PROTOCOL

TITLE:	**A CORNEAL ENDOTHELIAL CELLS SUBSTUDY IN ASSOCIATION WITH GR42691 STUDY (AVONELLE-X): A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	GR42691 Corneal Endothelial Cells Substudy
VERSION NUMBER:	*2*
IND NUMBER:	119225
NCT NUMBER:	*NCT04777201*
TEST PRODUCT:	Faricimab (RO6867461)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	*See electronic signature and date stamp on final page of this document.*

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	See electronic date stamp on the final page of this document.
1	7 February 2022

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol GR42691 Corneal Endothelial Cells (CEC) Substudy has been amended following a health authority request to include additional description of the test product, faricimab. The inclusion criteria have also been updated to facilitate study recruitment. Changes to the protocol, along with a rationale for each change, are summarized below:

- Investigational sites have been updated from those within the United States only, to also include global sites, for recruitment purposes (Section 3.1.1).
- The inclusion criteria have been updated to include main Study GR42691 patients willing to participate in the CEC Substudy for at least 48 weeks and have at least the first CEC visit while enrolled in main Study GR42691, to support recruitment efforts (Section 4.1.1.1).
- The exclusion criteria were updated to clarify the excluded severity of Fuchs endothelial corneal dystrophy Grade < 2
- Additional description of the Sponsor-supplied dosing form of the investigational medicinal product, faricimab, has been provided for clarity (new Sections 4.2.1.1, 4.2.2, 4.2.2.2, and 4.2.3 have been added).
- Text has been added to inform investigators that if a patient's participation extends beyond the duration of the main study, faricimab will continue to be reimbursed until the patient completes the CEC Substudy for the study eye (Section 4.2.3).
- The primary Medical Monitor has been updated to [redacted], M.D. (Protocol Title Page, Protocol Amendment Acceptance Form, and Section 5.4.1).
- Text has been added to clarify the circumstances in which reimbursement will be provided for use in the fellow eye of anti-VEGF therapies that are licensed for ocular use (Section 4.3.1).
- Text has been added to refer investigators to the main Study GR42691 protocol for guidance for safety assessments while also informing sites that the CEC Substudy will continue adverse event reporting until patients have completed the Substudy regardless of the completion status of the main Study GR42691 (new Section 5 has been added; subsequent sections have been renumbered; Appendix 1, the Schedule of Activities has been updated to include these changes).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A CORNEAL ENDOTHELIAL CELLS SUBSTUDY IN ASSOCIATION WITH GR42691 STUDY (AVONELLE-X): A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF FARICIMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	GR42691 Corneal Endothelial Cells Substudy
VERSION NUMBER:	*2*
IND NUMBER:	119225
NCT NUMBER:	*NCT04777201*
TEST PRODUCT:	Faricimab (RO6867461)
PHASE:	III (Long-term extension)
INDICATION:	Neovascular age-related macular degeneration
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

The primary objective for this substudy is to evaluate the impact of faricimab on corneal endothelial cell health on the basis of the following endpoints, as assessed by specular microscopy:

- Primary endpoint: Percent change in corneal endothelial cell density (ECD) from baseline at Year 1 (defined as the earliest substudy visit closest to Week 52 occurring between Week 48 and Week 64) in the study eye as compared with the fellow eye
- Secondary endpoint: Percent change in corneal ECD from baseline at substudy midpoint (defined as the earliest substudy visit closest to Week 24 occurring between Week 20 and Week 28) in the study eye as compared with the fellow eye
- Exploratory endpoints:
  - Percent change in the coefficient of variation (CV) of corneal endothelial cell area (standard deviation of the cell area/mean cell area) from baseline at substudy midpoint and Year 1 in the study eye as compared with the fellow eye
  - Percent change of hexagonal endothelial cells (HEX) from baseline at substudy midpoint and Year 1 in the study eye as compared with the fellow eye

STUDY DESIGN

DESCRIPTION OF STUDY

The *main* Study GR42691 is a multicenter long-term extension study designed to evaluate the long-term safety and tolerability of intravitreal faricimab 6 mg administered at a personalized treatment interval (PTI) to patients with neovascular age-related macular degeneration (nAMD) who enrolled in and completed one of the Phase III studies, GR40306 and GR40844. Patients enrolled in GR40306 or GR40844 were randomized in a 1:1 ratio to receive faricimab at a PTI up to Q16W (experimental arm) or aflibercept Q8W (comparator arm).

This substudy is designed to evaluate the impact of intravitreal faricimab 6 mg administered at a PTI on the health of the corneal endothelial cells in patients with nAMD. Fellow eyes of enrolled patients will be used as a comparator for corneal endothelial cells analyses.

NUMBER OF PATIENTS

Approximately 135 patients with nAMD will be enrolled at approximately 50 investigational *global* sites from the *main* Study GR42691.

