Medicinrådet

Bilag til direkte indplacering af faricimab i Medicinrådets behandlingsvejledning vedrørende lægemidler til retinal veneokklusion

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. faricimab
2. Ansøgers endelige ansøgning vedr. faricimab

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23.09.2024

DBS/HAS

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.10.2024
Leverandør	Roche
Lægemiddel	Vabysmo (faricimab)
Ansøgt indikation	Behandling af retinal veneokklusion
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse, Direkte indplacering i beh. vejledningen

Prisinformation

Amgros har følgende aftalepris på Vabysmo (faricimab):

Tabel 1: aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Vabysmo	120 mg/ml	0,24 ml	5.992,10	[redacted]	[redacted]

Aftaleforhold

Vabysmo er en del af udbuddet, som er baseret på behandlingsvejledningerne indenfor våd AMD, diabetisk maculaødem (DME) og retinal veneokkusion (RVO). Aftalen gælder indtil den 31.12.2024 og kan forlænges med 2 gange 6 måneder.

Konkurrencesituationen

Vabysmo bliver direkte indplaceret i behandlingsvejledningen for RVO på lige fod med de andre lægemidler til denne indikation, aflibercept samt ranibizumab, jf."Tillæg til Medicinrådets behandlingsvejledning vedrørende lægemidler til RVO"

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient i 20,3 md.

Lægemiddel	Styrke	Pakningsstørrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 20,3 måneder (SAIP, DKK)
Vabysmo	120 mg/ml	6 mg / 0,05 ml	6,3 sprøjter	[redacted]	[redacted]
Eylea	40 mg/ml	2 mg/0,05 ml	6,3 sprøjter	[redacted]	[redacted]
Lucentis	10 mg/ml	1,65 mg/0,165 ml	6,3 sprøjter	[redacted]	[redacted]

*Specifikationer ift. det kliniske sammenligningsgrundlag.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurderingen
England	Anbefalet	Link til anbefalingen

Konklusion

[redacted]

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or a new indication for an existing pharmaceutical, which will be assessed by updating an existing treatment guideline. The template is not exhaustive, companies must adhere to the current version of the relevant guideline alongside using this template when preparing their submission.

Please note the following requirements:

- Headings, subheadings and appendices must not be removed. Tables must not be edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process will be initiated when all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- The European Public Assessment Report (EPAR) should be submitted as soon as possible (draft versions will be accepted).

* Later in the appraisal process, once the application has received Day 0, the application must be assembled and sent to the DMC in one blinded version and one highlighted version (both in word and pdf).

Confidential information

- Please refer to DMC´s principles for use of unpublished data.

Version log

Version log		
Version	**Date**	**Change**
1.0	29 June 2023	Application form for pharmaceutical, which will be assessed by up-dating an existing treatment guideline, made available on the web-site of the Danish Medicines Council.

Application for the assessment of faricimab (Vabysmo) for the treatment of retinal vein occlusion (RVO)

Contact information

Contact information	
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Table of contents

Tables and Figures

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Abbreviations

Ang-2 - Angiopoietin-2

BCVA - Best corrected visual acuity

BRVO - Branch Retinal Vein Occlusion

CMH - Cochran-Mantel-Haenszel

CRVO - Central retinal vein occlusion

CST - Central Subfield Thickness

DMC - Danish Medicines Council

DME - Diabetic macular oedema

HRVO - Hemiretinal vein occlusion

ITT - Intention-to-treat

nAMD - Neovascular (wet) age-related macular degeneration

RVO - Retinal Vein Occlusion

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Faricimab
Generic name	Vabysmo
Therapeutic indication as defined by EMA	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).
Marketing authorization holder in Denmark	Roche Pharmaceuticals A/S
ATC code	S01LA09
Combination therapy and/or co-medication	N/A
(Expected) Date of EC approval	August 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Vabysmo is indicated for the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD). Vabysmo is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME).
Other indications that have been evaluated by the DMC (yes/no)	Yes, both of the above-mentioned EMA approved indications have been evaluated the Danish Medicines Council (DMC). Both indications have been approved by DMC to be placed into an already existing guideline.
Dispensing group	BEGR

Packaging – types, sizes/number of units and concentrations	0.24 mL sterile, solution in a glass vial with a coated rubber stopper sealed with an aluminum cap with a yellow plastic flip-off disk. Pack size of 1 vial and 1 blunt transfer filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm, 5 µm). Or A single-dose pre-filled syringe (expected CHMP positive opinion November 14th, 2024)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Vabysmo is indicated for the treatment of adult patients with visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO).
Dosage regiment and administration:	6 mg (0.05 mL solution) administered intravitreal every 4 weeks; 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualized with up to 4 months between injections, using a treat-and-extend approach.
Choice of comparator [if any]	Aflibercept
Most important efficacy endpoints (Difference/gain compared to comparator)	**BALATON** • Visual acuity, visual stabilisation measured as proportion of patients with visual loss of less than 15 ETDRS - letters: Faricimab: 99.6% (95% CI: 98.9%, 100.0) Aflibercept: 98.6% (95% CI: 97.2%, 99.9%) Absolute difference: 1.1% (95% CI: −0.5%, 2.6%) • Visual acuity, mean difference measured as mean change in number of ETDRS-letters: Faricimab: 16.9 (0.60) ETDRS letters (95% CI: 15.7, 18.1) Aflibercept: 17.5 (0.60) ETDRS letters (95% CI: 16.3, 18.6) Absolute difference: -0.6 (0.84) ETDRS letters (95% CI: -2.2, 1.1) • Central subfield thickness measured as mean change in central subfield thickness measured by OCT: Faricimab: −311.4 µm (95% CI: -316.4, -306.4) Aflibercept: −304.4 µm (95% CI: -309.3, -299.4) Absolute difference: −7.0 µm (95% CI: −14.1, 0.0)

	• Quality of life measured as mean change in patient-experienced quality of life rated by VFQ: Faricimab: 5.6 points (95% CI: 4.5, 6.7) Aflibercept: 5.9 points (95% CI: 4.8,7.1) Absolute difference: −0.4 points (95% CI: −1.9, 1.1) **COMINO** • Visual acuity, visual stabilisation measured as proportion of patients with visual loss of less than 15 ETDRS- letters: Faricimab: 96.2% (95% CI: 94.3%, 98.1%) Aflibercept: 96.7% (95% CI: 94.9%, 98.5) Absolute difference: -0.5% (95% CI: -3.2%, 2.2%) • Visual acuity, mean difference measured as mean change in number of ETDRS-letters: Faricimab: 16.9 (0.73) ETDRS letters (95% CI: 15.4, 18.3) Aflibercept: 17.3 (0.74) ETDRS letters (95% CI: 15.9, 18.8) Absolute difference: -0.4 (1.04) ETDRS letters (95% CI: -2.5, 1.6) • Central subfield thickness measured as mean change in central subfield thickness measured by OCT: Faricimab: −461.6 µm (95% Cl: -471.4, -451.9) Aflibercept: −448.8 µm (95% Cl: -458.6, -439.0) Absolute difference: −12.8 µm (95% CI: −26.7, 1.0) • Quality of life measured as mean change in patient-experienced quality of life rated by VFQ: Faricimab: 6.9 points (95% CI: 5.8, 8.0) Aflibercept: 8.1 points (95% CI: 7.0, 9.2) Absolute difference: −1.2 points (95% Cl:-2.7, 0.3)
Most important serious adverse events for the intervention and comparator	**BALATON** • Retinal vein occlusion: Faricimab: 0.4% Aflibercept: 0.4% • Retinal ischaemia: Faricimab: 0.7% Aflibercept: 0.0% • Vitreous haemorrhage: Faricimab: 0.0% Aflibercept: 0.4% • Cerebral infarction: Faricimab: 1.1% Aflibercept: 0.0%

COMINO

- Worsening of cystoid macular oedema:

  Faricimab: 0.5%
  Aflibercept: 0.6%

- Retinal ischaemia:

  Faricimab: 0.3%
  Aflibercept: 0.6%

- Retinal artery occlusion:

  Faricimab: 0.5%
  Aflibercept: 0.3%

- Uveitis:

  Faricimab: 0.5%
  Aflibercept: 0.0%

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Retinal vein occlusion (RVO) is a common group of chronic retinal vascular disorders characterized by obstruction of the retinal venous system. Blockage in the retinal veins caused by thrombus formation impairs the venous return of the retinal circulation (1). The levels of angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) in the retina increase with RVO (2, 3). This together with restricted blood flow lead to increased retinal capillary pressure, which results in increased capillary permeability and leakage of fluid and blood into the retina ultimately damaging the vision of the eye (1). The majority of RVO cases affect only one eye, however some patients may experience bilateral involvement at the time of disease presentation or over time (4).

RVO is divided into branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and hemicentral retinal vein occlusion (HRVO) which is an anatomic variant of CRVO. Whereas BRVO is a blockage of one of the tributaries of the central retinal vein, CRVO is an occlusion of the central retinal vein at the lamina cribosa or in its passage within the optic nerve posterior to the lamina cribosa (1, 4).

The main risk factor for RVO is increased age but systemic conditions such as hypertension, hyperlipidemia and diabetes also increase the risk of RVO (5). The prognosis for

patients with RVO depends on the severity of the occulation as well as the extent of the affected area in the retina. Generally, patients with CRVO have a worse prognosis than patients with BRVO (2). However, if left untreated both types of RVO can lead to permanent vision impairment or blindness (6). Early recognition and prompt treatment is key to preserve vision and achieve good outcomes. The primary aim of RVO treatment is to prevent further vision loss as compared to visual acuity at start of treatment. However, some patients may actually improve their vision following RVO treatment (2).

The scientific committee at the DMC estimates that approximately 2700 patients in Denmark are diagnosed with RVO each year. Of these approximately 820 patients, require treatment, namely 120 patients with CRVO and 700 patients with BRVO. These patients will all be candidates for treatment with faricimab (2).

In Denmark, the current standard treatment is either aflibercept (Eylea) 2 mg intravitreal injection or ranibizumab (Lucentis) 0.5 mg intravitreal injection (2). Aflibercept and ranibizumab have been given parity in the guideline and according to the DMC´s treatment recommendations for the treatment of RVO, these medicines should be used for at least 80% of the patients (7).

In the following aflibercept, which is the current standard treatment in Denmark is used as comparator to faricimab. Both aflibercept and ranibizumab are VEGF-inhibitors. Faricimab both block VEGF as well as ANG-2. Faricimab is considered equivalent with regards to effectiveness and safety compared with aflibercept.

3.2 The intervention

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

Overview of intervention	
Therapeutic indication relevant for the assessment	Vabysmo is indicated for the treatment of adult patients with visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO)
Method of administration	Intravitreal injection
Dosing	6 mg (0.05 mL solution)
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	6 mg (0.05 mL solution) administered every 4 weeks; 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualized with up to 4 months between injections, using a treat-and-extend approach.

Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Diagnostics needed for faricimab is the same as for aflibercept (current Danish clinical practice).
Package size(s)	0.24 mL sterile, solution in a glass vial with a coated rubber stopper sealed with an aluminum cap with a yellow plastic flip-off disk. Pack size of 1 vial and 1 blunt transfer filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm, 5 µm). Or A single-dose pre-filled syringe (expected available on market in November 2024)

3.2.1 The intervention in relation to Danish clinical practice

Faricimab is considered equivalent to existing treatments in Danish clinical practice (aflibercept and ranibizumab) with respect to effectiveness and safety, and thus can be placed directly into the treatment guideline in accordance with the newly published process guideline from the Medicines Council "Medicinrådets procesvejledning for vurdering af nye lægemidler i en behandlingsvejledning (direkte indplacering)".

4. Overview of literature

Two studies are relevant for this application namely the BALATON study and the COMINO study. Both studies provide a direct comparison between faricimab and aflibercept. Roche has developed and executed the clinical study program for faricimab treatment in RVO, and therefore there are no literature, other than the BALATON and COMINO study, available. Hence, a systematic literature review has not been performed. Furthermore, the majority of data extracted for this application are from the Clinical Study Reports for BALATON and COMINO (which are Roche Data on File). All data provided can be published by the DMC in the updated treatment guideline.

Table 1 provides an overview of the relevant literature based on BALATON and COMINO included in the assessment of efficacy and safety of faricimab vs. aflibercept.

Table 1: Relevant literature included in the assessment of efficacy and safety.

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
BALATON NCT04740905 Tadayoni R et al., Ophthalmology. 2024. (8) Tadayoni R et al., Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress. 2023. (9) Khanani AM et al., Macula Society 46th Annual Meeting I. 2023. (9, 10)	Phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group study.	24 weeks double-masked period follow by 48 weeks open lable (72 weeks in total). Patients that were randomized to aflipercept switched to faricimab after week 74	Start (FPI): 02/03/21 Completion (LPLV): 12/06/23 Data cut-off: 06/06/22 (up to week 24 follow-up) 30/08/23 (up to week 72 follow-up)	Adults ≥18 years with foveal center-involved macular edema due to branch retinal vein occlusion	Faricimab, intravitreal injection, 6 mg administered every 4 weeks; 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualized with up to 4 months between injections, using a treat-and-extend approach	Aflibercept, intravitreal injection, 2 mg administered every 4 weeks	1	• Proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Change from Baseline in Best-Corrected Visual Acuity (BCVA) at Week 24 [Time Frame: From Baseline to Week 24] • Change from baseline in Central Subfield Thickness at Specified Timepoints Through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Change from baseline in NEI VFQ-25 composite score

Tadayoni R et al., Angiogenesis, Exudation, and Degeneration 2024 Virtual Congress. 2024.								through Week 24 [Time Frame: Baseline and Week 24] • Safety
COMINO NCT04740931 Tadayoni R et al., Ophthalmology. 2024. (8) Tadayoni R et al., Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress. 2023. (9) Khanani AM et al., Macula Society 46th Annual Meeting I. 2023. (10) Tadayoni R et al., Angiogenesis, Exudation, and Degeneration 2024	Phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group study.	24 weeks double-masked period follow by 48 weeks open lable (72 weeks in total). Patients that were randomized to aflipercept switched to faricimab after week 74	Start (FPI): 02/03/21 Completion (LPLV): 12/07/23 Data cut-off: 06/07/22 (up to week 24 follow-up) 29/09/23 (up to week 72 follow-up)	Adults ≥18 years with foveal center-involved macular edema due to central retinal vein occlusion or hemiretinal vein occlusion	Faricimab, intravitreal injection, 6 mg administered every 4 weeks; 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualized with up to 4 months between injections, using a treat-and-extend approach	Aflibercept, intravitreal injection, 2 mg administered every 4 weeks	2	• Proportion of patients avoiding a loss of ≥15 letters in BCVA from baseline through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Change from Baseline in Best-Corrected Visual Acuity (BCVA) at Week 24 [Time Frame: From Baseline to Week 24] • Change from baseline in Central Subfield Thickness at Specified Timepoints Through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Change from baseline in NEI VFQ-25 composite score through Week 24 [Time Frame: Baseline and Week 24] • Safety

Virtual Congress.
2024. (11)

5. Clinical question 1

5.1 Efficacy of faricimab compared to aflibercept for adult patients with visual impairment due to branch RVO

5.1.1 Relevant studies

BALATON is a phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group study evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by IVT injection at 4-week intervals until Week 24 followed by a period of study without active control to evaluate faricimab administered according to a PTI dosing regimen, with up to 16-week intervals, in patients with macular edema (ME) secondary to BRVO.

