Official Title:	**STAIRWAY: SIMULTANEOUS BLOCKADE OF ANGIOPOIETIN-2 AND VEGF-A WITH THE BISPECIFIC ANTIBODY RO6867461 (RG7716) FOR EXTENDED DURABILITY IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
NCT Number:	**NCT03038880**
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PROTOCOL

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PROTOCOL NUMBER:	CR39521
VERSION NUMBER:	2
EUDRACT NUMBER:	N/A
IND NUMBER:	119225
TEST PRODUCT:	RO6867461 (RG7716)
MEDICAL MONITOR:	[redacted], M.B.B.S.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 7 November 2016
DATE AMENDED:	Version 2: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	14-Feb-2017 18:29:31

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol CR39521 has been amended to provide further clarity on certain aspects of protocol execution. Changes to the protocol, along with a rationale for each change, are summarized below.

- For assessment of active disease using optical coherence tomography (OCT), measurement of central foveal thickness (CFT) has been replaced with measurement of central subfield thickness (CST), as CST can be calculated using an automated program within the Heidelberg Spectralis® OCT instrument and has lower risk of measurement error compared to manual calculation of CFT on the same device (Sections 3.1.1 and 4.5.5.4).
- Language has been added to the study design (Section 3.1.1) to clarify that if the screening and Week 1/Day 1 visit occurs as a combined visit, informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.
- The location of choroidal neovascularization (CNV) in the study eye has been further clarified in an inclusion criterion (Section 4.1.1).
- To ensure consistency across study sites, specifications have been made for the timing for several of the inclusion/exclusion criteria (Sections 4.1.1 and 4.1.2).
- Language has been added and revised to provide guidance and explanation of the masked and unmasked roles at the site and study levels, and for biosamples (Section 4.2.2).
- Reimbursement by the Sponsor of commercial ranibizumab and other approved anti-VEGF treatments for the fellow eye has been clarified (Section 4.4.3).
- It has been specified that adverse events of special interest (immediately reportable to the Sponsor) can be non-serious or serious (Section 5.2.3).
- To adhere to current protocol template language for safety reporting, Section 5.3.5.7 has been updated.
- To provide sites the option to collect the whole blood DNA sample after the Week 1, Day 1 visit, language has been added to allow for this sample to be collected at any subsequent study visit where a blood draw is being performed (Appendix 1, footnote “n”).

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

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1.1: Overview of the Study Design

Patients will undergo a screening examination within 4 weeks of study treatment administration. The screening and Week 1/Day 1 (randomization) visit may occur as a combined visit if all assessments *(with the exception of informed consent)* are ~~conducted~~ *completed* within 48 hours. *Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.* Where screening and randomization are combined, assessments listed for both visits only need to be conducted once. …

Determination of active disease will be made if any of the following criteria are met (also see Section 4.5.5.4):

- Increase in central ~~foveal~~ *subfield* thickness (~~CFT~~*CST* of >50 μm on Spectralis® OCT compared to average ~~CFT~~ *CST* over last 2 visits (Weeks 16 and 20)

  Or

- Increase in ~~CFT~~ *CST* of ≥75 μm compared to lowest ~~CFT~~*CST* recorded at either Week 16 or Week 20 …

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

Ocular Criteria for Study Eye

- Subfoveal CNV or ~~CNV lesion component~~ *juxtafoveal CNV with a subfoveal component related to the CNV activity by FFA or SD-OCT (as evidenced by subretinal fluid, subretinal hyper-reflective material, evidence of leakage, or hemorrhage)*

General Criteria

- Age ≥50 years *on Day 1*

SECTION 4.1.2: Exclusion Criteria

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

Ocular Criteria for Study Eye

- Cataract surgery within 3 months of baseline assessments *(Day 1)*

Concurrent Ocular Conditions

- Active intraocular inflammation (grade trace or above) ***in the study eye*** *on Day 1 (prior to randomization)*

- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis *in either eye* *on Day 1 (prior to randomization)*

SECTION 4.2.2: Masking

This is a patient- and outcome assessor (BCVA and Central Reading Center)-masked study. The intent of this design allows for a single investigator per site to be present at a given visit to fulfill the masking requirements of this study.

