AMERICAN ACADEMY OF OPHTHALMOLOGY®

BALATON and COMINO: Phase III Randomized Clinical Trials of Faricimab for Retinal Vein Occlusion

Study Design and Rationale

Lars-Olof Hattenbach, MD, PhD,[1] Francis Abreu, PhD,[2] Pablo Arrisi, PhD,[3] Karen Basu, PhD,[4] Carl J. Danzig, MD,[5,6] Robyn Guymer, MD, PhD,[7] Zdenka Haskova, MD, PhD,[2] Jeffrey S. Heier, MD,[8] Aachal Kotecha, PhD,[3] Ying Liu, PhD,[2] Anat Loewenstein, MD,[9] András Seres, MD,[10] Jeffrey R. Willis, MD, PhD,[2] Charles C. Wykoff, MD, PhD,[11] Liliana P. Paris, MD, PhD[2]

Purpose: Dual inhibition of angiopoietin-2 and VEGF-A with faricimab (Vabysmo) offers excellent visual acuity gains with strong durability in patients with diabetic macular edema (ME) and neovascular age-related macular degeneration. The phase III BALATON/COMINO (NCT04740905/NCT04740931) trials will investigate the efficacy, safety, and durability of faricimab in patients with ME due to retinal vein occlusion (RVO).

Design: Two identically designed global, randomized, double-masked, active comparator–controlled studies.

Participants: Anti-VEGF treatment-naive patients with branch, central, or hemiretinal RVO.

Methods: Patients were randomized to 6 monthly injections of faricimab 6.0 mg or aflibercept 2.0 mg. From weeks 24 to 72, all patients received faricimab 6.0 mg administered in up to 16-week intervals using an automated treatment algorithm to generate a treat-and-extend–based personalized treatment interval dosing regimen. Personalized treatment interval adjustments were based on changes in central subfield thickness (CST) and best-corrected visual acuity (BCVA).

Main Outcome Measures: Primary end point was noninferiority of faricimab versus aflibercept in mean change from baseline in BCVA (week 24; noninferiority margin: 4 letters). Secondary end points (weeks 0–24) were mean change from baseline in BCVA, CST, and National Eye Institute Visual Function Questionnaire 25 composite score; proportion of patients gaining or avoiding loss of $\geq$ 15/$\geq$ 10/$\geq$ 5/$>$ 0 letters. Secondary end points (weeks 24–72) were treatment durability (week 68); continuation of weeks 0 to 24 end points. Ocular/nonocular adverse events will be assessed.

Results: In total, 1282 patients across 22 countries were enrolled (BALATON, 553 patients, 149 centers; COMINO, 729 patients, 193 centers).

Conclusions: Using a novel automated interval algorithm, BALATON/COMINO will evaluate the efficacy and safety of faricimab for ME secondary to RVO and provide key insights into how to personalize treatment.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Supplemental material available at www.ophthalmologyscience.org.

Retinal vein occlusion (RVO), including branch (BRVO), hemiretinal (HRVO), and central (CRVO) RVO, is a common retinal vascular disease that can result in varying degrees of visual loss.[1,2] Estimates from a 2018 analysis suggested there were approximately 28.1 million adults with RVO worldwide, including 23.4 million with BRVO and 4.7 million with CRVO.[3] Of note, after diabetic retinopathy, RVO is the second leading cause of retinal vascular disease and a common cause of vision loss.[2,4]

Macular edema (ME) is a leading cause of vision loss in RVO[5,6]; hence, treatment aimed at resolving ME is often utilized. To this end, intravitreal anti-VEGF injection is the most common first-line treatment for ME due to RVO.[7,8] Although efficacious, some patients with RVO require frequent long-term injections and monitoring to maintain the gains achieved during initial intensive treatment.[9,10] Early intervention has also been shown to be particularly important for better treatment outcomes.[10–13] Further to

https://doi.org/10.1016/j.xops.2023.100302
ISSN 2666-9145/23

the clinical trial findings, data from clinical-setting studies suggest many patients with RVO (both BRVO and CRVO) do not achieve the gains observed in clinical trials, at least partially due to suboptimal injection frequency.[14–19] Indeed, in a recent analysis, patients with CRVO from clinical-setting studies were found, on average, to be monitored less frequently, to receive fewer anti-VEGF injections, and to not have achieved the vision gains observed in patients with CRVO from clinical trials.[20] This decreased effectiveness in clinical settings is likely a reflection of the high burden associated with RVO treatment (and consequent decreased adherence), including the need for regular injections and appointments, and the associated costs.[21–23] Of note, patients with CRVO who achieve vision gains in clinical trials have also been shown to, on average, experience best-corrected visual acuity (BCVA) loss with subsequent pro re nata dosing, with less than monthly monitoring, in long-term extension studies.[20] Clearly, there is an unmet need for more efficacious and durable treatment options for RVO to decrease the treatment burden without visual compromise.

One means of ameliorating the treatment burden associated with RVO is to individualize treatment based on disease activity, resulting in the use of personalized treatment regimens, including treat-and-extend. Treat-and-extend–based approaches, originally used to individualize treatment based on disease activity in neovascular age-related macular degeneration (nAMD), are now commonly used in clinical practice for other indications[24] and have the potential to reduce the number of injections required and clinic visits while maintaining stable vision gains in most individuals being treated. However, there is currently limited[25] standardized evidence from large-scale clinical trials, including from diverse populations, supporting the use of treat-and-extend–based personalized treatment regimens in the management of RVO.

Targeting other pathways, in addition to VEGF, involved in mediating the underlying pathology of RVO may improve outcomes and durability. Angiopoietin-2 (Ang-2) is a growth factor that promotes vascular instability and is upregulated in RVO. Among patients with retinal vascular diseases, those with RVO were found to have higher vitreous concentrations of Ang-2 than those with diabetic ME (DME) or nAMD.[26] Together, Ang-2 and VEGF drive vascular instability characterized by vascular leakage, neovascularization, and inflammation,[27] the key mechanisms of disease progression in RVO.[27–29] Hence, dual inhibition of Ang-2 and VEGF may lead to more sustained stabilization of retinal vessels compared with VEGF inhibition alone, a hypothesis supported by data from preclinical studies.[30]

Faricimab (Vabysmo), the first humanized, bispecific, immunoglobulin G monoclonal antibody designed for intraocular use via intravitreal injection, independently binds and neutralizes both Ang-2 and VEGF-A, enabling dual inhibition of these pathways involved in RVO pathology. In the phase III YOSEMITE/RHINE trials (NCT03622580/NCT03622593) in patients with DME, faricimab given every 8 weeks (Q8W) or according to a personalized treatment interval (PTI), a protocol-driven treat-and-extend–based dosing regimen with intervals up to every 16 weeks (Q16W), demonstrated noninferior vision gains and improved anatomic outcomes compared with aflibercept Q8W at 1 year.[31] Likewise, in the phase III TENAYA/LUCERNE trials (NCT03823287/NCT03823300) in patients with nAMD, faricimab up to Q16W demonstrated noninferior vision gains compared with aflibercept Q8W at 1 year, with meaningful and comparable improvement in anatomic outcomes.[32] In both YOSEMITE/RHINE and TENAYA/LUCERNE, the vision gains with faricimab up to Q16W remained similar to those achieved with aflibercept through 2 years, with approximately 80% of patients on at least every-12-week (Q12W) dosing and > 60% of patients on Q16W dosing (Lim JI et al, conference presentation, American Society of Retina Specialists Annual Meeting, July 13–16, 2022, New York, NY; Khanani AM et al, conference presentation, American Society of Retina Specialists Annual Meeting, July 13–16, 2022, New York, NY).

