMD and DME pivotal studies.

Whilst there are no specific new safety signals identified, this topic remains an area of special interest for the CHMP. Thus, the MAH should continue to closely monitor this issue and provide specific updates in future PSURs.

In addition, the MAH discussed the feasibility to obtain longer term data on non-ocular safety and APTC events. The MAH 72-week RVO data presented in the BALATON and COMINO CSRs, in combination with the DME and nAMD LTE studies, and existing routine pharmacovigilance activities (i.e., adverse reaction reporting, Guided Questionnaires, signal detection and management activities) with all relevant safety data, reported in the PBRER have been considered sufficient to provide long-term safety and immunogenicity data for faricimab to cover the RVO indication for the following reasons:

• The commonality between the pathophysiology and risk factors in DME and RVO supports that data from LTE studies in DME is relevant to the RVO population.
• Long-term RWD studies from anti-VEGF products have not identified a difference in safety profile between the DME and RVO population.

• Data obtained to date from the ongoing faricimab LTE studies in the DME and nAMD.

Deaths

Before week 24

In Part 1 (before Week 24 visit) of the pooled BALATON and COMINO studies, a total of 4 patients had fatal events (2 patients [0.3%] in the faricimab Q4W arm and 2 patients [0.3%] in the aflibercept Q4W arm). The number of deaths was low and balanced across both treatment arms and none of the deaths were suspected by the investigators to be related to study treatment. The exposure-adjusted incidence rates (events per 100 patient years) of deaths were 0.68 in the faricimab Q4W arm and 0.68 in the aflibercept Q4W arm.

Week 24 through CCOD

Death was reported in **3 patients,** 1 (0.2%) in the faricimab Q4W to faricimab PTI arm and 2 (0.3%) in the aflibercept Q4W to faricimab PTI arm. The primary causes of death were COVID-19 in the faricimab Q4W to faricimab PTI arm and coronary artery disease and death (verbatim: unexplained death) in the aflibercept Q4W to faricimab PTI arm (please see the Table below). None of the deaths were suspected by the investigator to be related to study treatment and all the fatal events were confounded by either the underlying medical history of the patient or concurrent medical conditions.

Table 60. Patient Deaths After Week 24 to CCOD from the Phase III RVO Studies (Safety Evaluable Population)

Study: GR41984(BALATON)
Treatment: Aflibercept 2 mg Q4W to Faricimab 6 mg PTI

Center/ Patient ID Age/Sex/Race	Day of Death		Treatment Period	Number of Study Drug Administered prior to Death		Days from Last Dose Prior to Death to Death**	Causes of Death	AE Other Suspected Causes of Death	AE Suspected to be Caused by Masked Study Drug?	AE Suspected to be Caused by Fellow (Non-Study) Eye Anti-VEGF	Autopsy Performed?
	For Part 1	For Part 2		Part 1	Part 2						
330565/205301 67/M/White	363	166	Part2	6	2	107	Coronary artery disease		No	N/A	No
333812/204502 78/M/White	331	168	Part2	6	3	70	Death		No	No	Unknown
Study: GR41986(COMINO) Treatment: Faricimab 6 mg Q4W to Faricimab 6 mg PTI											
330666/304603 100/M/White	272	103	Part2	6	1	73	COVID-19		No	N/A	Unknown

Part 1 is the randomized treatment period through Week 24. Part 2 is the faricimab PTI period starting on the Week 24 dosing visit or after Day 168 for the faricimab Part 1 arm or, for aflibercept Part 1 arm, the date of the first faricimab dose to the CCOD. Part 2 no dose refers to the interval for some patients from the aflibercept arm in Part 1 have between the end of part 1 and the first faricimab dose in Part 2.
Day of Death Part 1: Study day of Death from first study treatment; Part 2: Study day of Death from start of Part 2.
Note: Day of Death study days past the start of Part 2 listed under the 'For Part 1' column represent the overall study day from baseline to the Day of Death occurring in the Part 2 treatment period Events with preferred term as Death are unexplained deaths.
Includes deaths that are occurring either, for faricimab Part 1 Arm, on Week 24 treatment (faricimab or sham) or dose hold or if none on Day 168 or, for aflibercept Part 1 Arm, the first faricimab dose to CCOD.
** Days from last dose derived from imputed onset date and/or end date.

Pooled Dataset Part 2

In the pooled Part 2 dataset, **5 patients** (0.8%) died in the faricimab Q4W to faricimab PTI arm (death [verbatim: unexplained death; 2 patients], aortic dissection, COVID-19, and myocardial infarction [1 patient each]), and **3 patients** (0.5%) died in the aflibercept Q4W to faricimab PTI arm (death [verbatim: unexplained death], cardiac failure, and coronary artery disease [1 patient each].

The exposure-adjusted incidence rate of deaths per 100 PY deaths was **0.88** in the faricimab Q4W to faricimab PTI arm and **0.59** in the aflibercept Q4W to faricimab PTI arm. The exposure-adjusted incidence rate of deaths per 100 PY in Part 2 was in line with the rate reported in Part 1 (**0.68** in both the faricimab and the aflibercept arms).

Table 61. Rate of Deaths Per 100 Patient Years by Study Part through Week 72 for Pooled BALATON and COMINO Studies, Safety- Evaluable Population

	Pooled (BALATON and COMINO)			
Primary Cause of Death	Faricimab 6 mg Q4W Part 1 (N=641)	Aflibercept 2 mg Q4W Part 1 (N=635)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=629)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=609)
Total Patient Years at Risk	295.4	292.1	567.2	506.1
Total Number of Deaths (Rate per 100 Patient Years)	2 (0.68)	2 (0.68)	5 (0.88)	3 (0.59)
Myocardial infarction	0	2 (0.68)	1 (0.18)	0
Cerebrovascular accident	1 (0.34)	0	0	0
Pneumonia	1 (0.34)	0	0	0
Aortic dissection	0	0	1 (0.18)	0
COVID-19	0	0	1 (0.18)	0
Cardiac failure	0	0	0	1 (0.20)
Coronary artery disease	0	0	0	1 (0.20)
Death	0	0	2 (0.35)	1 (0.20)

Total number of deaths is displayed, rate per 100 patient years is displayed in the bracket, calculated as [number of deaths/ total patient-years at risk] x 100.
For Part 1 the total patient-years at risk is the sum over all patients of the time intervals (in years) from the first dose of study treatment up until the patient withdraws prior to Week 24 or prior to Week 24 treatment or dose hold or if none prior to Day 168. For Part 2 the total patient-years at risk is the sum over all patients of the time intervals (in years) from the date of Week 24 treatment or dose hold for faricimab patients or the first dose of faricimab for aflibercept patients up until the patient completes/withdraws from the study. Includes deaths in the same period covered by patient-years at risk.

With regards to fatal cases, the CHMP noted 3 additional cases reported from Part II of both clinical studies. Two of these cases occurred in the subgroup of patients who had received aflibercept in Part I of the study and had been switched to faricimab PTI in part I,I and one case was reported in the faricimab 6mg Q4W group who had continued with faricimab 6mg PTI. The primary causes of death were COVID-19 in the faricimab Q4W to faricimab PTI arm and coronary artery disease and death (verbatim: unexplained death) in the aflibercept Q4W to faricimab PTI arm.

The MAH presented the total overall number of fatal cases in all patients exposed to faricimab (both part I exposure and part II exposure). A comparison was also provided highlighting those exposed to faricimab only in Part II. Given the inherent limitations in drawing meaningful conclusions from the non-comparator data from Part II of both studies, data were also provided as exposure-adjusted data.

A detailed update from the complete safety data set was subsequently presented by the MAH.

In the entire study dataset, **7 patients** (1.1%) died in the faricimab Q4W to faricimab PTI arm and **5 patients** (0.8%) died in the aflibercept Q4W to faricimab PTI arm. The exposure-adjusted incidence rate of deaths per 100 PY was lower (**0.81**) compared with other faricimab Phase III studies (**DME: 2.53** and **nAMD: 1.7)**.

None of the deaths were suspected by the investigator to be related to study treatment.
Therefore, it was agreed that no specific new safety issues arose from the cases presented. However, this matter should remain as a topic of special interest, closely monitored, and with regular updates presented in future PSURs.

Immunogenicity

Impact of Anti-Drug Antibody on Safety:

Through Week 24, there was no apparent impact of ADAs against faricimab observed on overall safety, including **IOI.** However, the clinical impact of ADA status on safety remained unclear. Therefore, the potential risk of immunogenicity in the context of IOI should continue to be monitored through routine signal detection in all ongoing Phase III faricimab studies.

Through Week 24, **54 patients** across BALATON and COMINO studies were **ADA-positive**, of which 6 (1.0%) patients were treatment-unaffected ADA-positive and 48 (8.0%) patients were treatment-emergent ADA-positive. The median time to onset of ADA was 24 weeks.

In the **BALATON** study the incidence of treatment-emergent ADAs against faricimab was low (6.9%). No apparent influence of ADA on overall safety was observed based on the available data. Overall, the incidence of ocular and non-ocular AEs, SAEs, AESIs, and deaths were comparable between the pooled ADA-positive and ADA-negative subgroups.

Through Week 24, the incidence of ocular AEs in the pooled ADA-positive subgroup was **22.2%,** vs **20.1%** in the pooled ADA-negative subgroup.

Of the patients who were ADA-positive and experienced ocular AEs, they were mainly non-serious, not suspected by the investigator to be related to study treatment, did not result in study withdrawal, and were not associated with severe IOI events. The incidence of patients with ocular SAEs and AESIs in the pooled ADA-positive subgroup was 3.7% and 1.9% vs 1.7% and 1.3% in the pooled ADA-negative subgroup. The serious AEs in the ADA positive subgroup were RAO and uveitis, both in the **COMINO** study. The event of **uveitis** was diagnosed on Day 97 and was confirmed as ADA positive at Week 24, with a titer of 10240. The **RAO** was reported at the Week 4 visit, at which point the patient tested ADA negative, and therefore the event is unlikely to be related to ADA status. The patient subsequently tested ADA-positive at Week 24 with a titer of 20 All IOI cases were in the **COMINO** study.

Overall, the incidence of IOI was comparable between the ADA-positive subgroup (1 event of serious uveitis, moderate intensity; 1/54; 1.9% and in the ADA-negative subgroup (8/543; 1.5%).

From Week 24 to CCOD, 2 events of IOI were reported in ADA positive patients. One non-serious event of Iritis reported on Day 337 which was confirmed as ADA positive at Week 24 with a titer of 1280, and one serious event of Iritis reported on Day 220 which was confirmed as ADA positive at Week 24 with a titer of 1280. The remaining 3 IOI events reported were all ADA negative, but the ADA status post-Week 24 was not yet available at the time of authoring this AR. Thus, conclusions about the impact of ADAs on safety from Week 24 could not be made.

Overall, the CHMP noted that:

- the incidence of IOI events was higher for the group treated with faricimab compared to aflibercept in the Comino study (8 patients [2.2%] and 4 patients [1.1%], respectively).
- In 6 patients the IOI event occurred shortly (i.e. ⩽10 days) after the first injection of faricimab, whereas in only one patient the IOI occurred soon (i.e. ⩽10 days) after first injection of aflibercept.

It was unclear why notable differences across the rate of IOI in the COMINO study to week 24 have been observed by the CHMP. The MAH discussed accordingly this observation, clarifying that, considering the overall low incidence of IOI, the comparability with previous registrational studies, and the mild clinical presentation of the events in the faricimab Q4W arm, the current data does not support a significant difference between treatment arms in Part 1 of COMINO (the treatment difference was 1.1%; 95% CI: -0.93%, 3.26%).