Hence, the BALATON study is composed of two parts (Figure 1):

- Part 1 (Day 1 through Week 24) to compare faricimab Q4W versus aflibercept Q4W. In Part 1, 276 and 277 patients were randomly assigned in a 1:1 ratio to receive 6 mg faricimab IVT injections or 2 mg aflibercept IVT injections, respectively Q4W from Day 1 through Week 20 resulting in a total of six injections.
- Part 2 (Week 24 through Week 72) to evaluate faricimab administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on PTI dosing criteria. In Part 2, all patients included in the study received 6 mg faricimab IVT injections, up to Q16W, using a PTI treat-and-extend dosing regimen from Week 24 through Week 68.

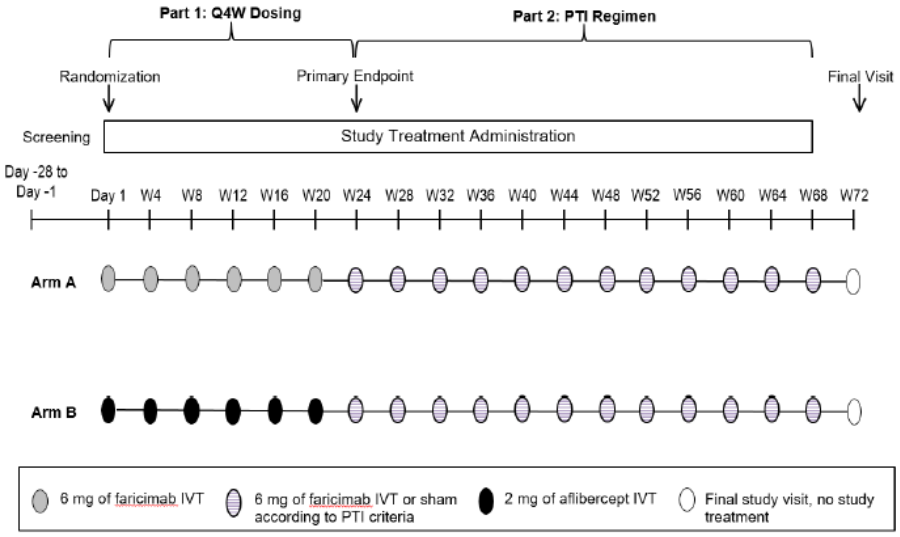

Figure 1: BALATON and COMINO study design (12).

The primary efficacy endpoint was change from baseline in best-corrected visual acuity (BCVA) at Week 24 as measured on the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter chart at a starting distance of 4 meters (8). Secondary efficacy endpoints which, according to the Medicines Council guideline protocol, is relevant for the assessment in the DMC, included proportion of patients with loss of fewer than 15 letters in BCVA score from baseline to Week 24 and change from baseline to Week 24 in central subfield thickness (CST). Relevant safety endpoints were incidence of serious ocular adverse events (AEs) and serious non-ocular AEs, and a relevant exploratory efficacy endpoint was change from baseline in National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) (2).

The first patient was enrolled in BALATON March 02, 2021 and patients were eligible for enrollment in the study if they were ≥18 years with foveal center-involved ME due to BRVO, had a BCVA of 73-19 letters and a CST ≥325 µm.

The primary analysis is based on Week 24 data with the clinical cut-off date (CCOD) of July 6, 2022, and the efficacy analysis is based on the ITT-population defined as all patients who were randomized in the study. Patients were grouped according to the treatment assigned at randomization. In BALATON, the ITT population was composed of a total of 535 patients with 276 patients in the faricimab Q4W arm and 277 patients in the aflibercept Q4W arm (8, 12, 13).

The safety analysis is based on the safety-evaluable population defined as all patients who received at least one injection of active study drug (either faricimab or aflibercept) in the study eye. Three patients, included in the ITT population, did not receive treatment and were thus not included in the safety-evaluable population. 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 randomised. Consequently, the safety evaluable population consists of 276 patients in the faricimab Q4W arm and 274 patients in the aflibercept Q4W arm (12).

Data from the primary analysis based on Week 24 data was first presented at Angiogenesis 2023 (9) and Macula Society 46th Annual Meeting I (10) and recently published by Tadayoni, R et al. (8). Follow-up data from Week 72 was presented earlier this year at Angiogenesis 2024 (11). Some data has not been published as of today (12). Please note that Week 24 data included in the latest presentation of the follow-up Week 72 data differ slightly from primary analysis. This is due to updates before database lock. In the following, however, data from the primary analysis of Week 24 data will be presented as this data has been peer-reviewed alongside with Week 72 data.

5.1.2 Comparability of studies

N/A.

This section is not relevant as efficacy and safety results of faricimab vs. aflibercept are compared directly in the BALATON study.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Baseline demographics and baseline ocular characteristics are listed in Table 2. Generally, patient demographics and baseline characteristics were well balanced and comparable across treatment arms. The median age was 65 and 64 years in the faricimab and aflibercept arm, respectively with slightly more patients ≥ 65 years in the faricimab arm (51.8%) compared to the aflibercept arm (48.0%). The proportion of males was 51.8% and 46.9% in the faricimab and aflibercept arm, respectively. Most patients were white in both arms namely 62.3% in the faricimab arm and 62.1% in the aflibercept arm. The median BCVA letters at baseline were 60.0 in both treatment arms. The mean CST (ILM-BM) was 558.32 microns in the faricimab arm and 558.12 microns in the aflibercept arm while the median CST (ILM-BM) was 518.00 microns and 505.00 microns in the two arms, respectively.

Table 2: Baseline characteristics of patients in the BALATON study.

	BALATON (8-12)		
	Faricimab 6 mg Q4W N=276	**Aflibercept 2 mg Q4W N=277**	**All patients N=553**
Age years - Median (min-max)	65.0 (35-93)	64.0 (28-88)	64.0 (28-93)
Age group – n (%)			
< 65	133 (48.2%)	144 (52.0%)	277 (50.1%)
≥ 65	143 (51.8%)	133 (48.0%)	276 (49.9%)
Gender – n (%)			
Female	133 (48.2%)	147 (53.1%)	280 (50.6%)
Male	143 (51.8%)	130 (46.9%)	273 (49.4%)
Race			
Black or African Americans	6 (2.2%)	7 (2.5%)	13 (2.4%)
White	172 (62.3%)	172 (62.1%)	344 (62.2%)
Asian	90 (32.6%)	94 (33.9%)	184 (33.3%)
American Indian or Alaska Native	3 (1.1%)	0 (0%)	3 (0.5%)

	BALATON (8-12)		
	Faricimab 6 mg Q4W N=276	**Aflibercept 2 mg Q4W N=277**	**All patients N=553**
Native Hawaiian or other Pacific Islander	1 (0.4%)	0 (0%)	1 (0.2%)
Unknown	4 (1.4%)	4 (1.4%)	8 (1.4%)
BCVA (letters)			
Median (min-max)	60.0 (19.0-76.0)	60.0 (21.0-73.0)	60.0 (19.0-76.0)
BCVA (letters) category			
≤ 34 letters (20/200 or worse)	N/A	N/A	N/A
> 34 (better than 20/200) - < 55 (worse than 20/80)	N/A	N/A	N/A
≤ 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 (min-max)	518.00 (281.0-1154.0)	506.00 (290.0-1208.0)	511.50 (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%)
Intraocular pressure (mmHg)			

	BALATON (8-12)		
	Faricimab 6 mg Q4W N=276	**Aflibercept 2 mg Q4W N=277**	**All patients N=553**
n	276	276	552
Mean (SD)	14.57 (2.88)	14.48 (2.94)	14.52 (2.91)
Median (min-max)	14.00 (7.0 - 21.0)	14.00 (7.0 - 22.0)	14.00 (7.0 - 22.0)

Abbreviations: BCVA - Best Corrected Visual Acuity; BM - Bruch's membrane; CST - Central Subfield Thickness; ILM - Internal Limiting Membrane; SD - Standard Deviation.

It has not been possible to find published literature on the above baseline characteristics in a Danish population. Roche has therefore consulted an epidemiologist (Marie Ørskov) within ophthalmology. According to the epidemiologist, there are several of the baseline characteristics included in the BALATON study that are in general either not registered in Denmark, or are registered in patient journals or potentially in an incomparable way. It cannot be excluded that there might exist some small databases where these baseline characteristics are registered. However, according to the epidemiologist, an unpublished study investigating social inequality, has examined 14041 Danish RVO-patients from 2000 – 2018. This study showed there were 50.8% females in the Danish RVO-population (N=7138), and that the mean age of a Danish RVO-patient was 69.9 years (sd: 12.9).

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

In this section, results on the following outcomes are presented from the BALATON study:

- Visual acuity, visual stabilization
- Visual acuity, mean difference
- Central subfield thickness
- Patient Reported Outcome, mean change in NEI VFQ-25 composite score
- Durability
- Adverse events
    - Serious adverse events
    - Intraocular inflammation
    - Qualitative description of safety profiles

Table 3: Overview of data requested in the Medicines Council protocol and Week 24 data from the BALATON study provided by Roche Pharmaceuticals A/S.

Data requested in DMC protocol (2)				Data provided by Roche Pharmaceuticals A/S
Outcome	Outcome measure	Significance	Minimum clinically relevant difference	Absolute difference between faricimab and comparator at Week 24 (8-10, 12, 13)
Visual acuity, visual stabilisation	Proportion of patients with visual loss of less than 15 ETDRS- letters	Critical	5%	1.1% (95% CI: −0.5%, 2.6%)
Visual acuity, mean difference	Mean change in number of ETDRS-letters	Important	10 ETDRS letters	-0.6 ETDRS letters (95% CI: -2.2, 1.1)
Central subfield thickness	Mean change in central subfield thickness measured by OCT	Critical	50 µm	−7.0 µm (95% CI: −14.1, 0.0)
Quality of life	Mean change in patient-experienced quality of life rated by VFQ	Important	5 points	−0.4 points (95% CI: −1.9, 1.1)
Side effects	Proportion of patients that experience serious side effects	Important	5%	-1.9% (95% CI: -6.1%, 2.3%)
	Proportion of patients that require treatment for inflammation		3%	0%
	Qualitative description of the types of treatment-related AEs with the purpose of assessing seriousness, manageability and weight		Narrative assessment	-

Abbreviations: AE - adverse event; ETDRS - Early Treatment of Diabetic Retinopathy Study; CI - confidence intervals; VFQ - Visual Function Questionnaire.

Visual acuity, visual stabilization

Visual stabilization measured as avoiding loss of ≥ 15 letters in BCVA from baseline was analysed using Cochran-Mantel-Haenszel (CMH) weights and stratified by baseline BCVA score (≤54 letters versus ≥55 letters) and region (United States and Canada, Asia, and the

rest of the world). Confidence intervals (CI) are two-sided and at the 95.03% level (rounded up to 95% in the text).

In BALATON, a comparable proportion of patients in the faricimab Q4W arm avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients in the aflibercept Q4W arm namely 99.6% and 98.6% in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference between treatment arms was 1.1% (95% CI: −0.5%, 2.6%) (8-10, 13). According to the Medicines Council protocol the significance of this outcome measure is termed *critical* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in BALATON is below the value considered clinically relevant difference.

The proportions of patients avoiding loss of ≥ 15 letters at Week 24 were maintained through Week 72 with an average over Week 64, 68 and 72 of 98.9% (95% CI: 97.7%, 100.0%) and 98.2% (95% CI: 96.7%, 99.8%) in faricimab and aflibercept switched to PTI faricimab (11-13).

Visual acuity, mean difference

BALATON met its primary efficacy endpoint defined as the change from baseline in BCVA at Week 24. BCVA was assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters and with a positive number of letters indicating an improvement. The primary analysis was performed using a mixed model for repeated measures (MMRM) which 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 randomisation stratification factors as fixed effects. CIs are two-sided and at the 95.03% level (rounded up to 95% in the text). 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.

The adjusted mean (SE) change in BCVA from baseline at Week 24 was 16.9 (0.60) ETDRS letters (95% CI: 15.7, 18.1) in the faricimab Q4W arm and 17.5 (0.60) ETDRS letters (95% CI: 16.3, 18.6) in the aflibercept Q4W arm with a difference of -0.6 (0.84) ETDRS letters (95% CI: -2.2, 1.1) between treatment arms (Figure 2) (8-10, 12, 13). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 10 ETDRS letters (2). Therefore,

the difference found in BALATON is below the value considered clinically relevant difference.

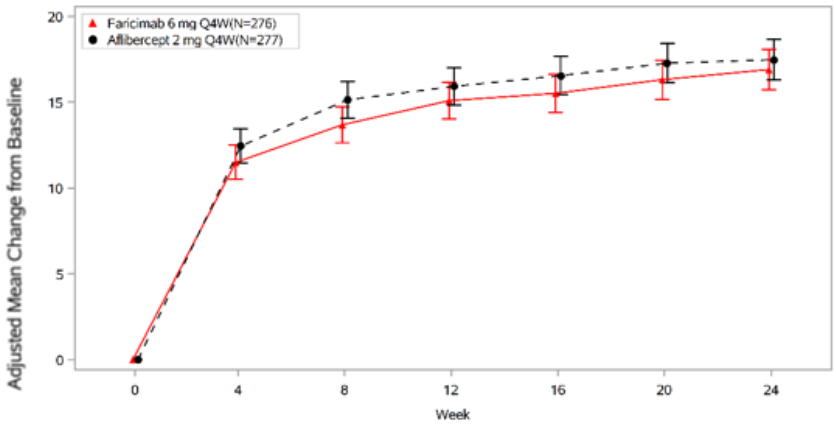

Figure 2: Change from baseline in BCVA in the ITT population overtime time up to Week 24 in the BALATON study.