The aim of the phase III BALATON (NCT04740905) and COMINO (NCT04740931) trials is to investigate the efficacy, safety, and durability of faricimab compared with aflibercept in patients with ME secondary to BRVO and CRVO/HRVO, respectively. Here, we summarize the rationale and methodology for these trials and elaborate on the unique design features, including implementation of the faricimab PTI, a protocol-driven treat-and-extend–based dosing regimen with treatment intervals up to Q16W.

BALATON and COMINO Study Design and Rationale

Study Overview

The BALATON and COMINO trials are 2 identically designed, double-masked, multicenter, randomized, parallel-group, registrational phase III studies designed to evaluate the efficacy, safety, and pharmacokinetics of intravitreal faricimab 6.0 mg for the treatment of ME secondary to BRVO and CRVO/HRVO, respectively. Patients were randomized 1:1 to receive faricimab 6.0 mg every 4 weeks (Q4W) or aflibercept 2.0 mg Q4W for the first 6 months. The primary end point was at week 24. From week 24 through to week 72, all patients received faricimab 6.0 mg according to protocol-driven treat-and-extend–based PTI dosing up to Q16W.

Input from global health authorities on the design of the trials was obtained. These trials were conducted in accordance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted. Written informed consent was obtained before initiation of study procedures, and the study protocol was approved by institutional review boards before the studies began (Supplementary Table 1 includes information for the 108 institutional review boards; available at www.ophthalmologyscience.org).

Part 1 of the trials (day 1 through week 24) compared faricimab Q4W versus aflibercept (active comparator) Q4W, with patients in each arm receiving a total of 6 injections (Fig 1 provides more detail). Part 2 of the trials (weeks 24–72) evaluated faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria (Fig 1). After screening, eligible patients were randomized 1:1 to the 2 treatment arms.

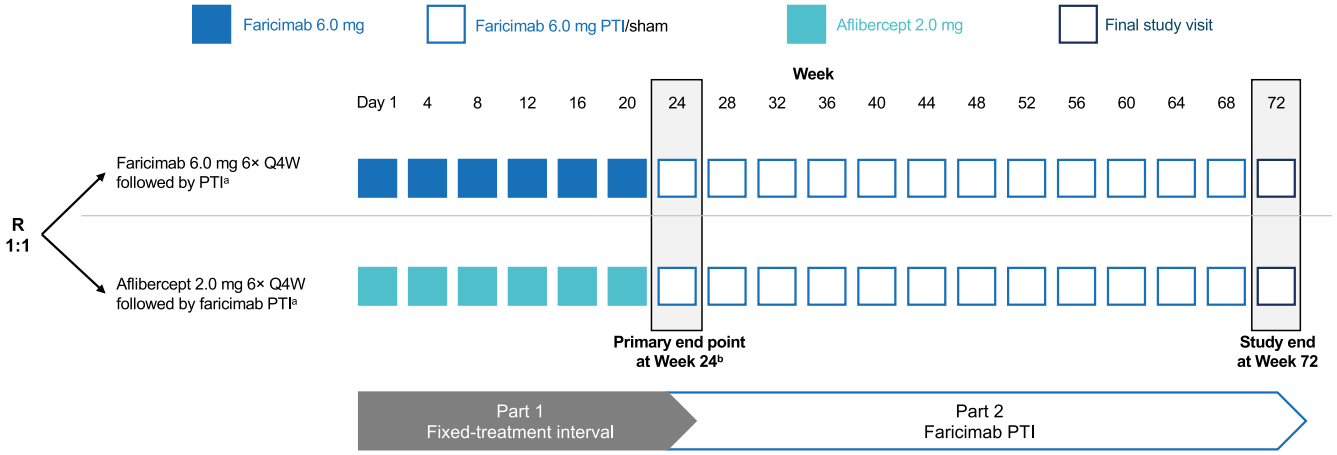

Figure 1. BALATON and COMINO: study design overview. [a] The personalized treatment interval (PTI) is a protocol-driven treat-and-extend–based regimen. Patients previously randomized to aflibercept moved directly to faricimab PTI without receiving any loading doses. [b] Change from baseline in best-corrected visual acuity, as measured on the ETDRS chart at a starting distance of 4 m. Q4W = every 4 weeks; R = randomization.

Randomization was stratified by baseline BCVA ETDRS letter score (BALATON: ≥ 55 letters vs. ≤ 54 letters; COMINO: ≤ 34 letters, 35–54 letters, and ≥ 55 letters) and region (United States and Canada, Asia, and the rest of the world). Different baseline BCVA categories were used for stratification in BALATON to account for patients with BRVO tending to have higher BCVA versus patients with CRVO[33] and thus ensure a more balanced distribution. The goal of stratification was to prevent an imbalance of these potentially confounding variables across the study arms that could affect the interpretation of study outcomes.

The BALATON and COMINO studies have their primary end point at week 24, and the total duration of the studies is 72 weeks. To preserve masking in part 2 of the studies, patients were seen Q4W and underwent a sham procedure at study treatment visits when they were not treated with active study drug. The sham procedure involved pressing the blunt end of an empty syringe, without a needle, against an anesthetized eye.

Principal investigators, assessor physicians, photographers and OCT technicians, masked study coordinators, and BCVA examiners were masked to the study treatment (part 1) and the treatment interval (part 2).

Study Participants and Eligibility Criteria

General inclusion and exclusion criteria are shown in full in Supplementary Table 2 (available at www.ophthalmologyscience.org). In brief, patients ≥ 18 years of age with foveal center-involved ME due to RVO were eligible to participate. Patients with ischemic RVO could be enrolled. General exclusion criteria included uncontrolled high blood pressure or a history of other systemic or ocular disease, physical examination findings, or clinical laboratory findings suggestive of a condition that would contraindicate use of any of the study drugs, may affect interpretation of the study results, or in the opinion of the investigator, would render the patient at high risk for treatment complications.

One eye per patient was designated as the study eye. Ocular exclusion and inclusion criteria for the study eye are shown in Table 3. Study eyes were required to have a BCVA of 73 to 19 letters and central subfield thickness (CST) of ≥ 325 μm. Eyes that had received any prior or current treatment, including anti-VEGF treatment for ME, macular neovascularization, or vitreomacular-interface abnormalities, were excluded from study entry. Central reading centers (CRCs) evaluated color fundus photography (CFP) and spectral domain-OCT (or swept-source OCT) images obtained at screening to provide an objective, masked assessment of whether patients' study eyes met the study eligibility criteria. If both eyes were eligible for inclusion, the eye with the worse BCVA at screening was selected as the study eye.

Anatomic Assessments

Retinal anatomic features were evaluated with OCT (spectral domain-OCT or swept-source OCT), CFP, fundus fluorescein angiography (FFA), and optional OCT angiography images. Because of the global nature of the trials, 2 CRCs (Duke Reading Center and Vienna Reading Center) were used to collect all OCT, CFP, FFA, and optional OCT angiography images. The Duke and Vienna CRCs graded all OCT images. The CFP and FFA images were transferred from the CRCs to a third reading center (The Wisconsin Reading Center) for evaluation.

Rationale for Choice of Comparator and Comparator Dosing (Part 1)

In part 1 of the trials, faricimab 6.0 mg was compared with the anti-VEGF agent aflibercept 2.0 mg. Eyes in the aflibercept arm received intravitreal aflibercept 2.0 mg Q4W from day 1 through week 20, for a total of 6 injections (Fig 1). Aflibercept was selected as a comparator as it is one of the standard-of-care anti-VEGF treatment options available globally to patients with RVO and was given as per the global label.

Rationale for Faricimab Dosing (Part 1)

In part 1 of the trials, eyes in the faricimab arm received intravitreal faricimab 6.0 mg Q4W from day 1 through week 20, for a total of 6 injections (Fig 1). Given that the downstream pathophysiology of hypoxia-driven ME with subsequent vision loss is similar in RVO and DME,[34] the 6-mg dose was selected based on the efficacy and safety findings of the phase II BOULEVARD trial[35] of faricimab in DME.