Limitations in the strategy for assessment of immunogenicity were noted by the CHMP. The incidence of ADAs through Week 24 was low and no apparent influence of ADA on overall safety or efficacy was observed, based on available data. However, most of the patients who developed ADAs still had persistent ADAs at Week 24 (94.4% in the BALATON study, and 96.7% in the COMINO study, respectively)and possibly beyond Week 24.

In **Part 2** a higher incidence of **IOI events** in the study eye was again reported, consistently with Part 1, with 10 patients (2.8%) in the faricimab Q4W to faricimab PTI arm and 5 patients **(1.5%)** in the aflibercept Q4W to faricimab PTI arms, respectively.

The MAH outlined the above was likely related to the greater severity of underlying **CRVO** disease compared with BRVO and in line with what observed in historical RVO pivotal trials. Majority of cases were non-serious, mild and moderate in severity and with no impact on visual outcomes. There was no clear relationship between injection day of study treatment and timing of the events observed, with the caveat that the number of IOI reported was small. There were no reported IOI events associated with retinal vasculitis or occlusive disease.
Additionally, IOI events associated with significant vision loss (≥ 15 letters or ≥ 30 letters) were infrequent (1 patient had a vision loss of ≥ 15 letters associated with a serious event of **vitritis** in the

faricimab Q4W to faricimab PTI arm and 1 patient had a vision loss of ≥ 15 letters associated with a non-serious event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm).

By **Week 72,** majority of **IOI** events were resolved or resolving. **Four events** (vitritis, non-infectious endophthalmitis, iritis, and iridocyclitis [1 event each]) in the faricimab Q4W to faricimab PTI arm and **1 event** of iridocyclitis in the aflibercept Q4W to faricimab PTI arm were not resolved by Week 72. Two of these events occurred at the end of the study; and therefore, they were still ongoing at the last study visit. One event of vitritis resulted in study discontinuation.

In the **pooled Part 2** dataset, the incidence of **IOI** events occurring in the study eye was low in both the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (**1.9%** and **1.3%,** respectively)

Immunogenicity results
In the **Balaton** study the incidence of treatment-emergent ADAs against faricimab from baseline to Week 72 in the faricimab Q4W to faricimab PTI arm was low (11.7%). No apparent influence of ADA on systemic exposure or efficacy was observed based on the available data. The clinical significance of anti-faricimab antibodies on overall safety is unclear at this time. The uncertainty is related to the low incidence of immunogenicity and the low incidence of IOI, for which all the events were of mild severity and had a reversible character.

In the **Comino** study the incidence of treatment-emergent ADAs against faricimab from baseline to Week 72 in the faricimab Q4W to faricimab PTI arm was low **(16.5%).** No apparent influence of ADA on systemic exposure or efficacy was observed based on the available data. Although **a higher incidence of IOI** was observed in **ADA-positive patients** compared with ADA-negative patients, the clinical significance of anti-faricimab antibodies on overall safety is unclear at this time. The uncertainty was related to the low incidence of immunogenicity and the low incidence of IOI, for which majority of the events were of mild to moderate severity and had a reversible character.

An overall higher incidence of treatment-emergent ADAs was noted in the COMINO study compared to the BALATON study. This correlated with a higher incidence of IOI events reported in ADA positive patients. This issue, discussed accordingly by the MAH, should be kept under monitoring over the longer term.

Other Ocular Assessments from the Pooled Phase III RVO Studies
Overall, 9 patients (1.4%) and 20 patients (3.1%) experienced an **intraocular pressure increase** AE in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively. One of the intraocular pressure increased AEs (in the aflibercept Q4W arm) was considered serious. This event was suspected by the investigator to be related to study treatment and resolved by Week 24.

Overall, 7 patients (1.1%) and 3 patients (0.5%) developed **ocular hypertension** in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively. None of ocular hypertension AEs were considered serious, all events were mild or moderate in severity; all events in the faricimab Q4W arm had either recovered or were recovering by Week 24, and all events in the aflibercept Q4W arm had not recovered by Week 24. No patient and 4 patients (0.6%) developed glaucoma in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively.

One AE of **open angle glaucoma** in the faricimab Q4W arm and 1 AE of open angle glaucoma and 1 AE of borderline glaucoma in the aflibercept Q4W arm were also reported (all in the **COMINO** study). None of glaucoma AEs were considered serious.

Week 24 through CCOD
Mean pre-dose IOP and mean IOP change from baseline over time from Week 24 through CCOD in the study eye were comparable across treatment 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 both 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. Overall, 13 patients (2.1%) and 11 patients (1.9%) experienced an intraocular pressure increased AE in the study eye in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively. None of the events were serious. Overall, 4 patients (0.6%) and 4 patients (0.7%) developed ocular hypertension in the study eye in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively. None of ocular hypertension AEs were considered serious. Overall, 5 patients (0.8%) and 5 patients (0.9%) developed glaucoma in the study eye in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively. One AE of open angle glaucoma and 1 AE of borderline glaucoma in the faricimab Q4W to faricimab PTI arm were also reported. None of glaucoma AEs were considered serious.

Intraocular Pressure
Intraocular pressure (IOP) was comparable between treatment arms at baseline. Mean pre-dose IOP were comparable across study visits **through Week 72** with mean pre-dose IOP change generally below 1 across visits for both arms. Overall, differences in pre-dose and post-dose IOP were within the limits of IOP measurement variability and consistent with expectations of IOP change following an intravitreal injection, and no trend or pattern was observed.

In Part 2, AEs of IOP increased in the study eye were reported in 13 patients (4.8%) and 8 patients (3.0%) in the faricimab Q4W to faricimab PTI arm and in the aflibercept Q4W to faricimab arm, respectively. All events were non-serious, and mild or moderate in severity.
Additionally, there were 2 AEs of ocular hypertension in the study eye reported in the faricimab Q4W to faricimab PTI arm. Both events were reported as non-serious.

There were 3 AEs of glaucoma in the faricimab Q4W to faricimab PTI arm. All were reported as non serious, and were also reported in the fellow eye.

Slit Lamp Examination
Through Week 24
The proportion of patients by grade for the worst post-baseline outcome in the study eye through Week 24 on slit lamp examination including intraocular inflammation (anterior chamber cell, anterior chamber flare, and vitreous flare), cataract and vitreous haemorrhage were comparable across the two treatment arms.

Week 24 through CCOD
There were 3 Grade 2 events of vitreous haemorrhage and 1 grade 3 in the faricimab Q4W to faricimab PTI arm and 1 grade 4 in aflibercept Q4W to faricimab PTI arm. There were no post-baseline Grade 4 findings of anterior chamber cell, anterior chamber flare and vitreous cell in either arm.

Worst **post-Week 24** findings in the study eye were cataract (1 patient and 3 patients with Grade 4 in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively) and Grade 4+ vitreous haemorrhage (1 patient in the aflibercept Q4W to faricimab PTI arm).

Indirect Ophthalmoscopy
Through Week 24
The proportion of patients having any post-baseline retinal break or retinal detachment through Week 24 in the study eye were low and comparable across the treatment arms. At baseline, 2 patients (0.3%) and 1 patient (0.2%) were reported to have a retinal break in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively. At baseline, 8 patients (1.2%) and 8 patients (1.3%) were reported to have a retinal detachment in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively. Five patients (0.8%) each in both the faricimab Q4W and aflibercept Q4W arms developed any post-baseline retinal break. Six (0.9%) and 8 patients (1.3%) developed any post-baseline retinal detachment in the study eye in the faricimab Q4W and aflibercept Q4W arms,

respectively. The vast majority of cases were identified by the investigator as having a serous macular detachment or break secondary to macular edema due to RVO.

Week 24 through CCOD
Overall, 1 patient (0.2%) in the faricimab Q4W to faricimab PTI arm experienced any new or worsened retinal break or detachment in the study eye.

In **Part 2**, one patient (0.4%) experienced a post-Week 24 retinal break in the study eye in the faricimab Q4W to faricimab PTI arm which was also reported as a mild and non-serious AE (retinal tear). One patient (0.4%) experienced a post-Week 24 rhegmatogenous detachment in the study eye in the faricimab Q4W to faricimab PTI arm. The AE of rhegmatogenous retinal detachment was reported in a patient with worsening of cataract who underwent cataract surgery after which he developed rhegmatogenous retinal detachment. Surgery and vitrectomy were performed. At the following visit, the investigator noticed a retinal tractional detachment. This was not assessed as treatment related. The study treatment was interrupted, the patient underwent vitrectomy and recovered. One patient (0.4%) experienced a post-Week 24 retinal break in the fellow eye in the aflibercept Q4W to faricimab PTI arm.

In relation to the available safety data, from ocular assessments, to week 24, the CHMP noted a relatively small number of patients who had developed AEs relating to increases in IOP, which were generally similar if not slightly higher in the aflibercept treatment group (faricimab Q4W n=9 patients (1.4%) and aflibercept Q4W n=20 patients (3.1%).

7 patients (1.1%) and 3 patients (0.5%) developed ocular hypertension in the study eye in the faricimab Q4W and aflibercept Q4W arms, respectively. These events were mild or moderate in severity.
Non-serious cases of glaucoma were reported in n=0 patients (faricimab Q4W) and N=4 patients (aflibercept Q4W arms 0.6%).

Based on the currently available data to CCOD, overall, 13 patients (2.1%) and 11 patients (1.9%) experienced an intraocular pressure increased AE in the study eye in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively. None of the events were serious. Overall, 4 patients (0.6%) and 4 patients (0.7%) developed non-serious ocular hypertension in the study eye in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.
Cases reporting non-serious glaucoma were noted in equal numbers n= 5 patients (0.8%) and n=5 patients (0.9%) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

Overall, no major imbalances were observed.

Laboratory findings
There were no clinically relevant imbalances across treatment arms for laboratory parameters.

Safety in special populations
No patient became pregnant during the study.

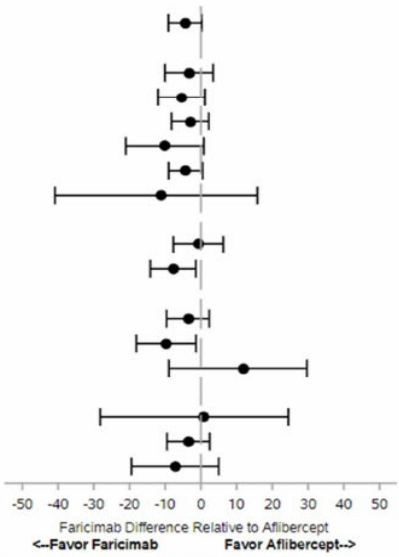
Subgroup Analyses
Analyses were performed to examine key safety across the subgroups defined by the following intrinsic factors, before the Week 24 visit:

- Age (< 65 and ≥ 65)Age (< 75 and ≥ 75)
- Age (< 85 and ≥ 85);
- Gender (female and male).
- Race (White, Asian and other); and
- Medical history (renal disease, cardiac disease, and vascular disease)

Overall, in the pooled data, differences in incidences of ocular AEs, incidences of non-ocular AEs, incidences of SAEs, and incidences of ocular AESI between the faricimab Q4W arm and the aflibercept Q4W arm were consistent across subgroups and with incidences in the overall safety-evaluable population. Subgroup analyses are provided in forest plots for the faricimab Q4W arm vs. aflibercept Q4W arm for ocular AEsin the Figure below.