Faricimab, thus demonstrated non-inferiority to aflibercept, as the lower bound of the 95.03% CI for the adjusted mean difference between the faricimab and aflibercept was greater than -4 letters .

Robust BCVA gains at Week 24 maintained through Week 72 for both arms with a mean change from baseline averaged over weeks 64, 68, and 72 being 18.1 (95% CI: 16.9, 19.4) for faricimab to faricimab and 18.8 (95% CI: 17.5, 20.0) for aflibercept to faricimab (Figure 3) (11, 13).

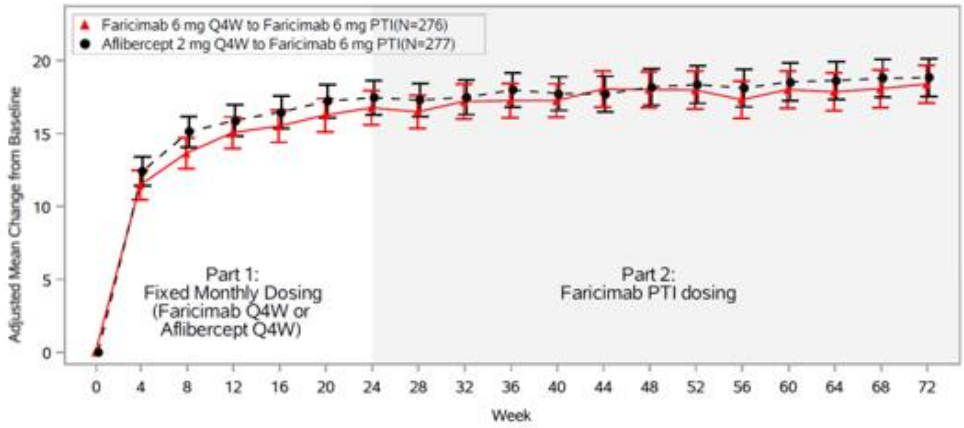

Figure 3: Change from baseline in BCVA in the ITT population overtime time up to week 72 in the BALATON study.

Central subfield thickness

The endpoint of CST, defined as the distance between the internal limiting membrane (ILM) and Bruch's membrane as asses by a central reading center, were analyzed using a

MMRM (adjusted as described above) with two-sided CI of 95.03% level (rounded up to 95% in the text).

Patients in the faricimab Q4W and aflibercept Q4W arms had comparable reductions in CST from baseline to Week 24. The adjusted mean change from baseline in CST was −311.4 µm (95% CI: -316.4, -306.4) in the faricimab Q4W arm and −304.4 µm (95% CI: -309.3, -299.4) in the aflibercept Q4W arm. The difference between treatment arms at Week 24 was −7.0 µm (95% CI: -14.1, 0.0) (Figure 4) (8-10, 12). According to the Medicines Council protocol the significance of this outcome measure is termed *critical* and the minimum clinically relevant difference is 50 µm (2). Therefore, the difference found in BALATON is below the value considered clinically relevant difference.

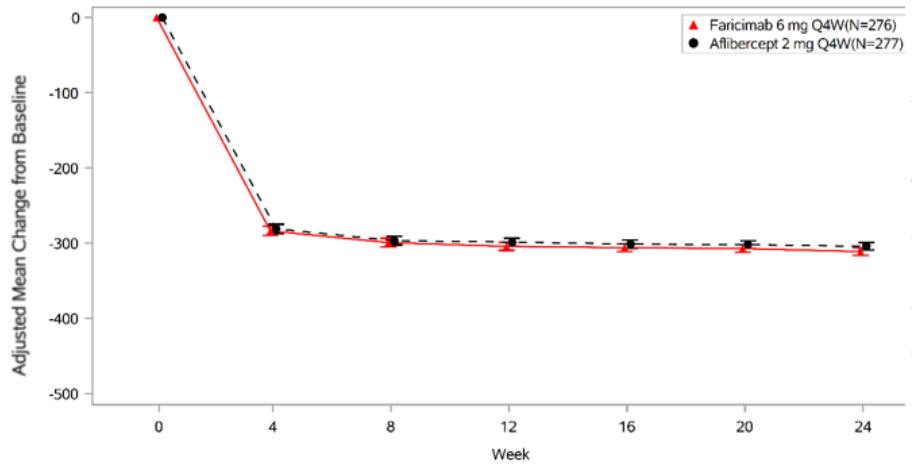

Figure 4: Change from baseline in CST from baseline the ITT population overtime time until Week 24 in the BALATON study.

Faricimab continued to show robust and sustained drying of the retina up to week 72, as patients maintained their reduction in CST in both arms with mean change from baseline averaged over Weeks 64, 68, and 72 being −307.0 µm (95% CI: -311.7, -302.3) and −310.9 µm (95% CI: -315.6, -306.3) (Figure 5) (11, 12).

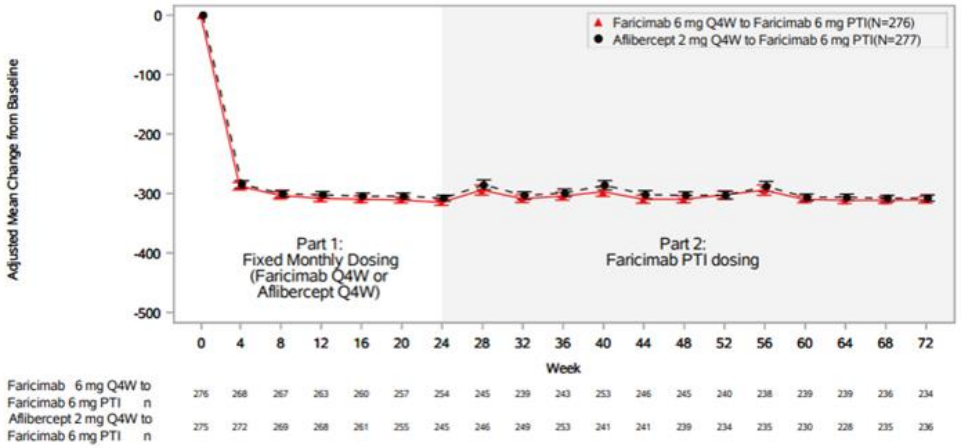

Figure 5: Change from baseline in CST from baseline the ITT population overtime time until Week 72 in the BALATON study.

Quality of Life

Patient reported outcome data were collected using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) to assess the treatment benefit of faricimab and analysed using a MMRM.

At Week 24, the adjusted mean change from baseline in NEI VFQ-25 composite score was 5.6 (95% CI: 4.5, 6.7) and 5.9 (95% CI: 4.8, 7.1) points in the faricimab Q4W and aflibercept Q4W arms, respectively with a difference of −0.4 points (95% CI: −1.9, 1.1) between treatment arms (Figure 6)(12, 13). Hence, patients treated with faricimab Q4W had comparable adjusted mean changes from baseline in the NEI VFQ-25 composite score compared with patients treated with aflibercept Q4W. According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5 points (2). Therefore, the difference found in BALATON is below the value considered clinically relevant difference.

Patient reported NEI VFQ-25 composite score for patients in the ITT population slightly increased though Week 72. At Week 72, adjusted mean changes from baseline in the NEI VFQ-25 composite score were 6.0 (95% CI: 4.8, 7.3) and 7.8 (95% CI: 6.6, 9.0) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (Figure 6) (12, 13).

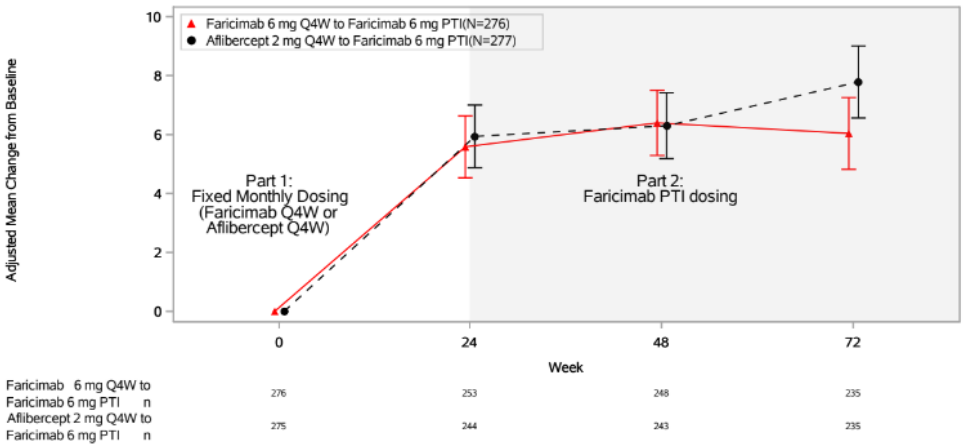

Figure 6: Adjusted mean change from baseline in NEI VFQ-25 composite score over time in the BALATON study.

Durability

Whereas patients up until Week 20 (Part I) received either 6 mg IVT faricimab Q4W or 2 mg IVT aflibercept Q4W, all patients from Week 24 onward, were treated with 6 mg IVT faricimab according to the PTI dosing regimen up to Week 68 (Part 2). Table 4 shows the proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68. Percentages are based on the randomized patients who have not discontinued the study at Week 68 and treatment interval at Week 68 is defined as the treatment interval decision followed at that visit. 95% is a rounding of 95.03%.

In BALATON, at Week 68, 64.1% of patients in the faricimab Q4W to faricimab PTI arm and 56.9% of patients in the aflibercept Q4W to faricimab PTI arm were on a Q12W or Q16W treatment interval (Table 4 (12) and Figure 7 (11)).

Table 4: The proportion of patients in the ITT population on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68 in BALATON study.

	Faricimab 6 mg PTI (Part 1: Faricimab 6 mg Q4W) N=276		Faricimab 6 mg PTI (Part 1: Aflibercept 2 mg Q4W) N=277	
Visit	Proportion n(%)	%95 CI of Proportion	Proportion n(%)	%95 CI of Proportion
Week 68				
N	248		244	
Q4W	56 (22.6%)	17.4%, 27.8%	61 (25.0%)	19.6%, 30.4%
Q8W	33 (13.3%)	9.1%, 17.5%	44 (18.0%)	13.2%, 22.9%
Q12W	29 (11.7%)	7.7%, 15.7%	23 (9.4%)	5.8%, 13.1%
Q16W	130 (52.4%)	46.2%, 58.6%	116 (47.5%)	41.3%, 53.8%

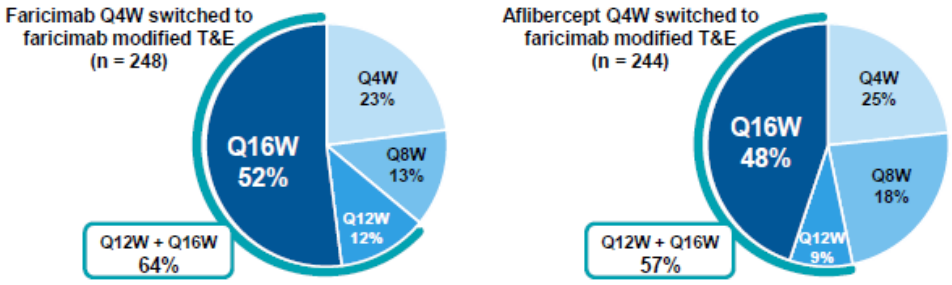

Figure 7: Proportion of patients on modified PTI at Week 68 in the BALATON study.

The majority (≥ 75%) of all patients extended their treatment intervals beyond Q4W with approximately 60% of all patients extending their treatment intervals to Q12W or Q16W, regardless of previous treatment (11-13). Following the longer intervals between injections with faricimab in maintenance treatment, faricimab will lower the cost of drugs and cost per patient as well as lower administration cost and ease capacity problems at ophthalmology departments compared to current standard of treatment.

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

Safety results are primarily reported separately as ocular or non-ocular events. Overall, treatment exposure in both the faricimab Q4W arm and the aflibercept Q4W arm was well balanced. The median duration of exposure was the same between both treatment arms, that is 20.1 weeks. The mean and median number of study drug administrations was the same in the faricimab Q4W and aflibercept Q4W arms, namely 5.8 and 6.0, respectively (13).

Serious adverse events

Through Week 24, the total numbers of patients with at least one serious AE (SAE) were 12 (4.3%) in the faricimab Q4W arm and 17 (6.2%) in the aflibercept Q4W arm. The difference between the faricimab Q4W arm when compared with the aflibercept Q4W arm was -1.9% (95% CI: -6.1%, 2.3%). The relative risk (faricimab vs aflibercept) was 0.70 (95% CI: 0.35, 1.42) (12). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in BALATON is below the value considered clinically relevant difference.

A further description of serious ocular and non-ocular adverse events is presented below.

Serious ocular adverse events

Through Week 24, the incidence of serious ocular AEs in the study eye was low and comparable between the treatment arms. The total numbers of patients with at least one serious ocular AE were 3 (1.1%) and 2 (0.7%) in the faricimab Q4W arm and aflibercept Q4W arm, respectively with a difference of 0.4% (95% CI: -10.9%, 2.6%) between treatment arms (8, 9, 12). In the faricimab Q4W arm, 2 patients (0.7%) experienced retinal ischaemia and 1 patient (0.4%) had RVO of which all were resolved by Week 24. In the

aflibercept Q4W arm, 1 patient (0.4%) experienced a worsening of RVO and 1 patient (0.4%) had vitreous haemorrhage of which neither were resolved by Week 24. The relative risk (faricimab vs aflibercept) was 1.49 (95% CI: 0.30, 7.42) (12). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in BALATON is below the value considered clinically relevant difference.

There were no serious ocular AEs suspected by the investigator to be related to study treatment in either arm (12).