TARGET POPULATION

Inclusion Criteria

In addition to the inclusion criteria specified in the *main* Study GR42691 (see *main* Study GR42691 Section 4.1.1.1), patients must meet the following criteria:

- Signed Informed Consent for this substudy
- *Must be able to participate for at least 48 weeks in the CEC Substudy and have at least the first CEC visit while enrolled in main Study GR42691*

General Inclusion Criteria

Patients must meet the following ocular inclusion criterion for substudy entry:

- Difference of $< 10\%$ in ECD at screening between the two eyes as measured by specular microscopy and determined by the independent reading center

Exclusion Criteria

In addition to all criteria specified in the *main* Study GR42691 protocol, patients will be excluded from this substudy if they meet the following criteria:

FELLOW (NON-STUDY) EYE

- Prior and/or current administration of faricimab
- Prior administration of brolucizumab

EITHER EYE

- Corneal ECD ≤ 1500 cells/mm^2 in either eye at screening as determined by the independent corneal reading center
- Fuchs endothelial corneal dystrophy Grade ≥ 2
- Previous ocular trauma (blunt or penetrating) and/or corneal endothelial cell damage, including from blunt or surgical trauma (including complicated cataract surgery resulting in complicated lens placement such as anterior chamber intraocular lens, sulcus intraocular lens, aphakia, etc.)
- Any ocular condition that precludes obtaining an analyzable specular microscopy image
- Active or history of corneal edema
- A*ny a*ctive or history of corneal dystrophies*, excluding Fuchs endothelial corneal dystrophy Grade < 2*
- Active or history of iridocorneal endothelial syndrome
- Active or history of pseudoexfoliation syndrome
- Active or history of herpetic keratitis or kerato-uveitis (including herpes simplex virus and herpes zoster virus)
- Intraocular laser therapy including selective laser trabeculoplasty, yttrium-aluminum garnet (YAG), prophylactic peripheral iridotomy within 1 year of screening, or YAG capsulotomy within 3 months of screening
- Prior vitrectomy surgery, submacular surgery, or other surgical intervention for age-related macular degeneration
- Prior pars plana vitrectomy surgery
- Previous intraocular device implantation excluding intraocular lenses
- Cataract surgery within 6 months of screening or planned for during the study
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery. Other types of prior glaucoma surgery are allowed providing that the surgery occur more than 6 months before screening
- Administration of topical Rho kinase inhibitors (e.g., Rhopressa eye drops) within 1 month prior to the screening visit
- Contact lens wear in either eye within 2 months of screening

- History of corneal transplantation, including partial-thickness corneal grafts (e.g., Descemet membrane endothelial keratoplasty, Descemet stripping endothelial keratoplasty)
- Active or history of iridocorneal endothelial syndrome
- Active or history of pseudoexfoliation syndrome

END OF SUBSTUDY

The end of this substudy is defined as the date when the last patient, last visit occurs.

LENGTH OF SUBSTUDY

The end of the substudy is expected to occur approximately 48 weeks after the last substudy patient is enrolled.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The investigational medicinal product(IMP) for this study is faricimab (test product). Faricimab will be supplied by the Sponsor as a sterile liquid for intravitreal injection in single-use glass vials.

Each single-use, 2 mL glass vial contains 6 mg (nominal) of faricimab formulated as 120 mg/mL in L-histidine/acetate buffer solution (approximately pH 5.5) containing sodium chloride, sucrose, L-methionine, and polysorbate 20 and is designed to provide a dose of 6 mg/0.05 mL for intravitreal injection.

STATISTICAL METHODS

PRIMARY ANALYSIS

The percent change in corneal ECD from baseline at Year 1 will be analyzed using the paired t-test. The 95% confidence intervals for Year 1 values as well as change-from-baseline at Year 1 will be calculated.

DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed for this substudy. A planned enrollment of approximately 135 patients from the *main* Study GR42691 was selected in order to obtain data from at least 100 patients through Year 1 to account for patients with missing data (e.g., missed visits, lost to follow-up). ECD, CV, and HEX will be assessed in the corneal endothelium evaluable set (Modified Intent to Treat [mITT] population), which includes all patients who were treated in the study eye and for whom specular microscopic images were interpretable in both the study and fellow eye both at baseline and at the substudy midpoint and/or Year 1 evaluations.

INTERIM ANALYSES

No interim analysis is planned for this substudy.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AMD	age-related macular degeneration
Ang2	angiopoietin-2
BCVA	best corrected visual acuity
CEC	*Corneal Endothelial Cells*
CV	coefficient of variation
DME	diabetic macular edema
ECD	endothelial cell density
FDA	Food and Drug Administration
HEX	hexagonal endothelial cells
IMP	investigational medicinal product
mITT	*modified intent-to-treat*
nAMD	neovascular age-related macular degeneration
PTI	personalized treatment interval
Q8W	every 8 weeks
Q16W	every 16 weeks
VEGF	vascular endothelial growth factor
SD	standard deviation
YAG	yttrium-aluminum garnet

1. BACKGROUND

1.1 BACKGROUND ON FARICIMAB

See *main* Study GR42691 Section 1.2.