At a site level:

- *Patients and BCVA examiners will be masked to treatment assignment. BCVA examiners will also be masked to study eye (see Section 4.5.5.1). All other site personnel that do not have a role in drug preparation and/or treatment delivery should be masked to study eye drug assignment.*
- *The investigator administrating the patient's treatment (RO6867461, comparator ranibizumab, or sham) and/or pharmacist/designated personnel responsible for drug preparation will be unmasked to treatment assignment.*

The number of unmasked study personnel should be limited to ensure the integrity of this masked study. All roles for each study staff member should be clearly documented in the site delegation log. The delegation log must be signed by the Principal Investigator. Unmasked personnel cannot switch to a masked role, but masked personnel can switch to an unmasked role. Any change should be documented in the delegation log.

~~Patients, study site personnel (with the exception of the investigator, and/or pharmacist/designated personnel responsible for drug preparation), BCVA examiners, imaging technicians,~~

At a study level:

The Central Reading Center personnel, study vendors, ~~Central Reading Center personnel,~~ and the Sponsor *(with the exception of a point person[s] to support unmasked site personnel and IMC members in the case of an optional interim analysis; Section 3.1.2 and Section 6.9)* and its agents will be masked to study eye drug assignment.

~~The number of unmasked study personnel should be limited to ensure the integrity of this masked study.~~

~~To maintain the masked design of the study, blood samples collected at timepoints specified in the schedule of activities (Appendix 1) will also be taken from all patients receiving ranibizumab per the RO6867461 schedule. The samples from these patients may or may not be analyzed.~~

For biosamples:

To maintain the masked design of the study, blood samples collected at timepoints specified in the schedule of activities (Appendix 1) will also be taken from all patients receiving ranibizumab per the RO6867461 schedule. The samples from these patients may or may not be analyzed. Unmasking for independent analysis of the relevant biosamples during the conduct of the study will be performed according the Sponsor's internal standard procedures in place to ensure integrity of the data. The number of Roche representative(s) and delegates unmasked will be kept to the minimum required to address the objective of the biosample analysis.

~~Sponsor personnel responsible for performing PK assays will be unmasked to patients' treatment assignments to identify appropriate PK samples to be analyzed.~~

SECTION 4.4.3: CNV Secondary to AMD in the Fellow Eye

When anti-VEGF therapy is recommended and ranibizumab warranted, every effort should be made to treat with ranibizumab. This treatment will be provided by the Sponsor as long as the patient remains in the study. When provided by the Sponsor, it will be in the commercial formulation for ranibizumab labelled for investigational use only (dispatched by IxRS). *Treatment with commercial supplies of ranibizumab may be reimbursed at the discretion and approval of the Sponsor.*

~~This treatment also~~ *Treatment with other approved anti-VEGF therapies* may be provided by the site ~~through commercial supplies~~. However, commercial supplies *of other approved anti-VEGF treatments* will not be reimbursed by the Sponsor.

SECTION 4.5.5.3: Ocular Imaging

For SD-OCT and optional OCT-A, images of *the study eye and* fellow eyes should ~~only~~ be captured and forwarded to the Central Reading Center at the screening, Week 24, Week 40, and Week 52 or early termination visits. At all other visits, only the study eye images need to be acquired and forwarded to the Central Reading Center.