The initial 6 faricimab intravitreal Q4W doses in the trials aimed to maximize visual acuity gains for the whole patient population, even though a subset of patients may have achieved stability with a lower number of initial injections. This dosing regimen was consistent with the regimens studied in the pivotal

Table 3. BALATON and COMINO: Ocular Exclusion and Inclusion Criteria for the Study Eye

Exclusion Criteria	Inclusion Criteria
• History of previous episodes of ME due to RVO or persistent ME due to RVO diagnosed > 4 mos before screening • Increase of ≥ 10 letters in BCVA ETDRS score between screening and day 1 • 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 ME 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 nonretinal conditions) • Current visually significant vitreous hemorrhage on day 1 • History of retinal detachment or macular hole (stage 3 or 4) • Tractional retinal detachment, vitreomacular traction, full thickness macular hole or epiretinal membrane involving the fovea or disrupting the macular architecture in the study eye, as evaluated by the CRC, and described in the CRC manual • Diagnosis of DR moderate nonproliferative or worse, proliferative DR, DME, nAMD, geographic atrophy, myopic choroidal neovascularization as assessed by the investigator • Active rubeosis, angle neovascularization, neovascular glaucoma • Aphakia or implantation of anterior chamber intraocular lens • Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG laser capsulotomy within 3 mos before day 1 • Any other intraocular surgery (e.g., pars plana vitrectomy, scleral buckle, glaucoma surgery, corneal transplant, or radiotherapy) • Any prior or current treatment for ME due to RVO, including intravitreal anti-VEGF treatment for ME due to RVO • Macular laser (focal/grid) in the study eye at any time before day 1 • Panretinal photocoagulation in the study eye within 3 mos before day 1 or anticipated within 3 mos of study start on day 1 • Any intravitreal treatment for any other retinal diseases that can lead to ME complication • Any prior or current treatment for ME; macular neovascularization, including DME and 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 vitreoretinal surgery including sheathotomy • Any prior steroid implant use, including Ozurdex (Allergan USA, Inc), or Iluvien (Alimera Sciences, Inc) implants • Prior periocular pharmacological or intravitreal treatment (including anti-VEGF medication) for other retinal diseases	• Foveal center-involved ME due to RVO,* diagnosed no longer than 4 mos before the screening visit and confirmed by CRC based on SD-OCT (or SS-OCT) images • BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 m (see the BCVA manual for additional details) on day 1 • CST ≥ 325 μm (defined as the distance between the internal limiting membrane and Bruch's Membrane), as measured on Spectralis SD-OCT (Heidelberg Engineering GmbH), Cirrus SD-OCT (Carl Zeiss Meditec), or Topcon SD-OCT (Topcon) (SS-OCT was acceptable after confirmation with CRC) • Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; C3F8 = perfluoropropane; CRC = central reading center; CRVO = central retinal vein occlusion; DME = diabetic macular edema; DR = diabetic retinopathy; HRVO = hemiretinal vein occlusion; ME = macular edema; nAMD = neovascular age-related macular degeneration; RVO = retinal vein occlusion; SD-OCT = spectral-domain OCT; SS-OCT = swept-source OCT; YAG = yttrium-aluminum-garnet.
*RVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system, or other biomicroscopic evidence of RVO (neovascularization, vitreous hemorrhages) in 1 quadrant or less of the retina drained by the affected vein (BRVO), the entire retina (CRVO), or 2 quadrants of the retina (HRVO).

anti-VEGF trials of ranibizumab and aflibercept, including BRAVO, CRUISE, GALILEO, COPERNICUS, and VIBRANT.[33,36–38]

Objective and Rationale for the Faricimab PTI Dosing (Part 2)

The objective of the PTI dosing in part 2 of the trials was to evaluate a treat-and-extend–based approach in a standardized manner suitable for use in a pivotal trial setting and to evaluate the durability of faricimab treatment. The faricimab PTI dosing was designed to closely follow the treat-and-extend approach commonly used by physicians in the clinical setting for the administration of the current standard-of-care anti-VEGF treatments. Of note, a treat-and-extend regimen was also shown to maintain vision gains from month 6 to month 12 in the SCORE2 trial (NCT01969708) of aflibercept or bevacizumab in patients with RVO.[25] The approach for BALATON/COMINO was developed based on the PTI regimen used in the phase III YOSEMITE/RHINE trials of faricimab for DME[31,39] and employed an automated treatment algorithm using an interactive voice or web-based response system (IxRS) to generate individualized treatment schedules for every patient based on standardized and objectively measured clinical parameters.

The faricimab RVO PTI (Fig 1) was a protocol-driven, automated, standardized, and objective regimen, with dosing interval extensions adjusted by 4-week intervals per prespecified CST and BCVA criteria (further detail to follow). As per the YOSEMITE/RHINE trials,[31,39] patients were able to receive treatment as frequently as Q4W up to Q16W. These treatment intervals were selected based on findings from the phase II BOULEVARD trial.[35] Specifically, time to disease reactivation findings (up to

16 weeks after the last dose) during the off-treatment observation period in BOULEVARD suggested that many patients could be maintained on Q12W or Q16W regimens.[35]

To allow for objective, unbiased assessment, masked graders at the Duke and Vienna CRCs received the OCT images from the sites and evaluated CST for all patients in all arms at every study visit and transferred these values into the IxRS. The ETDRS BCVA values were entered directly into the IxRS by site staff. Treatment interval decisions were then calculated automatically by the IxRS algorithm. Specifically, the IxRS used BCVA and CST data from active dosing visits, and not those from sham visits, to determine whether a patient's existing treatment interval was reduced by 4 weeks, reduced to Q4W, maintained, or extended by 4 weeks, up to a maximum of 16 weeks. This was to replicate what would happen in a setting outside clinical trials, where only data from treatment visits would be used.

In part 2 of the trials, all patients, including those previously on aflibercept, moved to faricimab PTI dosing (Fig 2). Faricimab contains an anti-VEGF arm, in addition to an anti−Ang-2 arm, which promotes synergistic effects on vascular permeability and stability, angiogenesis, and inflammation. The decision to switch all aflibercept patients to faricimab PTI after the first 6 months was based on both faricimab's mechanism of action and the efficacy results of the phase III faricimab studies in DME[31] and nAMD,[32] which showed faricimab to be noninferior to aflibercept, with comparable safety.

PTI Algorithm

In part 2 of the trials, all patients attended study visits every 4 weeks from week 24 through week 68 and received either sham treatment or intravitreal faricimab 6.0 mg (Fig 1), depending on their PTI dosing regimen. Week 24 was the first visit that a patient could receive sham treatment. Faricimab PTI decisions were made based on BCVA and CST data from the previous faricimab dosing visit and were automatically calculated by the IxRS. The BCVA and CST data collected at nondosing visits (i.e., when the patient received a sham procedure) were not used for any dosing decisions. Faricimab dosing visits were defined as visits when the patient received faricimab 6.0 mg per IxRS assignment.

Starting at week 24, if CST met the predefined reference CST threshold (< 325 μm) as determined by the CRC, and there was no decrease in BCVA of ≥ 10 letters, the patient's dosing interval was extended. If CST was ≥ 325 μm, the patient continued to receive faricimab Q4W until the reference CST threshold was met. The reference CST, defined as the CST value at week 20 or a later visit when the CST met the predefined reference CST threshold (< 325 μm), was used by the IxRS at faricimab dosing visits to determine the faricimab dosing interval. After a patient's initial reference CST was established, the patient was eligible to have the faricimab dosing interval increased in 4-week increments by the IxRS if the CST value was stable (i.e., had not increased or decreased by > 10%) with no associated loss of vision of ≥ 10 letters with respect to reference BCVA (Fig 2). Reference CST was adjusted if CST decreased by > 10% from the previous reference CST for 2 consecutive faricimab dosing visits, and the values obtained were within 30 μm. The CST value obtained at the latter visit served as the new reference CST, starting immediately at that visit. Reference BCVA was defined as the mean of the 3 best BCVA scores obtained at any prior dosing visit.