Figure 41. Subgroup Forest Plot of Ocular AEs in the Study Eye through Week 24 from Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

	Faricimab 6 mg n/m	%	Aflibercept 2 mg n/m	%	Difference (95% CI)
Overall	129/641	20.1%	156/635	24.6%	-4.4 (-9.1, 0.2)
Age					
<65	56/294	19.0%	67/299	22.4%	-3.4 (-10.1, 3.4)
>=65	73/347	21.0%	89/336	26.5%	-5.5 (-12.0, 1.1)
<75	103/507	20.3%	119/510	23.3%	-3.0 (-8.2, 2.2)
>=75	26/134	19.4%	37/125	29.6%	-10.2 (-21.0, 0.8)
<85	123/611	20.1%	151/619	24.4%	-4.3 (-9.0, 0.5)
>=85	6/30	20.0%	5/16	31.3%	-11.3 (-40.9, 15.8)
Gender					
Female	73/306	23.9%	76/309	24.6%	-0.7 (-7.7, 6.3)
Male	56/335	16.7%	80/326	24.5%	-7.8 (-14.2, -1.4)
Race					
White	92/414	22.2%	109/421	25.9%	-3.7 (-9.6, 2.3)
Asian	24/179	13.4%	42/181	23.2%	-9.8 (-18.1, -1.4)
Other	13/48	27.1%	5/33	15.2%	11.9 (-8.9, 29.7)
Medical History					
Renal Disease	3/23	13.0%	2/16	12.5%	0.5 (-28.2, 24.5)
Cardiac Disease	79/384	20.6%	98/406	24.1%	-3.6 (-9.5, 2.4)
Vascular Disease	21/111	18.9%	24/92	26.1%	-7.2 (-19.5, 4.9)

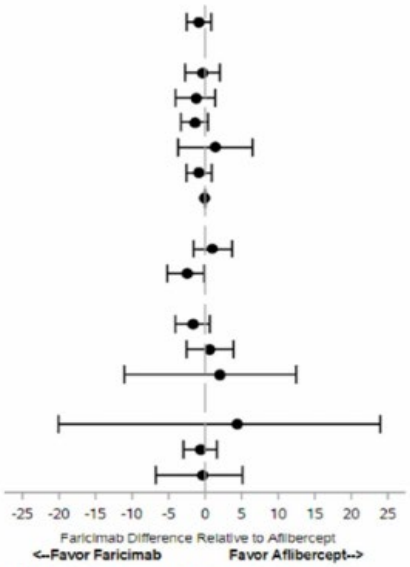


AE= Adverse Events; n = Number of patients with at least one applicable adverse event; m = Number of patients in the subgroup. Includes events with onset prior to Week 24 treatment or dose hold or if none prior to Day 168. Newcombe with continuity correction method is used for the difference and 95% CI.

Subgroup analyses are provided in forest plots for the faricimab Q4W arm vs. aflibercept Q4W arm for ocular AESIs are noted in the Figure below.

Figure 42. Subgroup Forest Plot of Ocular AEs of Special Interest in the Study Eye through Week 24 from Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)

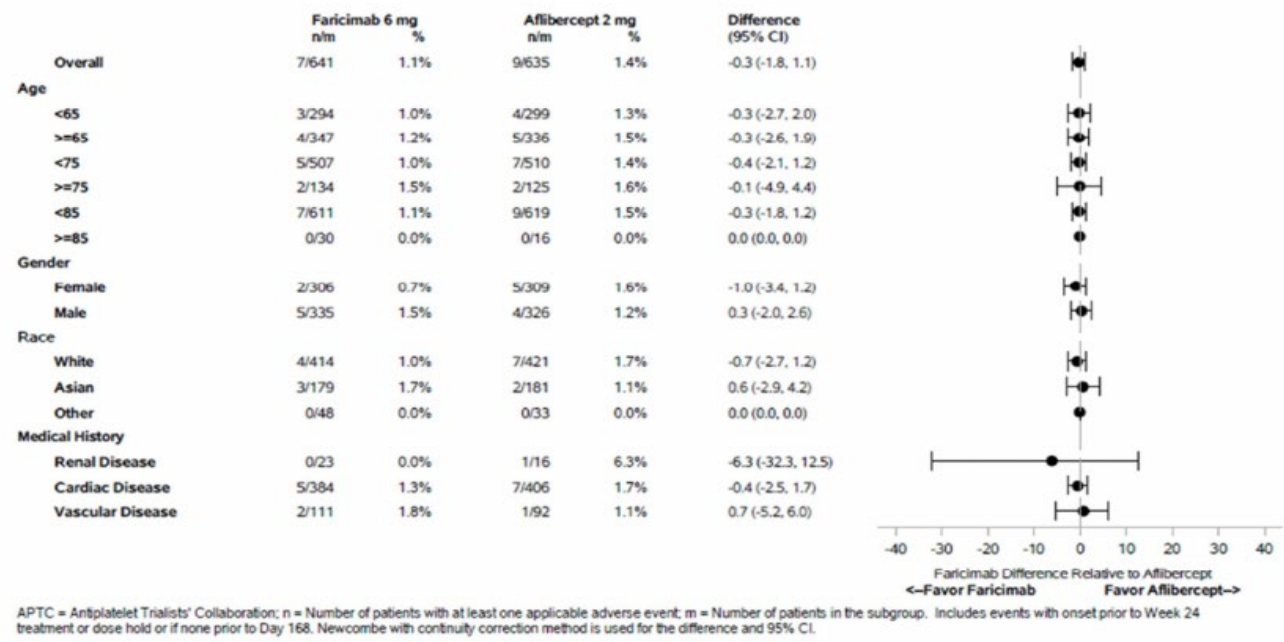
	Faricimab 6 mg n/m	%	Aflibercept 2 mg n/m	%	Difference (95% CI)
Overall	9/641	1.4%	14/635	2.2%	-0.8 (-2.5, 0.8)
Age					
<65	3/294	1.0%	4/299	1.3%	-0.3 (-2.7, 2.0)
>=65	6/347	1.7%	10/336	3.0%	-1.2 (-4.0, 1.4)
<75	5/507	1.0%	12/510	2.4%	-1.4 (-3.3, 0.4)
>=75	4/134	3.0%	2/125	1.6%	1.4 (-3.7, 6.5)
<85	9/611	1.5%	14/619	2.3%	-0.8 (-2.6, 0.9)
>=85	0/30	0.0%	0/16	0.0%	0.0 (0.0, 0.0)
Gender					
Female	7/306	2.3%	4/309	1.3%	1.0 (-1.6, 3.7)
Male	2/335	0.6%	10/326	3.1%	-2.5 (-5.2, -0.1)
Race					
White	6/414	1.4%	13/421	3.1%	-1.6 (-4.1, 0.6)
Asian	2/179	1.1%	1/181	0.6%	0.6 (-2.5, 3.9)
Other	1/48	2.1%	0/33	0.0%	2.1 (-11.0, 12.5)
Medical History					
Renal Disease	1/23	4.3%	0/16	0.0%	4.3 (-20.1, 24.0)
Cardiac Disease	6/384	1.6%	9/406	2.2%	-0.7 (-2.9, 1.6)
Vascular Disease	2/111	1.8%	2/92	2.2%	-0.4 (-6.8, 5.1)



AESI=Adverse Event of Special Interest; AE= Adverse Events; n = Number of patients with at least one applicable adverse event; m = Number of patients in the subgroup. Includes events with onset prior to Week 24 treatment or dose hold or if none prior to Day 168. Newcombe with continuity correction method is used for the difference and 95% CI.

Subgroup analyses are provided in forest plots for the faricimab Q4W arm vs. aflibercept Q4W arm for adjudicated-APTC events are outlined below.

Figure 43. Subgroup Forest Plot of APTC Events through Week 24 from Pooled Phase III RVO Studies (Pooled Safety-Evaluable Population)



APTC = Antiplatelet Trialists' Collaboration; n = Number of patients with at least one applicable adverse event; m = Number of patients in the subgroup. Includes events with onset prior to Week 24 treatment or dose hold or if none prior to Day 168. Newcombe with continuity correction method is used for the difference and 95% CI.

Table 62. Number of Patients by Hispanic and Non-Hispanic Subgroups through Week 72 in BALATON and COMINO (Safety-Evaluable Population)

Subgroup	Faricimab Q4W (no. of patients)		Aflibercept Q4W (no. of patients)	
BALATON	Part 1	Part 2	Part 1	Part 2
Hispanic	47	47	51	50
Non-Hispanic	224	218	221	215
COMINO				
Hispanic	66	64	73	66
Non-Hispanic	285	282	281	270

Q4W=every 4 weeks

Source: PR15689_t_ae_ci_SOCUL_PART_HISPSUB_SE_30AUG2023_41984; PR15689_t_ae_ci_SOCUL_PART_HISPSUB_SE_29AUG2023_41986

Overall, the MAH highlighted that there were no clinically meaningful differences in ocular and non-ocular safety between the Hispanic and non-Hispanic subgroups. While there appears to be some numerical differences in the proportions of ocular AEs and non-ocular AEs between the ethnic groups, it is difficult to draw any meaningful conclusions due to the small number of events within the Hispanic subgroup and the limitation that baseline characteristics may not be well balanced between the Hispanic and non Hispanic subgroups. Additionally, popPK analysis has shown no effect of race on the pharmacokinetics (ocular and systemic) of faricimab

The CHMP noted the analyses across various subgroups for age, gender, race and relevant medical history up to week 24. Although no major differences between faricimab and aflibercept were noted across most of the various subgroups, the MAH was asked to further discuss any potential adverse effect of **ethnicity,** particularly on the ocular safety of faricimab, based on their available safety data.
The non-ocular non-fatal stroke adjudicated APTC-defined ATEs in the entire pooled BALATON and COMINO studies were low across all racial subgroups. Additionally, the Pop PK analysis did not show any effect of race on the pharmacokinetics (ocular and systemic) of faricimab. Therefore, based on faricimab PK, no differences are expected.

In conclusion, the CHMP agreed that the MAH's available safety data did not suggest an association between faricimab safety profile and ethnicity.

The MAH was also requested to provide a **subgroup analysis** of the data from Part 2 of the clinical studies where pointed out that subgroups are generally consistent with the overall rates and across subgroups. While there appear to be some numerical differences in the proportions of ocular AEs, non-ocular AEs, and serious AEs by subgroup, the CHMP agreed it is difficult to draw any meaningful conclusions due to the small number of events within each subgroup. However, this topic should continue to be monitored by routine pharmacovigilance.

Safety related to drug-drug interactions and other interactions
No interaction studies have been conducted with this application.

Discontinuation due to adverse events
In **the Balaton study** in the ITT population, 12 patients (2.2%) discontinued study treatment with a comparable proportion between treatment arms (3.3% of patients in the faricimab Q4W arm and 1.1% of patients in the aflibercept Q4W arm). The reasons for study treatment discontinuation were lost to follow-up (1.8% in the faricimab Q4W arm and 0.7% in the aflibercept Q4W arm), withdrawal by subject (0.7% in the faricimab Q4W arm and 0.4% in the aflibercept Q4W arm), adverse event (0.4% in the faricimab Q4W arm) and death (0.4% in the faricimab Q4W arm).
The incidence of AEs leading to study treatment discontinuation was low (1 patient in each arm). There were no ocular AEs leading to study treatment discontinuation. The incidence of AEs leading to study discontinuation was low (2 patients and 1 patient in the faricimab Q4W and aflibercept Q4W arms, respectively).

There were no ocular AEs leading to study discontinuation. One patient in the faricimab Q4W arm died on Day 162. The patient's treatment discontinuation date was derived as the last treatment day (Day 132), which was before the start of the Week 24 window (Day 154); therefore, the patient was counted as discontinued study treatment. The patient's study discontinuation date was Day 162, which was beyond the analysis date of Day 154.