1.2 BACKGROUND ON CORNEAL ENDOTHELIAL CELLS

The corneal endothelium is a single layer of cells lining the posterior portion of the cornea that regulates the health and optical transparency of the cornea (Van den Bogerd et al. 2019). The structural and functional integrity of the corneal endothelium can be impacted by a variety of extrinsic and intrinsic factors, including genetics, race, age, corneal dystrophy, ocular trauma, intraocular surgery, ultraviolet radiation, and intraocular infection. Morphological changes in the corneal endothelium occur throughout life, including a significant decline in corneal endothelial cell density (ECD) and percentage of hexagonal cells with age (Bourne et al. 1997; Zavala et al. 2013). At birth, human ECD is approximately 5000 to 6000 cells/mm^2, and gradually decreases to about 3500 cells/mm^2 by 5 years of age, 3000 cells/mm^2 by 14 to 20 years of age, and 2500 cells/mm^2 in late adulthood due to an age-related increase in the corneal cell dimensions and normal senescence of the endothelial cells (Chaurasia and Vanathi 2021). Changes in normal human corneal endothelium in adult patients were studied for over 10 years and showed a calculated rate of cell loss at approximately 0.6% per year (Bourne et al. 1997). Additional factors can influence or induce corneal endothelial cell loss as seen, for example, by the exacerbation of loss following cataract surgery. Cell loss rates up to 10 years following cataract surgery (phacoemulsification) were reported as 2.5% per year, which is four times higher than the average rate due to the aging process alone (Choi and Han 2019). The greatest corneal endothelial cell loss occurs primarily in the first 1 to 3 months following cataract surgery (Bourne et al. 1997; Beato et al. 2021) and stabilizes approximately 6 months post-operatively (Dick et al. 1996; Bourne et al. 2004; Lass et al 2019; Kelkar et al. 2020).

Specular microscopy is an imaging modality that allows for direct assessment of the corneal ECD and morphology and is routinely used in the assessment of corneal endothelial cell health (Chaurasia and Vanathi 2021). Variables studied in the specular microscopy examination include ECD, percentage of hexagonal endothelial cells (HEX), and coefficient of variation (CV) of cell area and collectively allow the clinician to interpret the health status of the corneal endothelial cells (Chaurasia and Vanathi 2021). Human corneal endothelium consists of a monolayer of hexagonal cells situated in the posterior surface of the cornea (Schmedt et al. 2012) and healthy cornea has approximately 60% of HEX (Chaurasia and Vanathi 2021). The percentage of HEX decreases (pleomorphism) and the CV of cell area increases (polymegathism) with age and endothelial cell attrition due to various causes (Chaurasia and Vanathi 2021).

Corneal ECD is an important clinical parameter that enables assessment of the risk of functional decompensation of cornea and evaluation of the functional reserve of the

corneal endothelium in individual patients. Clinical observations indicate that an ECD of about 400 to 600 cells/mm^2 is a threshold at which corneal decompensation develops resulting in corneal edema accompanied by loss of corneal transparency (Arici et al 2014). The most common causes for corneal endothelial decompensation include cataract surgery or intraocular lens implantation-related complications and Fuchs endothelial corneal dystrophy (Ong Tone et al 2021).

Angiogenic Privilege of Corneal Endothelium

Maintenance of homeostasis between pro- and anti-angiogenic factors in the cornea regulates processes such as endothelial cell proliferation, survival, and apoptosis (Menzel-Severing 2012). In a recent literature search, no peer-reviewed literature was found showing Tie2 receptor expression on corneal endothelial cells. Tie2 receptor expression is absent on normal corneal endothelial cells, except in the instances of pathological corneal neovascularization. In this situation, Tie2 can be found expressed in the cornea only on the pathologically infiltrating vascular cells (Yan et al. 2017). Although high levels of Ang2 expression were detected in pathologically vascularized corneas, Ang2 levels in the corneal endothelial cells of normal corneas are low (Ferrari et al. 2016), and increased levels in the experimental pathological neovascularization corneal models could be reduced with anti-Ang2 treatment (Ferrari et al. 2016; Zhang et al. 2017). Under certain conditions (such as corneal injury or chemical burn, viral infection, other corneal inflammatory disorders, or surgical sutures in a predisposed high-risk corneal graft recipient), pathological triggers may tilt the balance between angiogenic and anti-angiogenic factors and lead to activation of the angiogenic cascade, resulting in neovascularization of the normally avascular cornea and overexpression of angiogenic growth receptors (Azar 2006). The majority of data on angiogenic factor expression in the cornea in the literature is related to the expression of pro-angiogenic factors and their receptors in pathologically neovascularized corneal tissue, and not in normal corneal tissue.

Potential Corneal Endothelial Cell Interactions with Intraocular Anti-VEGF Treatment

Medications administered via the intravitreal route can be eliminated from the vitreous body through both the blood-retinal barrier and the aqueous humor outflow, thus intravitreal medication can come in contact with corneal endothelial cells (Philipp et al. 2000; Del Amo et al. 2017; Lass et al. 2018). It has been postulated that VEGF receptors expressed in the corneal endothelium are in direct contact with the aqueous humor; therefore, anti-VEGF agents may potentially impact VEGF pathway dynamics within the aqueous humor and corneal endothelium (Menzel-Severing 2012; Guzel et al. 2015).

Both in vitro and in vivo studies have set out to address the potential influence of anti-VEGF antibodies on corneal endothelial cells. For instance, in vitro analysis of human donor corneas in the presence of anti-VEGF treatment showed no cytotoxic effects on the corneal endothelium up to 4 weeks post-treatment (Merz et al. 2018).