SECTION 4.5.5.4: Week 24 Assessment of Disease Activity

Determination of active disease will be made if any of the following criteria are met:

- Increase in ~~CFT~~ *CST* of >50 μm on Spectralis OCT compared to average ~~CFT~~*CST* over last 2 visits (Weeks 16 and 20)

  Or

- Increase in ~~CFT~~*CST* of ≥ 75 μm compared to lowest ~~CFT~~*CST* recorded at either Week 16 or Week 20 …

SECTION 5.2.3: Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious or serious ~~A~~*a*dverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). …

- Sight-threatening adverse events

  An adverse event *is* considered to be sight threatening *and* should be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; or reporting instructions) if it meets one or more of the following criteria: …

SECTION 5.3.3: Assessment of Severity of Adverse Events

The adverse event severity grading scale in Table 3 *will be used* ~~provides guidance~~ for assessing adverse event severity.

SECTION 5.3.5.7: Deaths

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 9.2: PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

… For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~
http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

APPENDIX 1: Schedule of Activities

Appendix 1 has been revised to reflect changes to the protocol, and to add footnote “n” to the whole blood sample for DNA assessment.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**STAIRWAY: SIMULTANEOUS BLOCKADE OF ANGIOPOIETIN-2 AND VEGF-A WITH THE BISPECIFIC ANTIBODY RO6867461 (RG7716) FOR EXTENDED DURABILITY IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
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MEDICAL MONITOR:	[redacted], M.B.B.S.
SPONSOR:	F. Hoffmann-La Roche Ltd

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 as instructed by the local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**STAIRWAY: SIMULTANEOUS BLOCKADE OF ANGIOPOIETIN-2 AND VEGF-A WITH THE BISPECIFIC ANTIBODY RO6867461 (RG7716) FOR EXTENDED DURABILITY IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	CR39521
VERSION NUMBER:	2
EUDRACT NUMBER:	N/A
IND NUMBER:	119225
TEST PRODUCT:	RO6867461 (RG7716)
PHASE:	Phase II
INDICATION:	Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of RO6867461 administered at 12- and 16-week intervals in patients with neovascular age-related macular degeneration (nAMD). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of RO6867461 on visual acuity when administered at 12- and 16-week intervals	• Mean change from baseline BCVA at Week 40 using the ETDRS-like charts
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of RO6867461 on additional visual acuity outcomes	• Mean change from baseline BCVA over time using the ETDRS-like charts • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters from baseline BCVA over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters from baseline BCVA over time • Proportion of patients with BCVA of 20/40 or better over time • Proportion of patients with BCVA of 20/200 or worse over time
• To evaluate the efficacy of RO6867461 on anatomic outcome measures using SD-OCT	• Mean change from baseline in CFT over time • Mean change from baseline in mean CST (1 mm diameter) over time • Proportion of patients with intraretinal fluid, subretinal fluid, cysts, or pigment epithelial detachment over time

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of RO6867461 on anatomic outcome measures using FFA	• Mean change from baseline in total area of CNV at Week 40 and Week 52 • Mean change from baseline in total area of CNV component at Week 40 and Week 52 • Mean change from baseline in total area of leakage at Week 40 and Week 52
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To investigate the incidence of disease activity at Week 24	• Proportion of patients with disease activity at Week 24
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of multiple IVT doses of RO6867461 at 12- and 16-week intervals	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events • Other safety data, including but not limited to, reasons for withdrawal from study, laboratory data, concomitant medications, vital signs, and physical examination results will be listed and summarized descriptively
Exploratory Pharmacokinetic/ Pharmacodynamic Objectives	**Corresponding Endpoints**
• To assess the systemic PK profile of RO6867461	• Plasma concentration of RO6867461 at specified timepoints
• To evaluate the RO6867461, ranibizumab, free VEGF-A, and Ang-2 profile in aqueous humor	• Relationship between aqueous humor RO6867461 concentrations or PK parameters and free VEGF-A and Ang-2 concentrations • Relationship between aqueous humor ranibizumab concentrations or PK parameters and free VEGF-A and Ang-2 concentrations • Time course of free VEGF-A and Ang-2 concentrations in aqueous humor
Immunogenicity Objective	**Corresponding Endpoints**
• To investigate the formation of plasma anti-RO6867461 antibodies	• Incidence of ADAs during the study
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To explore levels of potential biomarkers of angiogenesis and inflammation in aqueous humor at baseline and at additional timepoints to assess their response to RO6867461	• Relationship between aqueous humor concentration of potential biomarkers with primary and secondary endpoints