Overall, in **Balaton** study in the ITT population, 10.9% of patients discontinued study treatment prior to Week 72: 11.6% of patients in the faricimab Q4W to faricimab PTI arm and 10.2% of patients in the aflibercept Q4W to faricimab PTI arm; as reported in the Primary CSR, 3.3% and 1.1% of patients discontinued study treatment prior to Week 24 in the faricimab Q4W and aflibercept Q4W arms, respectively. Overall, 11.6% of patients withdrew from the study prior to Week 72: 11.2% in the faricimab Q4W to faricimab PTI arm and 11.9% in the aflibercept Q4W to faricimab PTI arm; as previously reported 1.3% and 1.4% discontinued from the study prior to Week 24 in the faricimab Q4W and aflibercept Q4W arms, respectively. In the **Comino** study, the incidence of all AEs (ocular and non-ocular AEs) leading to study treatment discontinuation was low across treatment arms (3 patients in each arm).
The incidence of ocular AEs leading to study treatment discontinuation was low across treatment arms (3 patients [0.8%] and 2 patients [0.6%] in the faricimab Q4W and aflibercept Q4W arms, respectively). Ocular AEs leading to study treatment discontinuation were uveitis (2 patients) and rhegmatogenous retinal detachment (1 patient) in the faricimab Q4W arm and endophthalmitis (1 patient) and RVO (1 patient) in the aflibercept Q4W arm.

The incidence of non-ocular AEs leading to study discontinuation was low across treatment arms (1 patient [0.3%] and 3 patients [0.8%] in the faricimab Q4W and aflibercept Q4W arms, respectively.

AEs and Ocular AEs Leading to Study Treatment or Study Discontinuation Pooled Part 2 Dataset
In the pooled Part 2 dataset, the incidence of ocular AEs leading to study treatment discontinuation was low in both treatment arms. All these events were single events that occurred in 1 patient each, with the exception of **vitritis** that occurred in 2 patients in the faricimab Q4W to faricimab PTI arm.

In the pooled Part 2 dataset, the incidence of ocular AEs leading to study discontinuation was also low in both treatment arms (3 patients [0.5%] in the faricimab Q4W to faricimab PTI arm and 2 patients [0.3%] in the aflibercept Q4W to faricimab PTI arm, respectively; All these events were single events that occurred in 1 patient each.

Entire Study
In the entire study dataset, the incidence of ocular AEs leading to study treatment discontinuation in the faricimab Q4W to faricimab PTI arm was low with 1.2%. The most common ocular AEs leading to study treatment discontinuation ($\geq$ 2 patients in any arm of pooled Entire Study dataset) were **uveitis** (3 patients in the faricimab Q4W to faricimab PTI arm) and **vitritis** (2 patients in the faricimab Q4W to faricimab PTI arm.
The incidence of ocular AEs leading to study discontinuation in the faricimab Q4W to faricimab PTI arm was low with 0.6%. All these events were single events that occurred in 1 patient each.

In summary, the CHMP noted that the overall incidence of ocular and non-ocular AEs leading to study discontinuation was low across treatment arms. The most common ocular AEs leading to study treatment discontinuation ($\geq$ 2 patients in any arm of pooled entire study dataset) were **uveitis** (3 patients in the faricimab Q4W to faricimab PTI arm) and **vitritis** (2 patients in the faricimab Q4W to faricimab PTI arm.

Post marketing experience
Faricimab has been approved in more than 50 countries worldwide to date. As of 27 January 2023, the total estimated cumulative patient exposure to faricimab from clinical trials (5,043 patients) and marketing experience (90,859 patients) is 95,902 patients.

2.5.1. Discussion on clinical safety

At the time of the initial submission of this application to extend the indication for use of faricimab in patients with RVO, the full safety data set from the pivotal clinical studies in patients with RVO was not yet available. The overall safety profiles of faricimab and aflibercept were generally comparable in Part 1 of the RVO pivotal studies to week 24. Based on the data to week 24, the overall incidence of ocular AEs in the study eye in the faricimab Q4W arm was comparable to the aflibercept Q4W arm (20.1% and 24.6% in the faricimab Q4W and aflibercept Q4W arms, respectively).

There was some uncertainty in relation to the conclusions on clinical safety of faricimab beyond 24 weeks treatment in this indication as there was no comparator arm beyond this timepoint and patients in part 2 of both phase III studies were treated with faricimab PTI so some ADR reports are confounded by some patients having received aflibercept in the 1st part of the RVO studies and then patients were subsequently exposed to faricimab in Part 2 of the studies. In this context, the MAH presented thereafter, as requested, the complete safety data set to facilitate the safety evaluation of the longer-term safety profile of faricimab in this indication.

In addition, at the time of the initial assessment, it was unclear how many patients were treated under each different dosing regimen as part of Faricimab PTI dosing and how many AEs were reported within the individual treatment schedules. This was further clarified by the MAH.

In the **Balaton** study the potential to extend treatment intervals with faricimab up to Q16W was demonstrated, with approximately 60% of patients on an extended dosing interval of Q12W or Q16W at Week 68, resulting in approximately **5 mean injections** in study **Part 2.** In the **Comino** study, the potential to extend treatment intervals with faricimab up to Q16W was demonstrated, with approximately 48% of patients on an extended dosing interval of Q12W or Q16W at Week 68, resulting in approximately **5.5 mean injections** in study **Part 2.**

Broadly speaking, the safety data provided in **Part 2** of the pivotal studies indicates that faricimab continues to be generally well tolerated. However, a number of uncertainties and points for clarification remained outstanding. As noted in the RVO initial clinical overview (CO), a slightly higher incidence of ocular AEs (including ocular SAEs) in both treatment arms continued to be reported in Part 2 in COMINO (C/HRVO) compared with BALATON (BRVO) which is consistent with historical RVO pivotal trials. Some uncertainties relating to longer term ocular and non-ocular safety, in addition to immunogenicity, also remain.

Extent of exposure
In the **Balaton** study the majority of randomized patients received at least one dose of study treatment (550 patients; 3 randomized patients did not receive any treatment and were excluded from the safety evaluable population).

As expected, due to study design, in study Part 1, the median duration of exposure (20.1 weeks), mean (5.8) and median (6.0) number of study drug administrations through Week 24 was the same for both treatment arms. In study Part 2, the median duration of exposure was 42.3 weeks and 37.8 weeks in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

The treatment exposure is longer in the faricimab Q4W to faricimab PTI arm than the aflibercept Q4W to faricimab PTI arm because the exposure is counted from Week 24 for the faricimab arm, and from the first faricimab dose on or after Week 24 for the aflibercept arm. While the faricimab PTI dosing regimen started at Week 24, most patients did not receive faricimab at Week 24 (7% [19/270] and 9% [24/267] received a faricimab dose at Week 24 in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively; the other patients received sham at Week 24).

The mean (median) number of study drug administrations were 4.8 (4.0) and 4.9 (4.0) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

In the **COMINO** study the majority of randomized patients received at least one dose of study drug (726 patients; 3 randomized patients did not receive any treatment and were excluded from the safety-evaluable population). As expected due to study design, the median duration of exposure (20.1 weeks), mean (5.7) and median (6.0) number of study drug administrations through Week 24 was the same for both treatment arms.

In study **Part 2**, the median duration of exposure was 42.3 weeks and 38.6 weeks in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arm, respectively. The treatment exposure is longer in the faricimab Q4W to faricimab PTI arm than the aflibercept Q4W to faricimab PTI arm because the exposure is counted from Week 24 for the faricimab Q4W to faricimab PTI arm, and from the first faricimab dose on or after Week 24 for the aflibercept Q4W to faricimab PTI arm. While the faricimab PTI dosing regimen started at Week 24, most patients did not receive faricimab at Week 24 (11% [39/359] and 12% [40/342] received a faricimab dose at Week 24 in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively; the other patients received sham at Week 24). The mean (median) number of study drug administrations were 5.6 (5.0) and 5.5 (4.0) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

In the **entire study** dataset, the median duration of exposure was 68.1 weeks in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (and the same duration in each study); the

mean (median) number of study treatment administrations (i.e., faricimab or aflibercept) in the pooled dataset was the same in each treatment arm (10.8 [10.0]; the mean (median) number of study treatment administrations was comparable between the BALATON and COMINO studies: 10.3 (9.0) and 11.2 (10.0) vs. 10.6 (10.0) and 10.9 (10.0) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

In the **All Faricimab** dataset, the median duration of exposure to faricimab was 44.1 weeks (same duration in each study); the mean (median) number of faricimab administrations in the pooled dataset was 8.1 (9.0) and was comparable between the studies (7.7 [9.0] in the BALATON study and 8.4 [9.0] in the COMINO study.

A total of 1,282 patients (553 in the BALATON study and 729 in the COMINO study) were enrolled in the two studies, with 1,276 patients treated with at least one dose through week 24 (641 with faricimab). Patient ages ranged from 28 to 93 with a mean [SD] of 64 [10.7] years, and 22 to 100 with a mean [SD] of 65 [13.2] years in the BALATON and COMINO studies, respectively.

In the pooled Part 2 dataset, 1,238 patients received at least one dose of faricimab (629 patients in the faricimab Q4W to faricimab PTI arm and 609 patients in the aflibercept Q4W to faricimab PTI arm and
the mean (median) number of faricimab administrations was similar in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (5.3 [4.0] and 5.2 [4.0], respectively).

In the separate studies, the mean (median) number of faricimab injections administered in Part 2 was generally comparable: in the BALATON study it was 4.8 (4.0) and 4.9 (4.0) vs. COMINO 5.6 (5.0) and 5.5 (4.0) in the faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm, respectively.

While focus is on the pooled Part 2 dataset (Week 24 through Week 72), of note, the faricimab Q4W to faricimab PTI arm in the entire study group has the longest, continuous faricimab treatment duration of any of the safety groups and it is therefore reasonable that these data can be used to support the consistency of safety profile in RVO with that in the DME (100 Weeks) and nAMD (112 Weeks), using exposure-adjusted AE rates from the faricimab arms in the other Phase III trials.

Ocular AEs
In relation to **ocular AEs**, the overall rates observed across the pooled phase III studies were generally balanced between faricimab and aflibercept to week 24.The exposure-adjusted incidence rate of ocular AEs per 100 PY was generally consistent with Part 1 for both arms (65.23 and 71.53 in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and 63.60 and 76.31 in the pooled faricimab and aflibercept arms in Part 1, respectively.

There was a higher incidence of ocular events in patients treated at the **Q4W** dosing interval compared to the **Q16W** dosing interval within each treatment arm. The higher incidence could be explained by a worse RVO disease status requiring more injections compared to the other dosing intervals throughout the study. The incidence of events in patients treated at the Q8W and Q12W dosing intervals should be interpreted with caution due to the comparatively low sample size.

Overall, considering the limitations of the by **treatment interval analysis**, the safety profile of faricimab remained similar across all treatment interval subgroups, and the nature and type of non-ocular AEs and ocular AEs in the study eye reported in patients assigned to Q8W, Q12W, and Q16W dosing was similar. By comparison, limited conclusions can be drawn from the data provided in patients treated with the Q8W and Q12W dosing intervals due to the low sample size.

In this context the limitations of the safety data in the RVO population should be reflected/strengthened in the PI, particularly for specific dosing regimens where safety data is currently limited.

In the **BALATON,** study there was an increased incidence of AEs and SAEs is observed in Part 2 (Week 24 through Week 72) compared to Part 1 (baseline through Week 24) as expected with the increased follow-up time, the safety results after treatment with a faricimab PTI dosing regimen were consistent with the safety results observed in Part 1, with faricimab continuing to be generally well tolerated with a low incidence of AEs leading to study treatment withdrawal.

In **Part 2**, the **most common ocular AEs** in the study eye (2% incidence in any treatment arm) by PT were: conjunctival haemorrhage, IOP increased, cataract, vitreous detachment, vitreous floaters, RVO [verbatim: worsening of CRVO, worsening of BRVO, exacerbation of BRVO, superior BRVO, accelerated worsening of BRVO, RVO aggravated], macular oedema [verbatim: worsening of MO], and epiretinal membrane. Information relating to these ocular ADRs is reflected accordingly in the PI.