Serious non-ocular adverse events

Similarly, the incidence of serious non-ocular AEs was low and comparable between the treatment arms through Week 24. The total numbers of patients with at least one AE were 9 (3.3%) and 16 (5.8%) in the faricimab Q4W and aflibercept Q4W arm, respectively with a difference of -2.6 (95% CI -6.6, 1.3) between treatment arms. The most common was cerebral infarction of which all 3 events (1.1%) occurred in the faricimab Q4W arm and all were reported as severe. The relative risk (faricimab vs aflibercept) was 0.56 (95% CI: 0.26, 1.22) (12).

The incidence of serious non-ocular AEs suspected by the investigator to be related to the study treatment was low, namely 2 patients (0.7%) in the faricimab Q4W arm with AEs of cerebral infarction, and 2 patients (0.7%) in the aflibercept Q4W arm in which 1 patient had acute myocardial infarction and coronary artery disease, and 1 patient with an AE of arteriosclerosis coronary artery (12).

Intraocular inflammation

In BALATON, intraocular Inflammation events included 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.

Through Week 24, there were no intraocular inflammation events occurring in the study eye of patients in the BALATON study. 1 patient in the faricimab Q4W arm had an event of vitreal cells reported but the verbatim term was 'non-inflammatory vitreous cells' and thus, not considered an intraocular inflammation event (8-10, 13).

According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 3% (2). There has been no events of intraocular inflammation occurring in the study eye of patients in the BALATON study, therefore there is no clinical relevant difference.

Qualitative description of safety profiles

Through week 24, the total numbers of patients with at least one AE were 125 (45.3%) and 128 (46.7%) in the faricimab Q4W and aflibercept Q4W arms, respectively (12).

Occular adverse events

The incidence of ocular AEs in the study eye was comparable between the treatment arms. Total numbers of patients with at least one ocular AE were 45 (16.3%) and 56 (20.4%) in the faricimab Q4W and aflibercept Q4W arms, respectively (8-10, 13). The most common ocular AEs ≥2% in any treatment arm (faricimab Q4W and aflibercept Q4W, respectively) were conjunctival haemorrhage (2.9% and 3.6%), dry eye (1.8% and 3.3%), vitreous floaters (2.2% and 2.2%) and intraocular pressure increase (0.4% and 2.6%) (13).

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. There were no patients with severe events in the faricimab Q4W arm, and 1 patient experienced a severe event of vitreous haemorrhage in the aflibercept Q4W arm (13).

The incidence of ocular AEs suspected by the investigator to be related to the study treatment was low with 1 patient (0.4%) and 2 patients (0.7%) in the faricimab Q4W and aflibercept Q4W arms, respectively. No patients had ocular AEs leading to study treatment discontinuation nor study discontinuation (13).

Lastly, the incidence of ocular adverse events of special interest (AESIs) in the study eye was low across treatment arms with 1 patient (0.4%) and 2 patients (0.7%) in the faricimab Q4W and aflibercept Q4W arms, respectively (8-10, 12, 13). None of these AESIs were suspected to be related to the study treatment (12).

Non-ocular adverse events

Through Week 24, the incidence of non-ocular AEs was comparable between treatment arms. The total numbers of patients with at least one AE were 90 (32.6%) and 97 (35.4%) in the faricimab Q4W and aflibercept Q4W arms, respectively (8, 12).The most common non-ocular AEs ≥ 2% in any treatment arm (the faricimab Q4W and aflibercept Q4W, respectively) were COVID-19 (3.6% and 5.8%), hypertension (6.2%and 2.6%), back pain (0.7% and 3.6%) and nasopharyngitis (2.2% and 2.2%) (12).

The incidence of non-ocular AEs suspected by the investigator to be related to the study treatment was low with 2 patients (0.7%) in each treatment arm. 1 patient (0.4%) in each study arm had non-ocular AEs leading to study treatment discontinuation. Similarly, the incidence of AEs leading to study discontinuation was low across treatment arms with 2 patients and 1 patient in the faricimab Q4W and aflibercept Q4W arms, respectively. No non-occular AESIs were reported (12).

Deaths

1 patient (0.4%) in the faricimab Q4W arm experienced an AE with a fatal outcome. The event was linked to a fatal cerebrovascular accident and was not considered related to study treatment as determined by the investigator (12).

Safety data from Part 1 of BALATON (baseline through Week 24) indicated that faricimab Q4W had a comparable safety profile to aflibercept Q4W, and faricimab was generally

well tolerated. An expected increased incidence of AEs and SAEs was observed in Part 2 (Week 24 through Week 72) compared to Part 1 (baseline through Week 24) are 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 (Table 5) (11, 12).

Table 5: Safety Summary through Week 72 by Study Part, Safety-Evaluable Population in BALATON study.

	Faricimab 6 mg Q4W Part 1 (N=276)	Aflibercept 2 mg Q4W Part 1 (N=274)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)
Total number of patients with at least one AE	128 (46.4%)	129 (47.1%)	172 (63.7%)	167 (62.5%)
Total number of AEs	236	293	557	475
Total number of patients with at least one SAE	12 (4.3%)	17 (6.2%)	29 (10.7%)	26 (9.7%)
Total number of SAEs	13	24	42	32
Total number of deaths	1 (0.4%)	0	1 (0.4%)	2 (0.7%)
Total number of patients withdrawn from study due to an AE	2 (0.7%)	0	0	5 (1.9%)
Total number of patients withdrawn from study treatment due to an AE	1 (0.4%)	0	0	4 (1.5%)
Total number of patients with at least one AESI	1 (0.4%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Ocular events: study eye total number of patients with at least one				
AE	45 (16.3%)	56 (20.4%)	76 (28.1%)	81 (30.3%)
SAE	3 (1.1%)	2 (0.7%)	4 (1.5%)	3 (1.1%)
AE leading to withdrawal from study treatment	0	0	0	1 (0.4%)
Treatment related AEs	1 (0.4%)	3 (1.1%)	7 (2.6%)	8 (3.0%)
Treatment related SAEs	0	0	0	0
AE of Special Interest	1 (0.4%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Drop in VA score >=30	1 (0.4%)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Ocular events: fellow eye total number of patients with at least one				
AE	25 (9.1%)	21 (7.7%)	37 (13.7%)	30 (11.2%)
SAE	0	0	0	0
AE of Special Interest	0	0	0	0
Drop in VA score >=30	0	0	0	0
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Non-ocular events total number of patients with at least one				
AE	94 (34.1%)	99 (36.1%)	136 (50.4%)	126 (47.2%)
SAE	9 (3.3%)	16 (5.8%)	25 (9.3%)	23 (8.6%)
AE leading to withdrawal from study treatment	1 (0.4%)	0	0	3 (1.1%)
AE of Special Interest	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	4 (1.4%)	4 (1.5%)	2 (0.7%)	8 (3.0%)
Non-fatal MI	1 (0.4%)	2 (0.7%)	1 (0.4%)	2 (0.7%)
Non-fatal Stroke	2 (0.7%)	2 (0.7%)	0	5 (1.9%)
Death	1 (0.4%)	0	1 (0.4%)	2 (0.7%)

Serious ocular adverse events through Week 72

In Part 2, the incidence of serious ocular AEs in the study eye was low with 4 patients (1.5%) in the faricimab Q4W to faricimab PTI arm and 3 patients (1.1%) in the aflibercept Q4W to faricimab PTI arm (Table 6) (12).

Table 6: Serious Ocular Adverse Events be Preferred Terms in the Study Eye through Week 72 by Study Part, Safety-Evaluable Population in BALATON study.

MedDRA Preferred Term	Faricimab 6 mg Q4W Part 1 (N=276)	Aflibercept 2 mg Q4W Part 1 (N=274)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=270)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=267)
Total number of patients with at least one adverse event	3 (1.1%)	2 (0.7%)	4 (1.5%)	3 (1.1%)
Total number of events	3	2	5	3
Retinal ischaemia	2 (0.7%)	0	0	2 (0.7%)
Retinal vein occlusion	1 (0.4%)	1 (0.4%)	0	0
Cataract	0	0	0	1 (0.4%)
Macular ischaemia	0	0	1 (0.4%)	0
Macular oedema	0	0	1 (0.4%)	0
Retinal neovascularisation	0	0	1 (0.4%)	0
Rhegmatogenous retinal detachment	0	0	1 (0.4%)	0
Tractional retinal detachment	0	0	1 (0.4%)	0
Vitreous haemorrhage	0	1 (0.4%)	0	0

In Part 2, there were no serious ocular AEs suspected by the investigator to be related to study treatment in any of the study arms (12).

Conclusion

Overall, safety data from BALATON demonstrated that faricimab is well tolerated and has a comparable safety profile to aflibercept through Week 24. No new or unexpected safety signals were identified. Furthermore, faricimab showed no significant changes in the safety profile from Week 24 to 72.

5.2.3 Method of synthesis

The BALATON study provides a direct comparison between faricimab and aflibercept.

5.2.4 Results from the comparative analysis

The BALATON study provides a direct comparison between faricimab and aflibercept and results can be used to address the clinical question. The comparative efficacy results for faricimab vs. aflibercept have been presented in section 5.2.1. The comparative safety results for faricimab vs. aflibercept have been presented in section 5.2.2.

Table 7: Results from BALATON: Direct comparison of faricimab vs. aflibercept for the ITT and safety population.

Outcome measure	Faricimab (N=276)	Aflibercept (N=277)	Results
Proportion of patients with visual loss of less than 15 ETDRS- letters, Week 24	99.6% (95% CI: 98.9%, 100.0%)	98.6% (95% CI: 97.2%, 99.9%)	Absolute difference: 1.1% (95% CI: −0.5%, 2.6%)
Mean change in number of ETDRS letters, Week 24	16.9 ETDRS letters (95% CI: 15.7, 18.1)	17.5 ETDRS letters (95% CI: 16.3, 18.6)	Absolute difference: -0.6 ETDRS letters (95% CI: -2.2, 1.1)
Mean change in central subfield thickness measured by OCT, Week 24	−311.4 µm (95% CI: -316.4, -306.4)	−304.4 µm (95% CI: -309.3, -299.4)	Absolute difference: −7.0 µm (95% CI: −14.1, 0)

Outcome measure	Faricimab (N=276)	Aflibercept (N=277)	Results
Mean change in patient-experienced quality of life rated by VFQ, Week 24	5.6 points (95% CI: 4.5, 6.7)	5.9 points (95% CI: 4.8,7.1)	Absolute difference: −0.4 points (95% CI: −1.9, 1.1)
Proportion of patients that experience serious side effects, Week 24	12/276 (4.3%)	17/274 (6.2%)	Absolute difference: -1.9% (95% CI: -6.1, 2.3) Relative risk: 0.70 (95% CI: 0.35, 1.42)
Proportion of patients that require treatment for inflammation, Week 24	0/276, 0%	0/274, 0%	N/A

6. Clinical question 2

6.1 Efficacy of faricimab compared to aflibercept for adult patients with central RVO

6.1.1 Relevant studies

The study design of COMINO is identical to the one of BALATON presented and showed in Figure 1 above. In COMINO, 366 patients were randomized to receive 6 mg faricimab IVT injections Q4W, and 363 patients to receive 2 mg aflibercept Q4W during Part 1 of the study before all patients crossed over to received 6 mg faricimab IVT injections according to a PTI dosing regimen in Part 2.

The primary efficacy endpoint and secondary efficacy endpoints relevant for the assessment in the DMC as well as relevant safety objectives relevant exploratory efficacy objective were the same in the COMINO study as the ones described above for BALATON.

In COMINO, the first patient was enrolled March 2, 2021. Patients were eligible for enrollment in the study if they were adults 18 years and older with foveal center-involved ME due to H/CRVO, had a BCVA of 73-19 letters and a central subfield thickness (CST) ≥ 325 µm. In COMINO, 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.

The primary analysis is based on Week 24 data with the CCOD of August 9, 2022. The efficacy analysis is based on the ITT population defined as all patients who were random-

ized in the study and patients were grouped according to the treatment assigned at randomization. The ITT population consists of a total of 729 patients with 366 patients in the faricimab Q4W arm and 363 patients in the aflibercept Q4W arm (8, 12, 13).

The safety analysis is based on the safety-evaluable population defined as all patients who received at least one injection of active study drug (either faricimab or aflibercept) in the study eye. Three patients, included in the ITT population, did not receive treatment and were thus not included in the safety-evaluable population. 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 randomised. Consequently, the safety evaluable population consists of 365 patients in the faricimab Q4W arm and 361 patients in the aflibercept Q4W arm (12).

6.1.2 Comparability of studies

This section is not relevant as efficacy and safety results of faricimab vs. aflibercept are compared directly in the COMINO study.

6.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Baseline demographics and baseline ocular characteristics are listed in Table 8. Generally, baseline characteristics across treatment arms were comparable. The median age was 67 and 66 years in the faricimab and aflibercept arm, respectively with similar proportions of patients ≥ 65 years in the faricimab arm (55.7% %) and in the aflibercept arm (56.5%). The proportion of males was 52.7% and 55.1% in the faricimab and aflibercept arm, respectively. Most patients were white in both arms namely 66.4% in the faricimab arm and 69.7% in the aflibercept arm. In the faricimab arm, 83.0% had central RVO and 17.0% had Hemiretinal Vein Occlusion while in the aflibercept arm the proportions were 81.9% and 18.1%, respectively. The median BCVA letters at baseline were 54.0 in both treatment arms. The mean CST (ILM-BM) was 702.21 microns in the faricimab arm and 721.07 microns in the aflibercept arm while the median CST (ILM-BM) was 668.00 microns and 701.00 microns in the two arms, respectively.

Table 8: Baseline characteristics of patients in COMINO.

