Official Title: A Phase III, Multicenter, Randomized, Double-masked, Active Comparator Controlled Studies to Evaluate the Efficacy and Safety of Faricimab in Patients with Macular Edema Secondary To Branch Retinal Vein Occlusion and Macular Edema Secondary To Central Retinal or Hemiretinal Vein Occlusion

NCT Number: NCT04740905 and NCT04740931

Document Date: Statistical Analysis Plan (SAP) Version 1: 03 October 2022

STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR CONTROLLED STUDIES TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION, AND MACULAR EDEMA SECONDARY TO CENTRAL RETINAL OR HEMIRETINAL VEIN OCCLUSION (BALATON AND COMINO)**

STUDY NUMBERS:	GR41984 (BALATON) and GR41986 (COMINO)
STUDY NAMES:	BALATON and COMINO
VERSION NUMBER:	1
ROCHE COMPOUND(S):	Faricimab (RO6867461)
EUDRACT NUMBER:	2020-000440-63 and 2020-000441-13
IND NUMBER:	119225
NCT NUMBER:	BALATON: NCT04740905/COMINO: NCT04740931
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STATISTICAL ANALYSIS PLAN APPROVAL

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DATE FINAL:	See electronic date stamp on the last page of this document

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

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SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on the last page of this document	Version 2, 3 April 2020

TABLE OF CONTENTS

1. INTRODUCTION 8
1.1 Objectives and Endpoints 9
1.1.1 Efficacy Objectives 9
1.1.1.1 Primary Efficacy Objective 9
1.1.1.2 Secondary Efficacy Objectives 10
1.1.1.3 Exploratory Efficacy Objective 11
1.1.2 Safety Objectives 11
1.1.3 Pharmacokinetic Objectives 11
1.1.4 Immunogenicity Objectives 12
1.1.5 Exploratory Biomarker Objectives 12
1.2 Study Design 12
1.2.1 Treatment Assignment and Masking 17
1.2.2 Independent Review Facility 18
1.2.3 Data Monitoring 18
2. STATISTICAL HYPOTHESES 19
2.1 Non-Inferiority Margin 19
3. SAMPLE SIZE DETERMINATION 20
3.1 Sample Size for the China Extension 21
4. ANALYSIS POPULATIONS/SETS 22
5. STATISTICAL ANALYSES 23
5.1 General ConsiderationS 23
5.2 Patient Disposition 24
5.3 Primary Endpoint(s) Analysis 24
5.3.1 Definition of Primary Endpoints 24
5.3.2 Main Analytical Approach for Primary Endpoint(s) 25
5.3.3 Sensitivity Analyses for Primary Endpoint(s) 25
5.3.4 Supplementary Analyses for Primary Endpoint(s) 26
5.3.5 Subgroup Analyses for Primary Endpoint(s) 28
5.4 Secondary EndpointS Analysis(ses) 29
5.4.1 Secondary Endpoints 29
5.4.1.1 Continuous Secondary Endpoints 34

5.4.1.2 Binary Secondary Endpoints 35
5.5 Exploratory Endpoint(s) Analysis 37
5.6 Safety Analyses 37
5.6.1 Extent of Exposure 37
5.6.2 Adverse Events 38
5.6.3 Laboratory Data 39
5.6.4 Vital Signs 39
5.6.5 Ocular Assessments 39
5.7 Other Analyses 40
5.7.1 Summaries of Conduct of Study 40
5.7.2 Summaries of Treatment Group Comparability 40
5.7.3 Pharmacokinetic Analyses 40
5.7.4 Pharmacodynamic Analyses 41
5.7.5 Immunogenicity Analyses 41
5.7.6 Biomarker Analyses 43
5.7.7 Analyses of China Subpopulation 43
5.8 Analyses for COVID-19 44
5.8.1 Study Conduct Analyses for COVID-19 44
5.8.2 Efficacy Analyses for COVID-19 44
5.8.3 Safety Analyses for COVID-19 45
5.9 Interim Analyses 46
6. REFERENCES 47

LIST OF TABLES

Table 1 Additional Estimand Attributes and Analysis Methods for Continuous Secondary Endpoints 30
Table 2 Additional Estimand Attributes and Analysis Methods for Binary Secondary Endpoints 32
Table 3 Roche COVID-19 SMQ (narrow) Preferred Terms for Confirmed Cases 45

LIST OF FIGURES

Figure 1 Study Schema 13
Figure 2 Algorithm for IxRS-Determined Faricimab Personalized Treatment Interval Dosing Intervals 16

LIST OF APPENDICES

Appendix 1 Protocol Synopsis for Study BALATON (GR41984)..... 49
Appendix 2 Protocol Synopsis for Study COMINO (GR41986)..... 58

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
Ang-2	angiopoietin-2
ANCOVA	analysis of covariance
APTC	anti-Platelet Trialists' Collaboration
AESI	adverse events of special interest
BCVA	best-corrected visual acuity
BM	Bruch's membrane
BRVO	branch retinal vein occlusion
CFP	color fundus photograph
CI	confidence interval
CMH	Cochran Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRC	central reading center
CRVO	central retinal vein occlusion
CSR	clinical study report
CST	central subfield thickness
DR	diabetic retinopathy
ETDRS	early treatment diabetic retinopathy study
FFA	fundus fluorescein angiography
HRVO	hemiretinal vein occlusion
iDMC	independent Data Monitoring Committee
IgG1	immunoglobulin G1
ILM	internal limiting membrane
IOI	intraocular inflammation
IOP	intraocular pressure
ITT	intent to treat
IVT	intravitreal
IxRS	interactive Voice/Web Response System
LOCF	last observation carried forward
LPLV	last patient last visit
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
NEI VFQ-25	National Eye Institute 25-Item Visual Functioning Questionnaire

NI	non-inferiority
OCT-A	optical coherence tomography angiography
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
PTI	personalized treatment interval
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SS-OCT	swept-source optical coherence tomography
SMQs	standardized MedDRA queries
VEGF -A	vascular endothelial growth factor –A

1. INTRODUCTION

Retinal vein occlusion (RVO) is one of the most common retinal vascular disorders and is associated with varying degrees of visual loss (Hayreh et al. 1994). RVO has been reported as the second leading cause of blindness for patients with retinal vascular disease, following diabetic retinopathy (DR) (Cugati et al. 2006; Klein et al. 2008; Rogers et al. 2010; Yasuda et al. 2010). The main types of RVO include branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO), and central retinal vein occlusion (CRVO). Patients with RVO were found to have the highest vitreous levels of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) among all retinal vascular diseases (Aiello et al 1994; Regula et al. 2016). Increased levels of Ang-2 and VEGF in retinal tissue result in pathological changes in the retina, and in many patients also leads to macular edema that is accompanied with a decrease in vision. A hallmark of RVO is the characteristic pattern of retinal hemorrhages, tortuous and dilated retinal veins across the affected area of retina (one quadrant in BRVO, two quadrants in HRVO and the entire retina in CRVO).

Despite anti-VEGF being the most effective therapy for macular edema due to RVO, data from anti-VEGF clinical trials showed that many patients do not achieve optimal best-corrected visual acuity (BCVA) and anatomical outcomes, and many require frequent long-term injections to maintain the gains achieved during initial intensive treatment. Moreover, real-world data analyses suggested that outside of trials many patients with RVO do not achieve the gains reached in clinical trials due to suboptimal injection frequency (Vaz-Pereira et al. 2017; Wecker et al. 2017; Jumper et al. 2018; Callizo et al. 2019; Pearce et al. 2020). The data suggest that many patients with macular edema due to BRVO and the majority of patients with macular edema due to CRVO require close monitoring and treatment for longer periods of time and that more durable and efficacious treatment options are needed (Bhisitkul et al. 2013; Scott et al. 2019).

Faricimab is a humanized full-length bispecific immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to all isoforms of VEGF-A (hereafter referred to as "VEGF") and Ang-2, key factors involved in mediating the pathophysiology of macular edema due to RVO. The Ang-2 and VEGF-binding variable regions of faricimab bind to Ang-2 and VEGF independently and simultaneously with high affinity. Based on the mechanism of action of faricimab, data from nonclinical and clinical trials, and the pathophysiology of macular edema due to RVO, it is hypothesized that faricimab may lead to stabilization of the pathological ocular vasculature and to improved visual and anatomical outcomes in RVO compared with anti-VEGF monotherapies.

The purpose of this document is to provide details of the planned analyses for Phase III Studies GR41984 (BALATON) for BRVO, and GR41986 (COMINO) for CRVO or HRVO.

The designs of these studies are identical with the exception of the inclusion/exclusion criteria, stratification factors and sample size. In this Statistical Analysis Plan (SAP), study equally refers to BALATON or COMINO. China Extension refers to China extension for COMINO. Protocol collectively refers to protocols for both BALATON and COMINO, unless otherwise specified. Study drug refers to faricimab or aflibercept, whereas study treatment refers to faricimab, aflibercept, or the sham procedure.

The analysis plan and the endpoints specified in this document supersede the analysis plan described in the study protocols. This document will address analysis for efficacy, safety, immunogenicity, biomarkers, pharmacokinetics (PK) and pharmacodynamics (PD). Detailed specifications of tables, figures and listings are provided in separate documents.

1.1 OBJECTIVES AND ENDPOINTS

BALATON and COMINO are comprised of two parts: Part 1 (Day 1 through Week 24) and Part 2 (Weeks 24-72). See Section 1.2 for details on the study design.

Part 1 of the trial will compare faricimab 6 mg intravitreal (IVT) every 4 weeks (Q4W) with aflibercept 2 mg IVT Q4W (active comparator) through Week 24 in adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO). The primary trial objective is to evaluate the efficacy of faricimab 6 mg IVT Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the change from baseline in BCVA at Week 24.

Part 2 of the trial will evaluate faricimab 6 mg IVT Q4W administered at masked treatment intervals of Q4W to every 16 weeks (Q16W) based on personalized treatment interval (PTI) dosing criteria. Patients in both Arms A and B will receive faricimab 6 mg IVT according to a PTI dosing regimen from Week 24 through Week 68. See Section 1.2 for details of PTI dosing criteria.

Secondary and exploratory endpoints over time include assessments at each study visit with the exception of endpoints on fundus fluorescein angiography (FFA), color fundus photographs (CFP) and National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25), which are assessed at Week 24, Week 48 and Week 72.

Endpoints evaluating proportions of patients meeting certain criteria over time refers to meeting the criteria at each time point, and summarized across timepoints.

1.1.1 Efficacy Objectives

1.1.1.1 Primary Efficacy Objective

The primary efficacy objective for Part 1 of the study is to evaluate the efficacy of faricimab 6 mg IVT Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the following endpoint: Change from baseline in BCVA at Week 24.

1.1.1.2 Secondary Efficacy Objectives

The secondary efficacy objective for Part 1 of this study (i.e., through Week 24) is to evaluate the efficacy of faricimab 6 mg Q4W compared with aflibercept 2 mg Q4W based on additional endpoints. The secondary efficacy objective for Part 2 of this study (i.e., Week 24 through Week 72) is to evaluate the efficacy of faricimab administered according to the PTI dosing regimen. The secondary endpoints (for both Part 1 and Part 2) are listed below.

Endpoints at both primary analysis (through Week 24) and the final analysis:

- Change from baseline in BCVA over time
- Proportion of patients gaining $\geq$ 15, $\geq$ 10, $\geq$ 5, or $>$ 0 letters in BCVA from baseline over time
- Proportion of patients avoiding a loss of $\geq$15, $\geq$10,or $\geq$5, letters in BCVA from baseline over time
- Proportion of patients achieving $\geq$ 84 letters (20/20 Snellen equivalent) in BCVA over time
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better (BCVA $\geq$ 69 letters) over time
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse (BCVA $\leq$ 38 letters) over time
- Change from baseline in central subfield thickness (CST) over time
  - CST is defined as the distance between internal limiting membrane (ILM) and Bruch's Membrane (BM), as measured in μm as assessed by CRC.
- Change from baseline in NEI VFQ-25 composite score over time
- Proportion of patients with absence of macular edema, defined as CST of $<$325 μmover time
  - CST for Cirrus spectral-domain optical coherence tomography (SD-OCT) or Topcon SD-OCT were standardized to Spectralis SD-OCT by the central reading center.
- Proportion of patients with absence of intraretinal fluid over time
  - Intraretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of subretinal fluid over time
  - Subretinal fluid is as measured in the central subfield (center 1 mm)
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time

Endpoints at the primary analysis:

- Proportion of patients gaining $\geq$ 15 letters in BCVA from baseline at Week 24

Endpoints at the final analysis:

- Change from baseline in BCVA averaged over Week 64, Week 68 and Week 72
- Proportion of patients on a Q4W, every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W treatment interval at Week 68
  - treatment intervals at Week 68 will be defined as the treatment interval decision followed at Week 68

Endpoints assessed in reference to Week 24 at the final analysis:

- Change from Week 24 in BCVA over time
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24 over time

1.1.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective is to evaluate the efficacy of faricimab based on additional endpoints. The exploratory endpoints are listed below and will be assessed at the primary analysis (through Week 24) and the final analysis.