In the **BALATON** study, in the faricimab Q4W to faricimab PTI arm, 35.7% of patients and 26.2% of patients experienced at least one ocular AE in the Q4W and Q16W dosing intervals, respectively. In the aflibercept Q4W to faricimab PTI arm, 34.4% of patients and 22.4% of patients experienced at least one ocular AE in the Q4W and Q16W dosing intervals, respectively.

Ocular AEs in the study eye which contributed to the higher incidence of AEs in patients treated at the faricimab PTI Q4W dosing interval compared to faricimab Q16W in either treatment arm (2% difference between Q4W and Q16W interval in either treatment arms) were: intraocular pressure increased, conjunctival haemorrhage, cataract, macular oedema, retinal vein occlusion, retinal haemorrhage, cystoid macular oedema, retinal ischaemia, visual acuity reduced, and glaucoma. As expected, the rates of ocular AEs in the Q4W dosing regimen were mainly driven by disease worsening of cystoid macular oedema, retinal vein occlusion and disease complication (e.g., glaucoma, retinal haemorrhage, retinal ischaemia).

Ocular AEs in the study eye in Q8W and Q12W varied across treatment arms (30.3% of patients and 47.7% of patients for Q8W and 27.6% of patients and 43.5% of patients for Q12W in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) which was likely due to the small sample size.

In the **COMINO** study an increased incidence of AEs and SAEs is observed in Part 2 (Week 24 through Week 72) compared to Part 1 (baseline through Week 24) as expected with the increased follow-up time, the safety results after treatment with a faricimab PTI dosing regimen were consistent with the safety results observed in Part 1, with faricimab continuing to be generally well tolerated with a low incidence of AEs leading to study treatment withdrawal.

In **Part 2** the **most common ocular AEs** in the study eye (2% incidence in any treatment arm) by PT were: IOP increased, cataract, cystoid macular oedema [verbatim: worsening of CMO], macular oedema [verbatim: worsening of MO], RVO [verbatim: worsening of CRVO, worsening of BRVO, exacerbation of BRVO, superior BRVO, accelerated worsening of BRVO, RVO aggravated], conjunctival haemorrhage, dry eye, epiretinal membrane, vitreous detachment, vitreous floaters, and glaucoma.

In the **COMINO** study, in the faricimab Q4W to faricimab PTI arm, 48.2% of patients and 27.9% of patients experienced at least one ocular AE in the Q4W and Q16W dosing interval, respectively. In the aflibercept Q4W to faricimab PTI arm, 39.6% of patients and 29.3% of patients experienced at least one ocular AE in the Q4W and Q16W dosing interval, respectively.

Ocular AEs in the study eye which contributed to the higher incidence of AEs in patients treated at the faricimab PTI Q4W dosing interval compared to faricimab Q16W in either treatment arm (2% difference between Q4W and Q16W interval in either treatment arms) were: cataract, cystoid macular oedema, macular oedema, retinal vein occlusion, epiretinal membrane, glaucoma, vitreous floaters, retinal neovascularization, and iritis. As expected, the rates of ocular AEs in the Q4W dosing regimen were mainly driven by disease worsening of cystoid macular oedema, retinal vein occlusion, and macular oedema events and study disease complication (e.g., glaucoma, epiretinal membrane).

Three cases of iritis were reported in the faricimab Q4W to faricimab PTI arm in the Q4W dosing subgroup; however, no clear relationship could be established between time of injection and event onset. Notably, one case of iritis was reported in the Q16W dosing regimen subgroup.

Ocular AEs in the study eye in Q12W varied across treatment arms (21.4% of patients in the faricimab Q4W to faricimab PTI arm and 51.4% of patients in the aflibercept Q4W to faricimab PTI arm) which was likely due to the small sample size.

In the **entire study** dataset, the incidence of **ocular AEs** in the faricimab Q4W to faricimab PTI arm representing the longer-term safety data for faricimab was **43.2%**. The majority of RVO disease worsening events (i.e. worsening of RVO, MO and CMO) were reported as non-serious, mild, and resolved by the end of the study. In the **entire study** dataset, the exposure-adjusted incidence **rates of ocular AEs** per 100 PY in the faricimab Q4W to faricimab PTI arm was **65.96.** This rate was consistent with the other faricimab Phase III studies (DME: **56.88** and nAMD: **68.90**). The rates of ocular AEs per 1000 injections in the faricimab Q4W to faricimab PTI arm was **82.18.** This rate was consistent with the other pooled faricimab treatment arms in the Phase III studies (DME: 81.68 and nAMD: 131.73).

The **ADRs** that were reported with a **frequency of ≥1%** in the BRVO and C/HRVO in the All faricimab group at **Week 72** were conjunctival haemorrhage, cataract, vitreous detachment, vitreous floaters, eye pain, and IOP increased.

The most **common pooled serious ADRs** in the RVO indications (≥2 patients) by PT were **uveitis** (3 patients in the faricimab Q4W to faricimab PTI arm for C/HRVO), **cataract** (1 patient each in the aflibercept Q4W to faricimab PTI arm for BRVO and C/HRVO, respectively), **rhegmatogenous retinal detachment** (1 patient each in the faricimab Q4W to faricimab PTI arm for BRVO and C/HRVO, respectively), and **vitreous haemorrhage** (2 patients in the faricimab Q4W to faricimab PTI arm for C/HRVO). The majority of the serious ADRs resolved, resolved with sequelae, or were resolving by Week 72 for BRVO and C/HRVO events, with the exception of **cataract** and **vitritis**).

The exposure-adjusted incidence **rate of serious ocular AEs** per 100 PY in Part 2 was consistent with Part 1 for both arms (**5.82** and **2.96** in the pooled faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms in Part 2, respectively and **5.38** and **4.77** in the pooled faricimab and aflibercept arms in Part 1, respectively. In the **entire study** dataset, the incidence of **serious ocular** AEs in the faricimab Q4W to faricimab PTI arm was **6.4%.** The rates of ocular SAEs were mainly driven by the disease worsening of **RVO** (1.2%), **CMO** (1.1%), and **MO** (0.6%). The majority were resolved or resolving by the end of the study (Week 72) and had no lasting impact on the patient's long-term vision.

AESIs

In part 1 the incidence of AESIs in the study eye in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms was 16 patients [2.5%] and 4 patients [0.7%], respectively.

In the **BALATON** study the incidence of ocular AESIs in the study eye was low across both arms (1 patient [0.4%] each). One patient in each treatment arm experienced an ocular AESI (macular oedema in the faricimab Q4W to faricimab PTI arm and cataract in the aflibercept Q4W to faricimab PTI arm) causing a decrease of 30 letters in VA score lasting more than 1 hour. No patients experienced an event in the other AESI categories of 'associated with severe intraocular inflammation' or 'required surgical or medical intervention to prevent permanent loss of sight'.

In the **COMINO** study ocular AESIs in the study eye occurred in 21 patients **[5.8%]** in the faricimab Q4W to faricimab PTI arm and 9 patients **[2.6%]** in the aflibercept Q4W to faricimab PTI arm.

Fifteen patients (4.2%) and 7 patients (2.0%) in the faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arm, respectively, experienced an ocular AESI in the study eye causing a decrease of ³30 letters in VA score lasting more than 1 hour.
The most common sight-threatening AEs in the study eye that caused a decrease of ³30 letters in VA score lasting more than 1 hour were almost all associated with disease worsening.

In the **pooled Part 2** dataset the majority of the ocular AESIs in the study eye occurred in the COMINO study; the majority of these events were associated with study disease worsening and were resolved or resolving by the end of study.

Sixteen patients (2.5%) and 8 patients (1.3%) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, experienced an ocular AESI causing a decrease of ≥ 30 letters in VA score lasting more than 1 hour. The majority were resolved or resolving by the end of the study.

Six patients (1.0%) and 1 patient (0.2%) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively, experienced an ocular AESI that required surgical or medical intervention to prevent permanent loss of sight. Four out of seven events were resolved by the end of the studies. One patient in the aflibercept Q4W to faricimab PTI arm experienced an event in the AESI category of 'associated with severe IOI' (endophthalmitis). This event was resolved by the end of the study.

In the entire study dataset, the incidence of AESIs in the faricimab Q4W to faricimab PTI arm was 4.7%. The exposure-adjusted incidence rates of AESIs per 100 PY in the Faricimab Q4W to Faricimab PTI arm was 3.71). This rate was consistent with other faricimab Phase III studies (DME: 3.05 and nAMD: 2.09) The rates of ocular AEs per 1000 injections in the Faricimab Q4W to Faricimab PTI arm was 4.62 This rate was consistent with other faricimab Phase III studies (DME: 4.38 and nAMD: 3.99).

IOI events
In the **BALATON** study the incidence of **IOI events** occurring in the study eye was low (2 patients [0.7%] and 3 patients [1.1%] in the faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arms, respectively). All the IOI events in the study eye were reported as non-serious and mild. There were no IOI events associated with retinal occlusive disease, and no reported events of retinal vasculitis or retinal occlusive vasculitis based on reported PTs in Part 1 or in Part 2. None of the IOI events was associated with a sustained vision loss of 15 letters or 30 letters. No events of endophthalmitis in the study eye were reported in either arm.

In the **COMINO** study it was critically noted that in part 1 the incidence of **IOI events** was higher for the group treated with faricimab compared to aflibercept in the Comino study (8 patients [2.2%] and 4 patients [1.1%], respectively). It is further noted that in 6 patients the IOI event occurred shortly (i.e. ≤10 days) after the first injection of faricimab, whereas in only one patient the IOI occurred soon (i.e. ≤10 days) after first injection of aflibercept.

In **Part 2** a higher incidence of **IOI events** in the study eye was again reported which is consistent with Part 1 with 10 patients **(2.8%)** in the faricimab Q4W to faricimab PTI arm and 5 patients **(1.5%)** in the aflibercept Q4W to faricimab PTI arms.

The MAH outlined that this is likely related to the greater severity of underlying **CRVO** disease compared with BRVO and that this is in line with what has been observed in historical RVO pivotal trials. The majority of cases were non-serious and mild and moderate in severity and had no impact on visual outcomes. There was no clear relationship between injection day of study treatment and the timing of the events observed with the caveat that the number of IOI events reported was small. There were no reported IOI events associated with retinal vasculitis or occlusive disease.

Additionally, IOI events associated with significant vision loss (≥ 15 letters or ≥ 30 letters) were infrequent (1 patient had a vision loss of ≥ 15 letters associated with a serious event of **vitritis** in the

faricimab Q4W to faricimab PTI arm and 1 patient had a vision loss of ≥ 15 letters associated with a non-serious event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm).

By **Week 72,** the majority of **IOI** events were resolved or resolving. **Four events** (vitritis, non-infectious endophthalmitis, iritis, and iridocyclitis [1 event each]) in the faricimab Q4W to faricimab PTI arm and 1 event of iridocyclitis in the aflibercept Q4W to faricimab PTI arm were not resolved by Week 72. Two of these events occurred at the end of the study and therefore were still ongoing at the last study visit. One event of vitritis resulted in study discontinuation.

In the **pooled Part 2** dataset, the incidence of **IOI** events occurring in the study eye was low in both the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms (**1.9%** and **1.3%,** respectively)

In the Entire Study dataset, the incidence of **IOI** in the faricimab Q4W to faricimab PTI arm was **3.0%.** The **IOI incidence** was higher in **CRVO,** but it is important to note that the majority of the IOI events reported in the COMINO study were non-serious, mild or moderate in severity, and had no impact on visual outcomes. There was no clear relationship between injection day of study treatment and the timing of the events observed with the caveat that the number of IOI reported were small. Nevertheless, this is a topic which requires ongoing monitoring and further characterization of the longer term safety profile specific to the proposed new indication.