The maximum and minimum treatment intervals that could be assigned were Q16W and Q4W, respectively. Patients who had previously had a dosing interval extension and who experienced disease worsening that triggered interval reduction were not allowed to extend the interval again, with the exception of patients who had dosing intervals reduced to Q4W; their interval could be extended again but only to an interval that was 4 weeks less than

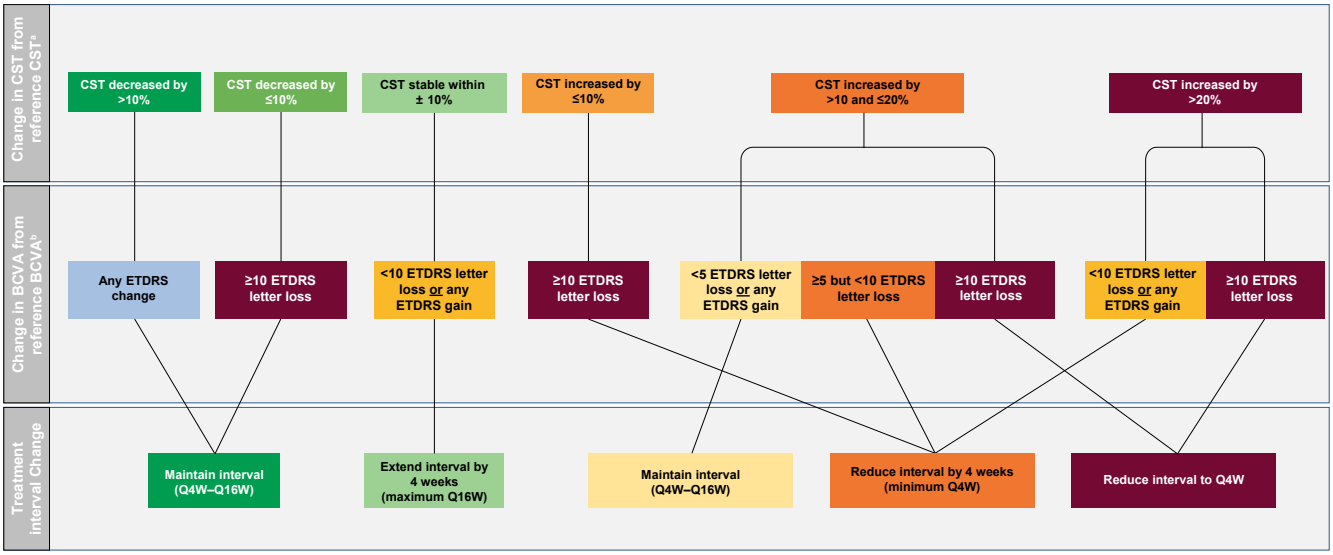

Figure 2. BALATON and COMINO: Decision tree for interactive voice or web-based response system (IxRS)-determined personalized treatment interval (PTI) dosing intervals. [a] Initial reference central subfield thickness (CST) = CST value when the initial CST threshold criteria are met, no earlier than week 20. Reference CST is adjusted if CST decreases by > 10% from the previous reference CST for 2 consecutive faricimab dosing visits and the values obtained are within 30 μm. The CST value obtained at the latter visit serves as the new reference CST, starting immediately at that visit. [b] Reference best-corrected visual acuity (BCVA) = the mean of the 3 best BCVA scores obtained at any previous active dosing visit.Q4W = every 4 weeks; Q16W = every 16 weeks.

Table 4. BALATON and COMINO: Algorithm for IxRS-Determined PTI Dosing Intervals, Initiated After ME Because RVO Was Clinically Controlled* (See Corresponding Fig 2)

Treat-and-Extend Principle	Change in Treatment Intervals, as Determined by Change in Reference CST† and BCVA‡ Values			
	Interval Extended by 4 Wks:	*Interval Maintained:*	*Interval Reduced by 4 Wks:*	*Interval Reduced to Q4W:*
Rationale for decision	Once ME is stable, increase treatment interval when anatomy is relatively unchanged	Once ME is stable, maintain existing interval if interval extension and reduction criteria are not met	Reduce existing treatment interval when there is evidence that it is associated with worsening of anatomy and/or vision	Significantly reduce existing treatment interval when there is evidence that it is associated with worsening of anatomy and significant vision loss
Criteria	CST value is increased or decreased by ≤ 10% without an associated ≥ 10-letter BCVA decrease	CST is decreased by > 10%§ or CST value is decreased by ≤ 10% with an associated ≥ 10-letter BCVA decrease or CST value is increased between > 10% and ≤ 20% without an associated ≥ 5-letter BCVA decrease	CST value is increased between > 10% and ≤ 20% with an associated ≥ 5- to < 10-letter BCVA decrease or CST value is increased by > 20% without an associated ≥ 10-letter BCVA decrease or CST value is increased by ≤ 10% with an associated ≥ 10-letter BCVA decrease	CST value is increased by > 10% with an associated ≥ 10-letter BCVA decrease

BCVA = best-corrected visual acuity; CST = central subfield thickness; IxRS = interactive voice- or web-based response system; ME = macular edema; PTI = personalized treatment interval; Q4W = every 4 wks; RVO = retinal vein occlusion.
*When CST (defined as the distance between the internal limiting membrane and Bruch's Membrane) meets the predefined reference CST threshold (< 325 μm) no earlier than wk 20.
†The reference CST, defined as the CST value when the initial CST threshold criteria are met (no earlier than wk 20) was used to determine the faricimab dosing interval. After a patient's initial reference CST was established, the patient was eligible to have the faricimab dosing interval increased in 4-wk increments if the CST value was stable (i.e., did not increase or decrease by > 10%) with no associated loss of vision of ≥ 10 letters with respect to reference.
‡The mean of the 3 best BCVA scores obtained at any previous study drug dosing visit.
§Anatomic improvements suggest ongoing benefit.

their original maximum extension. For example, if a patient's interval was reduced from Q12W to Q8W, this patient's interval could not be extended beyond Q8W for the remainder of the treatment period. If a patient's interval was reduced from Q16W to Q4W, this patient's interval could be extended up to Q12W but could not be extended back to Q16W.

The algorithm recognized 3 patterns using anatomic and functional measures of retinal stability (Fig 2, Table 4). If CST was stable (± 10% of the reference CST), the PTI algorithm extended the treatment interval by 4 weeks (to a maximum of Q16W), unless there was an accompanying decrease in BCVA of ≥ 10 letters. If CST improved by > 10% or by ≤ 10% with a decrease in BCVA of ≥ 10 letters, the PTI algorithm maintained the treatment interval. The treatment interval was maintained when CST improved by > 10% as this was taken to indicate continued benefit from treatment (i.e., the patient was not yet stable). If CST worsened by ≤ 10% with an accompanying decrease in BCVA of ≥ 10 letters, the PTI algorithm reduced the treatment interval by 4 weeks. If CST worsened by > 10% to ≤ 20%, the PTI algorithm maintained or reduced the treatment interval by 4 weeks or to Q4W depending on the magnitude of CST worsening and the change in BCVA. For example, the treatment interval was reduced by 4 weeks if BCVA decreased by ≥ 5 letters but < 10 letters. However, the treatment interval was reduced to Q4W if this CST change was accompanied by a BCVA decrease of ≥ 10 letters. If a patient's CST worsened by > 20%, the treatment interval was reduced by 4 weeks if there was a BCVA increase or if BCVA decreased by < 10 letters and was reduced to Q4W if BCVA decreased by ≥ 10 letters. Figure 2 depicts the treatment decision process in full, and Figure 3 highlights several theoretical PTI scenario examples.