	COMINO (8-12)		
	Faricimab 6 mg Q4W N=366	**Aflibercept 2 mg Q4W N=363**	**All patients N=729**
Age years - Median (min-max)	67.0 (22-100)	66.0 (27-95)	66.0 (22-100)
Age group – n (%)			

	COMINO (8-12)		
	Faricimab 6 mg Q4W N=366	**Aflibercept 2 mg Q4W N=363**	**All patients N=729**
< 65	162 (44.3%)	158 (43.5%)	320 (43.9%)
≥ 65	204 (55.7%)	205 (56.5%)	409 (56.1%)
Gender – n (%)			
Female	173 (47.3%)	163 (44.9%)	336 (46.1%)
Male	193 (52.7%)	200 (55.1%)	393 (53.9%)
Race			
Black or African Americans	10 (2.7%)	13 (3.6%)	23 (3.2%)
White	243 (66.4%)	253 (69.7%)	496 (68.0%)
Asian	89 (24.3%)	88 (24.2%)	177 (24.3%)
American Indian or Alaska Native	2 (0.5%)	3 (0.8%)	5 (0.7%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (0.3%)	1 (0.1%)
Unknown	21 (5.7%)	5 (1.4%)	26 (3.6%)
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 (letters)			
Median (min-max)	54.0 (19.0-87.0)	54.0 (19.0-73.0)	54.0 (19.0-87.0)
BCVA (letters) category			
≤ 34 letters (20/200 or worse)	79 (21.6%)	80 (22.0%)	159 (21.8%)

	COMINO (8-12)		
	Faricimab 6 mg Q4W N=366	**Aflibercept 2 mg Q4W N=363**	**All patients N=729**
> 34 (better than 20/200) - < 55 (worse than 20/80)	106 (29.0%)	105 (28.9%)	211 (28.9%)
≤ 54 (20/80 or worse)	N/A	N/A	N/A
≥ 55 (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 (min-max)	668.00 (266.0-1500.0)	701.00 (281.0-1419.0)	684.00 (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 (min-max)	15.00 (7.0 - 25.0)	15.00 (7.0 - 26.0)	15.00 (7.0 - 26.0)

Abbreviations: BCVA - Best Corrected Visual Acuity; BM - Bruch's membrane; CST - Central Subfield Thickness; ILM - Internal Limiting Membrane; SD - Standard Deviation.

Baseline characteristics of patients in the COMINO study are comparable to Danish patients eligible RVO-treatment – see also section 5.1.3.

6.2 Comparative analyses of efficacy and safety

6.2.1 Efficacy and safety – results per study

In this section, results on the following outcomes are presented:

- Visual acuity, visual stabilization
- Visual acuity, mean difference
- Central subfield thickness
- Patient Reported Outcome, mean change in NEI VFQ-25 composite score
- Durability
- Safety
    - Serious adverse events
    - Intraocular inflammation
    - Qualitative description of safety profiles

Table 9: Overview of data requested in the Medicines Council protocol and Week 24 data from the COMINO study provided by Roche Pharmaceuticals A/S.

Data requested in DMC protocol (2)				**Data provided by Roche Pharmaceuticals A/S**
Outcome	Outcome measure	Significance	Minimum clinically relevant difference	Absolute difference between faricimab and comparator at Week 24 (8-10, 12, 13)
Visual acuity, visual stabilisation	Proportion of patients with visual loss of less than 15 ETDRS- letters	Critical	5%	-0.5% (95% CI: -3.2%, 2.2%)
Visual acuity, mean difference	Mean change in number of ETDRS-letters	Important	10 ETDRS letters	-0.4 ETDRS letters (95% CI: -2.5, 1.6)
Central subfield thickness	Mean change in central subfield thickness measured by OCT	Critical	50 µm	−12.8 µm (95% CI: −26.7, 1.0)
Quality of life	Mean change in patient-experienced quality of life rated by VFQ	Important	5 points	−1.2 points (95% CI:-2.7, 0.3)
Side effects	Proportion of patients that experience serious side effects	Important	5%	-0.4% (95% CI: -4.8, 4.0)

	Proportion of patients that require treatment for inflammation		3%	0.3% (95% CI: -0.9%, 1.5%)
	Qualitative description of the types of treatment-related AEs with the purpose of assessing seriousness, manageability and weight		Narrative assessment	-

Abbreviations: AE - adverse event; ETDRS - Early Treatment of Diabetic Retinopathy Study; CI - confidence intervals; VFQ - Visual Function Questionnaire.

Visual acuity, visual stabilization

Visual stabilization was assessed and analyzed as described above for the BALATON study.

In COMINO, a comparable proportion of patients in the faricimab Q4W arm avoided a loss of ≥ 15 letters from baseline at Week 24 compared with patients in the aflibercept Q4W arm namely 96.2% and 96.7% in the faricimab Q4W and aflibercept Q4W arms, respectively. The difference between arms was –0.5% (95% CI: –3.2%, 2.2%) (8-10, 13). According to the Medicines Council protocol the significance of this outcome measure is termed *critical* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

The proportions of patients avoiding loss of ≥ 15 letters at Week 24 were maintained through Week 72 with an average over Week 64, 68 and 72 of 93.7% (95% CI: 91.3%, 96.2%) and 95.6% (95% CI: 93.5%, 97.7%) in faricimab and aflibercept switched to PTI faricimab, respectively (11-13).

Visual acuity, mean difference

COMINO met its primary efficacy endpoint defined as the change from baseline in BCVA at Week 24. The endpoint was assessed and analysed as described for the primary efficacy point of BALATON.

The adjusted mean (SE) change in BCVA from baseline at Week 24 was 16.9 (0.73) ETDRS letters (95% CI: 15.4, 18.3) in the faricimab Q4W arm and 17.3 (0.74) ETDRS letters (95% CI: 15.9, 18.8) in the aflibercept Q4W arm with a difference of -0.4 (1.04) ETDRS letters (95% CI: -2.5, 1.6) (Figure 8) (8-10, 12, 13). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 10 ETDRS letters (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

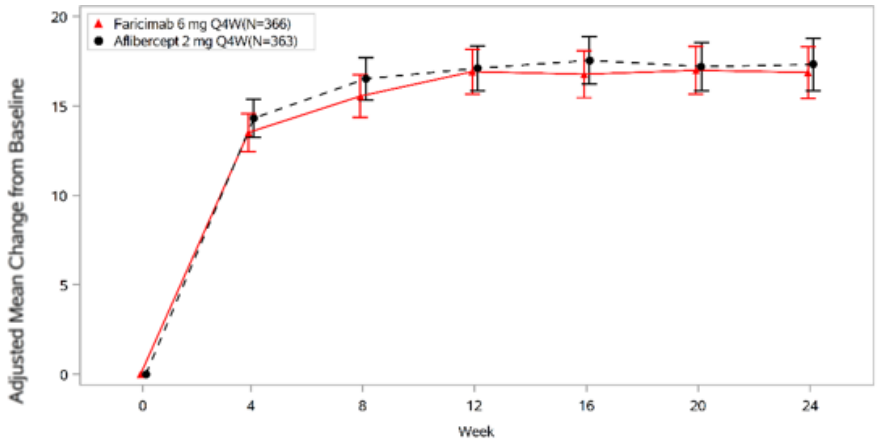

Figure 8: Change from baseline in BCVA in the ITT population overtime time until Week 24 in the COMINO study.

Faricimab, thus, demonstrated non-inferiority to aflibercept, as the lower bound of the 95.03% CI for the adjusted mean difference between the faricimab and aflibercept arms was greater than -4 letters.

The robust BCVA gains at Week 24 maintained through Week 72 for both arms with a mean change from baseline averaged over weeks 64, 68, and 72 being 16.9 (95% CI: 15.2, 18.6) and 17.1 (95% CI: 15.4, 18.8) (Figure 9).

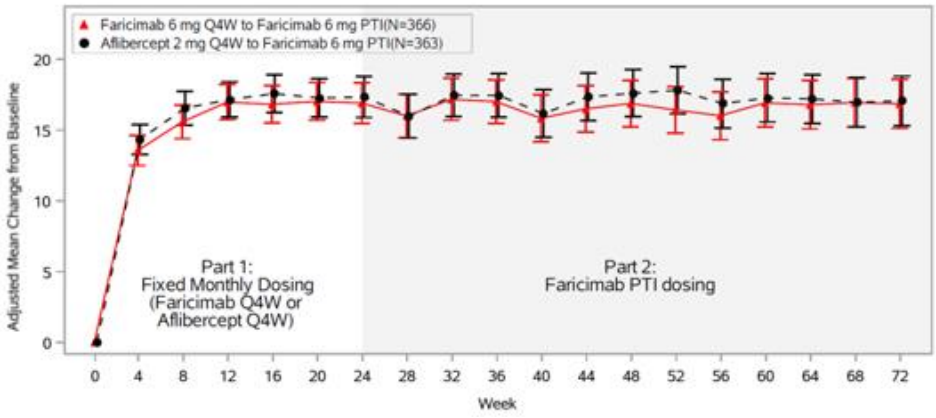

Figure 9: Change from baseline in BCVA in the ITT population overtime time until Week 72 in the COMINO study.

Central subfield thickness

The endpoint of CST was assessed and analyzed as described above for the BALATON study.

Patients in the faricimab Q4W and aflibercept Q4W arms had comparable reductions in CST from baseline at Week 24. The adjusted mean change from baseline in CST was −461.6 µm (95% CI: -471.4, -451.9) in the faricimab Q4W arm and −448.8 µm (95% CI: -458.6, -439.0) in the aflibercept Q4W arm. The difference between treatment arms at

Week 24 was −12.8 µm (95% CI: −26.7, 1.0) (Figure 10) (8-10, 12). According to the Medicines Council protocol the significance of this outcome measure is termed *critical* and the minimum clinically relevant difference is 50 µm (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

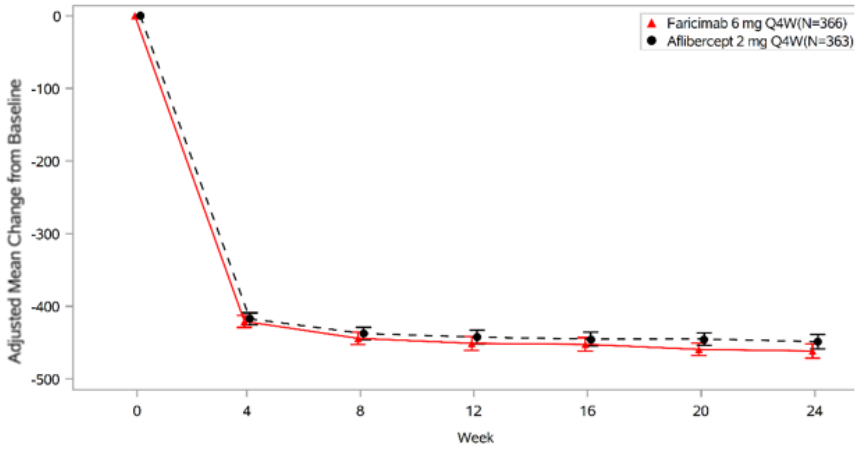

Figure 10: Change from baseline in CST from baseline the ITT population over time until Week 24 in the COMINO study.

Faricimab continued to show robust and sustained drying of the retina up to week 72, as patients maintained their reduction in CST in both arms with mean change from baseline averaged over Weeks 64, 68, and 72 being -465.9 µm (95% CI: -472.5, -459.3) and -460.6 µm (95% CI: -467.2, -453.9) (Figure 11) (11, 12).

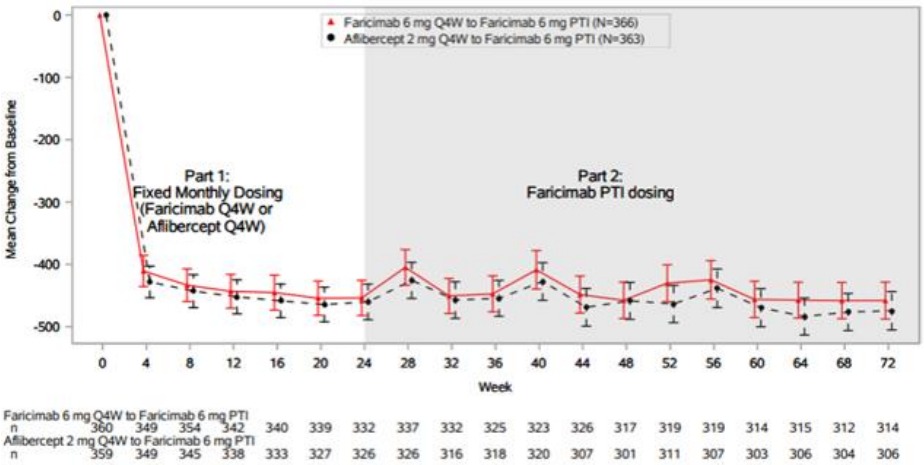

Figure 11: Change from baseline in CST from baseline the ITT population over time until Week 72 in the COMINO study.

Quality of Life

Patient reported outcome was evaluated as described for BALATON.

In COMINO, the adjusted mean change from baseline in NEI VFQ-25 composite score was 6.9 points (95% CI: 5.8, 8.0) and 8.1 points (95% CI: 7.0, 9.2) at Week 24 in the faricimab and aflibercept arms, respectively with a difference of −1.2 points (95% CI: -2.7, 0.3) between treatment arms (12, 13). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5 points (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

Patient reported NEI VFQ-25 composite score for patients in the ITT population slightly increased though Week 72. At Week 72, adjusted mean changes from baseline in the NEI VFQ-25 composite score were 7.8 points (95% CI: 6.5, 9.0) and 8.5 points (95% CI: 7.3, 9.8) in the faricimab Q4W to faricimab PTI and aflibercept Q4W to faricimab PTI arms, respectively (12, 13).

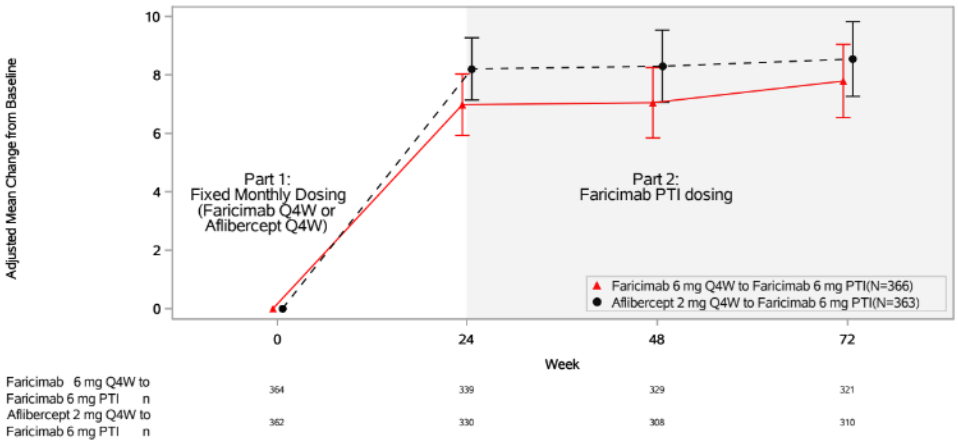

Figure 12: Adjusted mean change from baseline in NEI VFQ-25 composite score over time in the COMINO study.