Though anti-VEGF has been detected in aqueous humor following intravitreal injections (Wang et al. 2014; Celik et al. 2015; Hsu et al. 2016), a number of clinical studies have concluded that there is no substantial impact on the health of the corneal endothelium. No significant differences in corneal ECD, CV, and percent of HEX were identified in patients with neovascular age-related macular degeneration (nAMD) in comparisons preceding and either immediately following aflibercept loading doses (Atilgan et al. 2020) or after single dose of aflibercept at 1-, 3-, and 6-months follow-up (Muto and Machida 2019). Additionally, RE-VIEW was a Phase IV, open-label, single-arm study that evaluated corneal endothelial cell health by specular microscopy in eyes treated with repeated intravitreal aflibercept injection (Lass et al. 2018). Patients with nAMD received aflibercept intravitreal injections every 8 weeks (Q8W) after 3 monthly doses and had specular microscopy assessments performed at baseline and Weeks 24 and 52. RE-VIEW concluded that repeated intravitreal aflibercept injections compared to untreated fellow eyes had no significant impact on ECD, CV, and percent HEX at 1-year follow-up (Lass et al. 2018). Similarly, studies specifically using ranibizumab for intravitreal injections showed no significant impact on ECD, CV, and percentage of HEX up to 1-month (Joshi et al. 2019) and 6-months after injection (Perez-Rico et al. 2010). Conversely, a retrospective study of patients with age-related macular degeneration (AMD) receiving repeated treatments of either aflibercept or ranibizumab detected a statistically significant ECD loss from baseline up to 6-months after the first treatment (Urban et al. 2020); however, the authors noted that they had comparable measurements to multiple other studies where no statistically significant changes were detected. Collectively, safety analyses of pivotal trials for ranibizumab have detected no corneal toxicity and a majority of studies have shown that intravitreal anti-VEGF has no significant effect on the health of corneal endothelial cells.

Similarly, safety analyses from the Phase III studies GR40306 (TENAYA) and GR40844 (LUCERNE) of faricimab in patients with nAMD and from the Phase III studies GR40349 (YOSEMITE) and GR40398 (RHINE) of faricimab in patients with diabetic macular edema (DME) did not identify any clinically detectable cornea-related events that could be indicative of corneal endothelial cell toxicity, such as corneal edema; however, the direct impact of faricimab on the density of the corneal endothelium analyzed by specular microscopy has not yet been investigated.

1.3 SUBSTUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The four faricimab Phase III studies (GR40306 and GR40844 in patients with nAMD, and GR40349 and GR40398 in patients with DME) showed that faricimab 6 mg at intervals of up to every 16 weeks (Q16W) was non-inferior to aflibercept 2 mg Q8W for the primary endpoint of change from baseline in mean best corrected visual acuity (BCVA) at 1 year. Overall, all four studies indicated that faricimab was generally well tolerated and had a comparable safety profile to aflibercept, and a positive benefit-risk was established.

Although previous studies showed that anti-VEGF treatments do not significantly affect the health of the corneal endothelium (Benítez-Herreros et al. 2010; Perez-Rico et al. 2010; Joshi et al. 2019), the impact of faricimab, which inhibits both VEGF and Ang-2, on corneal endothelial cells has not been studied.

The aim of this substudy to *main* long-term extension Study GR42691 is to evaluate the corneal endothelial cells in the study eyes of patients with nAMD receiving faricimab to fulfill a U.S. Food and Drug Administration (FDA) post-marketing requirement. The fellow eyes of the same patients will serve as the controls, and will be permitted to receive standard of care anti-VEGF treatment (if needed).

2. OBJECTIVES AND ENDPOINTS

This substudy will evaluate the impact of faricimab on corneal endothelial cells in patients with nAMD. Specific objectives and corresponding endpoints for this substudy are outlined in the sections below.

2.1 SUBSTUDY OBJECTIVE

2.1.1 Primary Objective

The primary objective for this substudy is to evaluate the impact of faricimab on corneal endothelial cell health on the basis of the following endpoints, as assessed by specular microscopy:

- Primary endpoint: Percent change in corneal endothelial cell density from baseline at Year 1 (defined as the earliest substudy visit closest to Week 52 occurring between Week 48 and Week 64) in the study eye as compared with the fellow eye
- Secondary endpoint: Percent change in corneal endothelial cell density from baseline at substudy midpoint (defined as the earliest substudy visit closest to Week 24 occurring between Week 20 and Week 28) in the study eye as compared with the fellow eye
- Exploratory endpoints:
  - Percent change in the coefficient of variation of corneal endothelial cell area (standard deviation of the cell area/mean cell area) from baseline at substudy midpoint and Year 1 in the study eye as compared with the fellow eye
  - Percent change of hexagonal endothelial cells from baseline at substudy midpoint and Year 1 in the study eye as compared with the fellow eye

3. STUDY DESIGN

3.1 DESCRIPTION OF THE SUBSTUDY

The *main* Study GR42691 is a multicenter long-term extension study designed to evaluate the long-term safety and tolerability of intravitreal faricimab 6 mg administered at a PTI to patients with nAMD who enrolled in and completed one of the Phase III studies, GR40306 and GR40844. Patients enrolled in GR40306 or GR40844 were

randomized in a 1:1 ratio to receive faricimab at a PTI up to Q16W (experimental arm) or aflibercept Q8W (comparator arm).

This substudy is designed to evaluate the impact of intravitreal faricimab 6 mg administered at a PTI on the health of the corneal endothelial cells in patients with nAMD. Fellow eyes of enrolled patients will be used as a comparator for corneal endothelial cells analyses.