ADA = anti-drug antibody; Ang-2 = angiopoietin-2; BCVA = best corrected visual acuity; CFT = central foveal thickness; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FFA = fundus fluorescein angiography; IVT = intravitreal; PK = pharmacokinetic; SD-OCT = spectral domain optical coherence tomography; VEGF-A = vascular endothelial growth factor A.

Study Design

Description of Study

This is a Phase II, multicenter, randomized, active comparator-controlled, subject and outcome-assessor masked, parallel group, 52-week study to investigate the efficacy, safety, and pharmacokinetics of RO6867461 administered at 12- and 16-week intervals in treatment-naive patients with nAMD. Approximately 75 patients will be enrolled and randomized in a 2:2:1 ratio to one of three treatment arms:

- Arm A (Q12W): 6 mg RO6867461 intravitreally (IVT) every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 12 weeks up to Week 48 (injections at Weeks 24, 36, and 48; 3 injections)
- Arm B (Q16W): 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 16 weeks up to Week 48 (injections at Weeks 28 and 44; 2 injections)

  A protocol-defined assessment of disease activity at Week 24 requires Arm B patients with active disease (see criteria below) to switch to a 12-weekly dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.
- Arm C (comparator arm): 0.5 mg ranibizumab IVT every 4 weeks for 48 weeks (13 injections)

Only one eye will be chosen as the study eye.

The total duration of the study for each patient will be up to 56 weeks, divided as follows:

- Screening: up to 4 weeks prior to or on the same day as randomization
- Randomization: Day 1
- Study Treatment Administration: from Day 1 to Week 48
- Final Visit: Week 52

Patients will undergo a screening examination within 4 weeks of study treatment administration. The screening and Week 1/Day 1 (randomization) visit may occur as a combined visit if all assessments *(with the exception of informed consent)* are *completed* within 48 hours. *Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.* Where screening and randomization are combined, assessments listed for both visits only need to be conducted once. During screening (or the combined screening/Day 1 visit), the patient's eligibility will be assessed, including a central review of fundus photography (FP), spectral domain optical coherence tomography (SD-OCT), and fundus fluorescein angiography (FFA) to ensure that CNV secondary to AMD meets the predefined ocular criteria in the study.

Patients who were deemed ineligible based on screening results for any of the following reasons will be allowed to be re-screened:

- Uncontrolled blood pressure
- Administrative reason (e.g., unable to schedule Day 1 within 28 days from the screening visit)
- Not meeting eligibility criteria for the study eye (in the event the patient might be eligible to participate for the second eye after the initial screening period)

At re-screening, all screening visit assessments will be performed (except for FFA imaging collection), provided the Central Reading Center-eligible FFA images were taken within 4 weeks before the new Day 1 visit (randomization).

On Day 1, eligible patients will receive their first IVT administration of either RO6867461 or ranibizumab according to the randomization schedule described above and following established standard administration procedures. Patients will return to the eye clinic 7 days after their first IVT administration and then every 4 weeks for study treatment administration and assessments as outlined in the schedule of activities in the protocol. Sham IVT administration will be delivered to patients randomized to Arms A and B to maintain masking throughout the study period.

All patients will be assessed for disease activity at Week 24. Patients randomized to Arm B who have active disease at Week 24 (see criteria below) will switch to the Q12W dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.