Durability

Whereas patients up until Week 20 (Part I) received either 6 mg IVT faricimab Q4W or 2 mg IVT aflibercept Q4W, all patients from Week 24 onward, were treated with 6 mg IVT faricimab according to the PTI dosing regimen up to Week 68 (Part 2). Table 4 shows the proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68. Percentages are based on the randomized patients who have not discontinued the study at Week 68 and treatment interval at Week 68 is defined as the treatment interval decision followed at that visit. 95% is a rounding of 95.03%.

In COMINO, at Week 68, 45.5% of patients in the faricimab Q4W to faricimab PTI arm and 50.1% of patients in the aflibercept Q4W to faricimab T&E arm were on a Q12W or Q16W treatment interval, respectively (Table 10 (12) and Figure 13 (11)).

Table 10: The proportion of patients in the ITT population on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68 in COMINO study.

Visit	Faricimab 6 mg PTI (Part 1: Faricimab 6 mg Q4W) N=366		Faricimab 6 mg PTI (Part 1: Aflibercept 2 mg Q4W) N=363	
	Proportion n(%)	%95 CI of Proportion	Proportion n(%)	%95 CI of Proportion
Week 68				
N	330		315	
Q4W	114 (34.5%)	29.4%, 39.7%	102 (32.4%)	27.2%, 37.6%
Q8W	66 (20.0%)	15.7%, 24.3%	55 (17.5%)	13.3%, 21.7%
Q12W	28 (8.5%)	5.5%, 11.5%	35 (11.1%)	7.6%, 14.6%
Q16W	122 (37.0%)	31.8%, 42.2%	123 (39.0%)	33.7%, 44.4%

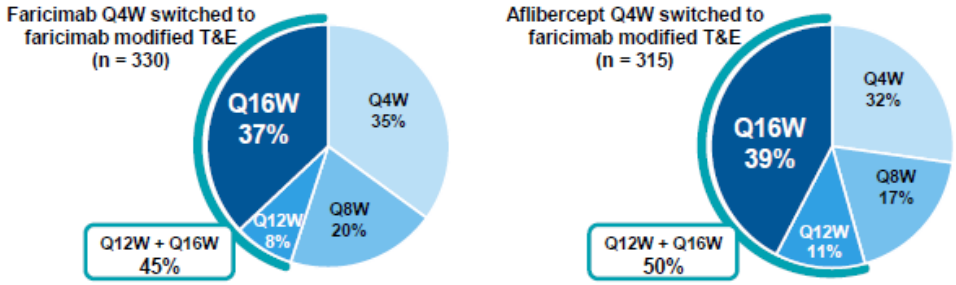

Figure 13: Proportion of Patients on Modified T&E Intervals at Week 68 in the COMINO study.

The majority (> 65%) of all patients extended their treatment intervals beyond Q4W with more than 45% of all patients extending their treatment intervals to Q12W or Q16W, regardless of previous treatment (11).

Both BALATON and COMINO showed that the majority of patients extended their treatment intervals after Week 24. The longer intervals between injections with faricimab in maintenance treatment, will lower the cost for the health system, alleviate capacity issues in the ophthalmology departments and place less treatment burden on the individual patient compared to current standard of treatment.

The expected health economic analysis is, due to the considered equivalent to existing treatments, a cost-minimization analysis that will be performed by the secretariat of the DMC. Roche expect the extended treatment comparison (det udvidede sammenlignings grundlag) to be updated due to the following two issues:

1. Duration of treatment/dosing frequency

Efficacy and safety are considered equal to the existing drugs in the treatment guideline, but frequency of treatment differs. Faricimab has a dosing interval of up to 16 weeks between injections in maintenance treatment. This must be reflected in the cost-minimization analysis due to

- lower cost of drugs due to longer treatment intervals

- lower cost for patients due to longer treatment intervals
- lower administration cost at ophthalmology departments

2. Number of treatments per vial (due to vial sharing) Current treatment of RVO is a combination of prefilled syringes and vials. Hospital pharmacies provide vial sharing to a certain level and deliver the drug in syringes to the ophthalmology departments. Vial sharing can be done as well with faricimab. Roche encourages that real world data from hospitals pharmacies on the exact number of treatments per vial for all drugs is included in the extended treatment comparison (det udvidede sammenligningsgrundlag) to ensure there is no discrepancy between the existing guideline estimations from Medicines Council and current Danish vial sharing practice.

6.2.2 Qualitative description of safety data

Safety results are primarily reported separately as ocular or non-ocular events. Overall, treatment exposure in all treatment arms was well balanced. The median duration of exposure was the same between both treatment arms, that is 20.1 weeks. The mean and median number of study drug administrations were the same in the faricimab Q4W and aflibercept Q4W arms namely 5.7 and 6.0, respectively (13).

Serious adverse events
Through Week 24, the total numbers of patients with at least one SAE were 32 (8.8%) in the faricimab Q4W arm and 33 (9.1%) in the aflibercept Q4W arm. The difference between treatment arms was -0.4% (95% CI: -4.8, 4.0). The relative risk (faricimab vs aflibercept) was 0.96 (95% CI: 0.61, 1.52) (12). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

A further description of serious ocular and non-ocular adverse events is presented below.

Serious ocular adverse events
Through Week 24, the incidence of serious ocular AEs in the study eye were comparable across treatment arms. The total numbers of patients with at least one serious ocular AE were 9 (2.5%) and 12 (3.3%) in the faricimab Q4W and aflibercept Q4W arms, respectively with a difference of -0.9% (95% CI: -3.7%, 1.9%) between treatment arms (8-10, 12). The most common serious ocular AEs (≥ 2 patients in any arm) (faricimab and aflibercept, respectively), were cystoid macular oedema (0.5% and 0.6%), retinal ischaemia (0.3% and 0.6%), retinal artery occlusion (0.5% and 0.3%), and uveitis (0.5% and 0%), with all other events occurring in single patients. By Week 24, the majority of serious ocular AEs had resolved or were resolving in both treatment arms and did not require a change in study treatment. The relative risk (faricimab vs aflibercept) was 0.76 (95% CI: 0.34, 1.68) (12). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 5% (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

Serious ocular AEs suspected by the investigator to be related to study treatment occurred in both treatment arms. In the faricimab Q4W arm, 2 patients experienced uveitis and 1 patient per event experienced the following (3 patients in total): cystoid macular oedema, retinal artery occlusion and retinal ischaemia. In the aflibercept Q4W arm, 1 patient experienced intraocular pressure increase and 1 patient experience retinal tear (12).

Serious non-ocular adverse events
Through Week 24, the incidence of non-ocular AEs was comparable between treatment arms. The total numbers of patients with at least one serious non-ocular AE were 22 (6.0%) and 23 (6.4%) in the faricimab Q4W and aflibercept Q4W arms, respectively with a difference of -0.3% (95% CI: -4.2%, 3.4%) between treatment arms (8-10, 12). The relative risk (faricimab vs. aflibercept) was 0.95 (95% CI: 0.54, 1.65) (12).

The incidence of serious non-ocular AEs suspected by the investigator to be related to the study treatment was low with 2 events of cerebrovascular accident in the same patient and 1 event of coronary artery disease in the faricimab Q4W arm, and 1 event of myocardial infarction and 1 event of acute myocardial infarction in the aflibercept Q4W arm (12).

Intraocular inflammation Events

In COMINO, intraocular inflammation events included events as mentioned for the BALATON study and includes events with an onset prior to Week 24 treatment or dose hold or if none onset prior to Day 168 (target day of Week 24 visit).

The proportion of patients who required treatment for intraocular Inflammation in the Study Eye through Week 24 was comparable between treatment arms. In the faricimab Q4W 3 patients (0.8%) (95% CI: 0.0%, 1.7%) required treatment while 2 patients (0.6%) (95% CI: 0.0%, 1.3%) required treatment for intraocular Inflammation in the study eye in the aflibercept Q4W treatment arm. The difference was 0.3% (95% CI: -0.9%, 1.5%) between treatment arms (with no rounding) (12). According to the Medicines Council protocol the significance of this outcome measure is termed *important* and the minimum clinically relevant difference is 3% (2). Therefore, the difference found in COMINO is below the value considered clinically relevant difference.

Qualitative description of safety profiles

Through week 24, the total numbers of patients with at least one AE were 174 (47.7%) and 200 (55.4%) in the faricimab Q4W and aflibercept Q4W arms, respectively (12).

Ocular adverse events
The incidence of ocular AEs in the study eye was comparable between the treatment arms. The total numbers of patients with at least one ocular AE were 84 (23.0%) and 100 (27.7%) in the faricimab Q4W and aflibercept Q4W arms, respectively (8-10, 12). The

most common ocular AEs that is ≥2% in any treatment arm (faricimab Q4W and aflibercept Q4W, respectively) were conjunctival haemorrhage (2.7% and 3.9%), intraocular pressure increase (2.2% and 3.6%) and vitreous detachment (3.0% and 2.5%) (12).

The majority of ocular events in the study eye were mild or moderate. However, in the faricimab Q4W arm, 6 patients (1.6%) experienced severe ocular events that is 2 patients had cystoid macular oedema, and 1 patient per event experienced the following: RVO (progression of CRVO), retinal artery occlusion, nonserious hypotony of eye, and macular ischaemia. A similar number of severe ocular events were seen in the aflibercept Q4W arm. Here 7 patients (1.9%) experienced severe ocular (1 patient per event) of the following; cystoid macular oedema, retinal exudates, retinal artery occlusion, retinal ischaemia, retinal artery embolism, intraocular pressure increase and endophthalmitis (12).

The incidence of ocular AEs suspected by the investigator to be related to the study treatment was low. The incidence was higher in the faricimab Q4W arm compared with the aflibercept Q4W arm namely 14 patients (3.8%) and 8 patients (2.2%), respectively. The overall most common ocular AE related to study treatment was intraocular pressure increase with 1 patient (0.3%) in the faricimab Q4W and 4 patients (1.1%) in the aflibercept Q4W arm. 3 patients (0.8%) had ocular AEs leading to treatment discontinuation in the faricimab Q4W while it was the case for 2 patients (0.6%) in the aflibercept Q4W arms (12).

Lastly, the incidence of ocular AESIs in the study eye was low and comparable across treatment arms with 8 patients (2.2%) and 12 patients (3.3%) in the faricimab Q4W and aflibercept Q4W arms, respectively (8, 9, 12). For 1 patient in the faricimab Q4W arm, and 2 patients in the aflibercept Q4W arm, the ocular AESIs were considered to be related to study treatment (12).

Non-ocular adverse events
Through Week 24, the incidence of non-ocular AEs was comparable between treatment arms. Total numbers of patients with at least one adverse event were 121 (33.2%) and 134 (37.1%) in the faricimab Q4W and aflibercept Q4W arms, respectively. There was no consistent pattern observed across treatment arms in regards to the most common non-ocular AEs (12).

The incidence of non-ocular AEs suspected by the investigator to be related to the study treatment was low with 2 patients (0.5%) and 3 patients (0.8%) in the faricimab Q4W and aflibercept Q4W arms, respectively. All events occurred in single patients with 1 patient experiencing 2 events of cerebrovascular accident. Similarly, the incidence of AEs leading to study discontinuation was low across treatment arms with 1 patient (0.3%) and 3 patient (0.8%) in the faricimab Q4W and aflibercept Q4W arms, respectively. No non-occular AESIs were reported (12).

Deaths
1 patient (0.3%) in the faricimab Q4W arm and 2 patients (0.6%) in the aflibercept Q4W arm experienced an AE with a fatal outcome. The causes of death were pneumonia for the patient in the faricimab Q4W arm and myocardial infarction for the patients in the

aflibercept Q4W arm. None of the deaths was considered related to study treatment by the investigators (12).

Safety data from Part 1 of COMINO (baseline through Week 24) indicated that faricimab Q4W had a comparable safety profile to aflibercept Q4W, and faricimab was generally well tolerated. An expected increased incidence of AEs and SAEs was observed in Part 2 (Week 24 through Week 72) compared to Part 1 (baseline through Week 24) which are 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 and faricimab continued to be generally well tolerated with a the low incidence of AEs leading to study treatment withdrawal (Table 11) (11, 12).

Table 11: Safety Summary through Week 72 by Study Part, Safety-Evaluable Population in COMINO study.

	Faricimab 6 mg Q4W Part 1 (N=365)	Aflibercept 2 mg Q4W Part 1 (N=361)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)
Total number of patients with at least one AE	178 (48.8%)	200 (55.4%)	247 (68.8%)	227 (66.4%)
Total number of AEs	423	466	782	723
Total number of patients with at least one SAE	32 (8.8%)	34 (9.4%)	55 (15.3%)	51 (14.9%)
Total number of SAEs	40	59	79	84
Total number of deaths	1 (0.3%)	2 (0.6%)	4 (1.1%)	1 (0.3%)
Total number of patients withdrawn from study due to an AE	2 (0.5%)	4 (1.1%)	9 (2.5%)	4 (1.2%)
Total number of patients withdrawn from study treatment due to an AE	3 (0.8%)	3 (0.8%)	8 (2.2%)	6 (1.8%)
Total number of patients with at least one AESI	9 (2.5%)	13 (3.6%)	22 (6.1%)	9 (2.6%)
Ocular events: study eye total number of patients with at least one				
AE	89 (24.4%)	98 (27.1%)	130 (36.2%)	118 (34.5%)
SAE	9 (2.5%)	13 (3.6%)	26 (7.2%)	12 (3.5%)
AE leading to withdrawal from study treatment	3 (0.8%)	2 (0.6%)	5 (1.4%)	3 (0.9%)
Treatment related AEs	15 (4.1%)	6 (1.7%)	14 (3.9%)	11 (3.2%)
Treatment related SAEs	3 (0.8%)	2 (0.6%)	4 (1.1%)	0
AE of Special Interest	8 (2.2%)	12 (3.3%)	21 (5.8%)	9 (2.6%)
Drop in VA score >=30	6 (1.6%)	6 (1.7%)	15 (4.2%)	7 (2.0%)
Associated with severe IOI	0	0	0	1 (0.3%)
Intervention req. to prevent permanent vision loss	2 (0.5%)	6 (1.7%)	6 (1.7%)	1 (0.3%)
Suspected transmission of infectious agent by study drug	0	0	0	0
Ocular events: fellow eye total number of patients with at least one				
AE	31 (8.5%)	33 (9.1%)	70 (19.5%)	51 (14.9%)
SAE	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
AE of Special Interest	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Drop in VA score >=30	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Non-ocular events total number of patients with at least one				
AE	123 (33.7%)	134 (37.1%)	191 (53.2%)	174 (50.9%)
SAE	22 (6.0%)	23 (6.4%)	30 (8.4%)	41 (12.0%)
AE leading to withdrawal from study treatment	0	1 (0.3%)	3 (0.8%)	3 (0.9%)
AE of Special Interest	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	5 (1.4%)	5 (1.4%)	8 (2.2%)	6 (1.8%)
Non-fatal MI	1 (0.3%)	2 (0.6%)	3 (0.8%)	2 (0.6%)
Non-fatal Stroke	4 (1.1%)	2 (0.6%)	3 (0.8%)	3 (0.9%)
Death	0	1 (0.3%)	2 (0.6%)	1 (0.3%)

Serious ocular adverse events through Week 72

The total numbers of patients through Week 72 with at least one serious ocular AE were 26 patients (7.2%) and 12 patients (3.5%) in the faricimab Q4W to faricimab PTI arm and the aflibercept Q4W to faricimab PTI arm, respectively (Table 12) (12).