Study Outcomes

The primary and secondary efficacy end points are summarized in Table 5.

The primary objective of the trials is to evaluate the efficacy of intravitreal faricimab 6.0 mg Q4W compared with intravitreal aflibercept 2.0 mg Q4W per the change from baseline in BCVA at week 24.

Secondary efficacy objectives in part 1 of the trials include evaluating the following over time (weeks 0−24) for faricimab compared with aflibercept: change from baseline in BCVA, CST, and National Eye Institute Visual Function Questionnaire 25 composite score and the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters from baseline. Other secondary efficacy objectives in part 1 include evaluating the proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA, BCVA Snellen equivalent of 20/40 (BCVA ≥ 69 letters) or better, and BCVA Snellen equivalent of 20/200 (BCVA ≤ 38 letters) or worse.

Secondary efficacy objectives in part 2 of the trials (weeks 24−72) include evaluating the following by original treatment arm at randomization (i.e. initially treated with aflibercept and initially treated with faricimab): proportion of patients on Q4W, Q8W, Q12W, or Q16W treatment intervals at week 68; change from baseline in BCVA, CST, and National Eye Institute Visual Function Questionnaire 25 composite score through week 72; and the proportion of patients gaining or avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters from baseline through week 72.

Exploratory efficacy objectives are to further evaluate the efficacy of faricimab on anatomic measures using spectral domain-OCT, FFA, OCT angiography, or a combination thereof, and to

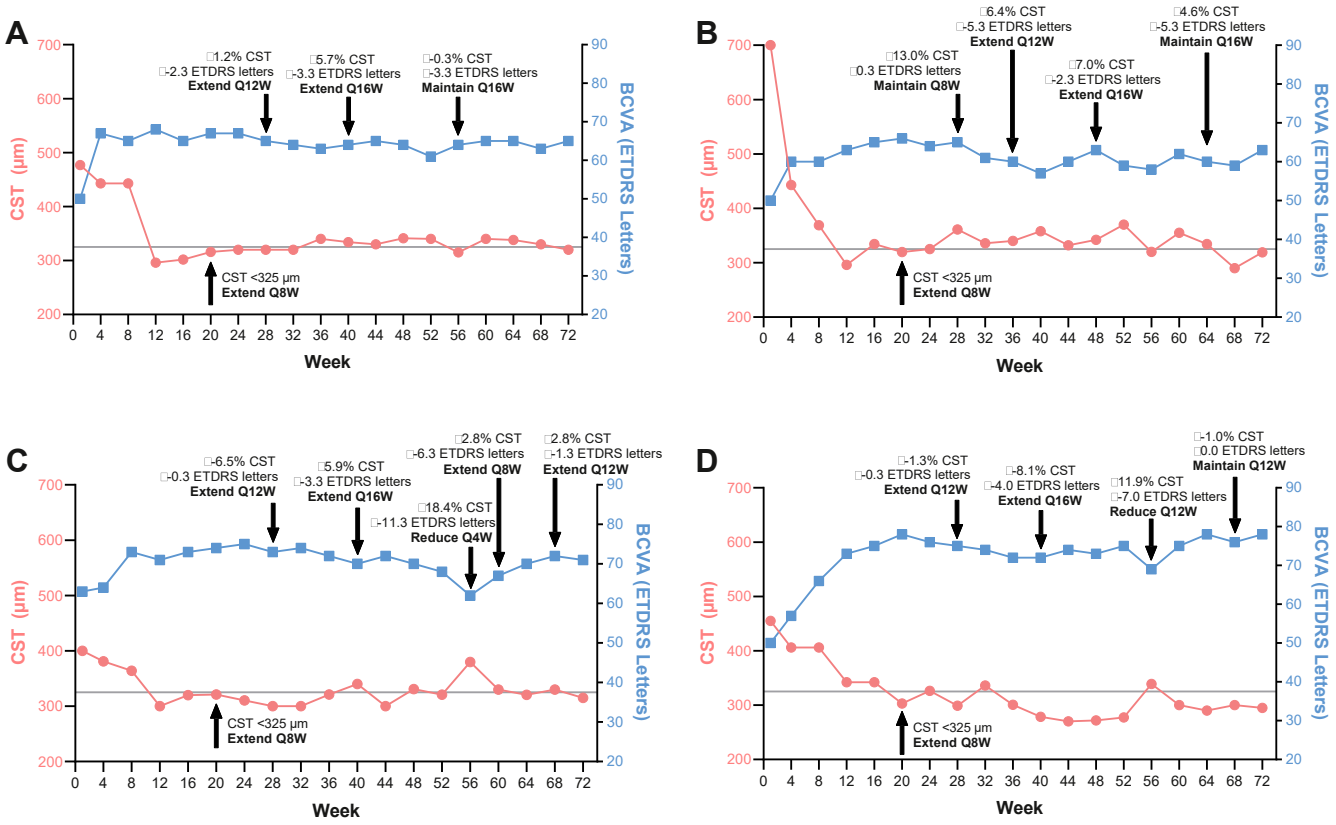

Figure 3. BALATON and COMINO: Personalized treatment interval (PTI) scenario examples. Horizontal line represents central subfield thickness (CST) threshold of 325 µm. **A,** week 20: CST < 325 µm (with no associated ≥ 10-letter best-corrected visual acuity [BCVA] decrease from reference BCVA), extend to every 8 weeks (Q8W); week 28: CST within ± 10% of reference CST[a] (with no associated ≥ 10-letter BCVA decrease from reference BCVA[b]), extend to every 12 weeks (Q12W); Week 40: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to every 16 weeks (Q16W); Week 56: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA) and patient is at the maximum treatment interval, maintain Q16W. **B,** week 20: CST < 325 µm (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q8W; week 28: CST increased by > 10% and ≤ 20% of reference CST (with an associated BCVA increase), maintain at Q8W; week 36: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q12W; week 48: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q16W; week 64: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA) and patient is at the maximum treatment interval, maintain Q16W. **C,** week 20: CST < 325 µm (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q8W; week 28: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q12W; week 40: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q16W; week 56: CST increased by > 10% and ≤ 20% of reference CST (with an associated ≥ 10-letter BCVA decrease from reference BCVA), reduce to every 4 weeks (Q4W); week 60: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q8W; week 68: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q12W. **D,** week 20: CST < 325 µm (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q8W; week 28: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q12W; week 40: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), extend to Q16W; week 56: CST increased by > 10% and ≤ 20% of reference CST (with associated ≥ 5- and < 10-letter BCVA decrease from reference BCVA), reduce to Q12W; week 68: CST within ± 10% of reference CST (with no associated ≥ 10-letter BCVA decrease from reference BCVA), maintain Q12W (interval cannot be further extended given the previous interval reduction from Q16W). [a] The first CST value that is < 325 µm, starting at week 20. Reference CST is adjusted if CST decreases by > 10% from the previous reference CST for 2 consecutive faricimab dosing visits and the values obtained are within 30 µm. The CST value obtained at the latter visit serves as the new reference CST. [b] The mean of the 3 best BCVA scores obtained at any previous active dosing visit.

further evaluate patient-reported outcomes using National Eye Institute Visual Function Questionnaire 25.

The key pharmacokinetic objective is to characterize the systemic pharmacokinetics of faricimab, whereas the exploratory pharmacokinetic objective is to explore the concentration-effect relationship between visual acuity and other end points (e.g., anatomic measures) over time.