Determination of active disease will be made if any of the following criteria are met:

- Increase in central *subfield* thickness (*CST* of >50 μm on Spectralis® OCT compared to average *CST* over last 2 visits (Weeks 16 and 20)

  Or
- Increase in *CST* of ≥75 μm compared to lowest *CST* recorded at either Week 16 or Week 20

  Or
- Decrease of at least 5 letters of best corrected visual acuity (BCVA) compared with average BCVA over last 2 visits (Weeks 16 and 20) due to nAMD disease activity

  Or
- Decrease of ≥10 letters of BCVA compared to highest BCVA recorded at either Week 16 or Week 20 due to nAMD disease activity

  Or
- Presence of new macular hemorrhage due to nAMD activity

If, in the opinion of the investigator, there is significant nAMD disease activity at Week 24 that requires immediate treatment, but does not meet the above criteria, the Medical Monitor should be contacted. In such cases, following approval by the Sponsor, patients randomized to Arm B will receive 6 mg RO6867461 at Week 24 and stay on repeated 12-weekly treatments at Weeks 36 and 48.

Patients who are withdrawn from the study early but have not withdrawn consent should return for an early termination visit 28 (+7) days following the last study treatment for assessments as well as monitoring of all adverse events.

Patients will return for a final visit at Week 52. After the final visit, adverse events should be followed up as outlined in the protocol. Assessments performed in case of an unscheduled visit(s) are at the discretion of the investigator.

Number of Patients

Approximately 75 treatment-naive patients with nAMD are expected to be enrolled and randomized in this study in the United States.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Ocular Criteria for Study Eye

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or *juxtafoveal CNV with a subfoveal component related to the CNV activity by FFA or SD-OCT (as evidenced by subretinal fluid, subretinal hyper-reflective material, evidence of leakage, or hemorrhage)*
- CNV lesion of all types (predominantly classic, minimally classic, or occult) with:

  Total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤6 disc areas by FFA

  And

  CNV component area of ≥ 50% of total lesion size by FFA

  And

  Active CNV confirmed by FFA (evidence of leakage)

  And

  CNV exudation confirmed by SD-OCT (presence of fluid)
- BCVA letter score of 73 to 24 letters (inclusive) on Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts (20/40 to 20/320 Snellen equivalent) *on Day 1*

- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

General Criteria

- Signed Informed Consent Form
- Age $\geq$ 50 years *on Day 1*
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<$1% per year during the treatment period and for at least 28 days after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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 acceptable methods of contraception.
- Patients must be willing not to participate in any other clinical trial including an investigational medicinal product (IMP) or device up to completion of the current study

Exclusion Criteria

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

Ocular Criteria for Study Eye

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Central serous chorioretinopathy at screening
- Retinal pigment epithelial tear involving the macula
- On FFA

  Subretinal hemorrhage of $>$50% of the total lesion area and/or that involves the fovea

  Fibrosis or atrophy of $>$50% of the total lesion area and/or that involves the fovea
- Any prior or concomitant treatment for CNV including (but not restricted to) IVT treatment (steroids, anti-vascular endothelial growth factor [VEGF], tissue plasminogen activator, ocriplasmin, C_3F_8 gas, air), periocular pharmacological intervention, argon LASER photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or surgical intervention
- Cataract surgery within 3 months of baseline assessments *(Day 1)*
- Any other intraocular surgery (pars plana vitrectomy, glaucoma surgery, corneal transplant, radiotherapy)
- Prior IVT treatment (including anti-VEGF medication) except for management of cataract complication with steroid IVT treatment
- Prior periocular pharmacological intervention for other retinal diseases

Concurrent Ocular Conditions

- Any concurrent intraocular condition *in the study eye* (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the course of the study
- Active intraocular inflammation (grade trace or above) *in the study eye* *on Day 1 (prior to randomization)*

- Current vitreous hemorrhage *in the study eye*
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure [IOP] ≥25 mmHg despite treatment with anti-glaucoma medication) *in the study eye*
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia *in the study eye*
- History of idiopathic or autoimmune-associated uveitis *in either eye*
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis *in either eye* *on Day 1 (prior to randomization)*