Table 12: Serious Ocular Adverse Events by Preferred Terms in the Study Eye through Week 72 by Study Part, Safety-Evaluable Population in COMINO study.

MedDRA Preferred Term	Faricimab 6 mg Q4W Part 1 (N=365)	Aflibercept 2 mg Q4W Part 1 (N=361)	Faricimab 6 mg Q4W to Faricimab 6 mg PTI Part 2 (N=359)	Aflibercept 2 mg Q4W to Faricimab 6 mg PTI Part 2 (N=342)
Total number of patients with at least one adverse event	9 (2.5%)	13 (3.6%)	26 (7.2%)	12 (3.5%)
Total number of events	13	13	28	12
Retinal vein occlusion	2 (0.5%)	1 (0.3%)	5 (1.4%)	3 (0.9%)
Cystoid macular oedema	2 (0.5%)	2 (0.6%)	5 (1.4%)	1 (0.3%)
Retinal artery occlusion	2 (0.5%)	1 (0.3%)	0	2 (0.6%)
Macular oedema	0	1 (0.3%)	3 (0.8%)	0
Retinal ischaemia	1 (0.3%)	2 (0.6%)	1 (0.3%)	0
Retinal tear	0	2 (0.6%)	1 (0.3%)	0
Uveitis	2 (0.5%)	0	1 (0.3%)	0
Macular hole	0	0	1 (0.3%)	1 (0.3%)
Retinal neovascularisation	0	0	1 (0.3%)	1 (0.3%)
Endophthalmitis	0	1 (0.3%)	0	1 (0.3%)
Retinal artery embolism	0	1 (0.3%)	1 (0.3%)	0
Macular ischaemia	1 (0.3%)	0	1 (0.3%)	0
Vitreous haemorrhage	1 (0.3%)	0	1 (0.3%)	0
Cataract	0	0	0	1 (0.3%)
Glaucoma	0	0	0	1 (0.3%)
Iris neovascularisation	0	0	0	1 (0.3%)
Epiretinal membrane	0	0	1 (0.3%)	0
Iridocyclitis	0	0	1 (0.3%)	0
Posterior capsule opacification	0	0	1 (0.3%)	0
Retinal detachment	0	0	1 (0.3%)	0
Visual acuity reduced	0	0	1 (0.3%)	0
Vitritis	0	0	1 (0.3%)	0
Intraocular pressure increased	0	1 (0.3%)	0	0
Non-infectious endophthalmitis	0	1 (0.3%)	0	0
Eye injury	1 (0.3%)	0	0	0
Rhegmatogenous retinal detachment	1 (0.3%)	0	0	0

The most common serious ocular AEs in the study eye (≥2 patients in any treatment arm) included that in the faricimab Q4W to faricimab PTI arm and the aflibercept Q4W to faricimab PTI arm 5 patients (1.4%) and 3 patients (0.9%) experienced retinal vein occlusion, and 5 patients (1.4%) and 1 patient (0.3%) experienced cystoid macular oedema, respectively. Furthermore, 3 patients (0.8%) experienced macular oedema in the faricimab Q4W to faricimab PTI arm, and 2 patients (0.6%) experienced retinal artery occlusion in the aflibercept Q4W to faricimab PTI arm (Table 12) (12).

By Week 72, the majority of serious ocular AEs had resolved or were resolving in both treatment arms.

The higher rates of ocular SAEs in Part 2 were driven by cystoid macular oedema, retinal vein occlusion and macular oedema events and were associated with worsening of study disease. All were assessed as not suspected to be related to study treatment.

4 patients experienced the serious ocular AEs uveitis, epiretinal membrane, iridocyclitis, and vitritis (1 patient each) in Part 2 of COMINO. These events were suspected by the investigator to be related to study treatment and occurred in the faricimab Q4W to faricimab PTI only (12).

Conclusion

Overall, safety data from COMINO demonstrated that faricimab is well tolerated and has a comparable safety profile to aflibercept through Week 24. No new or unexpected safety signals were identified. Further, faricimab showed no change in the safety profile from Week 24 to 72.

6.2.3 Method of synthesis

The COMINO study provides a direct comparison between faricimab and aflibercept.

6.2.4 Results from the comparative analysis

The COMINO study provides a direct comparison between faricimab and aflibercept and results can be used to address the clinical question. The comparative efficacy results for faricimab vs. aflibercept have been presented in section 6.2.1. The comparative safety results for faricimab vs. aflibercept have been presented in section 6.2.2.

Table 13: Results from COMINO: Direct comparison of faricimab vs. aflibercept for the ITT and safety population.

Outcome measure	Faricimab (N=366)	Aflibercept (N=363)	Result
Proportion of patients with visual loss of less than 15 ETDRS- letters, Week 24	96.2% (95% CI: 94.3%, 98.1)	96.7% (95% CI: 94.9%, 98.5)	Absolute difference: -0.5% (95% CI: -3.2%, 2.2%)
Mean change in number of ETDRS letters, Week 24	16.9 ETDRS letters (95% CI: 15.4, 18.3)	17.3 ETDRS letters (95% CI: 15.9, 18.8)	Absolute difference: -0.4 ETDRS letters (95% CI: -2.5, 1.6)
Mean change in central subfield thickness measured by OCT, Week 24	−461.6 µm (95% CI: -471.4, -451.9)	−448.8 µm (95% CI: -458.6, -439.0)	Absolute difference: −12.8 µm (95% CI: −26.7, 1.0)
Mean change in patient-experienced quality of life rated by VFQ, Week 24	6.9 points (95% CI: 5.8, 8.0)	8.1 points (95% CI: 7.0, 9.2)	Absolute difference: −1.2 points (95% CI:-2.7, 0.3)
Proportion of patients that experience serious side effects, Week 24	32/365 (8.8%)	33/361 (9.1%)	Absolute difference: -0.4% (95% CI: -4.8%, 4.0%) Relative risk: 0.96 (95% CI: 0.61, 1.52)
Proportion of patients that require treatment for inflammation, Week 24	0.8% (95% CI: 0.0%, 1.7%)	0.6% (95% CI: 0.0%, 1.3%)	Absolute risk: 0.3% (95% CI: -0.9%, 1.5%)

Conclusion

Danish RVO patients eligible for treatment with faricimab are currently treated with either ranibizumab or aflibercept according to the treatment guideline and recommendation issued by the DMC in 2020 and 2021, respectively (7). Both BALATON and COMINO demonstrated early and sustained vision improvement with faricimab, with both studies meeting their primary endpoints of non-inferior vision gains compared to aflibercept, the current standard of care.

In both studies, faricimab was generally well tolerated and the safety profile was consistent with previous studies. Importantly, both studies showed an increased durability of effect of faricimab in relation to comparators without compromising efficacy. Hence, patients treated with faricimab extended their treatment intervals up to 16 weeks while maintaining the vision gains achieved in the first 24 weeks of the studies. This is the first time that vision and anatomical improvements have been maintained for more than a year using a personalized treat-and-extend dosing regimen in global phase III studies for both BRVO and CRVO.

Consequently, the better vascular stability afforded by the unique dual mechanism of action of faricimab provides comprehensive disease control allowing physicians to extend treatment intervals up to every 16 weeks, thereby alleviating the burden that frequent injections currently impose on patients, caregivers, physicians, and the healthcare system.

7. References

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Appendix A. Main characteristics of studies included

Table 14: Main characteristic of the BALATON study

Trial name: BALATON	NCT number: NCT04740905
Objective	To evaluate the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24, followed by a double-masked period of study without active control to evaluate faricimab administered according to a personalized treatment interval dosing regimen in participants with macular edema due to branch retinal vein occlusion.
Publications – title, author, journal, year	Efficacy and Safety of Faricimab for Macular Edema due to Retinal Vein Occlusion: 24-Week Results from the BALATON and COMINO Trials, Tadayoni et al., Ophthalmology, 2024. (8) Faricimab in RVO: Results From the BALATON and COMINO Phase 3 Studies. Tadayoni et al., presented at the Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress, February 2023. (9) Efficacy and Safety of Faricimab in Macular Edema Due to Retinal Vein Occlusion: 24-Week Results From the Phase 3 BALATON and COMINO Trials, Khanani AM et al., presented at Macula Society 46th Annual Meeting, 2023. (10) Faricimab in RVO: 72-Week Results From the BALATON and COMINO Phase 3 Studies. Tadayoni et al., Angiogenesis, Exudation, and Degeneration 2024 Virtual Congress, February 2024. (9, 11) BALATON and COMINO: Phase III Randomized Clinical Trials of Faricimab for Retinal Vein Occlusion: Study Design and Rationale, Hattenbach LO et al. Ophthalmology Science, 2023. (14)
Study type and design	Phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group study. It composes of two parts: Part 1 (Day 1 through Week 24) compares faricimab every 4 weeks versus aflibercept every 4 weeks and Part 2 (Week 24 through Week 72) evaluates faricimab administered at masked treatment intervals of Q4W to every 16 weeks based on personalized treatment interval dosing criteria.
Sample size (n)	553
Main inclusion criteria	• Foveal center-involved macular edema due to branch retinal vein occlusion, diagnosed no longer than 4 months prior to the screening visit • Best-corrected visual acuity (BCVA) of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent) on Day 1

	• Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis • For women of childbearing potential: agreement to remain abstinent or use contraception, and agreement to refrain from donating eggs during the treatment period and for 3 months after the final dose of study treatment
Main exclusion criteria	• Any major illness or major surgical procedure within 1 month before screening • Uncontrolled blood pressure • Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1 • Pregnant or breastfeeding, or intending to become pregnant during the study 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 • Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than macular edema due to RVO in the study eye (e.g., ischemic maculopathy, Irvine-Gass syndrome, foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions) • Macular laser (focal/grid) in the study eye at any time prior to Day 1 • Panretinal photocoagulation in the study eye within 3 months prior to Day 1 or anticipated within 3 months of study start on Day 1 • Any prior or current treatment for macular edema; macular neovascularization, including diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD); and vitreomacular-interface abnormalities, including, but not restricted to, Intravitreal treatment with anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection • Any prior intervention with verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or vitreo-retinal surgery including sheatotomy • Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex) and fluocinolone acetonide intravitreal implant (Iluvien) Ocular Exclusion Criteria for Both Eyes: • Prior Intravitreal administration of faricimab in either eye • History of idiopathic or autoimmune-associated uveitis in either eye • Active periocular, ocular or intraocular inflammation or infection (including suspected) in either eye on Day 1
Intervention	276 patients will: In part 1 (from week 1 to week 20), receive 6 mg faricimab once every 4 weeks (a total of 6 injections).

	553 (276+277) patients will: In Part 2 (from Week 24 to Week 68), receive 6 mg faricimab according to a personalized treatment interval dosing regimen.
Comparator(s)	277 patients will: In part 1 (from week 1 to week 20), received 2 mg aflibercept once every 4 weeks (a total of 6 injections).
Follow-up time	CCOD of July 6, 2022 – up to Week 24 follow-up. CCOD of August 30, 2023 – up to Week 72 follow-up.
Primary, secondary and exploratory endpoints	Primary endpoint • Change From Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 24 [Time Frame: From Baseline through Week 24] Secondary endpoints • Change from baseline in BCVA in the study eye at specified time points through Week 24 (part 1) and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Change from week 24 in BCVA in the study eye at specified time points through Week 72 (part 2) [Time Frame: Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients gaining ≥15 letters in BCVA from baseline in the study eye at Week 24 (part 1) [Time Frame: Baseline and Week 24] • Proportion of patients gaining ≥15, ≥10, ≥5 or >0 Letters in BCVA from baseline in the study eye at specified time points through week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients avoiding a loss of ≥15 Letters in BCVA from baseline in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Proportion of patients avoiding a Loss of ≥15, ≥10, ≥5 or >0 Letters in BCVA from baseline in the study eye at specified time points through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients achieving ≥84 Letters in BCVA (20/20 or Better Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients achieving ≥69 Letters in BCVA (20/40 or Better Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]

- Proportion of patients achieving ≤38 Letters in BCVA (20/200 or Worse Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Change from baseline in Central Subfield Thickness in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of macular edema, defined as CST of < 325 µm, in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2)[Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of intraretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of subretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of intraretinal fluid and subretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Change from baseline in National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) Composite Score at Week 24 (part 1) [Time Frame: Baseline and Week 24] and through Week 72 (part 2) [Time Frame: Baseline and Weeks 24, 48, and 72]
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68 [Time Frame: Week 68]

Exploratory endpoint

- Proportion of patients with absence of macular ischemic non perfusion (capillary loss) on FFA over time (where 'absence' is defined as an area of ischemic non perfusion within the macula of 0 to 0.1 mm^2)
- Change from baseline in the area of ischemic non perfusion within the macula on FFA over time
- Proportion of patients with absence of macular leakage on FFA over time (where 'absence' is defined as an area of leakage within the macula of 0 mm^2)
- Change from baseline in vascular leakage area on FFA in the macula over time
- Proportion of patients requiring panretinal photocoagulation
- Change from baseline in NEI VFQ-25 near activities-subscale score and distance activities-subscale scores over time [Time Frame: Baseline, Weeks 24, 48, and 72]