3.1.1 Overview of the Substudy

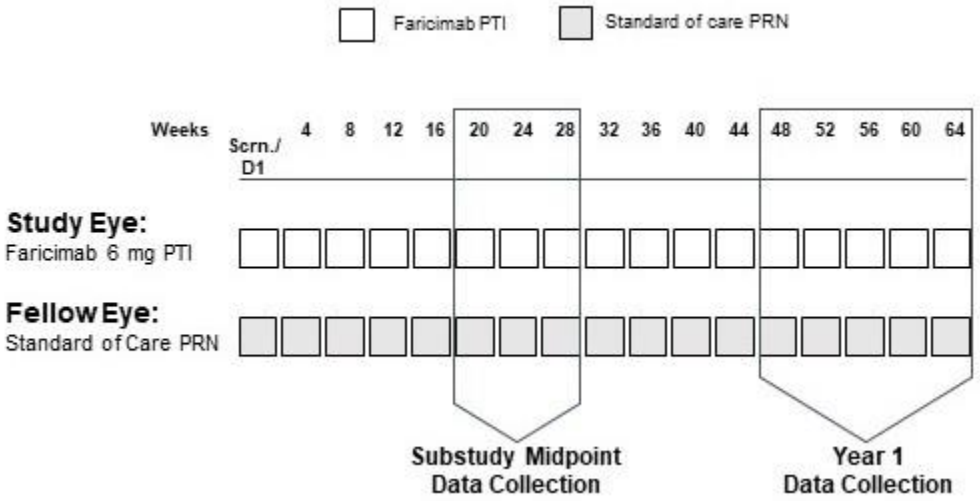
Approximately 135 patients with nAMD will be enrolled at approximately 50 investigational *global* sites from the *main* Study GR42691. Study GR42691 patients must have at least 48 weeks remaining in Study GR42691.

Patients in the *main* Study GR42691 will be eligible to screen for participation in this substudy. During the substudy screening visit, eligibility to participate will be determined based on the inclusion and exclusion criteria for this substudy.

Patients who do not meet the criteria for participation in this substudy (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 90 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (Section 4.4.1).

Figure 1 presents an overview of the substudy design. A schedule of activities is provided in Appendix 1.

Figure 1 Substudy Assessment Schema



D1 = Day 1; PRN = pro renata (as needed); PTI = personalized treatment interval; Scrn = screening visit.

Substudy midpoint data collection timepoint is defined as the earliest substudy visit closest to Week 24 occurring between Week 20 and Week 28. Year 1 data collection timepoint is defined as the earliest substudy visit closest to Week 52 occurring between Week 48 and Week 64.

3.1.2 Enrollment

Each consented patient must satisfy all eligibility criteria of the *main* Study GR42691 (see *main* Study GR42691 Sections 4.1.1 and 4.1.2), and the eligibility criteria of this substudy (see Section 4.1.1 and Section 4.1.2), including receipt of all substudy screening images and confirmation of substudy eligibility by the independent corneal reading center.

3.1.3 Corneal Endothelial Cells Assessments

When possible, patients will follow the scheduled assessments per the *main* protocol (see *main* Study GR42691 Appendix 1). However, for some patients, an additional visit may need to be scheduled in between *main* protocol visits for the substudy midpoint visit. Substudy patients will undergo specular microscopy imaging in both eyes to assess number/density of corneal endothelial cells at screening, substudy midpoint, and Year 1 prior to the application of any topical ophthalmic anesthetic, tonometry, or any other study treatment.

Patients should attend all scheduled visits; however, if there are extenuating circumstances that preclude attendance at a scheduled visit, the patient may come in for specular microscopy imaging at an unscheduled visit up to 4 weeks after the missed visit.

3.1.4 Substudy or Study Withdrawal

If the patient withdraws from the substudy only, then the patient may remain in the *main* Study GR42691.

If the patient withdraws from the *main* Study GR42691, then the patient will also be withdrawn from this substudy.

If the patient discontinues treatment in the *main* Study GR42691 but remains in the *main* Study GR42691 for follow-up, then the patient will remain in this substudy. All patients who remain in this substudy will be strongly encouraged to complete specular microscopy imaging at substudy midpoint and Year 1.

3.2 END OF SUBSTUDY AND LENGTH OF SUBSTUDY

The end of this substudy is defined as the date when the last patient, last visit occurs. The end of the substudy is expected to occur approximately 48 weeks after the last substudy patient is enrolled.

In addition, the Sponsor may decide to terminate the substudy at any time.

3.3 RATIONALE FOR SUBSTUDY DESIGN

3.3.1 Rationale for Faricimab Dose and Schedule

See *main* Study GR42691 Section 3.3.1.

3.3.2 Rationale for Patient Population

The patient population for this substudy mirrors the patient population of the *main* Study GR42691, with the exceptions listed in Section 4.1.1 for Inclusion Criteria and Section 4.1.2 for Exclusion Criteria.

The aim of this substudy is to assess whether the health of corneal endothelial cells is affected by faricimab in eyes of patients with nAMD, and therefore the patient population for this substudy, which includes patients with nAMD who will receive faricimab in one eye with fellow eye as a control comparison, is appropriate.