General Criteria

- Any major illness or major surgical procedure within 1 month before screening
- Uncontrolled blood pressure ([BP] defined as systolic >180 mmHg and/or diastolic >100 mmHg while patient at rest). 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 BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke or myocardial infarction within 3 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated 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 treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Known hypersensitivity to ranibizumab, fluorescein, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used
- Treatment with investigational therapy within 3 months prior to initiation of study treatment

End of Study

The end of the study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur 52 weeks after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 18–19 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

RO6867461 Drug Product (120 mg/mL) will be provided as a sterile, colorless to brownish liquid and contains no preservatives. Each single-use, 2-mL vial with a nominal 0.5-mL fill contains 60 mg (nominal) of RO6867461 formulated as a 120-mg/mL in L-histidine/HCl buffer solution (approximately pH 6.0) containing sodium chloride, sucrose, and polysorbate 20.

RO6867461 Drug Product required for completion of this study will be provided by the Sponsor.

RO6867461 Drug Product packaging will be overseen by the Roche clinical trial supplies department and bear labels with the identification required by local law, the protocol number, drug identification, and strength.

The packaging and labeling of RO6867461 Drug Product will be in accordance with Roche standard and local regulations.

RO6867461 Drug Product must be stored according to the details on the product label and the information provided in the Pharmacy Manual.

Upon arrival of the masked investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

For further details, see the RO6867461 Investigator's Brochure.

Comparator

Ranibizumab (nominal content 0.5 mg/0.05 mL) required for completion of this study will be provided by the Sponsor as a solution formulated at 10 mg/mL, and supplied as a single-use 2-mL vial.

Ranibizumab packaging will be overseen by the Roche clinical trial supplies department and bear labels with the identification required by local law, the protocol number, drug identification, and strength.

The packaging and labeling of ranibizumab will be in accordance with Roche standard and local regulations.

Ranibizumab must be stored according to the details on the product label and the information provided in the Pharmacy Manual.

Upon arrival of the masked investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

Sham Administration

A sham administration is a procedure that mimics an IVT administration of study drug, except that the blunt end of an empty syringe is pressed against an anesthetized eye instead of a needle attached to a study drug-filled syringe. Empty boxes identical to the other study treatment boxes will be supplied for sham administration.

Upon arrival of the masked material at the site, site personnel should check sham boxes for damage and verify proper identity and quantity, and report any deviations or product complaints to the monitor upon discovery.

Refer to the protocol for additional details on dosage, administration, and compliance for RO6867461, ranibizumab, and sham.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is BCVA change from baseline at Week 40. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance will be used to account for within-patient correlation, but another variance-covariance structure, such as AR(1), may be selected in case of convergence issues.

Means for RO6867461 and ranibizumab arms, difference of the means relative to ranibizumab, and the corresponding two-sided 80% confidence intervals will be computed. There will not be formal correction for multiple testing.

Determination of Sample Size

The focus of this trial is estimation rather than hypothesis testing. The sample size was determined largely based on logistical considerations. Assuming a common standard deviation for BCVA change from baseline of 13.5 letters, the distance from the difference of the means between RO6867461 ($n=30$) and ranibizumab ($n=15$) to the 80% two-sided confidence interval bounds is estimated to be 5.5 letters.

Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by the Sponsor IMC and appropriate senior management personnel who will be unmasked at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
Ang-1	angiopoietin-1
Ang-2	angiopoietin-2
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
AUC	area under the concentration–time curve
BCVA	best corrected visual acuity
BP	blood pressure
CFT	central foveal thickness
C_{max}	maximum concentration observed
CNV	choroidal neovascularization
CRO	contract research organization
CST	central subfield thickness
DLE	dose-limiting event
DMC	Data Monitoring Committee
DME	diabetic macular edema
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDI	enhanced depth imaging
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
FP	fundus photography
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HCT	hematocrit
ICH	International Council on Harmonisation
IgG1	immunoglobulin G1
IMC	Internal Monitoring Committee
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (application)
INR	international normalized ratio
IOP	intraocular pressure
IRB	Institutional Review Board
IVT	intravitreal(ly)
IxRS	Interactive Voice and Web Response System
LPLV	last patient, last visit
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MMRM	Mixed Model for Repeated Measurement
nAMD	neovascular age-related macular degeneration
NGS	next-generation sequencing
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PD	pharmacodynamics
PK	pharmacokinetic
PT	prothrombin time
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
RBR	Research Biosample Repository
SD-OCT	spectral domain optical coherence tomography
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor A
wAMD	wet age-related macular degeneration
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION

Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD; also known as neovascular AMD [nAMD] or wet AMD [wAMD]) is a form of advanced AMD that can result in rapid and severe visual impairment, and remains a leading cause of vision loss and visual morbidity (Bourne et al. 2013; Wong et al. 2014). According to the National Eye Institute (2016), more than 2 million people in the United States had some form of advanced AMD in 2010, and this number is expected to grow to 2.95 million by 2020 and 3.6 million by 2030. nAMD is characterized by the proliferation of abnormal choroidal vessels that penetrate Bruch's membrane in the form of choroidal neovascular membranes leading to the exudation of fluid and blood into and underneath the retina. This exudative process causes disruption to the normal retinal architecture and severe visual impairment.

The treatment of nAMD was revolutionized by the introduction of biological molecules that targeted an important factor in pathological angiogenesis, vascular endothelial growth factor A (VEGF-A; Brown et al. 2006; Rosenfeld et al. 2006). Although anti-VEGF therapies have set a new efficacy paradigm in terms of preventing further visual loss or blindness, some patients with nAMD do not gain vision or continue to lose vision despite anti-VEGF therapy (Brown et al. 2006; Rosenfeld et al. 2006; CATT Research Group 2016). Even under trial conditions with regular monitoring visits and frequent injections, many eyes with nAMD fail to regain lost vision with approximately 20% continuing to deteriorate and over 60% failing to achieve 20/40 vision (Schmidt-Erfurth et al. 2014; European Medicines Agency 2016; CATT Research Group 2016). Therefore, there is a need for more efficacious therapies that can increase vision gains and reduce the risk of further sight loss. Neovascularization in AMD is a multifactorial process; therefore, targeting an additional soluble factor that is essential to angiogenesis, such as angiopoietin-2 (Ang-2), in addition to VEGF, may help to improve efficacy and treatment outcomes.

To maintain vision gains, currently available anti-VEGF treatments require frequent and long-term administration (Heier et al. 2012; CATT Research Group 2016). Real-world data suggest that many patients with nAMD do not receive optimal treatment frequency, and this under-treatment in clinical practice is associated with lower visual acuity gains compared with randomized in controlled clinical trials (Cohen et al. 2013; Finger et al. 2013; Holz et al. 2015). Under-treatment in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system (Gohil et al. 2015; Prenner et al. 2015; Varano et al. 2015; CATT Research Group 2016; Vukicevic et al. 2016).

Partly because some patients continue to lose vision despite regular treatment, and partly due to fewer injections being delivered in clinical practice than in clinical trials

(Holz et al. 2015), AMD remains a leading cause of blindness and visual morbidity despite the improved outcomes provided by anti-VEGF therapy (Bourne et al. 2014). The current treatment paradigm requires frequent administration for several years to maintain optimal results. Clinical evaluation of alternative anti-angiogenic targets or mechanisms of action are warranted to improve upon the clinical benefit of approved anti-VEGF therapies and to reduce treatment burden.

1.2 BACKGROUND ON RO6867461

RO6867461 (also known as RG7716) is a novel humanized bispecific immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively binds VEGF-A and Ang-2. The VEGF-binding component binds all isoforms of VEGF-A with high affinity, and the Ang-2-binding component binds Ang-2, also with high affinity.