- 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

1.1.2 Safety Objectives

The safety objective for this study is to evaluate the safety and tolerability of faricimab on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to Adverse Event (AE) Severity Grading Scale (as defined in Protocol Table 2)
- Incidence and severity of non-ocular adverse events, with severity determined according to AE Severity Grading Scale (as defined in Protocol Table 2)

1.1.3 Pharmacokinetic Objectives

The PK objective for this study is to characterize the faricimab PK profile on the basis of the following endpoint: Plasma concentration of faricimab over time.

The exploratory PK objective for this study is to explore the concentration--effect relationship for visual acuity and other endpoints (e.g., anatomic measures) on the basis of the following endpoint: Concentration of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time.

1.1.4 Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the antibody immune response to faricimab on the basis of the following endpoint: Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint: Relationship between ADA status and efficacy, safety, or PK endpoints.

1.1.5 Exploratory Biomarker Objectives

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time
- Relationship between anatomic measures and visual acuity

1.2 STUDY DESIGN

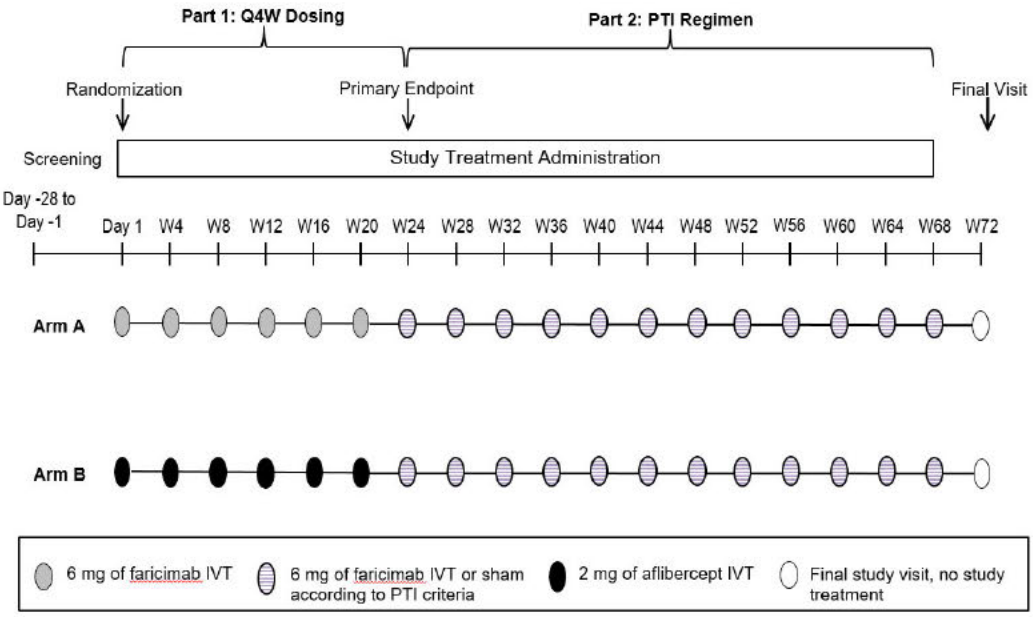
The Protocol Synopsis for BALATON and COMINO are in Appendix 1 and Appendix 2, respectively.

BALATON and COMINO are Phase III, multicenter, randomized, double-masked, active comparator-controlled, parallel-group studies evaluating the efficacy, safety, and pharmacokinetics of faricimab administered by IVT 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 PTI dosing regimen in patients with macular edema due to BRVO (BALATON), and CRVO or HRVO (COMINO). The study schema is shown in Figure 1.

BALATON and COMINO are comprised of two parts: Part 1 (Day 1 through Week 24) will compare faricimab Q4W versus aflibercept (active comparator) Q4W; Part 2 (Weeks

24-72) will evaluate faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria where all patients receive faricimab PTI dosing.

Figure 1 Study Schema



IVT = intravitreal; PTI = personalized treatment interval; Q4W = every 4 weeks; W = Week.

In Part 1 (Q4W Dosing), approximately 570 patients for BALATON and 750 patients for COMINO will be randomized during the global enrollment phase of the study in a 1:1 ratio to one of two treatment arms, with treatment defined as follows:

- Arm A: Patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20 (6 injections).
- Arm B (comparator arm): Patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20 (6 injections).

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

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

After completion of the global enrollment phase, additional participants may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan to ensure a total of approximately 62 and 82 participants in the China subpopulation for BALATON and COMINO, respectively. The global population will

include all participants enrolled during the global enrollment phase (including participants enrolled in mainland China, Hong Kong, and Taiwan during that phase), and the China subpopulation will include all patients enrolled in mainland China, Taiwan and Hong Kong (during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation (see Section 5.7.7 for China subpopulation analyses).

The primary analysis for the global population will be performed when all patients from the global enrollment phase have either completed the study through Week 24 or have discontinued from the study prior to Week 24, whichever comes later (i.e., timing is defined as the primary analysis last patient last visit [LPLV]), and all data collected prior to the primary LPLV in the global enrollment phase are in the database, and cleaning and verification of critical variables have been completed. At the time of the primary analysis, the study will be ongoing. Results of the primary analysis, summarized by treatment group, may be reported to the public before completion of the study. However, patients, masked study site personnel, and central reading center (CRC) personnel will remain masked to individual treatment assignment until the global study clinical study report through Week 72 is completed.

The final analysis for the global population will be performed when all patients from the global enrollment phase have either completed the study through Week 72 or have discontinued early from the study, whichever comes later, and all data from the global enrollment phase are in the database, and cleaning and verification of critical variables have been completed.

Primary analysis for the China subpopulation of each study will be performed when all patients from China (i.e., during both the global enrollment phase and the China extension) within a specific study have either completed the study through Week 24 or have discontinued from the study prior to Week 24, whichever comes later, and all data collected are in the database, and cleaning and verification of critical variables have been completed.

A final analysis for the China subpopulation of each study will be performed when all patients from China (i.e., during both the global enrollment phase and the China enrollment phase) within a specific study have either completed the study through Week 72 or have discontinued early from the study, whichever comes later, and all data are in the database, and cleaning and verification of critical variables have been completed.

Faricimab Interval Determination for Part 2 (PTI Regimen)

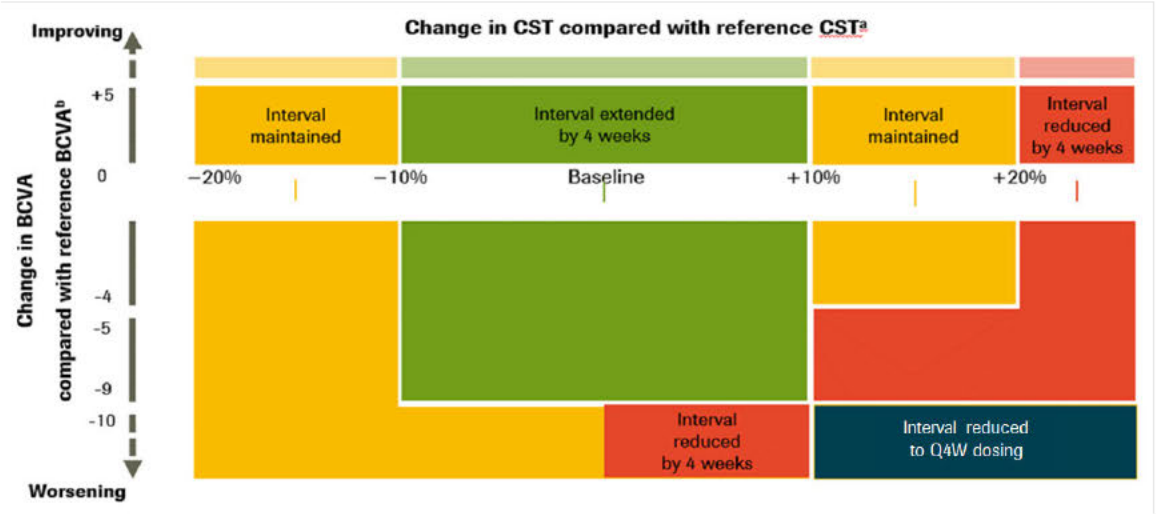
In Part 2 of the study, all patients will visit the clinic Q4W from Week 24 through Week 68 and receive either sham treatment or faricimab 6 mg IVT, depending on their PTI dosing regimen. The first visit that a patient could receive sham treatment is Week 24. Faricimab PTI decisions will be automatically calculated by the interactive

Voice/Web Response System (IxRS) based on the PTI criteria described in this section. Faricimab dosing visits are defined as those visits when the patient receives faricimab 6 mg IVT 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 compared with the reference BCVA, 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 (Figure 2). Reference CST was adjusted if CST decreased by >10% from the previous reference CST for two 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 three 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 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.

Figure 2 Algorithm for IxRS-Determined Faricimab Personalized Treatment Interval Dosing Intervals



BCVA = best-corrected visual acuity; CST = central subfield thickness between internal limiting membrane (ILM) to Bruch's membrane (BM); IxRS = interactive web-based response system; Q4W = every 4 weeks.

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

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

The algorithm used by the IxRS for interval decision-making, which is based on the relative change of the CST and BCVA at faricimab dosing visits compared with the reference CST and reference BCVA, is outlined below and in Figure 2. The faricimab dosing interval will be extended, maintained, or reduced as follows.

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

  - If the CST value is increased by $>20\%$ without an associated ≥ 10-letter BCVA decrease
  - If the CST value is increased by $\leq 10\%$ with an associated BCVA decrease of ≥ 10-letters
- Interval reduced to Q4W
  - If the CST value is increased by $>10\%$ with an associated ≥ 10-letter BCVA decrease

1.2.1 Treatment Assignment and Masking

Patients will be randomized in a 1:1 ratio to one of two study treatment arms (faricimab Q4W or aflibercept Q4W through Week 20). After randomization and at each study treatment visit (i.e., including Day 1), the IxRS will assign the appropriate study treatment kit to be used.

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

BALATON (BRVO):

- Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (≥ 55 letters vs. ≤ 54 letters)
- Region (United States and Canada, Asia, and the rest of the world)

COMINO (C/HRVO):

- Baseline BCVA ETDRS letter score (≤ 34 letters, 35-54 letters, and ≥ 55 letters)
- Region (United States and Canada, Asia, and the rest of the world)

A stratified permuted-block randomization scheme will be used to obtain approximately a 1:1 ratio among the treatment groups overall and within each of the above strata. For analyses, the stratification factors as recorded in IxRS will be used.

The randomization method implemented in the China extension study will be the same as that implemented in the global population.

Statistics Collaborative, Inc. (StatCollab), as an independent Data Coordinating Center (iDCC), conducted randomization audits of the randomization and kit allocation data provided by Signant Health (IxRS vendor). Two randomization audits were performed (first review in July 2021 and second review in February 2022). No major randomization issues were found. For all audit findings, appropriate corrective and preventive actions were undertaken. The corresponding report will be provided by the iDCC at study end, the report will be filled to the electronic Trial Master File.

This is a double-masked study, and only site staff members in unmasked roles, as specified in Section 4.2.2.2 of the protocol, are unmasked in both Part 1 and Part 2. There must be a minimum of two investigators per site to fulfill the masking requirements

of this study and both investigators are required to be present at each scheduled study visit.

To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered.

1.2.2 Independent Review Facility

Ocular Imaging

All ocular images are obtained by trained site personnel at the study sites and forwarded to CRCs, for independent analysis and storage. As part of the screening process, the CRCs evaluate CFPs and SD-OCT (or swept-source optical coherence tomography [SS-OCT]) images to provide an objective assessment of patient eligibility. The diagnosis of macular edema due to RVO must be confirmed by the CRC. During the study treatment period, the CRCs provide a masked evaluation of all ocular images including CFP, FFA, SD-OCT or SS-OCT, and optional coherence tomography angiography (OCT-A). The data resulting from this masked review of ocular images are forwarded to the Sponsor and additionally, the SD-OCT CST values are forwarded to the IxRS for treatment interval determination.