3.3.3 Rationale for Use of Patient Fellow Eye as the Comparator

Documented changes occur in the morphology, cell density, and percent hexagonal cells in the corneal endothelium due to the natural progression of aging (Bourne et al. 1997). Large inter-patient variability in corneal endothelium morphology can be due to factors such as age, gender, ethnicity, and ocular and non-ocular disorders (Carlson et al. 1988; Snellingen et al. 2001; Shi et al. 2019); therefore, comparison of corneal endothelial cells' health between two eyes of the same patient (one eye treated with faricimab, the other eye without) is appropriate to account for changes that would typically occur in a given patient.

Current evidence suggests that intravitreally administered anti-VEGF agents, as described in Section 1.2, have no negative impact on corneal endothelial health. However, safety data have shown that treatment with brolucizumab is associated with intraocular inflammation that could lead to retinal vasculitis or retinal artery occlusion. Therefore, patients who previously received brolucizumab in the fellow eye will be excluded (see Section 4.1.2) but there will be no other specific exclusion of patients who have received previous treatment in the fellow eye with other intravitreal anti-VEGF agents.

4. MATERIALS AND METHODS

4.1 PATIENTS

The planned enrollment is approximately 135 patients with nAMD who meet eligibility criteria for both the *main* Study GR42691 and this substudy.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

In addition to the inclusion criteria specified in the *main* Study GR42691 (see *main* Study GR42691 Section 4.1.1.1), patients must meet the following criteria:

- Signed Informed Consent for this substudy

*Must be able to participate for a*t least 48 weeks *in the CEC Substudy and have at least the first CEC visit while enrolled* in the *main* Study GR42691.

4.1.1.2 Ocular Inclusion Criteria

Patients must meet the following ocular inclusion criterion for substudy entry:

- Difference of $<10\%$ in ECD at screening between the two eyes as measured by specular microscopy and determined by the independent reading center

4.1.2 Exclusion Criteria

In addition to all criteria specified in the *main* Study GR42691 protocol, patients will be excluded from this substudy if they meet the following criteria:

Fellow (Non-Study) Eye

- Prior and/or current administration of faricimab
- Prior administration of brolucizumab

Either Eye

- Corneal ECD ≤ 1500 cells/mm^2 in either eye at screening as determined by the independent corneal reading center
- Fuchs endothelial corneal dystrophy Grade ≥ 2
- Previous ocular trauma (blunt or penetrating) and/or corneal endothelial cell damage, including from blunt or surgical trauma (including complicated cataract surgery resulting in complicated lens placement such as anterior chamber intraocular lens, sulcus intraocular lens, aphakia, etc.)

- Any ocular condition that precludes obtaining an analyzable specular microscopy image
- Active or history of corneal edema
- *Any* active or history of corneal dystrophies*, excluding Fuchs endothelial corneal dystrophy Grade <2*
- Active or history of iridocorneal endothelial syndrome
- Active or history of pseudoexfoliation syndrome
- Active or history of herpetic keratitis or kerato-uveitis (including herpes simplex virus and herpes zoster virus)
- Intraocular laser therapy including selective laser trabeculoplasty, yttrium-aluminum garnet (YAG), prophylactic peripheral iridotomy within 1 year of screening, or YAG capsulotomy within 3 months of screening
- Prior vitrectomy surgery, submacular surgery, or other surgical intervention for AMD
- Prior pars plana vitrectomy surgery
- Previous intraocular device implantation excluding intraocular lenses
- Cataract surgery within 6 months of screening or planned for during the study
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery. Other types of prior glaucoma surgery are allowed providing that the surgery occur more than 6 months before screening
- Administration of topical Rho kinase inhibitors (e.g., Rhopressa eye drops) within 1 month prior to the screening visit
- Contact lens wear in either eye within 2 months of screening
- History of corneal transplantation, including partial-thickness corneal grafts (e.g., Descemet membrane endothelial keratoplasty, Descemet stripping endothelial keratoplasty)
- Active or history of iridocorneal endothelial syndrome
- Active or history of pseudoexfoliation syndrome

4.2 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE SUBSTUDY DESIGN

The investigational medicinal product (IMP) for this study is faricimab (test product).

4.2.1 *Study Treatment Formulation and Packaging*

4.2.1.1 Faricimab

Faricimab will be supplied by the Sponsor as a sterile liquid for intravitreal injection in single-use glass vials.

Each single-use, 2 -mL glass vial contains 6 mg (nominal) of faricimab formulated as 120 mg/mL in L-histidine/acetate buffer solution (approximately pH 5.5) containing sodium chloride, sucrose, L-methionine, and polysorbate 20 and is designed to provide a

dose of 6 mg/0.05 mL for intravitreal injection. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.2.2 *Investigational Medicinal Product Handling and Accountability*

See main Study GR42691 Section 4.3.3.

4.2.3 *Continued Access to Faricimab*

See main Study GR42691 Section 4.3.4. If a patient's participation extends beyond the duration of the main study faricimab will continue to be reimbursed until the patient completes the CEC Substudy for the study eye.

4.3 CONCOMITANT THERAPY

See *main* Study GR42691 Section 4.4.

4.3.1 Permitted Therapy

See *main* Study GR42691 Section 4.4.1. *As faricimab is made commercially available globally, the requirements for ongoing reimbursement of other anti-VEGF therapies licensed for ocular use that are used in the fellow eye have been revised, and reimbursement must be approved by the Sponsor unless the patient is enrolled in the CEC Substudy. Reimbursements will cease if the patient is discontinued from the faricimab study treatment or once the patient has completed the trial or the CEC substudy, whichever occurs last.*

4.3.2 Prohibited Therapy

See *main* Study GR42691 Section 4.4.2.