The exposure-adjusted incidence rate of IOIs per 100 PY in the faricimab Q4W to faricimab PTI arm was 2.67. This rate was somewhat consistent with other faricimab Phase III studies but it is notable that the overall exposure adjusted incidence rate of IOIs in the RVO indication is noted to be numerically higher than the rates in other approved indications (DME: 1.13 and nAMD: 1.94). This topic requires continuous monitoring.

Immunogenicity
In the **Balaton** study the incidence of treatment-emergent ADAs against faricimab from baseline to Week 72 in the faricimab Q4W to faricimab PTI arm was low (11.7%). No apparent influence of ADA on systemic exposure or efficacy was observed based on the available data. The clinical significance of anti-faricimab antibodies on overall safety is unclear at this time. The uncertainty is related to the low incidence of immunogenicity and the low incidence of IOI, for which all the events were of mild severity and had a reversible character.

In the **Comino** study the incidence of treatment-emergent ADAs against faricimab from baseline to Week 72 in the faricimab Q4W to faricimab PTI arm was also low **(16.5%).** No apparent influence of ADA on systemic exposure or efficacy was observed based on the available data. Although **a higher incidence of IOI** was observed in **ADA-positive patients** compared with ADA-negative patients, the clinical significance of anti-faricimab antibodies on overall safety is unclear at this time. The uncertainty is related to the low incidence of immunogenicity and the low incidence of IOI, for which the majority of the events were of mild to moderate severity and had a reversible character.

An overall higher incidence of treatment-emergent ADAs was noted in the COMINO study compared to the BALATON study. This correlated with a higher incidence of IOI events reported in ADA positive patients. This issue requires ongoing monitoring over the longer term.

Non-ocular safety
BALATON
The incidence of non-ocular AEs was comparable between treatment arms (32.6% and 35.4% in the faricimab Q4W and aflibercept Q4W arms, respectively). A higher incidence of events occurred in the faricimab Q4W arm compared with the aflibercept Q4W arm in the Vascular Disorders system organ class (SOC; **6.5%** vs. **3.6%** in the faricimab Q4W and aflibercept Q4W arms, respectively), mainly driven by patients with **hypertension** events.

In **Part 1** (before Week 24 visit) the incidence of hypertension events was higher in the faricimab Q4W arm (20 patients [7.2%]) compared to the aflibercept Q4W arm (7 patients [2.6%]) All events were reported as non-serious and none were assessed as related to the study treatment by the investigators or required a change in study treatment. In **Part 2**, (Week 24 to Week 72): the incidence of hypertension events were 14 patients (5.2%) in the faricimab Q4W to faricimab PTI arm and 8 patients (3.0%) in the aflibercept Q4W to faricimab PTI arm.

In the **COMINO** study, the incidence of non-ocular AEs was comparable between treatment arms (33.2% and 37.1% in the faricimab Q4W and aflibercept Q4W arms, respectively). A higher incidence of events occurred in the faricimab Q4W arm in the Nervous System Disorder system organ class (SOC; 5.8% vs. 3.0% in the faricimab Q4W and aflibercept Q4W arms, respectively; with no single PT driving the difference).

Across both phase III studies, non-ocular AEs were generally reported at a similar rate across both treatment arms up to week 24. The exception is reports of '**hypertension'** which were reported with a higher numerical frequency in the faricimab treatment arm in the **BALATON** study. Although some of the relevant cases had confounding factors, as requested the MAH discussed and clarified further why this imbalance might have occurred and has provided an update on cases reporting 'hypertension' from the full data set.

Overall, in the All faricimab group 43 **hypertension** events were reported in 40 patients receiving faricimab through Week 72. All of the events were reported as non-serious with the majority being of mild (n=25/43) or moderate (n=17/43) severity. None of the 43 events were assessed as related to the study treatment by the investigators or required a change in study treatment.

In the absence of an imbalance of hypertension events in other population treated with faricimab (nAMD and DME) and considering that (1) majority of the cases reported in the faricimab RVO studies had risk factors associated with the events of hypertension, and that (2) the baseline medical history of patients with RVO, and (3) the rates of hypertension in published data for this population, the numerically higher rate of hypertension events in the faricimab Q4W arm was considered by the MAH as isolated findings in the BALATON study.

Hypertension is a major risk factor for RVO; the overall rate of hypertension reported in Balaton and COMINO was in line or lower than published data in this patient population.

Non-Ocular AEs Pooled Part 2 Dataset
In the pooled Part 2 dataset, the incidence of **non-ocular AEs** in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms was **52%** and **49.3%,** respectively. The majority of non-ocular AEs were mild or moderate in severity.

Consistent with Part 1, the most common non-ocular AEs in **Part 2** (≥ 2% incidence in any treatment arm of the pooled Part 2 dataset: faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively) by PT were **COVID-19** (12.4% and 11.7%), **nasopharyngitis** (2.9% and 4.3%), **hypertension** (4.3% and 2.6%), **upper respiratory tract infection** (2.2% and 2.8%), **back pain** (2.4% and 1.3%), and **influenza** (1.9% and 2.6%).

In the **pooled Part 2** dataset, the exposure-adjusted **incidence rate of non-ocular AEs** per 100 patient years was consistent with Part 1. (**145.10** and **141.68** in the pooled faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arms in Part 2, respectively; and **126.19** and **156.02** in the pooled faricimab and the aflibercept arms in **Part 1**, respectively.

In the **entire study** dataset, the incidence of **non-ocular AEs** in the faricimab Q4W to faricimab PTI arm was **63.2%.** The exposure-adjusted incidence **rate of non-ocular AEs per 100 PY** was **140.50** which was consistent with other faricimab Phase III studies (DME: **172.42** and nAMD: **139.29).**

The incidence of **serious non-ocular AEs** was low and comparable between the treatment arms (9 patients [3.3%] and 16 patients [5.8%] in the faricimab Q4W and aflibercept Q4W arms, respectively; The most common (≥ 1% of patients in any arm) was **cerebral infarction** (3 events in the faricimab Q4W arm; All cerebral infarction events were reported as severe, of which **2 were assessed as related to the study treatment** and 1 assessed as related to other cause (concurrent illness)-see LoQ.

Cases reporting **serious non-ocular events** were similar across the faricimab and aflibercept treatment arms in Part I of both phase III studies. Of note, **three serious** cases of **cerebral infarction** were reported in the faricimab treatment arm in the Balaton study up to week 24. No similar cases were reported for the comparator group aflibercept or for either faricimab or aflibercept groups in the Comino study to week 24. From review of the narratives of the three serious cases of cerebral infarction**,** it is noted that these cases were all reported in the Faricimab arm in the Balaton study up to week 24 in Asian males aged in their 60's.

The MAH was requested to further discuss this finding and present the totality of the safety data in respect of all cerebral infarction cases, including any available updates on the above highlighted narratives. It was also asked to discuss if any difference in safety could be expected depending on ethnicity.

The MAH acknowledged this reference to the important potential risk of arterial thromboembolic events and CNS haemorrhagic events of faricimab and of all anti-VEGFs and provided in their additional information on the 3 cases of cerebral infarction.

All of the **cerebral infarction** events across treatment arms in the BALATON and COMINO studies noted above were reported in Asian patients with a majority from China (5 out of 6 patients); however, other non-ocular non-fatal stroke adjudicated Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic event (ATEs) (ischemic stroke, cerebrovascular accident, and haematoma) were reported in the other racial subgroups (i.e., white, unknown and black or African American).

The MAH further discussed these findings and presented the totality of safety data in respect of all cerebral infarction cases including the available updates on the above highlighted narratives. It also discussed if any difference in safety could be expected depending on ethnicity and whilst this does not seem likely, particularly as no differences in PK can be expected, this is a topic which should continue to be closely monitored.

Additionally, the PopPK analysis did not shown any effect of race on the pharmacokinetics (ocular and systemic) of faricimab. Therefore, based on faricimab PK, no differences are expected in the population of Asian origin. The APTC rates reported in the entire study were consistent with the previous faricimab Phase III studies in nAMD and DME, and the rate of non-fatal strokes observed in Part 2 was consistent with Part 1. RVO is associated with cardiovascular risk factors which are also well-known risks for stroke and this should be reflected in the PI. The overall rate is in line with event rates for cerebrovascular accidents in patients with RVO reported in the literature.

The MAH's available data did not suggest an association between the faricimab safety profile and ethnicity. However, this issue should continue to be monitored by routine pharmacovigilance.
In the **pooled Part 2** dataset, the incidence of **serious non-ocular AEs** was low in both treatment arms. There were **no serious non-ocular AEs** with ≥ 1% incidence in any treatment arm of the pooled **Part 2** dataset.

In the **entire study** dataset, the incidence of **serious non-ocular AEs** in the faricimab Q4W to faricimab PTI arm was **12.6%.** The exposure-adjusted incidence rates of serious non-ocular AEs per 100 PY was **14.26** which is consistent with other faricimab Phase III studies (nAMD: 17.06 and DME: 27.83).

Fatal cases
In the entire study dataset, 7 patients (1.1%) **died** in the faricimab Q4W to faricimab PTI arm and 5 patients (0.8%) died in the aflibercept Q4W to faricimab PTI arm. The exposure-adjusted incidence rate of deaths per 100 PY was lower **(0.81)** compared with other faricimab Phase III studies (DME: 2.53 and nAMD: 1.7) Overall, in the entire pooled BALATON and COMINO studies through Week 72, 10 patients (0.8%) in the All Faricimab group had fatal events. None of the deaths were suspected by the investigator to be related to study treatment.

In conclusion: overall, the safety profile of faricimab in patients with RVO has been well characterized to week 24. Additional safety data to week 72 has also been provided, although some uncertainties remain in relation to the longer term safety aspects in the RVO indication.

In the Phase III faricimab arms, 36.2% (BALATON study) and 48.5% (COMINO study) of patients in the faricimab arms experienced ocular AEs, of which the majority were mild or moderate in severity. In Part 2 (Week 24 through Week 72) when all patients were on the faricimab adjustable T&E type regimen, the safety results were overall consistent with those observed in Part 1. ADRs for faricimab are well characterized, including those previously treated with aflibercept. No new ADRs have been identified in the RVO study populations. The overall faricimab safety profile in the RVO studies is considered to be broadly in line with the known safety profile from the approved faricimab indications, although some imbalances were noted in the part II safety data set.

Of note, the absence of a comparator treatment after 24 weeks is still seen as a limitation in drawing firm conclusions on the longer term safety of faricimab in RVO, based on the evaluation of the safety data beyond week 24 in Part II of the studies. Nevertheless, it is acknowledged that the MAH presented accordingly the safety data in Part II of the clinical studies in order to facilitate evaluation and provided an overview of relevant findings from the safety evaluations in the approved nAMD and DME indications for context.

However, due to remaining uncertainties, the longer-term safety of faricimab in the RVO should be closely followed over the longer term.
In addition, a focused review of relevant safety topics of interest should be presented in future PSURs.

The MAH should also review the need to strengthen the PI in relation to any specific safety considerations relevant to the RVO patient population going forward, in order to optimise the safe use of faricimab in these patients.

2.5.2. Conclusions on clinical safety

Overall, based on the pooled safety data from both pivotal phase III studies BALATON and COMINO, the available safety data from faricimab treatment in the RVO indication indicates that the ocular and non-ocular safety profiles of faricimab and aflibercept are broadly comparable up to week 24 and the safety profile of faricimab to week 72 is generally well characterised and broadly in line with the established safety data from the DME and nAMD indications. However, it is highlighted that some uncertainties remain and a number of imbalances were noted in the comparative safety data which warrant further close monitoring.