Anti-Platelet Triallists' Collaboration (APTC)

APTC events that are identified during the study are externally adjudicated on an ongoing basis. A dossier of available information on each case of interest is provided to the external expert adjudicators for their review and assessment.

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) monitors safety and study conduct on an ongoing basis and the iDMC's responsibility of monitoring ends after the primary analysis. Members of the iDMC are external to the Sponsor and follow a charter that outlines the iDMC's roles and responsibilities. The iDMC meets approximately every 6 months (frequency adjustable as required) to evaluate unmasked ocular and non-ocular safety events. After reviewing the data, the iDMC provides a recommendation to the Sponsor as described in the iDMC Charter. Final decisions rest with the Sponsor. Any outcome of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

A nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary analysis, it is estimated that three safety interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses would be performed with a family-wise significance level of 0.0497. The actual adjustment will depend on the actual number of iDMC interim safety reviews. This type I error adjustment is not expected to impact sample size or power.

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint is the change from baseline in BCVA at Week 24. The following hypothesis will be tested:

- Non-inferiority (NI) of faricimab Q4W compared with aflibercept Q4W at Week 24 in the intent to treat (ITT) population as defined in Section 4 (at a one-sided 0.02485 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population (at a two-sided 0.0497 significance level)

The hypotheses on the primary endpoint will be tested in the order shown above, proceeding sequentially starting from the non-inferiority test and only testing the superiority after achieving statistical significance on the non-inferiority test. There is no impact on the type I error rate for the superiority test following the NI test, therefore a claim of superiority after NI can be made without multiplicity adjustment (Ke et al. 2012).

The null and alternative hypotheses for NI test are as follows:

- The null hypothesis (H_0) is: $\mu^{faricimab} - \mu^{aflibercept} \leq -4$ letters
- The alternative hypothesis (H_a) is: $\mu^{faricimab} - \mu^{aflibercept} > -4$ letters

where $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA at Week 24 for the faricimab Q4W arm and the active comparator (aflibercept Q4W) arm, respectively.

If the lower bound of a two-sided 95.03% confidence interval (CI) for the difference of two treatments is greater than −4 letters (the NI margin), the test is considered positive and IVT 6 mg faricimab administered Q4W is considered non-inferior to IVT 2 mg aflibercept administered Q4W.

The null and alternative hypotheses for superiority test are as follows:

- The null hypothesis (H_0) is: $\mu^{faricimab} - \mu^{aflibercept} = 0$ letters
- The alternative hypothesis (H_a) is: $\mu^{faricimab} - \mu^{aflibercept} \neq 0$ letters

where $\mu^{faricimab}$ and $\mu^{aflibercept}$ are the expected change from baseline in BCVA at Week 24 for the faricimab Q4W arm and the active comparator (aflibercept Q4W) arm, respectively.

If the lower bound of a two-sided 95.03% CI for the difference of two treatments is greater than 0 letters, the test is considered positive and IVT 6 mg faricimab administered Q4W is considered superior to IVT 2 mg aflibercept administered Q4W.

2.1 NON-INFERIORITY MARGIN

Non−inferiority hypothesis testing for the primary endpoint of the change from baseline in BCVA at Week 24 (Month 6) will be performed using a 4−letter NI margin for both BRVO

and CRVO (includes HRVO cases) studies. The NI margin is selected based upon the aflibercept pivotal trials in BRVO and CRVO. The pathological states are part of the spectrum of the same disease caused by obstruction in central, hemi-central, or branch retinal vein, with CRVO presenting as the most severe form. While there is only one BRVO study of aflibercept versus control available, there are multiple CRVO studies of aflibercept versus sham available. The NI margin rationale is therefore built upon the past BRVO and CRVO study results.

The VIBRANT study (Campochiaro et al. 2015) in BRVO randomized 183 patients in a 1:1 ratio to 2 mg IVT aflibercept or laser control. At Week 24 (Month 6), patients receiving aflibercept Q4W gained on average 17 letters from baseline compared to 6.9 letters in the control arm, with a 95% CI for the difference between treatments of [7.1, 14.0] letters.

The COPERNICUS (Boyer et al. 2012) and GALILEO (Holz et al. 2013) studies in CRVO randomized 189 and 177 patients respectively in a 3:2 ratio to 2 mg IVT aflibercept or sham procedure. At Month 6 in the COPERNICUS study, patients receiving aflibercept Q4W gained on average 17.3 letters from baseline compared to a loss of 4 letters in the control arm, for a 95% CI for the difference between treatments of [17.3, 26.1]. The corresponding results for the GALILEO study were a gain on average of 18 letters for aflibercept versus 3.3 letters from the control arm, with a 95% CI for the difference between treatments of [10.7, 18.7].

The NI margin of 4 letters for the mean change from baseline in BCVA at Week 24 is chosen based on the statistical rationale of preserving approximately 50% of the benefit compared with sham control as estimated by the lower limit of a 95% CI. Based on the aflibercept pivotal trials described, the proposed NI margin of 4 letters preserves between 44% (calculated as [(7.1−4)/7.1]=43.7%) and 77% (calculated as [(17.3−4)/17.3]=76.9%) of the least estimated benefit of aflibercept relative to control.

This NI boundary is also supported from a clinical perspective and is in alignment with the general considerations highlighted in Section 2 of the European guidance document (EMA 2005). The NI margin should be small enough to allow a conclusion that the new treatment is not inferior to the active control to an unacceptable extent on the basis of a combination of clinical judgment and statistical reasoning. From a clinical perspective, a loss of 5 letters (one ETDRS line) between treatments would be considered clinically relevant, and therefore a NI margin of 4 letters provides assurance that there would be no important loss of efficacy if the new treatment is used instead of the reference product.

3. SAMPLE SIZE DETERMINATION

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately 570 patients for BALATON

and 750 patients for COMINO. Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B). The primary comparison will be between the active comparator (aflibercept Q4W) and the faricimab Q4W arm at Week 24.

A sample size of approximately 285 patients for BALATON and 375 patients for COMINO in each arm will provide $>90\%$ power to show NI of faricimab to aflibercept in the change in BCVA at Week 24 in the ITT population, using a NI margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between the two treatment arms
- Standard deviation (SD) of 13 letters for BALATON and 15 letters for COMINO for the change from baseline in BCVA at Week 24
- Two-sample t-tests
- 2.5% one-sided type I error rate
- 10% dropout rate

Furthermore, a sample size of approximately 285 patients for BALATON and 375 patients for COMINO per arm will provide greater than 80% power to show a 3.5-letter superiority of faricimab over aflibercept, under the same SD, test, and dropout assumptions above, and a two-sided type I error rate of 5%.

The enrollment ended after 553 and 730 patients were enrolled in BALATON and COMINO, respectively. The planned sample size aimed to also provide adequate power for the Per Protocol analysis accounting for potential impact of coronavirus disease-19 (COVID-19); however, as the COVID-19 impact was less than originally anticipated, the Sponsor decided to stop recruitment with an under-recruitment of about 3%. The final sample size provided $>90\%$ power for the NI assessment and $>80\%$ power for the superiority test.

3.1 SAMPLE SIZE FOR THE CHINA EXTENSION

After the global enrollment phase has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the People's Republic of China. It is anticipated that approximately 62 patients will be enrolled (including patients who have already enrolled during the global enrollment phase) for BALATON, and approximately 82 patients will be enrolled (including patients who have already enrolled during the global enrollment phase) for COMINO. The data from China patients enrolled during the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses but will be included in the China subpopulation analysis.

4. ANALYSIS POPULATIONS/SETS

The analysis populations presented in this section are based on patients enrolled during the global enrollment phase of the study and will not include the China extension, unless otherwise specified. The analysis plans for the China extensions are presented in Section 5.7.7.

The following populations are defined:

Population	Definition
ITT	All patients who are randomized in the study. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization. Note: Subjects who were wrongly randomized to one study (BALATON or COMINO), discontinued without treatment, and then randomized to the other study (COMINO or BALATON respectively) are included in the latter study only.
Per-Protocol	All patients randomized in the study who receive at least one dose of study treatment and who do not have a major protocol violation that impacts the efficacy evaluation. Patients will be grouped according to actual treatment received through Week 20. If by error, a patient receives a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group will be as randomized. Prior to study unmasking, protocol deviations will be reviewed and a determination of the definition of the population for per protocol analysis will be made.
Safety-Evaluable	All patients who receive at least one injection of active study drug (faricimab or aflibercept) in the study eye. Patients will be grouped according to actual treatment received through Week 20. If by error a patient receives a combination of different active study drugs (faricimab and aflibercept) in the study eye, the patient's treatment group will be as randomized.
Pharmacokinetic-Evaluable	Safety-evaluable patients with at least one plasma sample, and if sufficient dosing information (dose and dosing time) is available. Patients will be grouped according to actual treatment received (as defined for Safety-Evaluable population)
Faricimab Pharmacokinetic-Evaluable	Pharmacokinetic-Evaluable patients from faricimab treatment group (as defined for Pharmacokinetic-Evaluable population)
Immunogenicity Analysis	The immunogenicity prevalence set will consist of all patients randomized to or who received faricimab with at least one determinant anti-drug antibody (ADA against faricimab) assessment. Patients will be grouped according to actual treatment received as described for the Safety-Evaluable population or if no treatment is received prior to study discontinuation, according to treatment assigned. The immunogenicity incidence set will consist of all patients who received faricimab with at least one determinant ADA assessment after the initiation of faricimab treatment. Patients will be grouped according to actual treatment received as described for the Safety-Evaluable population.

5. STATISTICAL ANALYSES

Unless otherwise specified, the analyses described in this section are based on patients enrolled during the global enrollment phase (excluding the China extension). Details of the planned analyses, including any additional analyses needed to support China marketing applications, will be provided in Section 5.7.7.

The analyses timing for primary and final analyses are provided in Section 1.2.

5.1 GENERAL CONSIDERATIONS

Efficacy analyses will be based on the ITT population and grouped according to the treatment assigned at randomization unless otherwise specified. A supplementary analysis based on the per-protocol population will also be conducted for the primary endpoint. At the primary analysis, efficacy analysis will be based on data through Week 24 (efficacy endpoints at Week 24 are measured before the Week 24 injection and will be included in the comparative analysis).

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by the following stratification factors, as recorded in IxRS:

- Baseline BCVA ETDRS letter score, as assessed on Day 1 ($\geq$55 letters vs. $\leq$54 letters for BALATON; and $\leq$ 34 letters, 35–54 letters, and $\geq$ 55 letters for COMINO)
- Region (United States and Canada, Asia, and the rest of the world).

Continuous outcomes will be analyzed using a mixed model for repeated measures (MMRM) unless otherwise specified. Binary secondary endpoints will be analyzed using stratified estimation for binomial proportions. Nominal superiority p-values will be provided for secondary and exploratory endpoints where applicable for reference purposes. The estimates and CIs will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment arm and for the difference in means or proportions between the aflibercept Q4W arm and the faricimab Q4W arm (where applicable). All CIs will be two-sided and at the 95.03% level.

Invalid BCVA (BCVA values that are confirmed to be inaccurate, due to the BCVA test being performed incorrectly) will be excluded from the analyses. Non-standard BCVA data (such as assessed by ETDRS BCVA testing with prior visit refraction, BCVA test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor) will be included in the analyses.

Central Subfield Thickness is assessed by the CRCs and standardized to Spectralis SD-OCT (distance measured between ILM and BM). Analysis will be based on the same type of read over time within patient. When available, algorithmic reads with a predefined centerpoint (as opposed to manual reads) of CST values will be used for analysis.

All safety analyses will be performed in the safety-evaluable population unless otherwise specified. At the primary analysis, safety analysis will be based on data before the Week 24 visit date, with the exception of assessments measured at Week 24 but before the administration of the Week 24 injection such as labs, vital signs (where applicable) and ocular assessments in Section 5.6.5, where data through Week 24 will be used.

Baseline for non-safety analyses is defined as the last available measurement obtained on or prior to randomization. Baseline for safety analyses is defined as the last available measurement prior to first exposure to study drug. Patients with missing baseline assessments will not be imputed. Data collected in scheduled and unscheduled visits will be mapped to visits that appear in the schedule of assessments per the protocol using the actual study day of assessment. If there are multiple values in the same visit window, the value closest to the target study day will be used in the analysis.