Immunogenicity objectives are to evaluate anti-drug antibody status at baseline and at time points after baseline, whereas the exploratory immunogenicity objectives include evaluating the relationship between anti-drug antibody status and efficacy, safety, or pharmacokinetic end points.

The exploratory biomarker objective is to identify and/or evaluate biomarkers that are predictive of response to faricimab,

Table 5. BALATON and COMINO: Summary of Primary and Selected Secondary Efficacy End Points

Primary Efficacy End Point
- Change from baseline in BCVA at wk 24

Secondary Efficacy End points

Part 1 (Fixed Treatment Interval: wks 0–24)
- Change from baseline in BCVA over time
- Proportion of patients gaining/avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters from baseline over time
- Change from baseline in CST over time
- Change from baseline in NEI VFQ-25 composite score over time

Part 2 (PTI: wks 24–72)
- Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at week 68
- Change from baseline in BCVA over time
- Proportion of patients gaining/avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters from baseline over time
- Change from baseline in CST over time
- Change from baseline in NEI VFQ-25 composite score over time

BCVA = best-corrected visual acuity; CST = central subfield thickness; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire 25; PTI = personalized treatment interval; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks.

associated with progression to a more severe disease state, and associated with susceptibility to developing adverse events (AEs) or can lead to improved AE monitoring or investigation, provide evidence of faricimab activity, or increase the knowledge and understanding of disease biology and drug safety.

Safety Assessments

The safety objective of the trials is to evaluate the ocular and systemic safety and tolerability of faricimab. Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, were performed throughout the studies. An independent data monitoring committee proactively monitored safety and study conduct until the primary analysis.

The following safety summaries are planned for the primary analysis up to week 24 (safety-evaluable population: all patients who receive ≥ 1 dose of study treatment in the study eye) and for the final analysis: AEs (ocular and nonocular), serious AEs (ocular and nonocular), AEs leading to discontinuation of study treatment, and deaths and descriptive summaries of ocular assessments and laboratory test findings and vital sign abnormalities. All AEs, including serious AEs and AEs of special interest, are required to be reported to the sponsor via AE electronic case reporting forms by the study investigators.

Statistical Approaches

The global enrollment phase enrolled approximately 276 patients per arm for BALATON and 365 patients per arm for COMINO. These enrollment numbers will provide > 90% power to demonstrate the noninferiority of faricimab to aflibercept for the change from baseline in BCVA at week 24 in the intention-to-treat population, using a noninferiority margin of 4 letters and under the following assumptions: no difference in the mean change from baseline in BCVA between treatment arms, a standard deviation of 13 letters for BALATON and 15 letters for COMINO for the change from baseline in BCVA at week 24, 2-sample *t* tests, 2.5% 1-sided type I error rate, and a 10% dropout rate. The noninferiority margin of 4 letters was selected with reference to findings from the pivotal aflibercept trials in patients with BRVO[40] and CRVO[41,42] and is based on the statistical rationale of preserving approximately 50% of the least estimated benefit of aflibercept relative to control, using the lower limit of the 95% confidence interval.

The primary efficacy end point is the change from baseline in BCVA at week 24. For the primary estimand, all patients randomized will be included and grouped by treatment arm assigned at randomization. For intercurrent events (discontinuation of study treatment due to AEs or lack of efficacy and use of any prohibited systemic treatment or prohibited therapy in the study eye), a treatment policy strategy will be applied, whereby all observed values will be used regardless of occurrence of the intercurrent event.

The primary comparison will be between the active comparator (aflibercept 2.0 mg Q4W) and faricimab 6.0 mg Q4W at week 24. The following hypotheses will be tested: noninferiority of faricimab Q4W compared with aflibercept Q4W at week 24 (at a 1-sided 0.02485 significance level) and superiority of faricimab Q4W compared with aflibercept Q4W at week 24 (at a 2-sided 0.0497 significance level). A nominal type I error penalty of 0.0001 (2-sided) was taken for each of the 3 independent data monitoring committee safety interim reviews of unmasked data before the formal analysis of the primary efficacy end point, for a final 2-sided α of 0.0497.

Changes from baseline in BCVA (the primary end point) will be assessed using a mixed model for repeated measures (MMRM). The model will include the change from baseline at weeks 4 to 24 as the response variable and include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), and randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. Missing data will be implicitly imputed by the MMRM model assuming a missing at random mechanism.

A sensitivity analysis will be performed, where missing primary end point BCVA data will be imputed via multiple imputation. A supplementary per protocol analysis will also be performed and will include all patients randomized who receive ≥ 1 dose of study treatment and who do not have a major protocol violation impacting the efficacy evaluation. Further supplementary analyses will be performed using alternative approaches for the definition and handling of intercurrent events.

Continuous secondary efficacy outcomes in both parts of the trials will be analyzed using an MMRM, whereas binary secondary end points will be analyzed using stratified estimation for binomial proportions using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by the randomization stratification factors of baseline BCVA score and region with Cochran-Mantel-Haenszel weights. The estimates and confidence intervals will be determined for the mean (continuous variables) or proportion (binary variables) for each treatment arm and for the difference in means or proportions between the aflibercept Q4W arm and the faricimab Q4W arm (this

applies to part 1 of the trials only as all patients will be on faricimab in part 2; arms will not be compared in part 2). All confidence intervals will be 2 sided and at the 95.03% level. Durability outcomes (proportion of patients on Q4W, Q8W, Q12W, or Q16W treatment intervals) will be analyzed using descriptive statistics.

Study Status

The BALATON trial commenced recruitment in March 2021, and primary end point completion occurred in July 2022. The COMINO trial commenced recruitment in March 2021 and primary end point completion occurred in August 2022. The anticipated trial completion dates are June 2023 for BALATON and July 2023 for COMINO.

The BALATON and COMINO trials enrolled 1282 patients across 22 countries (BALATON, 553 patients across 149 centers; COMINO, 729 patients across 193 centers).

Discussion

The global phase 3 BALATON and COMINO trials were designed to evaluate whether dual inhibition of Ang-2 and VEGF-A with faricimab improves outcomes beyond anti-VEGF monotherapy in treatment-naive patients with ME due to RVO. The protocol-driven treat-and-extend-based PTI phase of the trials was designed to examine the potential for individualized faricimab therapy with extended treatment intervals up to Q16W, tailored according to patient needs, to reduce treatment burden while maintaining efficacy.

Personalized treatment regimens, such as treat-and-extend, have the potential to decrease treatment burden without visual compromise in patients with RVO; however, there is currently limited standardized evidence from clinical trials. The SCORE2 trial of patients with ME due to CRVO or HRVO compared the efficacy of monthly aflibercept with monthly bevacizumab through 6 months.[43] From month 6 onward, patients who responded to aflibercept/bevacizumab were rerandomized to continue treatment with the same drug, either on a monthly regimen or a treat-and-extend regimen through month 12. Patients on the treat-and-extend regimen who met predefined anatomical criteria had their dosing intervals extended in 2-week increments up to a maximum of Q10W. The visual gains achieved at month 6 were maintained through month 12, with both monthly and treat-and-extend regimens.[25] Further, patients on the treat-and-extend regimen had 1 to 2 fewer injections over the 6-month period, demonstrating a decreased treatment burden. The findings from SCORE2 provided evidence that a treat-and-extend–based regimen could provide similar efficacy to monthly treatment, thus informing the decision to evaluate a treat-and-extend-based regimen in BALATON/COMINO. In contrast to the treat-and-extend phase of the SCORE2 trial,[25] which only included patients who had a good response to anti-VEGF therapy in the first 6 months of the trial, all patients will be included in the treat-and-extend-based PTI phase of BALATON/COMINO. Hence, these trials will provide additional insight on the use of treat-and-extend–based approaches in patients with RVO.