Of note, the absence of a comparator treatment after 24 weeks is still seen as a limitation in drawing firm conclusions on the safety of faricimab based on the evaluation of the safety data beyond week 24 in Part II of the studies. Nevertheless, it is acknowledged that the MAH presented accordingly the safety data in Part II of the clinical studies in order to facilitate data evaluation and provided an overview of relevant findings from the safety evaluations in the approved nAMD and DME indications for context.

Overall, the faricimab safety profile in the RVO studies is considered to be broadly in line with the known safety profile from the approved faricimab indications. Nevertheless, it is considered that a degree of uncertainty remains in relation to the longer-term safety profile of faricimab in the RVO

indication, particularly due to the absence of a comparator arm beyond week 24 and since some patients were treated with both aflibercept and faricimab. In this context, it is recommended that the longer-term safety of faricimab in the RVO should be closely followed over the longer term. The MAH is therefore asked to present a focused review of relevant safety topics of interest in future PSURs. Furthermore, it should continue to review the need to strengthen the PI in relation to any specific safety considerations relevant to the RVO patient population going forward, in order to optimise safe use of faricimab in RVO patients.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP with this EoI application to include the primary analysis (Week 24) results from Studies GR41984 (BALATON) and GR41986 (COMINO) to support the registration of faricimab for the treatment of adult patients with visual impairment due to macular edema secondary to retinal vein occlusion (RVO; branch RVO or central RVO). No new important identified and potential risks were identified by the MAH as part of this procedure.

Safety Concerns

Table 63. Summary of the 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

No changes to the summary of safety concerns were made as part of this procedure. Considering the data in the safety specifications, the safety concerns listed above remains appropriate.

Pharmacovigilance plan

Table 64. Ongoing and Planned Additional Pharmacovigilance Activities

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 Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Date(s)**
Category 3 (cont.)				
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
Study CR45271 (real-world data study): A secondary data use, retrospective observational study to evaluate the incidence of RV and ROV.	The primary objective of this study is to assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO events across eyes treated with different approved IVT anti-VEGF agents after diagnosis of nAMD or DME, as recorded in an EHR database.	Intraocular inflammation	Last data extraction	Planned 30 June 2024
			Final Clinical Study Report	Planned 31 March 2025

ATE=arterial thromboembolic events; CHMP=Committee for Medicinal Products for Human Use; DME=diabetic macular edema; EHR = electronic health records; FPFV=first patient first visit; GR40306=TENAYA; GR40349=YOSEMITE; GR40398=RHINE; GR40844=LUCERNE; IOI = intraocular inflammation; IVT =intravitreal; LTE=long-term extension; nAMD=neovascular age-related macular degeneration; NCA=National Competent Authority; PRAC=Pharmacovigilance Risk Assessment Committee; RO = retinal vascular occlusion; RV = retinal vasculitis; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

Two long-term extension studies (AVONELLE-X and RHONE-X) in patients with nAMD and DME, respectively, are currently ongoing to evaluate the long-term safety and tolerability of intravitreal faricimab, which will address the missing information of long-term safety of faricimab, and will provide a cumulative 4 years of exposure data. In addition, data from these two long--term extension studies will also further characterize the important potential risk of ATE/CNS haemorrhagic events. No changes were made to the Pharmacovigilance plan , as no new safety concerns were identified within this procedure.

The 72-week RVO data presented in the BALATON and COMINO CSRs in combination with the DME and nAMD LTE studies and existing routine pharmacovigilance activities (i.e., adverse reaction reporting, Guided Questionnaires, signal detection and management activities) with all relevant safety data being reported in the PBRER are considered sufficient in providing long-term safety and immunogenicity data for faricimab to cover the RVO indication for the following reasons:

- The commonality between the pathophysiology and risk factors in DME and RVO supports that data from LTE studies in DME is relevant to the RVO population.
- Long-term RWD studies from anti-VEGF products have not identified a difference in safety profile between the DME and RVO population.
- Data obtained to date from the ongoing faricimab LTE studies in the DME and nAMD.

However, the MAH should keep the above issues, in particular, intraocular inflammation (IOI) events and immunogenicity in the RVO indication, as topics of special interest in future PSURs. The MAH should also continuously review the need to strengthen current information (e.g. in the PI) on these topics, if necessary.

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV plan is sufficient to identify and characterise the risks of the product

Risk minimisation measures

Table 65. Summary of Pharmacovigilance and Risk Minimisation Activities by Safety Concern

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 PIL Section 2 What you need to know before you use Vabysmo	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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:** Study CR45271

Safety concern	Risk minimization measures	Pharmacovigilance activities
Arterial thromboembolic events and central nervous system hemorrhagic events	**Routine risk minimization measures:** • SmPC Section 4.4 Special Warnings and Precautions for Use • PIL Section 2 What you need to know before you use Vabysmo 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) **Final Study Report Due Dates:** AVONELLE-X (GR42691): Q1 2025 RHONE-X (GR41987): Q4 2024
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) **Final Study Report Due Dates:** AVONELLE-X (GR4691): Q1 2025 RHONE-X (GR41987): Q4 2024
Use in pregnancy	**Routine risk minimization measures:** • SmPC Section 4.6 Fertility, pregnancy and lactation • PIL Section 2 What you need to know before you use Vabysmo **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.

RMP Part V was updated to include the RVO population as part of the target audience of the additional risk minimization measure already in place for Vabysmo (patient/carer guide).
Accordingly, Annex 6,7,8 of the RMP and Annex II-D of the Product Information were also revised. The key elements of the additional risk minimization activity of the patient/carer guide have been updated to indicate that a description of branch/central RVO will be provided.

Conclusion on the RMP

The CHMP concluded that Vabysmo RMP version 5.1 is acceptable.

2.7. Update of the Product Information

As a result of this variation procedure, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to reflect information relating to the proposed new indication in RVO. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a **full user consultation** with target patient groups on the package leaflet was submitted by the MAH and found acceptable for the following reasons:

- In 2021, a Full User Testing (Report 1804) was conducted to support Vabysmo Marketing Authorisation Application (MAA) for the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD) based on results of 2 pivotal clinical studies TENAYA and LUCERNE and for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) based on YOSEMITE and RHINE.

- The results of the Full User Testing demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to understand the information.

- The proposed type II variation is based on the results from the two Phase III studies; BALATON (GR41984) in patients with branch retinal vein occlusion (BRVO) and COMINO (GR41986) in patients with central retinal vein occlusion (CRVO) or hemi-retinal vein occlusion (HRVO).

The Marketing Authorisation Holder (MAH) considered justified not conducting a **novel User Consultation** for the Package Leaflet for this application because:

- No significant changes impacting the readability of the package leaflet are made. In particular, key safety messages are not affected by this variation. The additional text follows the same structure and uses similar descriptions and terminology as used in the approved package leaflet.

- The posology section wording in this application follows the same structure and uses the same descriptions and terminology as in the approved indications for Vabysmo.

- As Vabysmo must be administered by a qualified healthcare professional trained in intravitreal injections, the target group of users (i.e., HCP specialising in ophthalmology) will be similar between the approved indication (nAMD, DME) and the applied indication (RVO).

The MAH's justification is acceptable.

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

RVO is one of the most common retinal vascular disorders and is associated with varying degrees of visual loss (Hayreh et al. 1994). RVO has been reported as the second leading cause of blindness for patients with retinal vascular disease, following diabetic retinopathy (DR) (Cugati et al. 2006; Klein et al. 2008; Rogers et al. 2010; Yasuda et al. 2010). The main types of RVO include BRVO, HRVO, and CRVO. As of 2015, approximately 28.06 million adults worldwide were affected by any type RVO, of which 4.67 million are CRVO patients and 23.38 million are BRVO patients. The estimated global prevalence of RVO increased with advanced age but did not show significant differences between sexes (Song et al. 2019).
The most common presenting complaint of RVO is an abrupt, painless decrease of central vision, due to macular oedema. Less frequently, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over several days to weeks before being followed by a permanent decrease in vision. Metamorphopsia and visual field defects have also been described (Achiron et al. 2015; Manabe et al. 2017).

The most recognised risk factors for RVO are age and systemic vascular disorders. In over half of the cases, the age of onset is over 65 years. Systemic diseases such as hypertension, hyperlipidemia and diabetes mellitus are very strongly associated with the development of RVO.

3.1.2. Available therapies and unmet medical need

Anti-VEGF pharmacotherapy is the current mainstay of treatment in macular oedema due to RVO and has demonstrated efficacy across several pivotal, randomised clinical studies, although macular laser and intravitreal steroids-especially steroid implants are also used in some cases. Ranibizumab (Lucentis SmPC, Lucentis USPI) and aflibercept (Eylea SmPC, Eylea USPI) are the most widely used globally approved treatments for RVO.

3.1.3. Main clinical studies

Clinical evidence supporting the efficacy, safety, and favourable benefit-risk assessment of faricimab is mainly based on the primary analysis results of two pivotal Phase III studies:

- Study GR41984 (hereafter referred to as BALATON) in patients with macular edema due to branch retinal vein occlusion (BRVO)
- Study GR41986 (hereafter referred to as COMINO) in patients with macular edema due to central retinal vein occlusion or hemi-retinal vein occlusion (C/HRVO).

3.2. Favourable effects

Key favourable effects
In both pivotal studies investigating patients with branch retinal vein occlusion (BALATON study) and patients with central or hemi-retinal vein occlusion (COMINO study), the primary endpoint was met as the patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W, as the lower bound of the 95% confidence

interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than − 4 letters.

In the **BALATON study**, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.5 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was −0.6 letters (95% CI: −2.2, 1.1).

In the **COMINO study**, at Week 24, in the ITT population, the adjusted mean change from baseline in BCVA was 16.9 and 17.3 letters in the faricimab Q4W and aflibercept Q4W arms, respectively; the difference was -0.4 letters (95% CI: -2.5, 1.6).
In both pivotal studies, the results of the primary analysis were also supported by supplementary analyses performed by the MAH such as the analysis based on the PP population, an analysis distinguishing COVID and non-COVID intercurrent events and an analysis using hypothetical strategy for all intercurrent events.

Supportive outcomes
These effects are supported by similar effects results as reported for secondary endpoints investigated in studies.

In relation to the effect on additional BCVA outcomes including the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline, patients achieving ≥ 84, 69 letters or ≤ 38 letters, all assessed at week 24, in both pivotal studies the results were comparable between the treatment groups.

The graph of change from baseline in visual acuity vs. time shows that, in both group, visual acuity sharply improves by Month 4, and gradually continues to improve thereafter.

In the Balaton study, at Week 24, 56.1% and 60.4% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was −4.3% (95% CI: −12.3%, 3.8%). In the Comino study, at week 24, 56.6% and 58.1% of patients gained at least 15 letters in BCVA score from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in the adjusted proportion of patients who gained at least 15 letters from baseline between the faricimab Q4W arm and the aflibercept Q4W arm at Week 24 was -1.5% (95% CI: -8.4%, 5.3%).

Also, a similar proportion of patients treated with faricimab Q4W avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients treated with aflibercept Q4W. In the Balaton study, at Week 24, 99.6% and 98.6% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively. In the Comino study, at Week 24, 96.2% and 96.7% of patients avoided a loss of ≥ 15 letters in BCVA from baseline in the faricimab Q4W and aflibercept Q4W arms, respectively.

In relation the effect on anatomic outcome measures macular oedema was reduced with a clinically meaningful reduction in both treatment groups, which was also reflected by an increase in the proportion of patients with absence of macular oedema, or absence of intraretinal subretinal fluid. Of note, at baseline, macular oedema was more significant in patients with central or hemi-retinal vein occlusion, or in those with branch retinal vein occlusion and improvements seen in patients with central or hemi-retinal vein occlusion was higher.

In the BALATON study, at Week 24, the adjusted mean change from baseline in CST was −311.4 µm and −304.4 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −7.0 µm (95% CI: −14.1, 0).