Due to extended exportation timelines of PD, PK, and ADA samples from mainland China, a small percentage of data from these samples may not be included in the primary analysis. All PD, PK, and ADA data will be included in the final analysis.

5.2 PATIENT DISPOSITION

The number of patients randomized will be tabulated by country, site, and treatment arm. At the primary and final analysis, patient disposition (the number of patients randomized, treated, and completing through the primary endpoint timing, as well as overall through the end of study) will be tabulated by treatment arm in the ITT population. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

5.3 PRIMARY ENDPOINT(S) ANALYSIS

5.3.1 Definition of Primary Endpoints

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

- Population: Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population)
- Variable: Change from baseline in BCVA at Week 24
- Treatments (as randomized):
  - Experimental: Faricimab 6 mg IVT Q4W
  - Control: Aflibercept 2 mg IVT Q4W
- Intercurrent events prior to Week 24:
  - Discontinuation of study treatment due to AEs or lack of efficacy

- Use of any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of Protocol)

- Handling of intercurrent events:
  - A treatment policy strategy will be applied to all intercurrent events.

5.3.2 Main Analytical Approach for Primary Endpoint(s)

The rationale of using ITT population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including use of prohibited therapies) is administered. Additional analysis applying hypothetical strategy to all intercurrent events, applying hypothetical strategy to COVID-19 related intercurrent events and treatment policy strategy to non-COVID-19 related intercurrent events, and analysis on the per-protocol population will also be provided (details see Section 5.3.4).

The main analysis for the primary endpoint will be performed using a MMRM. The model will include the change from baseline at Weeks 4-24 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), as well as randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an autoregressive (AR) (1) covariance structure may be fitted.

Missing data will be implicitly imputed by the MMRM model assuming missing at random (MAR). Additional analyses using different missing data handling approaches will be included as sensitivity analyses (Section 5.3.3). The proportion of patients who receive prohibited therapy or who discontinue study drug due to lack of efficacy or adverse events is anticipated to be low.

5.3.3 Sensitivity Analyses for Primary Endpoint(s)

The following sensitivity analysis using a different handling of missing data will be performed for the primary efficacy endpoint to evaluate the robustness of the main analysis of the primary endpoint finding:

Multiple imputation:

The population, intercurrent events, and handling of intercurrent events will be the same as in the main analysis, however missing primary endpoint BCVA data will be imputed via multiple imputation. The analysis will be performed using an analysis of covariance (ANCOVA) model with adjustment for the following covariates: treatment group, baseline BCVA (continuous), as well as randomization stratification factors. The dependent variable in the ANCOVA model is the Week 24 assessment in change from baseline in BCVA score.

Missing BCVA data will be assumed to be missing not at random (MNAR). Each arm will be imputed separately. Imputation will only be performed for patients with missing BCVA data at Week 24.

An approximate Bayesian bootstrap method will be used for imputation. These patients will be assumed to have worse outcomes compared to the rest of the population and will be imputed from patients with non-missing BCVA data with the worst outcomes.

Suppose there are n_1 patients with an assessment from at Week 24 (i.e., patients with non-missing primary endpoint data), and n_0 patients that are missing the Week 24 assessment. The imputation steps will be as follows:

1. Among patients with an assessment at Week 24, identify 20% of the patients with the worst values for change in BCVA score from baseline at Week 24. Call this Y_{obs}.
2. Draw n_1 observations randomly with replacement from Y_{obs} to create a new data set Y_{obs}*.
3. Draw n_0 values randomly with replacement from Y_{obs}* to obtain the missing values.

The imputation will be implemented in statistical analysis system (SAS) using the three standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step. The number of imputations will be set to 100.

1. The missing data will be filled in 100 times to generate 100 imputed datasets.
2. Each of the 100 imputed datasets will be analyzed using the ANCOVA model.
3. The results from the 100 imputed data sets will be combined for inference following the methodology developed by (Rubin 1987).

The SAS codes for multiple imputation will be added to a separate table/listing/graph mockup document (Data Analysis Plan – Module 2) prior to the study unmasking; and will also be included in the Analysis Data Reviewer's Guide.

5.3.4 Supplementary Analyses for Primary Endpoint(s)

The following supplementary analyses will be performed for the primary efficacy endpoint to provide further understanding of the treatment effect.

1. Per-protocol analysis:

The per-protocol analysis will follow the same intercurrent events, handling of intercurrent events, analysis method and handling of missing data as the main analysis for the primary endpoint (Section 5.3.2) with the exception that the analysis will be based on the per-protocol population (Section 4). Patients with major protocol deviations that impact the efficacy evaluation will be excluded from the analysis.

2. Analysis distinguishing COVID-19 and non-COVID-19 related intercurrent events. The estimand is defined as follows:

- Population: Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population)
- Variable: Change from baseline in BCVA at Week 24
- Treatments (as randomzied):
  - Experimental: Faricimab 6 mg IVT Q4W
  - Control: Aflibercept 2 mg IVT Q4W
- Intercurrent events prior to Week 24:
  - Discontinuation of study treatment due to AEs or lack of efficacy not due to COVID-19
  - Use of any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of Protocol) not due to COVID-19
  - Discontinuation of study treatment due to COVID-19
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19
  - Missed dose(s) with potentially major impact on efficacy due to COVID-19
  - COVID-19 death
- Handling of intercurrent events:
  - A treatment policy strategy will be applied to intercurrent events not related to COVID-19, where all observed values will be used regardless of the occurrence of the intercurrent event
  - A hypothetical strategy will be applied to intercurrent events related to COVID-19, where all values will be censored after the intercurrent event
- Population-level summary: Difference in adjusted means between treatment groups

All observed data will be included in the analysis regardless of whether or not a patient has experienced an intercurrent event unrelated to COVID-19; the treatment policy strategy is applied in a best attempt to approximate the effectiveness of the treatment under real world conditions (in the absence of COVID-19). If a patient experiences an intercurrent event related to COVID-19, all values following the intercurrent event will be set to missing. The rationale for applying the hypothetical strategy for COVID-19 related intercurrent events is to discard potentially confounding impacts of the pandemic, and estimate the treatment effect in the absence of COVID-19 assuming COVID-19 will not be present or will not have the same impact in the future.

Data censored after intercurrent events following hypothetical strategy and missing data due to reasons other than intercurrent events will both be implicitly imputed by the MMRM model assuming MAR. The rationale of MAR assumption for data censored after COVID-19 related intercurrent events following hypothetical strategy is based on the assumption that patients would behave similarly to other patients in the same

treatment group with similar covariates, had the patients not had such intercurrent events.

3. Analysis using hypothetical strategy for all intercurrent events:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 5.3.2). However, all intercurrent events will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event, to estimate a treatment effect in the absence of intercurrent events. Data censored after intercurrent events following hypothetical strategy and missing data due to reasons other than intercurrent events will both be implicitly imputed by the MMRM model assuming MAR.

5.3.5 Subgroup Analyses for Primary Endpoint(s)

The following subgroups will be analyzed with respect to the primary efficacy endpoint using the same method as specified above for the primary endpoint within each subgroup (except in the case of baseline BCVA and region subgroup where the baseline covariate consisting of the BCVA stratification factor and region stratification, respectively, will be removed from the model). A forest plot will be presented to summarize the results. The subgroup categories may be combined if there is not enough representation of a specific subpopulation.

- Baseline BCVA (based on stratification factors)
  - BALATON (BRVO): ≤54 letters and ≥55 letters
  - COMINO (C/HRVO): ≤34 letters, 35-54 letters, and ≥55 letters
- Baseline BCVA (low vision of ≤23 letters and ≥ 24 letters)
  - Analysis will be performed should a sufficient sample size be available to draw meaningful conclusions.
- Region (United States and Canada, Asia, and the rest of the world)
- Age (<65 years and ≥65 years)
- Gender (female and male)
- Race (White, Asian, and other)
- Baseline RVO status (CRVO and HRVO)
  - Only applies to COMINO.

At the final analysis, analyses in Section 5.3 will be performed for the endpoint of BCVA change from baseline averaged over Weeks 64, 68 and 72, with the exception that no comparisons between treatment groups will be made since all patients will receive faricimab during Part 2 of the study. Differences between groups will not be assessed and nominal p-values will not be provided.

5.4 SECONDARY ENDPOINTS ANALYSIS(SES)

5.4.1 Secondary Endpoints

The following intercurrent events and handling of intercurrent events will be used for all secondary endpoints unless specified otherwise. Note that the time period of intercurrent events may differ for different secondary endpoints, see details in Table 1 and Table 2.

- Intercurrent events:
  - Discontinuation of study treatment due to AEs or lack of efficacy
  - Use of any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of Protocol)
- Handling of intercurrent events (same as the main analysis for the primary endpoint):

A treatment policy strategy will be applied to all intercurrent events.

Table 1 and Table 2 provide additional attributes of the estimand and analysis methods for the continuous and binary secondary endpoints, respectively. Details of the estimand and analysis methods will be provided in the subsequent sections.

At the primary analysis, nominal superiority p-values will be included for secondary endpoints for reference purposes. No formal superiority test will be performed for secondary endpoints. At the final analysis, no comparisons between treatment groups will be made since all patients will receive faricimab during Part 2 of the study. Differences between groups will not be estimated and nominal p-values will not be provided.

At the final analysis, secondary endpoints will be summarized over time from baseline to Week 72, and selected secondary endpoints will be summarized by the average over Weeks 64, 68 and 72 as appropriate.

Table 1 Additional Estimand Attributes and Analysis Methods for Continuous Secondary Endpoints

Continuous Secondary Endpoint	Estimand* and Analysis methods	Primary analysis	Final analysis
Group 1 (Endpoints are over time and averaged over Weeks 64, 68 and 72): Change from baseline in BCVA Change from baseline in CST	Variable	Same as endpoint, from baseline through Week 24	Same as endpoint, from baseline through Week 72
	Treatments	Faricimab Q4W, Aflibercept Q4W	F-F PTI, A-F PTI
	Intercurrent Events	Prior to Week 24	Entire study
	Population-level summary	Difference in adjusted means between treatment groups	Adjusted means of each treatment group
	Analysis methods	MMRM as the main analysis of the primary endpoint	MMRM as the main analysis of the primary endpoint
Group 2 (Endpoints are over time): Change from baseline in NEI VFQ-25 composite score	Variable	Same as endpoint, at Week 24	Same as endpoint, at Week 24, 48 and 72
	Treatments	Faricimab Q4W, Aflibercept Q4W	F-F PTI, A-F PTI
	Intercurrent Events	Prior to Week 24	Entire study
	Population-level summary	Difference in adjusted means between treatment groups	Adjusted means of each treatment group
	Analysis methods	ANCOVA	MMRM as the main analysis of the primary endpoint

Table 1 Additional Estimand Attributes and Analysis Methods for Continuous Secondary Endpoints (cont.)

Continuous Secondary Endpoint	Estimand* and Analysis methods	Primary analysis	Final analysis
Group 3 (Endpoints are over time and averaged over Weeks 64, 68 and 72): Change from Week 24 in BCVA	Variable	NA	Same as endpoint, from Week 24 through Week 72
	Treatments	NA	F-F PTI, A-F PTI
	Intercurrent Events		From Week 24 onwards
	Population-level summary		Adjusted means for all patients
	Analysis methods		MMRM as the main analysis of the primary endpoint for ITT patients with the response variables of change in BCVA from Week 24 (patients without evaluable Week 24 BCVA will be excluded)

BCVA=best corrected visual acuity; CST=central subfield thickness; F-F PTI= Faricimab PTI (Faricimab Q4W in Part 1); A-F PTI= Faricimab PTI (Aflibercept Q4W in Part 1 crossover); MMRM= mixed model for repeated measures; NA=not applicable; NEI-VFQ-25= National Eye Institute 25-Item Visual Functioning Questionnaire.

*Intercurrent events and handling of intercurrent events are not listed as they are the same (unless otherwise specified) for all secondary endpoints.