	• Number of study drug injections received in the study eye from Week 24 through Week 72 [Time Frame: From Week 24 to Week 72] • Incidence and Severity of Ocular Adverse Events, With Severity Determined According to Adverse Event Severity Grading Scale [Time Frame: From Baseline until end of study (up to 72 weeks)] • Incidence and Severity of Non-Ocular Adverse Events, With Severity Determined According to Adverse Event Severity Grading Scale [Time Frame: From Baseline until end of study (up to 72 weeks)] • Plasma Concentration of Faricimab Over Time [Time Frame: Predose at Day 1, Weeks 4, 24, 28, 52, and 72] • Number of Participants With Anti-Drug Antibodies (ADAs) to Faricimab at Baseline and During the Study [Time Frame: Predose at Day 1 (Baseline), Weeks 4, 24, 28, 52, and 72] **Endpoints included in this application:** As per DMC's protocol for treatment guideline for RVO • Proportion of patients with visual loss of less than 15 ETDRS- letters • Mean change in number of ETDRS-letters • Mean change in central subfield thickness measured by OCT • Proportion of patients that experience serious side effects • Qualitative description of safety profile • Patient-reported outcomes
Method of analysis	Visual stabilisation was analysed using Cochran-Mantel-Haenszel (CMH). Confidence intervals (Cl) are two-sided and at the 95.03% level. Visual acuity, mean difference: BCVA was assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters. The analysis was performed using a mixed model for repeated measures (MMRM) which 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 randomisation stratification factors as fixed effects. CIs are two-sided and at the 95.03% level. Central subfield thickness was analyzed using a MMRM with two-sided Cl of 95.03% level. Patient reported outcome data were collected using NEI VFQ-25 and analysed using a MMRM.
Subgroup analyses	N/A
Other relevant information	N/A

Table 15: Main characteristic of the COMINO study

Trial name: COMINO	NCT number: NCT04740931
Objective	To evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by intravitreal injection at 4-week intervals until Week 24, followed by a double-masked period of study without active control to evaluate faricimab administered according to a personalized treatment interval dosing regimen in patients with macular edema due to central retinal vein occlusion or hemiretinal vein occlusion.
Publications – title, author, journal, year	Efficacy and Safety of Faricimab for Macular Edema due to Retinal Vein Occlusion: 24-Week Results from the BALATON and COMINO Trials, Tadayoni et al., Ophthalmology, 2024. (8) Faricimab in RVO: Results From the BALATON and COMINO Phase 3 Studies. Tadayoni et al., presented at the Angiogenesis, Exudation, and Degeneration 2023 Virtual Congress, February 2023. (9) Efficacy and Safety of Faricimab in Macular Edema Due to Retinal Vein Occlusion: 24-Week Results From the Phase 3 BALATON and COMINO Trials, Khanani AM et al., presented at Macula Society 46th Annual Meeting, 2023. (9, 10) Faricimab in RVO: 72-Week Results From the BALATON and COMINO Phase 3 Studies. Tadayoni et al., Angiogenesis, Exudation, and Degeneration 2024 Virtual Congress, February 2024. (11) ALATON and COMINO: Phase III Randomized Clinical Trials of Faricimab for Retinal Vein Occlusion: Study Design and Rationale, Hattenbach LO et al. Ophthalmology Science, 2023. (14)
Study type and design	Phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group study. It composes of two parts: Part 1 (Day 1 through Week 24) compares faricimab every 4 weeks versus aflibercept every 4 weeks and Part 2 (Week 24 through Week 72) evaluates faricimab administered at masked treatment intervals of Q4W to every 16 weeks based on personalized treatment interval dosing criteria.
Sample size (n)	729
Main inclusion criteria	• Foveal center-involved macular edema due to central retinal vein occlusion or hemiretinal vein occlusion, diagnosed no longer than 4 months prior to the screening visit • Best-corrected visual acuity (BCVA) of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent) on Day 1 • Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis • For women of childbearing potential: agreement to remain abstinent or use contraception, and agreement to refrain from donating eggs during the treatment period and for 3 months after the final dose of study treatment

Main exclusion criteria	• Any major illness or major surgical procedure within 1 month before screening • Uncontrolled blood pressure • Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1 • Pregnant or breastfeeding, or intending to become pregnant during the study 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 • Any current ocular condition which, in the opinion of the investigator, is currently causing or could be expected to contribute to irreversible vision loss due to a cause other than macular edema due to RVO in the study eye (e.g., ischemic maculopathy, Irvine-Gass syndrome, foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions) • Macular laser (focal/grid) in the study eye at any time prior to Day 1 • Panretinal photocoagulation in the study eye within 3 months prior to Day 1 or anticipated within 3 months of study start on Day 1 • Any prior or current treatment for macular edema; macular neovascularization, including diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD); and vitreomacular-interface abnormalities, including, but not restricted to, Intravitreal treatment with anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air or periocular injection • Any prior intervention with verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or vitreo-retinal surgery including sheatotomy • Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex) and fluocinolone acetonide intravitreal implant (Iluvien) Ocular Exclusion Criteria for Both Eyes: • Prior Intravitreal administration of faricimab in either eye • History of idiopathic or autoimmune-associated uveitis in either eye • Active periocular, ocular or intraocular inflammation or infection (including suspected) in either eye on Day 1
Intervention	366 patients will: In part 1 (from week 1 to week 20), receive 6 mg faricimab once every 4 weeks (a total of 6 injections). 729 (366+363) patients will: In Part 2 (from Week 24 to Week 68), receive 6 mg faricimab according to a personalized treatment interval dosing regimen.
Comparator(s)	363 patients will: In part 1 (from week 1 to week 20), received 2 mg aflibercept once every 4 weeks (a total of 6 injections).

Follow-up time	CCOD of August 9, 2022 – up to Week 24 follow-up. CCOD of August 29, 2023 – up to Week 72 follow-up.
Primary, secondary and exploratory endpoints	Primary endpoint • Change From Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 24 [Time Frame: From Baseline through Week 24] Secondary endpoints • Change from baseline in BCVA in the study eye at specified time points through Week 24 (part 1) and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Change from week 24 in BCVA in the study eye at specified time points through Week 72 (part 2) [Time Frame: Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients gaining ≥15 letters in BCVA from baseline in the study eye at Week 24 (part 1) [Time Frame: Baseline and Week 24] • Proportion of patients gaining ≥15, ≥10, ≥5 or >0 Letters in BCVA from baseline in the study eye at specified time points through week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients avoiding a loss of ≥15 Letters in BCVA from baseline in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] • Proportion of patients avoiding a Loss of ≥15, ≥10, ≥5 or >0 Letters in BCVA from baseline in the study eye at specified time points through Week 24 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients achieving ≥84 Letters in BCVA (20/20 or Better Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients achieving ≥69 Letters in BCVA (20/40 or Better Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Proportion of patients achieving ≤38 Letters in BCVA (20/200 or Worse Snellen Equivalent) in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72] • Change from baseline in Central Subfield Thickness in the study eye at specified time points through Week 24 (part 1) [Time Frame:

Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]

- Proportion of patients with absence of macular edema, defined as CST of < 325 µm, in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2)[Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of intraretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of subretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 (part 2) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Proportion of patients with absence of intraretinal fluid and subretinal fluid in the study eye at specified time points through Week 24 (part 1) [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, and 24] and through Week 72 [Time Frame: Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72]
- Change from baseline in National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) Composite Score at Week 24 (part 1) [Time Frame: Baseline and Week 24] and through Week 72 (part 2) [Time Frame: Baseline and Weeks 24, 48, and 72]
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68 [Time Frame: Week 68]

Exploratory endpoint

- Proportion of patients with absence of macular ischemic non perfusion (capillary loss) on FFA over time (where 'absence' is defined as an area of ischemic non perfusion within the macula of 0 to 0.1 mm^2)
- Change from baseline in the area of ischemic non perfusion within the macula on FFA over time
- Proportion of patients with absence of macular leakage on FFA over time (where 'absence' is defined as an area of leakage within the macula of 0 mm^2)
- Change from baseline in vascular leakage area on FFA in the macula over time
- Proportion of patients requiring panretinal photocoagulation
- Change from baseline in NEI VFQ-25 near activities-subscale score and distance activities-subscale scores over time [Time Frame: Baseline, Weeks 24, 48, and 72]
- Number of study drug injections received in the study eye from Week 24 through Week 72 [Time Frame: From Week 24 to Week 72]
- Incidence and Severity of Ocular Adverse Events, With Severity Determined According to Adverse Event Severity Grading Scale [Time Frame: From Baseline until end of study (up to 72 weeks)]

	• Incidence and Severity of Non-Ocular Adverse Events, With Severity Determined According to Adverse Event Severity Grading Scale [Time Frame: From Baseline until end of study (up to 72 weeks)] • Plasma Concentration of Faricimab Over Time [Time Frame: Predose at Day 1, Weeks 4, 24, 28, 52, and 72] • Number of Participants With Anti-Drug Antibodies (ADAs) to Faricimab at Baseline and During the Study [Time Frame: Predose at Day 1 (Baseline), Weeks 4, 24, 28, 52, and 72] **Endpoints included in this application:** As per DMC's protocol for treatment guideline for RVO • Proportion of patients with visual loss of less than 15 ETDRS- letters • Mean change in number of ETDRS-letters • Mean change in central subfield thickness measured by OCT • Proportion of patients that experience serious side effects • Qualitative description of safety profile • Patient-reported outcomes
Method of analysis	Visual stabilisation was analysed using Cochran-Mantel-Haenszel (CMH). Cls are two-sided and at the 95.03% level. Visual acuity, mean difference: BCVA was assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters. The analysis was performed using a mixed model for repeated measures (MMRM) which 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 randomisation stratification factors as fixed effects. CIs are two-sided and at the 95.03% level. Central subfield thickness was analyzed using a MMRM with two-sided Cl of 95.03% level. Patient reported outcome data were collected using NEI VFQ-25 and analysed using a MMRM.
Subgroup analyses	N/A
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 16: Results from BALATON (12)

Results of BALATON (NCT04740905)											
				Estimated absolute difference in effect			Estimated relative difference in effect*			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Visual acuity, visual stabilisation measured as proportion of patients with visual loss of less than 15 ETDRS- letters	Faricimab	276	99.6% (98.9%-100.0%)	1.1%	−0.5%-2.6%	0.1816	-	-	-	The weighted estimate is 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 Last Observation Carried Forward (LOCF). Proportion is calculated after LOCF imputation. N in the header is the number of patients randomized (used as the denominator when calculating proportion). 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 are excluded.	(8, 12)
	Aflibercept	277	98.6% (97.2%-99.9%)								(8, 12)

Results of BALATON (NCT04740905)											
				Estimated absolute difference in effect			Estimated relative difference in effect*			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Visual acuity, mean difference measured as mean change in number of ETDRS-letters	Faricimab	276	16.9 ETDRS letters (15.7, 18.1)	-0.6 ETDRS letters	-2.2, 1.1	0.4978	-	-	-	For the Mixed-Model Repeated-Measures (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.	(8, 12)
	Aflibercept	277	17.5 ETDRS letters (16.3, 18.6)								(8, 12)
Central subfield thickness measured as mean change in central subfield thickness measured by OCT	Faricimab	276	−311.4 µm (-316.4, -306.4)	−7.0 µm	−14.1, 0.0	0.0495	-	-	-	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.	(8, 12)
	Aflibercept	277	−304.4 µm (-309.3, -299.4)								(8, 12)

Results of BALATON (NCT04740905)												
				Estimated absolute difference in effect			Estimated relative difference in effect*			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										95% CI is a rounding of 95.03% CI.	
Quality of life measured as mean change in patient-experienced quality of life rated by VFQ	Faricimab	276	5.6 points (4.5, 6.7)	−0.4 points	−1.9, 1.1	0.6370	-	-	-	For the ANCOVA analysis, the model uses the non-missing change from baseline in BCVA at Weeks 24 as the response variables adjusted for the treatment group, baseline NEI VFQ-25 Composite Score(continuous), baseline BCVA score (<=54 letters vs. >=55 letters) and region (U.S. and Canada, Asia, and the rest of the world). Observed NEI VFQ-25 assessments were used regardless of the occurrence of intercurrent events. Missing data were not imputed. 95% CI is a rounding of 95.03% CI.	(8, 12)
	Aflibercept	277	5.9 points (4.8, 7.1)								(8, 12)

* Relative risk is not calculated due to adjusted numbers.

Table 17: Results from COMINO

Results of **COMINO (NCT04740931)**											
				Estimated absolute difference in effect			**Estimated relative difference in effect***			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Visual acuity, visual stabilisation measured as proportion of patients with visual loss of less than 15 ETDRS- letters	Faricimab	366	96.2% (94.3%, 98.1%)	–0.5%	–3.2%, 2.2%	0.7170	-	-	-	Same as described for the BALATON study in Table 16	(8, 12)
	Aflibercept	363	96.7% (94.9%, 98.5%)								(8, 12)
Visual acuity, mean difference measured as mean change in number of ETDRS-letters	Faricimab	366	16.9 (15.4, 18.3)	-0.4	-2.5, 1.6	0.6715	-	-	-	Same as described for the BALATON study in Table 16	(8, 12)
	Aflibercept	363	17.3 (15.9, 18.8)								(8, 12)
Central subfield thickness measured as mean	Faricimab	366	-461.6 (-471.4, -451.9)	-12.8	-26.7, 1.0	0.0684	-	-	-	Same as described for the BALATON study in Table 16	(8, 12)

change in central subfield thickness measured by OCT	Aflibercept	363	-448.8 (-458.6, -439.0)								(8, 12)
Quality of life measured as mean change in patient-experienced quality of life rated by VFQ	Faricimab	366	6.9 (5.8, 8.0)	-1.2	-2.7, 0.3	0.1088	-	-	-	Same as described for the BALATON study in Table 16	(8, 12)
	Aflibercept	363	8.1 (7.0, 9.2)								(8, 12)

* Relative risk is not calculated due to adjusted numbers.

Appendix C. Comparative analysis of efficacy

N/A.

All comparative results can be found in Appendix B as both BALATON and COMINO provides a direct comparison.

Appendix D. Literature searches for the clinical assessment

N/A.

No literature search has been performed. because the BALATON study and the COMINO study provides a sufficient base for comparison with current Danish standard of care.

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