In the COMINO study, at Week 24, the adjusted mean change from baseline in CST was −461.6 µm and −448.8 µm in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference in adjusted mean change from baseline in CST between the faricimab Q4W when compared to the aflibercept Q4W arm at Week 24 was −12.8 µm (95% CI: −26.7, 1.0).As indicated by the MAH, the majority of patients in Part 2 of the studies were treated using Q12W or Q16W dosing interval. Between Week 24 and Week 68, 81.5% and 74.0% of patients achieved a faricimab Q12W or Q16W dosing interval in BALATON and COMINO, respectively. The proportion of patients who only received Q4W dosing through Week 68 in BALATON and COMINO was low (1.2% and 2.5%, respectively.

Despite the lower frequency of the treatment in Part 2 of the study, the efficacy was maintained.
In the BALATON study, at Week 64/68/72, in the ITT population, the adjusted mean change from baseline in BCVA was 18.1 and 18.8 letters in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively.

3.3. Uncertainties and limitations about favourable effects

There are no major uncertainties in relation to the efficacy. The posology as proposed by the MAH is acceptable.

3.4. Unfavourable effects

In relation to clinical safety, the following ocular and non-ocular AEs were observed in the pooled integrated safety data from the two pivotal phase III studies (BALOTAN and COMINO) which evaluated the safety and tolerability of faricimab in the treatment of patients with RVO.
The most common ocular AEs in the study eye (> 2% incidence in any treatment arm) by PT were: IOP increased, cataract, cystoid macular oedema [verbatim: worsening of CMO], macular oedema [verbatim: worsening of MO], RVO [verbatim: worsening of CRVO, worsening of BRVO, exacerbation of BRVO, superior BRVO, accelerated worsening of BRVO, RVO aggravated], conjunctival haemorrhage, dry eye, epiretinal membrane, vitreous detachment, vitreous floaters, and glaucoma.
Ocular adverse events of special interest (AESIs) in the study eye occurred in 21 patients [5.8%] in the faricimab Q4W to faricimab PTI arm and 9 patients [2.6%] in the aflibercept Q4W to faricimab PTI arm. Fifteen patients (4.2%) and 7 patients (2.0%) in the faricimab Q4W to faricimab PTI and the aflibercept Q4W to faricimab PTI arm, respectively, experienced an ocular AESI in the study eye causing a decrease of >30 letters in VA score lasting more than 1 hour.

The overall incidence of **IOI events** in the study eye in Part 2 (Week 24 through Week 72) of the pivotal studies was n=10 patients (2.8%) in the faricimab Q4W to faricimab PTI arm and 5 patients (1.5%) in the aflibercept Q4W to faricimab PTI arms.

Two patients reporting IOI events had a significant vision loss of >15 letters associated with an IOI event: one serious event of vitritis in the faricimab Q4W to faricimab PTI arm and one event of iridocyclitis in the aflibercept Q4W to faricimab PTI
arm.

One case of endophthalmitis in the study eye was reported in the aflibercept Q4W to faricimab PTI arm.

The incidence of treatment-emergent ADAs against faricimab from baseline to Week 72 in the faricimab Q4W to faricimab PTI arm was 16.5%.

A higher incidence of IOI was observed in ADA-positive patients compared with ADA-negative patients, Although the clinical significance of anti-faricimab antibodies on overall safety is unclear at this time.

Non-ocular safety
In Part1, the incidence of **serious non-ocular AEs** was generally low and comparable between the treatment arms (9 patients [3.3%] and 16 patients [5.8%] in the faricimab Q4W and aflibercept Q4W arms, respectively; The most common (≥ 1% of patients in any arm) was **cerebral infarction** (3 events in the faricimab Q4W arm; All cerebral infarction events were reported as severe, of which **2 were assessed as related to the study treatment** and 1 assessed as related to other cause (concurrent illness).

In Part 2 (Week 24 through Week 72), there was 1 patient (0.4%) in each treatment arm (faricimab Q4W to faricimab PTI arm and aflibercept Q4W to faricimab PTI arm) that experienced a cerebral infarction event. The one event in the aflibercept Q4W to faricimab PTI arm occurred on Study Day 417 (Week 59) and was considered serious, suspected by the investigator to be related to the study treatment, and resolved by Week 72; the dose remained unchanged from the event.

3.5. Uncertainties and limitations about unfavourable effects

In view of inherent limitations in interpreting the part II safety data and some imbalances noted in the comparative safety profiles provided, the MAH is asked to continue to closely monitor the longer-term safety and immunogenicity profiles of faricimab specific to the RVO indication. A number of imbalances were initially identified in relation to a number of ocular and non-ocular AEs and these issues were further discussed by the MAH in their responses. As a result, follow up safety monitoring over the longer term is requested and should be a focus of the PSURs.

In relation to cases reporting cerebral infarction, from review of the narratives of the three serious cases of cerebral infarction, it is noted that these cases were all reported in the faricimab arm in the BALATON study up to week 24, in Asian males aged in their 60's. The MAH further discussed these findings and presented the totality of the safety data in respect of all cerebral infarction cases including the available updates on the above highlighted narratives. The MAH also discussed if any difference in safety could be expected depending on ethnicity and whilst this does not seem likely, particularly as no differences in PK can be expected, this is a topic which should continue to be monitored.

RVO is associated with cardiovascular risk factors which are also well-known risks for strokes. Of note, the overall rate is generally in line with event rates for cerebrovascular accidents in patients with RVO.

Whilst the safety profile of faricimab in the RVO indication is considered generally well characterised over the shorter term, the longer-term safety profile requires ongoing monitoring in order to be more fully characterised. In addition, the MAH is asked to present a focused review of relevant safety topics of interest in the PSURs. In addition, the MAH should present a focused review of relevant safety topics of interest in the PSURs.

3.6. Effects Table

Table 66. Effects Table for faricimab versus aflibercept to week 24

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
BCVA at week	Change from Baseline in BCVA in the Study Eye		Faricimab 6 mg Q4W	Afilbercept 2 mg Q4W	Difference in Adjusted Means (95% CI)	**BALATON study** Non- inferiority design, non

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
24	at Week 24		16.9 (15.7, 18.1)	17.5 (16.3, 18.6)	-0.6 (-2.2, 1.1)	inferiority margin – 4 letters,
BCVA at week 24	Change from Baseline in BCVA in the Study Eye at Week 24		Faricimab 6 mg Q4W 16.9 (15.4, 18.3)	Afilbercept 2 mg Q4W 17.3 (15.9, 18.8)	Difference in Adjusted Means (95% CI) -0.4 (-2.5, 1.6)	**COMINO study** Non- inferiority design, non inferiority margin – 4 letters,
Unfavourable Effects						
Ocular safety	Conjunctival haemorrhage Intraocular pressure increased Vitreous detachment Dry eye IOI (COMINO only)	%	Faricimab Q4W arm 2.8% 1.4% 2.3% 1.6% 3.03 exposure adjusted incidence rate	Aflibercept Q4W arm 3.8% 3.1% 1.7% 2.4% 1.36	Interim data-	Integrated summary of safety for Pooled data **BALATON and COMINO** **COMINO CSR**
Non-ocular safety	Hypertension	%	4.7%	2.7%	Interim data-	Integrated summary of safety for Pooled data BALATON and COMINO
APTC event	Total events	%	1.1%	1.4%	Interim data-	Integrated summary of safety for Pooled data BALATON and COMINO

Abbreviations: APTC (Antiplatelet Trialists' Collaboration); BCVA (best-corrected visual acuity); CI (Confidence interval); CSR (Clinical study report); IOI (intraocular inflammation); Q4W (every 4 weeks)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In both pivotal studies investigating patients with branch retinal vein occlusion (BALATON study) and patients with central or hemi-retinal vein occlusion (COMINO study), the primary endpoint was met as the patients treated with faricimab Q4W had a non-inferior change from baseline in BCVA at Week 24 compared with patients treated with aflibercept Q4W (i.e. the lower bound of the 95% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than − 4 letters). This non-inferiority was discussed and broadly agreed during the scientific advice.
The proposed posology is considered acceptable.

In general, the study population is overall representative of the target population with expectations of patients with most severe symptoms, a long history and those who failed a previous treatment.
A number of imbalances were initially identified in relation to a number of ocular and non-ocular AEs and these issues were further discussed by the MAH in their responses. As a result, follow up safety monitoring over the longer term is deemed necessary and should be a focus of the PSURs.

In relation to cases reporting cerebral infarction, from review of the narratives of the three serious cases of cerebral infarction, it is noted that these cases were all reported in the faricimab arm in the BALATON study up to week 24, in Asian males aged in their 60's. The MAH further discussed these findings and presented the totality of the safety data in respect of all cerebral infarction cases including the available updates on the above highlighted narratives. The MAH also discussed if any difference in safety could be expected depending on ethnicity and whilst this does not seem likely, particularly as no differences in PK can be expected, this is a topic which should continue to be closely monitored.

In addition, clarification was requested in relation to the number of patients who were treated with faricimab under each different dosing regimen as part of faricimab PTI dosing and how many AEs were reported within the individual treatment schedules. The available safety data from Part II of the pivotal RVO studies were presented. It is highlighted that limited data is available in the less frequent dosing regimens (QW8 and QW12) and, again, it is recommended that long term safety in these subgroups is further monitored.

The MAH considers that the long-term safety and immunogenicity data of faricimab in patients with RVO is covered by the safety data presented in the 72-week BALATON and COMINO CSRs and can be reasonably supplemented by the data generated in the DME and nAMD LTE studies (CSRs expected to be available in Q4 2024 and Q1 2025, respectively). Furthermore, the long-term safety data (including IOI, endophthalmitis, ATE, CNS haemorrhagic events, and in the elderly population) for all indications of faricimab, including RVO, will continue to be collected from post marketing sources, monitored and provided using the routine pharmacovigilance activities (i.e., adverse reaction reporting, guided questionnaires, signal detection, and management activities) with all relevant data being reported in the PBRER.
Overall, the safety profile of faricimab in the RVO indication is considered generally well characterised over the shorter term; the longer-term safety profile in the RVO patient population requires ongoing monitoring in order to be more fully characterised. In particular the MAH is requested to keep APTC events, IOI events and immunogenicity as topics of special interest in the PSURs.

3.7.2. Balance of benefits and risks

In both pivotal studies investigating patients with branch retinal vein occlusion (BALATON study) and patients with central or hemi-retinal vein occlusion (COMINO study), the primary endpoint was met and faricimab Q4W was found to be non-inferior to aflibercept Q4W.

In conclusion, the safety profile of faricimab in the RVO indication is considered to be generally well characterised over the shorter term; the longer-term safety profile in the RVO patient population requires ongoing monitoring in order to be more fully characterised.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Vabysmo in the treatment of patients in the proposed RVO indication is **positive.**

4. Recommendations

Outcome

Based on the review of submitted data, the CHMP considers the Extension of indication (EoI) as acceptable and therefore recommends the variation to the terms of the marketing authorisation (MA), concerning the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) for Vabysmo, based on results from the two phase 3 studies: GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and GR41986 (COMINO) in patients with central retinal vein occlusion (CRVO) or hemi-retinal vein occlusion (HRVO). These are global, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety, and PK of faricimab.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to the Summary of Product Characteristics (SmPC), amendments to Annex(es) I, II and IIIB and to the Risk Management Plan (RMP) are recommended.

Conditions or restrictions with regards 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.

In addition, 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), diabetic macular edema (DME), and retinal vein occlusion (RVO).
- 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
Not applicable

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR the le 8 "*steps after the authorisation*" will be updated as follows:

Scope
Please refer to the Recommendations section above.

Summary
Please refer to the Scientific Discussion.

Attachments
- PI as adopted by the CHMP on 27 June 2024