Table 2 Additional Estimand Attributes and Analysis Methods for Binary Secondary Endpoints

Binary Secondary Endpoints	Estimand* and Analysis Methods	Primary analysis	Final analysis
Group 1: Proportion of patients gaining ≥ 15 letters in BCVA from baseline at Week 24	Variable	Same as endpoint	NA
	Treatments	Faricimab Q4W, Aflibercept Q4W	
	Intercurrent Events	Prior to Week 24	
	Population-level summary	Difference in weighted proportions between treatment groups	
	Analysis methods	CMH**	
Group 2 (Endpoints are over time and averaged over Weeks 64, 68 and 72): Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline Proportion of patients avoiding a loss of ≥ 15, ≥ 10, or ≥ 5 letters in BCVA from baseline Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA Proportion of patients with BCVA Snellen equivalent of 20/40 (BCVA-ETDRS 69 letters) or better Proportion of patients with BCVA Snellen equivalent of 20/200 (BCVA-ETDRS≤ 38 letters) or worse Proportion of patients with absence of macular edema, defined as CST of <325 μm Proportion of patients with absence of intraretinal fluid Proportion of patients with absence of subretinal fluid Proportion of patients with absence of both intraretinal fluid and subretinal fluid	Variable	Same as endpoint, from baseline through Week 24	Same as endpoint, from baseline through Week 72
	Treatments	Faricimab Q4W, Aflibercept Q4W	F-F PTI, A-F PTI
	Intercurrent Events	Prior to Week 24	Entire study
	Population-level summary	Difference in weighted proportions between treatment groups	Weighted proportions of each treatment group
	Analysis methods	CMH**	CMH**

Table 2 Additional Estimand Attributes and Analysis Methods for Binary Secondary Endpoints (cont.)

Binary Secondary Endpoints	Estimand* and Analysis Methods	Primary Analysis	Final Analysis
Group 3 (Endpoints are over time and averaged over Week 64, 68 and 72): Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24	Variable	NA	Same as endpoint, from Week 24 through Week 72
	Treatments		F-F PTI, A-F PTI
	Intercurrent Events		From Week 24 onwards
	Population-level summary		Weighted proportions for all patients after Week 24
	Analysis methods		CMH** for ITT population patients with evaluable Week 24 BCVA
Group 4: Proportion of patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68	Variable	NA	Same as endpoint
	Treatments		F-F PTI, A-F PTI
	Intercurrent Events		Entire study
	Population-level summary		Proportions of each treatment group and for all patients
	Analysis methods		Descriptive Statistics

BCVA=best corrected visual acuity; CMH=Cochran Mantel-Haenszel; ETDRS=Early Treatment Diabetic Retinopathy Study; ITT population=full analysis set; A-F PTI= Faricimab PTI (Aflibercept Q4W in Part 1 crossover); F-F PTI= Faricimab PTI (Faricimab Q4W in Part 1); NA=not applicable; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

*Intercurrent events and handling of intercurrent events are not listed as they are the same (unless otherwise specified) for all secondary endpoints.

** The proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factor using the CMH weights. No formal superiority test will be performed. Nominal superiority p-values will be included as appropriate, using a CMH test stratified by the same stratification factors.

5.4.1.1 Continuous Secondary Endpoints

5.4.1.1.1 Continuous secondary endpoints at the primary analysis

Continuous secondary endpoints (Table 1) at the primary analysis will be analyzed using the same estimand and analysis methods for the main analysis of the primary endpoint (Section 5.3.1 and Section 5.3.2), with the exception that change from baseline in NEI VFQ-25 composite score will be analyzed using ANCOVA analysis.

5.4.1.1.2 Continuous secondary endpoints at the Final Analysis

Continuous secondary endpoints (Table 1) at the final analysis will be analyzed using the same analysis methods for the main analysis of the primary endpoint (Section 5.3.2) with the exception that treatment difference will not be estimated and nominal p-values will not be provided, and the same intercurrent events and intercurrent events handling strategies described in Section 5.4.1 with the following additional attributes.

- Population:
  - Change from baseline in BCVA and CST, and NEI VFQ-25 endpoints (Table 1, Group 1 and Group 2): Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population)
  - Change from Week 24 in BCVA (Table 2, Group 3): Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population) with an evaluable Week 24 BCVA.
- Variable: Same as endpoint
- Treatments (as randomized):
  - Experimental: Faricimab PTI (Faricimab Q4W in Part 1)
  - Experimental: Faricimab PTI (Aflibercept Q4W in Part 1 crossover)
- Intercurrent events time period:
  - Change from baseline in BCVA and CST, and NEI VFQ-25 endpoints (Table 1 Group 1 and Group 2): Intercurrent events measured throughout the study will be accounted for
  - Change from Week 24 in BCVA (Table 2 Group 3): Intercurrent events occurring prior to Week 24 will not be accounted for
- Population-level summary: Adjusted means of each treatment group and adjusted means for all patients after Week 24
  - Change from baseline in BCVA and CST, and NEI VFQ-25 endpoints (Table 1 Group 1 and Group 2): Adjusted means of each treatment group
  - Change from Week 24 in BCVA (Table 2 Group 3): Adjusted means for all patients after Week 24

5.4.1.2 Binary Secondary Endpoints

5.4.1.2.1 Binary Secondary Endpoints at Primary Analysis

Binary secondary endpoints (Table 2, Group 1 and Group 2) at the primary analysis will be analyzed using the same population, treatments, intercurrent events and intercurrent handling strategies described in Section 5.4.1 and the following additional attributes:

- Variable: Same as endpoint
- Population-level summary: Difference in weighted proportions between treatment groups

The proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factor of baseline BCVA score and region (as defined in Section 1.2.1) using the Cochran Mantel-Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959). The endpoints on proportion of patients with BCVA Snellen equivalent of 20/200 (BCVA-ETDRS $\leq$ 38 letters) or worse over time will be estimated using a different baseline BCVA strata (BCVA $\leq$ 38 vs. BCVA $>$ 38 letters). Confidence intervals of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrotra and Railkar 2000). No formal superiority tests will be performed. Nominal superiority p-values will be included as appropriate, using a CMH test stratified by the same stratification factors. If the response rate is low, an unstratified analysis may also be performed.

All intercurrent events will be handled using a treatment policy strategy and all observed data will be used. For CMH method, missing data will be imputed using last observation carried forward (LOCF).

In addition, a supplementary analysis will be performed for the following secondary endpoints at the primary analysis.

- Proportion of patients gaining $\geq$ 15 letters in BCVA from baseline at Week 24
- Proportion of patients avoiding a loss of $\geq$15 letters in BCVA from baseline at Week 24

The above supplementary analyses will be analyzed using the same estimand, analysis method as the main analysis for binary secondary endpoints with the following differences:

  - Handling of intercurrent events: A composite variable strategy will be applied where patients with any intercurrent event are assumed to be failures after the intercurrent event

- Missing data (without intercurrent events) handling rules: If BCVA at Week 16, 20 and 24 are all missing, patients will be assumed to be failures at Week 24. Otherwise, missing data will be imputed using LOCF.

5.4.1.2.2 Binary Secondary Endpoints at Final Analysis

Binary secondary endpoints (Table 2, Group 2, Group 3 and Group 4) at the final analysis will be analyzed using the same intercurrent events and intercurrent events handling strategies described in Section 5.4.1, unless otherwise specified, with the following additional attributes:

- Population:
  - Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24 (Table 2, Group 3): Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population) with an evaluable Week 24 BCVA
  - Proportions of patients on Q4W, Q8W, Q12W, or Q16W treatment interval and other binary endpoints (Table 2, Group 2 and Group 4): Adult patients with macular edema due to BRVO (for BALATON), CRVO or HRVO (for COMINO), as defined by the inclusion and exclusion criteria (ITT population)
- Variable: Same as endpoint
- Treatments (as randomized):
  - Experimental: Faricimab PTI (Faricimab Q4W in Part 1)
  - Experimental: Faricimab PTI (Aflibercet Q4W in Part 1 crossover)
- Intercurrent events time period:
  - Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24 (Table 2, Group 3): Intercurrent events occurring prior to Week 24 will not be accounted for
  - Proportions of patients on Q4W, Q8W, Q12W, or Q16W treatment interval and other binary endpoints (Table 2, Group 2 and Group 4): Intercurrent events measured throughout the study will be accounted for
- Population-level summary:
  - Binary BCVA endpoints in reference to baseline (Table 2, Group 2): Weighted proportions of each treatment group
  - Binary BCVA endpoint in reference to Week 24 (Table 2 Group 3): Weighted proportions for all patients after Week 24
  - Proportions of patients on Q4W, Q8W, Q12W, or Q16W treatment interval (Table 2, Group 4): Proportions of each treatment group and for all patients

Binary endpoints (Table 2, Group 2 and Group 3) at the final analysis will be analyzed using the same analysis methods for the binary BCVA endpoints at the primary analysis

(Section 5.4.1.2.1) with the exception that the treatment differences will not be estimated and nominal p-values will not be provided after Week 24.

Proportions of patients on Q4W, Q8W, Q12W, or Q16W treatment interval at Week 68 (Table 2, Group 4) will be analyzed using descriptive statistics. Percentage will be based on the patients who have not discontinued the study at Week 68.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS

Exploratory endpoints will be summarized for the ITT population at the primary analysis and the final analysis (if applicable). All observed data will be used and missing data will not be imputed. For the final analysis, no comparisons between treatment groups will be made since all patients will receive faricimab during Part 2 of the study. Differences between groups will not be assessed.

The exploratory endpoints will be summarized using descriptive statistics by including the mean, SD, median, and range for continuous endpoints, and counts and percentages for categorical endpoints.

5.6 SAFETY ANALYSES

Safety data will be summarized for the Safety-Evaluable population (see Section 4).

Safety will be assessed through descriptive summary of ocular and non-ocular AEs, deaths, and ocular assessments. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as AEs and evaluated as part of the AE assessments.

At the primary analysis, safety summaries will be performed based on data before the Week 24 visit in the safety-evaluable population by treatment group. At the final analysis, safety summaries will be summarized by the following groups: Faricimab Q4W before Week 24 visit, Aflibercept Q4W before Week 24 visit, Faricimab PTI (Faricimab Q4W in Part 1) on and after Week 24 visit, Faricimab PTI (Aflibercept Q4W in Part 1 crossover) on and after the first dose of faricimab, all patients who received at least one dose of faricimab with safety data on and after the first dose of faricimab.

Missing data for safety analyses will not be imputed.

5.6.1 Extent of Exposure

At the primary analysis, exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment group for the study eye based on data before the Week 24 visit for the safety-evaluable population.

Duration of treatment is the time from first study drug (faricimab or aflibercept) to the earlier of:

- Date of treatment discontinuation before the Week 24 visit
- Date of last dose of study drug or last dose hold before the Week 24 visit

At the final analysis, exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment group and by period for the study eye through Week 72 for the safety-evaluable population.

Duration of treatment for Faricimab PTI (Faricimab Q4W in Part 1) and Faricimab PTI (Aflibercept Q4W in Part 1 crossover) from Week 24 onwards is the time from the first study treatment (faricimab or sham) on or after Week 24 to the earlier of:

- Date of treatment discontinuation
- Date of last dose of study drug or last dose hold prior to Week 72

Duration of treatment for patients who received at least one dose of faricimab is the time from first dose of faricimab to the earlier of:

- Date of treatment discontinuation
- Date of last dose of study drug or last dose hold prior to Week 72

5.6.2 Adverse Events

All verbatim AEs terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), and the incidence and severity will be summarized by treatment arm.

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. A treatment-emergent AE is defined as any new AE reported or any worsening of an existing condition on or after the first dose of study drug (faricimab or aflibercept) for the Safety-Evaluable population. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the start date of the reporting period.

Frequency tables, including patient incidence rates by treatment arm, will be provided for the events listed below. In addition, graphical presentations will be included, as applicable. For ocular AEs, events in the study eye and fellow eye will be summarized separately:

- Ocular AEs and serious adverse events (SAEs)
- Non-ocular AEs and SAEs
- Adverse events of special interest (AESI) defined as follows:

  - Cases of potential drug-induced liver injury that include elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6 of Protocol)
  - Suspected transmission of an infectious agent by the study drug
  - Sight-threatening AEs (see Section 5.2.3 of Protocol for definitions)
- AEs leading to discontinuation of study treatment
- AEs leading to discontinuation from the study
- AEs leading to study treatment interruption
- Treatment related ocular AEs and SAEs as determined by the Investigator
- Non-Ocular Adverse Events of Arterial Thromboembolic Event (ATE) and Cerebrovascular Haemorrhagic Adverse Events
- Externally adjudicated APTC events
- Intraocular inflammation (IOI)
- Retinal vascular occlusive disease
- Deaths

There is no standardized MedDRA queries (SMQ) that encompasses the medical concepts of IOI or retinal vascular occlusive disease. These definitions will be assessed based on the masked review of clinical database preferred terms (PTs) before the primary analysis and final analysis, and with subsequent MedDRA version updates, to ensure no event terms are missed.