Administration of topical Rho kinase inhibitors (e.g., Rhopressa eye drops) during the substudy and for at least 1 month prior to screening is prohibited.

Administration of the following therapies to the fellow eye is also prohibited during the substudy:

- faricimab
- brolucizumab (Beovu®)
- bevacizumab (Avastin®)
- Port Delivery System implantation (Susvimo™)

4.4 SUBSTUDY ASSESSMENTS

The schedule of activities to be performed during the substudy is provided in Appendix 1. All activities should be performed and documented for each patient.

4.4.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the substudy must be obtained before performing any substudy-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened, to document eligibility or record reasons for screening failure, as applicable.

4.4.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

See *main* Study GR42691 Section 4.5.2 for the medical history, baseline conditions and demographic data.

4.4.3 Vital Signs

See *main* Study GR42691 Section 4.5.3.

4.4.4 Ocular Assessments

See *main* Study GR42691 Section 4.5.4.

Ocular Imaging

A corneal reading center will provide sites with the corneal reading center manual and training materials for specified substudy ocular images. Before any substudy images are obtained, site personnel, test images, systems, and software (where applicable) will be certified and validated by the reading center as specified in the corneal reading center manual. All ocular image results will be obtained by trained site personnel at the study sites and forwarded to the corneal reading center for independent analysis and/or storage and will later be transferred to the Sponsor.

If a patient misses all the substudy visits within the visit window in which specular microscopy imaging can be scheduled (i.e., Weeks 20 through 28 for substudy midpoint and Weeks 48 through 64 for Year 1), the images should be obtained at an unscheduled visit up to 4 weeks after the last missed visit of the window (i.e., Week 28 for substudy midpoint and Week 64 for Year 1) or at the next scheduled in-person *main* Study GR42691 visit, whichever comes first. If the images need to be repeated due to quality reasons, this should be done within the visit window or within 4 weeks, whichever comes first.

Scans of both eyes will be collected from all substudy patients, according to the corneal reading center image acquisition protocol.

4.4.5 Concurrent Ocular Procedures

See *main* Study GR42691 Section 4.5.5.

4.5 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Study Treatment Discontinuation

See Section 3.1.4 and *main* Study GR42691 Section 4.6.1.

4.5.2 Patient Discontinuation from the Study

See *main* Study GR42691 Section 4.6.2.

4.5.3 Study Discontinuation

See Section 3.1.4 and *main* Study GR42691 Section 4.6.3.

4.5.4 Site Discontinuation

See *main* Study GR42691 Section 4.6.4.

5. *ASSESSMENT OF SAFETY*

5.1 *SAFETY PLAN*

See main Study GR42691 Section 5.1. If a patient's duration on the CEC Substudy extends beyond the duration of the main study, safety data will continue to be collected per the same reporting mechanism, which will remain available until the final CEC visit.

5.2 *SAFETY PARAMETERS AND DEFINITIONS*

See main Study GR42691 Section 5.2.

5.3 *METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS*

See main Study GR42691 Section 5.3.

5.4 *IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR*

See main Study GR42691 Section 5.4.

5.4.1 *Medical Monitors and Emergency Medical Contact*

Contact Information for All Sites

Medical Monitor/Emergency Medical Contact: [redacted] (Primary)

Mobile Telephone No.: [redacted]

5.4.2 *Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest*

See main Study GR42691 Section 5.4.2. If a patient's duration on the CEC Substudy extends beyond the duration of the main study, safety data will continue to be collected per the same reporting mechanism, which will remain available until the final CEC visit.

5.4.3 *Reporting Requirements for Pregnancies*

See main Study GR42691 Section 5.4.3.

5.5 *FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS*

See main Study GR42691 Section 5.5.

5.6 *ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

See main Study GR42691 Section 5.6.

5.7 *EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES*

See main Study GR42691 Section 5.7.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed for this substudy. A planned enrollment of approximately 135 patients from the *main* Study GR42691 was selected in order to obtain data from at least 100 patients through Year 1 to account for patients with missing data (e.g., missed visits, lost to follow-up). ECD, CV, and HEX will be assessed in the corneal endothelium evaluable set (modified intent-to-treat [mITT] population), which includes all patients who were treated in the study eye and for whom specular microscopic images were interpretable in both the study and fellow eye both at baseline and at the substudy midpoint and/or Year 1 evaluations.

For additional details, refer to *main* Study GR42691.

6.2 ANALYSIS POPULATIONS

6.2.1 Modified Intent-to-Treat Population

The mITT population will comprise all eligible patients enrolled into this substudy who received at least one injection of faricimab during the substudy. For analyses using the GR40306 or GR40844 (hereinafter referred to as *main* Phase III study) treatment group, patients will be grouped according to the treatment assigned at randomization in the *main* Phase III study. In the *main* Phase III studies, patients were randomized to one of

two regimens: faricimab administered up to Q16W or aflibercept administered at a fixed interval of Q8W.

6.2.2 Per-Protocol Population

The per-protocol population is defined as all mITT patients who do not have a major protocol violation that impact the efficacy evaluation in the substudy. For analyses using the *main* Phase III study treatment group, patients will be grouped according to the treatment assigned at randomization in the *main* Phase III study.