The RVO PTI algorithm in BALATON/COMINO is similar to the DME PTI algorithm used in the YOSEMITE/RHINE trials,[31,39] but with additional criteria for treatment interval reduction. This approach was taken to ameliorate any potential risk of deterioration given the higher likelihood of destabilization having a negative impact on functional outcomes in patients with RVO, in particular CRVO, compared with patients with DME.[44] Specifically, patients with RVO who had CST worsen by $\leq$ 10% with a BCVA decrease of $\geq$ 10 letters had their treatment interval reduced by 4 weeks, whereas similar patients with DME had their treatment maintained. Further, patients with RVO who had CST worsen by $>$ 10% with a BCVA decrease of $\geq$ 10 letters had their treatment interval reduced to Q4W, whereas similar patients with DME had their treatment interval reduced by 8 weeks. Another difference between the DME and RVO PTI algorithms is that patients with RVO could not re-extend their dosing interval after interval reduction due to disease worsening. An exception was if the interval was reduced to Q4W, in which cases patients could re-extend to an interval 4 weeks less than their original maximum extension.

The BALATON and COMINO studies are the first phase III registration trials in patients with RVO to include automated protocol-prespecified PTI dosing based on the treat-and-extend approach. The design of these trials is in keeping with clinical practice in that treatment decisions during the PTI phase occurred during the dosing visits only (not during sham visits) and were dictated by the results of functional and anatomic assessments. Notably, the PTI was fully automated, standardized, and objective, thus limiting the potential for any confounding effects due to subjective decisions. Further, the PTI was applied across a large global RVO population, thereby allowing for evaluation of possible treatment benefits across a diverse patient population. The use of masked CRC graders during the trials allowed for unbiased and objective clinical assessments.

In conclusion, the BALATON and COMINO trials will provide key insights on the efficacy and safety of faricimab for the treatment of RVO. Faricimab targets VEGF-A and Ang-2, both of which play an underlying role in retinal vascular disease progression and are present in higher vitreous concentrations in patients with RVO than in patients with other retinal vascular diseases. In addition to efficacy and safety, the trials will also provide important information on the possible benefits of an algorithm-based PTI faricimab regimen, allowing for up to Q16W dosing with 4-week extensions and hence a reduced treatment burden for patients.

Footnotes and Disclosures

Originally received: October 29, 2022.
Final revision: March 20, 2023.
Accepted: March 22, 2023.
Available online: March 27, 2023. Manuscript no. XOPS-D-22-00235R2.

[1] Augenklinik des Klinikums Ludwigshafen, Ludwigshafen, Germany.

[2] Genentech, Inc., South San Francisco, California.

[3] Roche Products Ltd., Welwyn Garden City, UK.

[4] Roche Products (Ireland), Dublin, Ireland.

[5] Rand Eye Institute, Deerfield Beach, Florida.

[6] Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida.

[7] The Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, East Melbourne, Australia.

[8] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[9] Tel Aviv Medical Center, Tel Aviv University, Tel Aviv, Israel.

[10] Budapest Retina Associates, Budapest, Hungary.

[11] Retinal Consultants of Texas, Houston, Texas.

Information in this manuscript has been presented, in part, at the following:

136th Asia-Pacific Academy of Ophthalmology 2021 Congress; Virtual; September 5−11, 2021.

21st European Society of Retina Specialists Congress; Virtual; September 10−12, 2021.

The 14th Congress of the Asia-Pacific Vitreo-retina Society; Virtual; December 11−12, 2021.

126th Annual Meeting of the Japanese Ophthalmological Society; Osaka, Japan; April 14−17, 2022.

World Ophthalmology Congress; Virtual; September 9−12, 2022.

120th Deutsche Ophthalmologische Gesellschaft Congress; Berlin, Germany; September 29−October 2, 2022.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

L.-O.H.: Consultant/lecture fees − Alcon, Allergan, Bausch + Lomb, Bayer, Novartis, Roche, ZEISS; Grant support − Apellis, Novartis, PIXIUM VISION, Roche.

F.A.: Employee − Genentech, Inc.

P.A.: Employee − F. Hoffmann-La Roche Ltd.

K.B.: Employee − F. Hoffmann-La Roche Ltd.

C.J.D.: Consultant − Adverum, Dutch Ophthalmic Research Center, Genentech, Inc., Iveric Bio, Novartis, Regeneron; Regenxbio; Grant support − Adverum, Alexion, Bayer, Genentech, Inc., Gyroscope, Iveric Bio, Kodiak Sciences, Novartis, Regeneron, Regenxbio, Roche, Unity; Speaker − Genentech, Inc., Novartis.

R.G.: Advisory board − Apellis, Bayer, Novartis, Roche/Genentech, Inc.; Consultant − Roche/Genentech, Inc.; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events − Apellis, Bayer, Novartis, Roche/Genentech, Inc.; Support for attending meetings and/or travel − Roche/Genentech, Inc.

Z.H.: Employee − Genentech, Inc.

J.S.H.: Advisory board − Roche; Board of Directors member − Ocular Therapeutix; Consultant − 4D Molecular Therapeutics, Adverum, AffaMed, Applied Genetic Technologies Corporation, Akouos, Allegro, Allergan, Annexon, Apellis, AsclepiX, Bionic Vision, DTx, Gemini, Gyroscope, Iveric Bio, Janssen R&D, jCyte, Nanoscope, NGM Bio, Notal Vision, Novartis, Ocuphire, OcuTerra, Palatin, Perceive Biotherapeutics, Ray Therapeutics, Regeneron, Regenxbio, RetinAI, RevOpsis, Roche/Genentech, Inc., Stealth, Thea, Unity, Vanotech, Vinci, Vitranu.

A.K.: Employee − F. Hoffmann-La Roche Ltd.

Y.L.: Employee − Genentech, Inc.

A.L.: Advisory board − Roche; Consultant − Allergan, Bayer, Beyeonics, ForSight Labs, Notal Vision, Novartis, Roche.

A.S.: Advisory board − Roche; Consultant − Novartis, Roche, Syneos Health.

J.R.W.: Employee − Genentech, Inc.

C.C.W.: Consultant − AbbVie, Adverum, Aerie, Allergan, Allegenesys, Alnylam, Annexon, Apellis, Arrowhead, Bausch + Lomb, Bayer, Bionic Vision, Chengdu Kanghong, Clearside Biomedical, EyePoint, Genentech, Inc., Gyroscope, Iveric Bio, Janssen, Kato, Kodiak Sciences, Long Bridge Medical, NGM Bio, Novartis, OccuRx, Ocular Therapeutix, ONL, Opthea, Palatin, Perfuse, PolyPhotonix, RecensMedical, Regeneron, Regenxbio, Roche, Surrozen, Takeda, Valo, Verana Health, Vitranu; Grant support − Adverum, Aerie, Aldeyra, Alimera, Alkahest, Allergan, Amgen, Annexon, Apellis, AsclepiX, Bayer, Boehringer Ingelheim, Chengdu Kanghong, Clearside Biomedical, Gemini, Genentech, Inc., Graybug, Gyroscope, Ionis, iRenix, Iveric Bio, Kodiak Sciences, Lowy Medical Research Institute, Nanoscope, Neurotech, NGM Bio, Novartis, Ocular, Opthea, Oxurion, RecensMedical, Regeneron, Regenxbio, Roche, SamChunDang, Taiwan Liposome Company, Xbrane; Equity owner − ONL, PolyPhotonix, RecensMedical, Visgenx.

L.P.P.: Employee − Genentech, Inc.

Supported by F. Hoffmann-La Roche Ltd., Basel, Switzerland. The sponsor participated in the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the paper for publication. Funding was provided by F. Hoffmann-La Roche Ltd. for the study and third-party writing assistance, which was provided by Luke Carey, PhD, CMPP, of Envision Pharma Group.