5.6.3 Laboratory Data

Laboratory data will be collected at baseline and Week 24 only (Section 4.5.7 of Protocol). Laboratory assessments will be summarized by treatment group and timepoint, using descriptive summaries.

5.6.4 Vital Signs

Vital signs will be collected at screening, randomization, Week 72 or early termination visit. These data can be used for interpretation of AEs, no general summary is planned.

5.6.5 Ocular Assessments

Results of the following ocular assessments will be summarized by treatment group, by timepoint, by eye (Study vs. Fellow) using descriptive summaries and graphical presentations (as applicable):

- intraocular pressure (IOP)
- slitlamp examination
- indirect ophthalmoscopy

Changes from baseline in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will be summarized. The presence of IOI and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade (according to grading scales for flares and cells in Appendix 4 of Protocol). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

Conduct of study will be summarized for the ITT population at the primary analysis and the final analysis.

Eligibility criteria deviations and other major protocol deviations will be summarized by treatment arm.

Pre-treatment and concomitant systemic medications, ocular medications for the study eye, and ocular medications for the fellow eye will be summarized separately by treatment group.

5.7.2 Summaries of Treatment Group Comparability

Treatment group comparability will be summarized for the ITT population at the primary analysis and will not be summarized at the final analysis. Demographic and baseline characteristics such as age, sex, race/ethnicity and region, and baseline disease characteristics (such as baseline BCVA, ocular assessments, and medical history) will be summarized using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

5.7.3 Pharmacokinetic Analyses

At the primary analysis, PK summaries will be based on the faricimab PK-evaluable population (see Section 4) using data from Day 1 up to Week 24 by treatment group. At the final analysis, PK summaries will be based on the PK-evaluable population (see Section 4) using data from Day 1 up to Week 72 by treatment group.

Summaries of individual plasma and aqueous humor faricimab (RO6867461) concentrations will be provided by treatment arm with summary statistics. Mean faricimab (RO6867461) plasma and aqueous humor concentration versus time data will be plotted.

In addition, a population PK analysis will be performed including co-variate analysis and assessment of potential effect of ADA on the kinetics of faricimab. Details of the population PK analyses will be described in a Modeling and Simulation Analysis Plan.

The result of the population PK analyses will be reported in a document separate from the Clinical Study Report (CSR) and may include data from the China extensions.

5.7.4 Pharmacodynamic Analyses

PD analyses will be based on the Safety-Evaluable population (see Section 4).

At the primary analysis, PD summaries will be based on data from Day 1 up to Week 24 by treatment group. At the final analysis, PD summaries will be based on data from Day 1 up to Week 72 by treatment group.

PD biomarker analyses will be focused primarily on, but not limited to, the change in Ang-2 and VEGF. Graphical displays and summaries of the absolute values or change from baseline (or as appropriate, percent change from baseline) will be provided. The data collected from this study may be pooled with data from previous studies and the results of such analyses will be reported in a document separate from the CSR. The effect of exposure or dosing information on BCVA, CST, aqueous humor free VEGF-A and Ang-2 may be explored using a longitudinal modeling approach if appropriate. The influence of various baseline covariates on model parameters may be investigated. The PK-PD or dose-PD relationship will be characterized as appropriate and results will be reported in a document separate from the CSR.

5.7.5 Immunogenicity Analyses

Immunogenicity analyses will be based on the Immunogenicity-Analysis population (see Section 4).

At the primary analysis, ADA summaries will be based on data through Week 24 for patients in the Faricimab Q4W arm in Part 1. At the final analysis, ADA summaries will be based on data from Day 1 to week 72 for patients in the Faricimab Q4W arm in Part 1 followed by Faricimab PTI in Part 2. For patients in the Aflibercept Q4W arm in Part 1 followed by Faricimab PTI in Part 2, ADA summaries will be based on data on Day 1, and from Week 24 to Week 72.

The following properties of each sample will be listed by patient: ADA status (from the confirmatory assay): ADA positive (yes) or ADA negative (no) and titer value for the ADA positive sample.

The ADA status at baseline will be summarized using the Immunogenicity prevalence set and summarized according to treatment received. For patients in the Aflibercept Q4W arm in Part 1 followed by Faricimab PTI in Part 2, ADA status at Week 24 will also be summarized using the Immunogenicity prevalence set.

The ADA status will be listed by patient using the Immunogenicity incidence set and summarized according to actual treatment received. For the immunogenicity incidence set, baseline for patients in the Faricimab Q4W arm refers to study Day 1 and baseline

for patients in the Aflibercept Q4W arm in Part 1 followed by Faricimab PTI in Part 2 refers to Week 24.

- Treatment-boosted ADA-positive: number and percent of patients with at least one treatment-boosted ADA-positive sample. The numerator is the number of patients with an ADA-positive sample at baseline and with post-baseline samples with a titer that is equal or greater than 4-fold baseline titer. The denominator is the total number of patients in the immunogenicity incidence set summarized according to treatment received.
- Treatment-induced ADA-positive: number and percent of patients with at least one treatment-induced ADA-positive sample. The numerator is the number of patients with an ADA-negative or missing sample at baseline and any post-baseline positive sample. The denominator is the total number of patients in the immunogenicity incidence set. Among the treatment –induced ADA-positive, the number of patients with transient (ADA-positive result detected (a) at only one post-baseline sampling time point (excluding last timepoint) OR (b) at 2 or more timepoints during treatment where the first and last ADA-positive samples are separated by a period of $<$ 16 weeks, irrespective of any negative samples in between) and persistent (ADA-positive result detected (a) at the last post-baseline sampling time point, OR (b) at 2 or more time points during treatment where the first and last ADA-positive samples are separated by a period of $\geq$ 16 weeks, irrespective of any negative samples in between) will be listed.
- Treatment-unaffected ADA-positive patient: number and percent of patients with an ADA-positive baseline sample (level of pre-existing ADAs) that does not change following drug administration. The numerator is the number of patients with ADA-positive sample and with all post-baseline titers lower than 4-fold the ADA-positive baseline titer. The denominator is the total number of patients in the immunogenicity incidence set.
- ADA-negative: number and percent of patients without positive ADA during the study period or if they are ADA-positive at baseline but without positive ADA post baseline (numerator). The denominator is the total number of patients in the immunogenicity incidence set.
- ADA incidence (i.e., ADA-positive in %): number and percent of patients with at least one treatment-induced or treatment-boosted ADA-positive sample. The numerator is the number of patients positive for boosted or induced ADA. The denominator is the total number of patients in the immunogenicity incidence set.

Of note, ADA-positive is defined as treatment-boosted ADA-positive, treatment-induced ADA-positive or treatment-unaffected ADA-positive (see definition above).

The following summaries, both overall and by time point (including baseline) will be provided using the Immunogenicity prevalence set:

- ADA prevalence: number and percent of patients with at least one ADA-positive sample at any timepoint (including baseline). The numerator is the number of

ADA-positive patients at each timepoint and overall timepoints. The denominator is the total number of evaluable patients in the study at corresponding timepoints.

The relationship between ADA status and safety and efficacy will be analyzed and reported using descriptive statistics.

5.7.6 Biomarker Analyses

Biomarker analyses will be based on the Safety-Evaluable population (see Section 4).

Baseline values will be used to evaluate predictive biomarkers in the context of efficacy, PK, safety, and/or immunogenicity endpoints. In addition, whole genome sequencing data will be analyzed in the context of this study and may be explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and faricimab treatment response, and guide the development of new therapeutic approaches. The results from these analyses will be reported in a document separate from the CSR.

Details of the biomarker analyses will be described in a separate Analysis Plan.

5.7.7 Analyses of China Subpopulation

Separate analyses will be performed for each China subpopulation, where data from all patients enrolled in mainland China, Hong Kong, or Taiwan for each study (i.e., during both the global enrollment phase and China extension) will be summarized individually for each study.

Analyses described in this section will include data from the China subpopulation as defined in Section 1.2.

The analysis populations will be equally defined as per Section 4 but will be based only on patients who enroll in mainland China, Hong Kong, or Taiwan. Analyses of study conduct will be performed as described in Section 5.7.1. Summaries of demographics, stratification factors, disease history, baseline disease characteristics, and patient treatment history will be produced as described in Section 5.7.2. Primary and key efficacy endpoints for the China subpopulation will be summarized using descriptive statistics. Similarly, key PK, ADA and safety data for the China subpopulation will also be summarized.

No formal statistical testing of the comparison between faricimab and the active comparator aflibercept is planned for the China subpopulation and the clinical data will be descriptively summarized. The China subpopulation results will be interpreted in the context of results from the global enrollment phase. Thus, the consideration of whether the China subpopulation data is consistent with the results from the global population will be based on the totality of the data, including the direction of efficacy and safety profiles.

5.8 ANALYSES FOR COVID-19

Based on the first reports of COVID-19 infection globally, the Sponsor determined that the window for all analyses of COVID-19 associated events would start from 1 December 2019.

The impact of COVID-19 will be assessed for study conduct, efficacy analyses and safety events.

5.8.1 Study Conduct Analyses for COVID-19

In order to assess the impact of COVID-19 on study conduct, the following metrics will be recorded:

- BCVA not performed per protocol (non-standard BCVA) due to COVID-19 or related precautions
- Major protocol deviations due to COVID-19, including, but not limited to:
  - Missed visits reported as due to COVID-19 or related precautions on or prior to Week 24
  - Missed injections reported as due to COVID-19 or related precautions on or prior to Week 20
  - Use of prohibited therapies due to COVID-19
- Discontinuations from treatment and/or study due to COVID-19, which includes:
  - Indirect COVID-19 pandemic-related aspects (e.g., patients leaving the study due to fear of going to the site during the pandemic) as collected on the disposition or study drug early discontinuation electronic Case Report Form (eCRF), and
  - Direct COVID-19 pandemic-related aspects (Safety events related to COVID-19 as specified in Section 5.8.3).

5.8.2 Efficacy Analyses for COVID-19

A supplementary analysis for the primary endpoint applying a hypothetical strategy for COVID-19 related intercurrent events, where all values will be censored after such intercurrent events, will be performed. A supplementary analysis on the per-protocol population will also be conducted to help assess pandemic related impacts (Section 5.3.4).

For data integrity of efficacy analyses, the following will be summarized by treatment arm at the primary and final analysis:

- Discontinuation of study treatment due to COVID-19
- Use of prohibited therapy due to COVID-19
- Missed doses with a potentially major impact on efficacy due to COVID-19
- Death due to COVID-19

5.8.3 Safety Analyses for COVID-19

Following the MedDRA 24.0 release, a COVID-19 SMQ (narrow) is available. This SMQ includes terms relevant to COVID-19 infection. Patients with AEs from this COVID-19 SMQ (narrow) will be considered to have a confirmed or suspected COVID-19 infection.

For the patients identified from the search as having confirmed or suspected COVID-19 infection, outputs to evaluate safety events will be produced as follows:

- Summary table and listing of confirmed and suspected COVID-19 AEs

In addition to presenting the suspected/confirmed COVID-19 infections, the Sponsor developed a broad search strategy for AEs associated with COVID-19 infection to further evaluate the confirmed events of COVID-19 and reported AEs that could be considered complications of the disease. This search strategy includes both the AEs of a confirmed or suspected COVID-19 infection and any AEs considered associated with COVID-19. The Sponsor identified associated AEs as those reported ≤7 days before and ≤30 days after any reported AE suggesting a confirmed COVID-19 infection (PTs listed in Table 3).

Table 3 Roche COVID-19 SMQ (narrow) Preferred Terms for Confirmed Cases

Congenital COVID-19
Coronavirus Infection
Coronavirus Test Positive
COVID-19
COVID -19 Pneumonia
COVID-19 Treatment
Multisystem Inflammatory Syndrome in Children
Post-acute COVID-19 Syndrome
SARS-CoV-2 RNA Decreased
SARS-CoV-2 RNA Fluctuation
SARS-CoV-2 RNA Increased
SARsS-Cov-2 Test Positive
SARS-CoV-2 sepsis
SARS-CoV-2 viraemia
Vaccine Derived SARS-CoV-2 Infection

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

For the patients identified from the search as having COVID-19 associated AEs, outputs to evaluate these safety events will be produced as follows:

- Summary table and listing of COVID-19 Associated Events: including all of the above confirmed/suspected COVID-19 infections plus, for those patients with

confirmed COVID-19 infection or positive polymerase chain reaction test flag, any other AEs occurring within ≤ 7 days before and ≤ 30 days after start date of all the confirmed COVID-19 events in Table 3.