6.3 SUMMARIES OF CONDUCT OF STUDY

Summaries of conduct of study will be based on the mITT population and will be presented overall and by *main* Phase III study treatment group. The number and percentage of patients who enroll (including from which treatment group of the *main* Phase III study) will be summarized by site. The number and percentage of patients who enroll in (including from which treatment group of the *main* Phase III study), discontinue from, or complete this substudy will be also summarized. Reasons for premature substudy withdrawal will be listed and summarized. Eligibility criteria exceptions and other major protocol deviations will be listed and evaluated for their potential impact on the interpretation of the substudy results.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline disease characteristics will be summarized using the mITT population and will be presented overall and by *main* study Phase III treatment group.

- Demographic data (e.g., sex and race or ethnicity) will originate from the *main* Phase III studies.
- Baseline ocular and non-ocular disease characteristics (e.g., baseline BCVA, central subfield thickness [CST]) will be done both with values originating from the *main* Phase III study treatment group and from the *main* study GR42691 study overall.

Baseline ocular characteristics collected at the substudy screening visit will be summarized by eye (study eye versus control eye).

Exposure to study drug (number of treatments and duration of treatment) will be summarized as the exposure during the substudy only. Exposure will be presented overall and by *main* Phase III study treatment groups for the safety-evaluable population.

The difference between study eye and fellow eye ECD, CV, and HEX will be summarized by using means, standard deviations, medians, and ranges for study and fellow eye at baseline. Descriptive statistics for continuous data will include number of observations, arithmetic mean, SD, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and/or percent.

6.5 IMAGING ANALYSES

Imaging analyses will be performed among the subset of patients who had an interpretable baseline specular microscopic image in both eyes and at least one post-baseline specular microscopic image for both eyes either at substudy midpoint and/or at Year 1.

6.5.1 Primary Efficacy Endpoint

The percent change in corneal ECD from baseline at Year 1 will be analyzed using the paired t-test. The 95% confidence intervals for Year 1 values as well as change-from-baseline at Year 1 will be calculated.

6.5.2 Secondary Efficacy Endpoint

The percent change in corneal ECD from baseline at substudy midpoint will be analyzed using the paired t-test. The 95% confidence intervals for baseline and substudy midpoint values as well as for change-from-baseline at substudy midpoint will be calculated.

6.5.3 Exploratory Efficacy Endpoints

The percent change in CV of corneal endothelial cell area and percent change of HEX cells from baseline at substudy midpoint and Year 1 will be analyzed using the paired t-test. The 95% confidence intervals for baseline, substudy midpoint, and Year 1 values as well as for change-from-baseline at each timepoint will be calculated.

6.5.3.1 Subgroup Analyses

The percent change in corneal ECD from baseline at Year 1, the percent change in CV of corneal endothelial cell area from baseline at substudy midpoint and Year 1, and the percent change of HEX cells from baseline at substudy midpoint and Year 1 will be analyzed separately using the paired t-test within each of the following subgroups:

- Baseline age (<65, ≥ 65 to <75, and ≥ 75 years)
- Number of faricimab injections received during substudy (≤ 5, >5 injections)

6.6 INTERIM ANALYSIS

No interim analysis is planned for this substudy.

7. DATA COLLECTION AND MANAGEMENT

See *main* Study GR42691 Section 7.

8. ETHICAL CONSIDERATIONS

See *main* Study GR42691 Section 8.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

See *main* Study GR42691 Section 9.

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Appendix 1 Schedule of Activities

Assessments	Screening and Enrollment Visit [a, b]	Substudy Midpoint [a, c]	Year 1 [a, d] (Final Substudy Visit)	Unscheduled Visit
Substudy (Week[s])	1	20 to 28	48 to 64	
Visit window (days) [a]	Any *week within main* Study GR42691 *and* ≥ 7 days after last anti-VEGF or other IVT injection in either eye	—	—	—
Informed consent [e]	x			
Review of inclusion and exclusion criteria	x			
Specular microscopy [f]	x	x	x	x

IVT = intravitreal; VEGF = vascular endothelial growth factor.

[a] Refer to *main* Study GR42691 Schedule of Activities (Appendix 1) for *main* study assessments, visit schedule, and study visit windows. Please note that substudy visits will also be based on the patient's personalized treatment interval determined during the *main* Study GR42691.

[b] Screening and enrollment visit will be Day 1 of this substudy.

[c] Substudy midpoint assessment is defined as the earliest substudy visit closest to Week 24 occurring between Week 20 and Week 28. *However, patients are allowed to complete the CEC visit at any time between Week 20 and Week 28.*

[d] Year 1 assessment is defined as the earliest substudy visit closest to Week 52 occurring between Week 48 and Week 64.

[e] Patients must sign the substudy Informed Consent Form prior to performing protocol-mandated assessments. Consent may be obtained on or prior to the screening visit. *However, patients are allowed to complete the Corneal Endothelial Cells study visit at any time between Week 48 and Week 64.*

[f] Perform specular microscopy for both eyes prior to application of any topical ophthalmic anesthetic, tonometry, or any other study treatment on the same day for the evaluation of endothelial cell density. Specular microscopy imaging must be performed prior to study treatment administration.

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