HUMAN SUBJECTS: Human subjects were included in this study. IRB approved: These trials were conducted in accordance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted. Written informed consent was obtained before initiation of study procedures, and the study protocol was approved by institutional review boards before the studies began (Supplementary Table 1 includes information for the 108 institutional review boards; available at www.ophthalmologyscience.org).

No animal subjects were used in this study.

Author Contributions:

Conception and design: Abreu, Basu, Haskova, Heier, Liu, Seres, Wykoff,

Analysis and interpretation: Hattenbach, Abreu, Arrisi, Basu, Danzig, Guymer, Haskova, Heier, Kotecha, Liu, Loewenstein, Seres, Willis, Wykoff, Paris

Data collection: Hattenbach, Abreu, Basu, Danzig, Guymer, Heier, Loewenstein, Seres, Willis, Wykoff, Paris

Obtained funding: N/A

Overall responsibility: Hattenbach

Abbreviations and Acronyms:
AE = adverse event; **Ang-2** = angiopoietin 2; **BCVA** = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **CFP** = color fundus photography; **CRC** = central reading center; **CRVO** = central retinal vein occlusion; **CST** = central subfield thickness; **DME** = diabetic macular edema; **FFA** = fundus fluorescein angiography; **HRVO** = hemiretinal vein occlusion; **IxRS** = interactive voice- or web-based response; **ME** = macular edema; **MMRM** = mixed model for repeated measures; **nAMD** = neovascular age-related macular edema; **PTI** = personalized treatment interval; **Q4W** = every 4 weeks; **Q8W** = every 8 weeks; **Q12W** = every 12 weeks; **Q16W** = every 16 weeks; **RVO** = retinal vein occlusion.

Keywords:
Angiopoietin-2, Faricimab, Macular edema, Retinal vein occlusion, Vascular endothelial growth factor receptor.

Correspondence:
Liliana P. Paris, MD, PhD, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080. E-mail: paris-pereira.liliana@gene.com.

References

1. Ip M, Hendrick A. Retinal vein occlusion review. *Asia Pac J Ophthalmol (Phila)*. 2018;7:40−45.
2. Scott IU, Campochiaro PA, Newman NJ, Biousse V. Retinal vascular occlusions. *Lancet*. 2020;396:1927−1940.
3. Song P, Xu Y, Zha M, et al. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health*. 2019;9:010427.
4. Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. *Eye (Lond)*. 2011;25:981−988.
5. Rhoades W, Dickson D, Nguyen QD, Do DV. Management of macular edema due to central retinal vein occlusion - the role of aflibercept. *Taiwan J Ophthalmol*. 2017;7:70−76.
6. Cochran ML, Mahabadi N, Czyz CN. Branch retinal vein occlusion. StatPearls. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/pubmed/30570991. Accessed October 20, 2022.
7. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2019;242:123−162.
8. Flaxel CJ, Adelman RA, Bailey ST, et al. Retinal vein occlusions Preferred Practice Pattern(R). *Ophthalmology*. 2020;127:288−320.
9. Campochiaro PA, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology*. 2014;121:209−219.
10. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology*. 2012;119:802−809.
11. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011;118:2041−2049.
12. Tadayoni R, Waldstein SM, Boscia F, et al. Individualized stabilization criteria-driven ranibizumab versus laser in branch retinal vein occlusion: six-month results of BRIGHTER. *Ophthalmology*. 2016;123:1332−1344.
13. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER study. *Ophthalmology*. 2017;124:1778−1787.
14. Vaz-Pereira S, Marques IP, Matias J, et al. Real-world outcomes of anti-VEGF treatment for retinal vein occlusion in Portugal. *Eur J Ophthalmol*. 2017;27:756−761.
15. Wecker T, Ehlken C, Bühler A, et al. Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV. *Br J Ophthalmol*. 2017;101:353−359.
16. Callizo J, Ziemssen F, Bertelmann T, et al. Real-world data: ranibizumab treatment for retinal vein occlusion in the OCEAN study. *Clin Ophthalmol*. 2019;13:2167−2179.
17. Pearce I, Clemens A, Brent MH, et al. Real-world outcomes with ranibizumab in branch retinal vein occlusion: the prospective, global, LUMINOUS study. *PLOS ONE*. 2020;15:e0234739.
18. Ciulla T, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in macular oedema due to retinal vein occlusion: a real-world analysis of 15 613 patient eyes. *Br J Ophthalmol*. 2021;105:1696−1704.
19. Jumper JM, Dugel PU, Chen S, et al. Anti-VEGF treatment of macular edema associated with retinal vein occlusion: patterns of use and effectiveness in clinical practice (ECHO study report 2). *Clin Ophthalmol*. 2018;12:621−629.
20. Bhisitkul RB, Blotner S, Steffen V, Haskova Z. Clinical trial versus real-world outcomes with anti-VEGF therapy for central retinal vein occlusion. *Invest Ophthalmol Vis Sci*. 2020;61:1304.
21. Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. *Clin Ophthalmol*. 2016;10:939−946.
22. Suñer IJ, Margolis J, Ruiz K, Tran I, et al. Direct medical costs and resource use for treating central and branch retinal vein occlusion in commercially insured working-age and Medicare populations. *Retina*. 2014;34:2250−2258.
23. Fekrat S, Shea AM, Hammill BG, et al. Resource use and costs of branch and central retinal vein occlusion in the elderly. *Curr Med Res Opin*. 2010;26:223−230.
24. Rezaei KA, Stone TW. 2015 global trends in retina survey. https://www.asrs.org/content/documents/2015_global_trends_in_retina_survey_-_for_website.pdf. Accessed October 20, 2022.
25. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: secondary outcomes from the SCORE2 randomized clinical trial. *JAMA Ophthalmol*. 2018;136:337−345.
26. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2016;8:1265−1288.
27. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16:635−661.
28. Klaassen I, Van Noorden CJ, Schlingemann RO. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. *Prog Retin Eye Res*. 2013;34:19−48.
29. Campochiaro PA. Ocular neovascularization. *J Mol Med (Berl)*. 2013;91:311−321.
30. Joussen AM, Ricci F, Paris LP, et al. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)*. 2021;35:1305−1316.
31. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*. 2022;399:741−755.

32. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399:729–740.
33. Thach AB, Yau L, Hoang C, Tuomi L. Time to clinically significant visual acuity gains after ranibizumab treatment for retinal vein occlusion: BRAVO and CRUISE trials. *Ophthalmology*. 2014;121:1059–1066.
34. Dysli M, Rückert R, Munk MR. Differentiation of underlying pathologies of macular edema using spectral domain optical coherence tomography (SD-OCT). *Ocul Immunol Inflamm*. 2019;27:474–483.
35. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-a with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*. 2019;126:1155–1170.
36. Korobelnik JF, Holz FG, Roider J, et al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the phase 3 GALILEO study. *Ophthalmology*. 2014;121:202–208.
37. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. *Ophthalmology*. 2014;121:1414–1420.e1.
38. Clark WL, Boyer DS, Heier JS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the VIBRANT study. *Ophthalmology*. 2016;123:330–336.
39. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical trials of faricimab for diabetic macular edema: study design and rationale. *Ophthalmol Sci*. 2022;2:100111.
40. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122:538–544.
41. Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97:278–284.
42. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. *Am J Ophthalmol*. 2013;155:429–437.e7.
43. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA*. 2017;317:2072–2087.
44. Douglas VP, Douglas KAA, Vavvas DG, et al. Short- and long-term visual outcomes in patients receiving intravitreal injections: the impact of the coronavirus 2019 disease (covid-19)-related lockdown. *J Clin Med*. 2022;11:2097.