In addition, the following outputs will be produced:

- Listing of Adverse Events associated with COVID-19 Leading to Study Treatment Discontinuation
- Listing of Adverse Events associated with COVID-19 Leading to Study Discontinuation
- Listing of adverse Events associated with COVID-19 Resulting in Death

5.9 INTERIM ANALYSES

No interim efficacy or futility analyses are planned or conducted. The iDMC reviewed interim safety analyses approximately every 6 months, 3 interim safety analyses before the primary analysis are expected.

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Appendix 1 Protocol Synopsis for Study BALATON (GR41984)

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION**
PROTOCOL NUMBER:	GR41984
STUDY NAME	BALATON
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2020-000440-63
IND NUMBER:	119225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	III
INDICATION:	Macular edema secondary to branch retinal vein occlusion
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab compared with aflibercept in patients with macular edema due to branch retinal vein occlusion (BRVO) up to the primary endpoint at Week 24. Efficacy, safety, and pharmacokinetics of faricimab administered according to the personalized treatment interval (PTI) dosing regimen (i.e., from every 4 weeks [Q4W] to every 16 weeks [Q16W]) will be assessed during the study period from Weeks 24 to 72. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

For efficacy endpoint evaluation, best-corrected visual acuity (BCVA) will be assessed on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a starting test distance of 4 meters.

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the efficacy of faricimab 6 mg intravitreal (IVT) Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the following endpoint:

- Change from baseline in BCVA at Week 24

SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objective for Part 1 of this study (i.e., through Week 24) is to evaluate the efficacy of faricimab compared with aflibercept on the basis of the following endpoints:

- Change from baseline in BCVA at specified timepoints through Week 24
- Proportion of patients $gaining \geq 15$ letters in BCVA $from\ baseline$ at Week 24
- Proportion of patients $gaining \geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA $from\ baseline$ at specified timepoints through Week 24

- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at specified timepoints through Week 24
- Proportion of patients achieving $\geq$ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints through Week 24
- Change from baseline in central subfield thickness (CST) at specified timepoints through Week 24
- Change from baseline in National Eye Institute 25Item Visual Functioning Questionnaire (NEI VFQ-25) composite score at specified timepoints through Week 24

The secondary efficacy objective for Part 2 of this study (i.e., Week 24 through Week 72) is to evaluate the efficacy of faricimab administered according to the PTI dosing regimen on the basis of the following endpoints*:*

- Change from baseline in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients *gaining* $\geq$15 letters in BCVA *from baseline* at Week *72*
- Proportion of patients *gaining* ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA *from baseline* at specified timepoints from Week 24 through Week 72
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from baseline at specified timepoints from Week 24 through Week 72
- Proportion of patients achieving $\geq$ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints from Week 24 through Week 72
- Change from Week 24 in BCVA at specified timepoints through Week 72
- Proportion of patients avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or > 0 letters in BCVA from Week 24 through Week 72
- Proportion of patients on a Q4W, every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W treatment interval at Week 72
- Number of study drug injections received from Week 24 through Week 72
- Change from baseline in CST at specified timepoints from Week 24 through Week 72
- Change from baseline in NEI VFQ-25 composite score at specified timepoints from Week 24 through Week 72

EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to evaluate the efficacy of faricimab on the basis of the following endpoints*:*

- Proportion of patients with absence of retinal ischemia on fundus fluorescein angiography (FFA) and on optical coherence tomography angiography (OCT-A) (optional) over time (at specified timepoints)
- Change from baseline in area of retinal ischemia on FFA and on OCT-A (optional) over time
- Proportion of patients with vascular leakage on FFA and on OCT-A (optional) over time
- Change from baseline in area of vascular leakage on FFA, and on OCT-A (optional) over time
- Change from baseline in foveal avascular zone and other exploratory outputs defined in *the* Statistical Analysis Plan *(SAP)* on OCT-A (optional) over time

- Proportion of patients with absence of retinal neovascularization *over time* (per investigator assessment)
- Proportion of patients with absence of vitreal, preretinal, or subretinal hemorrhage over time (per investigator assessment)
- Proportion of patients with absence of anterior segment (iris and anterior chamber angle) neovascularization over time
- Proportion of patients requiring panretinal photocoagulation at any time during *the* study
- Proportion of patients with absence of macular edema, defined as CST of $\leq$325 μm for Spectralis spectral-domain optical coherence tomography (SD-OCT), or $\leq$315 μm for Cirrus SD-OCT or Topcon SD-OCT, over time
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time
- Proportion of patients with absence of intraretinal cysts over time
- Change from baseline in NEI VFQ-25 near activities–subscale score and distance activities–subscale scores over time

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of faricimab on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale
- Incidence and severity of non-ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the faricimab PK profile on the basis of the following endpoint:

- Plasma concentration of faricimab over time

The exploratory PK objective for this study is to explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomic measures) on the basis of the following endpoint:

- Concentration of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the *antibody* immune response to faricimab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time
- Relationship between anatomic measures and visual acuity

EXPLORATORY SUBSTUDY

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GR41984 protocol. Each substudy will be documented in a separate substudy protocol and will have a separate associated Informed Consent Form.

STUDY DESIGN

DESCRIPTION OF STUDY

This 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 double-masked period of study without active control to evaluate faricimab administered according to a PTI dosing regimen in patients with macular edema due to BRVO.

This study is comprised of two parts: Part 1 (Day 1 through Week 24) will compare faricimab Q4W versus aflibercept (active comparator) Q4W; Part 2 (Weeks 24–72) will evaluate faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria.

The study will consist of a screening period of up to 28 days (Days –28 to –1) and an approximately 68-week treatment period (Parts 1 and 2), followed by the final study visit at Week 72. All patients will complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered.

Only one eye will be assigned as the study eye. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected as the study eye, unless the investigator deems the other eye to be more appropriate for treatment in the study.

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

Patient recruitment is expected to take longer in China; therefore, a specific China enrollment plan may be established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at National Medical Products Administration (NMPA)-recognized sites. All Chinese patients enrolled in the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses.

NUMBER OF PATIENTS

Approximately *570 patients* with macular edema due to BRVO will be enrolled during the global enrollment phase of this study.

TARGET POPULATION

INCLUSION CRITERIA

General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 3 months after the final dose of study treatment. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For patients enrolled in the extended China enrollment phase at NMPA-recognized sites: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

Ocular Inclusion Criteria for Study Eye

Patients must also meet the following ocular criteria for study entry:

- Foveal center–involved macular edema due to BRVO diagnosed no longer than 4 months prior to the screening visit and confirmed by central reading center (CRC) based on SDOCT (or SS-OCT) images

  BRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in one quadrant or less of the retina drained by the affected vein
- BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters (see the BCVA manual for additional details) on Day 1
- CST $\geq$325 μm, as measured on Spectralis SD-OCT, or $\geq$315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (SS-OCT acceptable after confirmation with CRC)
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

EXCLUSION CRITERIA

General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for > 12 months
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2 (Prohibited Therapy)
- Systemic treatment for suspected or active systemic infection on Day 1

  Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor.
- Any systemic corticosteroid use (e.g., oral or injectable) within 1 month of the screening visit

- Uncontrolled blood pressure, defined as systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 110 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or historical or current clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study drug. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study- related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used during the study
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1

Ocular Exclusion Criteria for Study Eye

Patients who meet any of the following ocular exclusion criteria for the study eye will be excluded from study entry:

- History of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed more than 4 months before screening
- Increase of $\geq$ 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 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)
- 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 diabetic retinopathy (DR) moderate non-proliferative or worse, proliferative DR, diabetic macular edema (DME), neovascular age-related macular degeneration (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 (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to 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 macular edema due to RVO, including anti–vascular endothelial growth factor (VEGF) IVT for macular edema due to RVO
- 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 IVT treatment for any other retinal diseases that can lead to macular edema complication
- Any prior or current treatment for macular edema; macular neovascularization, including DME and nAMD; and vitreomacular-interface abnormalities, including, but not restricted to, IVT 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 *sheathotomy*
- Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex®) and fluocinolone acetonide intravitreal implant (Iluvien®)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

Ocular Exclusion Criteria for Fellow (Non-Study) Eye

Patients who meet the following ocular exclusion criterion for the fellow (non-study) eye at both screening and Day 1 will be excluded from study entry:

- Non-functioning fellow eye, defined as either one of the following:

  BCVA 20/320 or worse

  No physical presence of fellow eye (i.e., monocular)

Ocular Exclusion Criteria for Both Eyes

Patients who meet any of the following ocular exclusion criteria for both eyes will be excluded from study entry:

- Prior IVT 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

END OF STUDY

The study consists of two enrollment phases: the global enrollment phase, during which patients are recruited globally; and an optional China extension phase, during which additional patients may be recruited in China to support registration in China.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, including patients from the optional China extension. The end of the study is expected to occur approximately 72 weeks after the last patient is randomized.

The Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the study (excluding the China extension) from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 34 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

In Part 1 of the study, patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

In Part 2 of the study, patients randomly assigned to both Arms A and B will receive faricimab 6 mg IVT administered according to a PTI dosing regimen in intervals between Q4W and Q16W. At faricimab dosing visits, treatment intervals will be maintained or adjusted (i.e., increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values. Patients will therefore receive between 3 and 12 injections during the period from Week 24 through Week 68.

COMPARATOR

In Part 1 of the study, patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

SHAM PROCEDURE

During Part 2 of the study, to preserve the masking of faricimab treatment intervals, the sham procedure will be administered to patients in both Arms A and B during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered. The sham vial is empty and will remain empty throughout the sham treatment. The sham is a procedure that mimics an IVT injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary and secondary efficacy analyses will be based on the intent-to-treat (ITT population) population, unless otherwise specified, with patients grouped according to the treatment assigned at randomization. Additional analysis based on the per-protocol population will also be conducted for the primary endpoint.

The primary comparison will be between the active comparator (aflibercept Q4W) and faricimab Q4W at Week 24. The following hypothesis will be tested:

- Non-inferiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population population (at a 1-sided 0.025 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population population (at a 2-sided 0.05 significance level)

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 24. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The MMRM model will include the change from baseline at Weeks 4–24 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, a heterogeneous compound symmetry or an AR(1) covariance structure may be fITT populationed.

DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately $570\ patients$. Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B).

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

- No difference in the mean change from baseline in BCVA between the two treatment arms
- SD of 13 letters for the change from baseline in BCVA at Week 24
- Two-sample $t\text{-}tests$
- 2.5% one-sided type I error rate
- 10% dropout rate

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

INTERIM ANALYSES

There are no prospectively planned interim efficacy or futility analyses.

Appendix 2 Protocol Synopsis for Study COMINO (GR41986)

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FARICIMAB IN PATIENTS WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL OR HEMIRETINAL VEIN OCCLUSION**
PROTOCOL NUMBER:	GR41986
STUDY NAME:	COMINO
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2020-00044*1-1*3
IND NUMBER:	119225
NCT NUMBER:	To be determined
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	III
INDICATION:	Macular edema secondary to central retinal or hemiretinal vein occlusion
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of faricimab compared with aflibercept in patients with macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO) up to the primary endpoint at Week 24. Efficacy, safety, and pharmacokinetics of faricimab administered according to the personalized treatment interval (PTI) dosing regimen (i.e., from every 4 weeks [Q4W] to every 16 weeks [Q16W]) will be assessed during the study period from Weeks 24 to 72. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

For efficacy endpoint evaluation, best-corrected visual acuity (BCVA) will be assessed on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a starting test distance of 4 meters.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of faricimab 6 mg intravitreal (IVT) Q4W compared with aflibercept 2 mg IVT Q4W on the basis of the following endpoint:

- Change from baseline in BCVA at Week 24

Secondary Efficacy Objectives

The secondary efficacy objective for Part 1 of this study (i.e., through Week 24) is to evaluate the efficacy of faricimab compared with aflibercept on the basis of the following endpoints*:*

- Change from baseline in BCVA at specified timepoints through Week 24
- Proportion of patients *gaining* ≥15 letters in BCVA *from baseline* at Week 24

- Proportion of patients *gaining* $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA *from baseline* at specified timepoints through Week 24
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from baseline at specified timepoints through Week 24
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints through Week 24
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints through Week 24
- Change from baseline in central subfield thickness (CST) at specified timepoints through Week 24
- Change from baseline in National Eye Institute 25Item Visual Functioning Questionnaire (NEI VFQ-25) composite score at specified timepoints through Week 24

The secondary efficacy objective for Part 2 of this study (i.e., Week 24 through Week 72) is to evaluate the efficacy of faricimab administered according to the PTI dosing regimen on the basis of the following endpoints*:*

- Change from baseline in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients *gaining* ≥ 15 letters in BCVA *from baseline* at Week *72*
- Proportion of patients *gaining* $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA *from baseline* at specified timepoints from Week 24 through Week 72
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from baseline at specified timepoints from Week 24 through Week 72
- Proportion of patients achieving ≥ 84 letters (20/20 Snellen equivalent) in BCVA at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/40 or better at specified timepoints from Week 24 through Week 72
- Proportion of patients with BCVA Snellen equivalent of 20/200 or worse at specified timepoints from Week 24 through Week 72
- Change from Week 24 in BCVA at specified timepoints through Week 72
- Proportion of patients avoiding a loss of $\geq 15, \geq 10, \geq 5$, or > 0 letters in BCVA from Week 24 through Week 72
- Proportion of patients on a Q4W, every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W treatment interval at Week 72
- Number of study drug injections received from Week 24 through Week 72
- Change from baseline in CST at specified timepoints from Week 24 through Week 72
- Change from baseline in NEI VFQ-25 composite score at specified timepoints from Week 24 through Week 72

EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to evaluate the efficacy of faricimab on the basis of the following endpoints*:*

- Proportion of patients with absence of retinal ischemia on fundus fluorescein angiography (FFA) and on optical coherence tomography angiography (OCT-A) (optional) over time (at specified timepoints)
- Change from baseline in area of retinal ischemia on FFA and on OCT-A (optional) over time
- Proportion of patients with vascular leakage on FFA and on OCT-A (optional) over time
- Change from baseline in area of vascular leakage on FFA, and on OCT-A (optional) over time

- Change from baseline in foveal avascular zone and other exploratory outputs defined in the Statistical Analysis Plan (SAP) on OCT-A (optional) over time
- Proportion of patients with absence of retinal neovascularization over time (per investigator assessment)
- Proportion of patients with absence of vitreal, preretinal, or subretinal hemorrhage over time (per investigator assessment)
- Proportion of patients with absence of anterior segment (iris and anterior chamber angle) neovascularization over time
- Proportion of patients requiring panretinal photocoagulation at any time during the study
- Proportion of patients with absence of macular edema, defined as CST of $\leq$325 μm for Spectralis spectral-domain optical coherence tomography (SD-OCT), or $\leq$315 μm for Cirrus SD-OCT or Topcon SD-OCT, over time
- Proportion of patients with absence of intraretinal fluid over time
- Proportion of patients with absence of subretinal fluid over time
- Proportion of patients with absence of both intraretinal fluid and subretinal fluid over time
- Proportion of patients with absence of intraretinal cysts over time
- Change from baseline in NEI VFQ-25 near activities–subscale score and distance activities–subscale scores over time

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of faricimab on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale
- Incidence and severity of non-ocular adverse events, with severity determined according to Adverse Event Severity Grading Scale

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the faricimab PK profile on the basis of the following endpoint:

- Plasma concentration of faricimab over time

The exploratory PK objective for this study is to explore the concentration–effect relationship for visual acuity and other endpoints (e.g., anatomic measures) on the basis of the following endpoint:

- Concentration of faricimab and the change in BCVA or other endpoints (e.g., anatomical markers) over time

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the antibody immune response to faricimab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to faricimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of faricimab activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between baseline anatomic measures and the change in BCVA or other endpoints (e.g., the frequency of faricimab administration) over time
- Relationship between anatomic measures and visual acuity

EXPLORATORY SUBSTUDY

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GR41986 protocol. Each substudy will be documented in a separate substudy protocol and will have a separate associated Informed Consent Form.

STUDY DESIGN

DESCRIPTION OF STUDY

This 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 double-masked period of study without active control to evaluate faricimab administered according to a PTI dosing regimen in patients with macular edema due to CRVO or HRVO.

This study is comprised of two parts: Part 1 (Day 1 through Week 24) will compare faricimab Q4W versus aflibercept (active comparator) Q4W; Part 2 (Weeks 24–72) will evaluate faricimab administered at masked treatment intervals of Q4W to Q16W based on PTI dosing criteria.

The study will consist of a screening period of up to 28 days (Days –28 to –1) and an approximately 68-week treatment period (Parts 1 and 2), followed by the final study visit at Week 72. All patients will complete scheduled study visits Q4W for the entire study duration (72 weeks). To preserve the masking of faricimab treatment intervals for Week 24 through Week 68, a sham procedure will be administered during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered.

Only one eye will be assigned as the study eye. If both eyes are considered eligible, the eye with the worse BCVA, as assessed at screening, will be selected as the study eye, unless the investigator deems the other eye to be more appropriate for treatment in the study.

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

Patient recruitment is expected to take longer in China; therefore, a specific China enrollment plan may be established. After the global enrollment phase of the study has been completed, additional patients may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. The China extension may include current residents of mainland China, Hong Kong, or Taiwan enrolled at National Medical Products Administration (NMPA)-recognized sites. All Chinese patients enrolled in the global enrollment phase of the study will be included in the primary analysis of the study. Data from patients enrolled during the China extension will not be included in the primary analyses.

NUMBER OF PATIENTS

Approximately *750 patients* with macular edema due to CRVO or HRVO will be enrolled during the global enrollment phase of this study.

TARGET POPULATION

INCLUSION CRITERIA

General Inclusion Criteria

- Patients must meet the following criteria for study entry:
- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 3 months after the final dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For patients enrolled in the extended China enrollment phase at NMPA-recognized sites: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

Ocular Inclusion Criteria for Study Eye

- Patients must also meet the following ocular criteria for study entry:
- Foveal center–involved macular edema due to CRVO or HRVO diagnosed no longer than 4 months prior to the screening visit and confirmed by central reading center (CRC) based on SD-OCT (or SS-OCT) images

  CRVO or HRVO is defined by retinal hemorrhages, telangiectatic capillary bed, dilated venous system or other biomicroscopic evidence of retinal vein occlusion (RVO; neovascularization, vitreous hemorrhages) in the entire retina (CRVO) or two quadrants of the retina (HRVO)
- BCVA of 73 to 19 letters, inclusive (20/40 to 20/400 approximate Snellen equivalent), as assessed on the ETDRS visual acuity chart at a starting test distance of 4 meters (see the BCVA manual for additional details) on Day 1
- CST $\geq$325 μm, as measured on Spectralis SD-OCT, or $\geq$315 μm, as measured on Cirrus SD-OCT or Topcon SD-OCT at screening (SS-OCT acceptable after confirmation with CRC)
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

EXCLUSION CRITERIA

General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any major illness or major surgical procedure within 1 month before screening
- Active cancer within the 12 months prior to Day 1 except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen for > 12 months
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2 (Prohibited Therapy)
- Systemic treatment for suspected or active systemic infection on Day 1

Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the Medical Monitor.

- Any systemic corticosteroid use (e.g., oral or injectable) within 1 month of the screening visit
- Uncontrolled blood pressure, defined as systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 110 mmHg while a patient is at rest on Day 1

  If a patient's initial reading exceeds these values, a second reading may be taken later on the same day or on another day during the screening period. If the patient's blood pressure is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke (cerebral vascular accident) or myocardial infarction within 6 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or historical or current clinical laboratory findings giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to initiation of study drug. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the faricimab or aflibercept injections, study- related procedure preparations (including fluorescein), dilating drops, or any of the anesthetic and antimicrobial preparations used during the study
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 3 months prior to Day 1

Ocular Exclusion Criteria for Study Eye

Patients who meet any of the following ocular exclusion criteria for the study eye will be excluded from study entry:

- History of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed more than 4 months before screening
- Increase of $\geq$ 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 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)
- 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 diabetic retinopathy (DR) moderate non-proliferative or worse, proliferative DR, diabetic macular edema (DME), neovascular age-related macular degeneration (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 (yttrium-aluminum-garnet) laser capsulotomy within 3 months prior to 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 macular edema due to RVO, including anti–vascular endothelial growth factor (VEGF) IVT for macular edema due to RVO
- 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 IVT treatment for any other retinal diseases that can lead to macular edema complication
- Any prior or current treatment for macular edema; macular neovascularization, including DME and nAMD; and vitreomacular-interface abnormalities, including, but not restricted to, IVT 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 *sheathotomy*
- Any prior steroid implant use including dexamethasone intravitreal implant (Ozurdex®) and fluocinolone acetonide intravitreal implant (Iluvien®)
- Prior periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases

Ocular Exclusion Criteria for Fellow (Non-Study) Eye

Patients who meet the following ocular exclusion criterion for the fellow (non-study) eye at both screening and Day 1 will be excluded from study entry:

- Non-functioning fellow eye, defined as either one of the following:

  BCVA 20/320 or worse

  No physical presence of fellow eye (i.e., monocular)

Ocular Exclusion Criteria for Both Eyes

Patients who meet any of the following ocular exclusion criteria for both eyes will be excluded from study entry:

- Prior IVT 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

END OF STUDY

The study consists of two enrollment phases: the global enrollment phase, during which patients are recruited globally; and an optional China extension phase, during which additional patients may be recruited in China to support registration in China.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, including patients from the optional China extension. The end of the study is expected to occur approximately 72 weeks after the last patient is randomized.

The Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the study (excluding the China extension) from screening of the first patient to the LPLV for patients from the global enrollment phase is expected to be approximately 34 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

In Part 1 of the study, patients randomly assigned to Arm A will receive faricimab 6 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

In Part 2 of the study, patients randomly assigned to both Arms A and B will receive faricimab 6 mg IVT administered according to a PTI dosing regimen in intervals between Q4W and Q16W. At faricimab dosing visits, treatment intervals will be maintained or adjusted

(i.e., increased by 4 weeks or decreased by 4, 8, or 12 weeks), based on CST and BCVA values. Patients will therefore receive between 3 and 12 injections during the period from Week 24 through Week 68.

COMPARATOR

In Part 1 of the study, patients randomly assigned to Arm B will receive aflibercept 2 mg IVT Q4W from Day 1 through Week 20, for a total of 6 injections.

SHAM PROCEDURE

During Part 2 of the study, to preserve the masking of faricimab treatment intervals, the sham procedure will be administered to patients in both Arms A and B during study visits at which (according to the PTI dosing regimen) no faricimab treatment is administered. The sham vial is empty and will remain empty throughout the sham treatment. The sham is a procedure that mimics an IVT injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary and secondary efficacy analyses will be based on the intent-to-treat (ITT population) population, unless otherwise specified, with patients grouped according to the treatment assigned at randomization. Additional analysis based on the per-protocol population will also be conducted for the primary endpoint.

The primary comparison will be between the active comparator (aflibercept Q4W) and faricimab Q4W at Week 24. The following hypothesis will be tested:

- Non-inferiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population population (at a 1-sided 0.025 significance level)
- Superiority of faricimab Q4W compared with aflibercept Q4W at Week 24 in the ITT population population (at a 2-sided 0.05 significance level)

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 24. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The MMRM model will include the change from baseline at Weeks 4–24 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, a heterogeneous compound symmetry or an AR(1) covariance structure may be fITT populationed.

DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on patients enrolled in the global enrollment phase. The global enrollment phase will enroll approximately $750\ patients$. Patients will be randomized in a 1:1 ratio to receive treatment with faricimab (Arm A) or aflibercept (Arm B).

A sample size of approximately $375\ patients$ in each arm will provide $>90\%$ power to show non-inferiority of faricimab to aflibercept in the change in BCVA at Week 24 in the ITT population population, using a non-inferiority margin of 4 letters, and under the following assumptions:

- No difference in the mean change from baseline in BCVA between the two treatment arms
- SD of 13 letters for the change from baseline in BCVA at Week 24
- Two-sample $t\text{-}tests$
- 2.5% one-sided type I error rate
- 10% dropout rate

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

INTERIM ANALYSES

There are no prospectively planned interim efficacy or futility analyses.

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Approval Task	[redacted] Company Signatory 03-Oct-2022 12:51:20 GMT+0000