VEGF-A is a signal protein produced by cells that stimulate vasculogenesis and angiogenesis. Uncontrolled VEGF-A expression results in growth of new blood vessels, which fail to mature, and show a number of abnormalities including tortuosity and reduced number of pericytes. These structural defects in the newly formed retinal vessels can result in fragility, hyperpermeability, and a propensity for exudation and bleeding, all of which are key features of pathological neovascularization, and can lead to photoreceptor damage and vision impairment.

Angiopoietin-1 (Ang-1) and Ang-2 are of key importance in the homeostasis of the vascular compartment, functioning as ligands of the Tie-2 receptor tyrosine kinase that is expressed on endothelial cells (Davis et al. 1996; Maisonpierre et al. 1997; Fiedler et al. 2003). Ang-1 is a Tie-2 receptor agonist, and acts as a homeostatic factor that stabilizes the mature vasculature by promoting recruitment of pericytes and smooth muscle cells to the vessel wall. In contrast, Ang-2 is an antagonist of Tie-2, and acts as a vascular destabilization factor by blocking Ang-1–dependent Tie-2 activation, which leads to dissociation of pericytes from existing vessels, thus increasing vessel plasticity, rendering vasculature amendable to endothelial barrier breakdown and sprouting of new vessels (Davis et al. 1996; Maisonpierre et al. 1997; Fiedler et al. 2003). Ang-2 levels can be upregulated by other pro-angiogenic factors, including VEGF-A, and were shown to be increased during angiogenic stress triggered by hypoxia or hyperglycemia. Ang-2 also functions as a pro-inflammatory cytokine. Since upregulation of Ang-2 is associated with the release of inflammatory cytokines, adhesion of leukocytes to endothelial cells, and migration of leukocytes into the retina, its inhibition may also have additional anti-inflammatory benefits.

Nonclinical studies have shown that VEGF-A and Ang-2 act in concert to regulate the vasculature and cooperate to increase retinal endothelial cell permeability in vitro. Pharmacological evaluation in vivo demonstrated that simultaneous inhibition of VEGF and Ang-2 with the bispecific antibody RO6867461 led to a greater reduction in the size, number, and severity of CNV lesions in a laser-induced CNV model in non-human primates compared to ranibizumab (anti-VEGF-A) or anti-Ang-2 alone. Earlier

experiments using a mouse model of spontaneous CNV showed that dual inhibition of VEGF-A and Ang-2 consistently outperformed monotherapeutic inhibition of either target alone in terms of reduction in vascular growth, leakage, edema, and photoreceptor loss (Regula et al. 2016).

In addition, vitreous concentrations of both VEGF-A and Ang-2 were shown to be upregulated in diabetic retinopathy, retinal vein occlusion, and to a lesser extent, in patients with nAMD (Regula et al. 2016). Therefore, simultaneous neutralization of both targets, VEGF-A and Ang-2, may further normalize the pathological ocular vasculature as compared to the current standard of care, anti-VEGF monotherapy.

A multicenter, Phase I, open-label, single-ascending-dose (0.5, 1.5, 3, or 6 mg) and multiple-ascending-dose (3 or 6 mg) study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO6867461 administered intravitreally (IVT) in patients with nAMD has been completed (Study BP28936). Patients recruited in the Phase I study had already received anti-VEGF treatment ($\geq$3 IVT treatments in the preceding 6 months) but showed an insufficient response, as defined by best corrected visual acuity (BCVA) $\leq$20/40 and presence of fluid on optical coherence tomography (OCT). While the primary focus of this study was safety and tolerability following a single dose and three sequential doses of RO6867461, 4 weeks apart, there were signals of activity in both visual acuity and anatomical endpoints.

The current ongoing Phase II program includes two studies: Study BP30099 (BOULEVARD; ClinicalTrials.gov number NCT02699450) investigating RO6867461 in patients with diabetic macular edema (DME) and Study BP29647 (AVENUE; ClinicalTrials.gov number NCT02484690) in patients with nAMD.

In Study BP30099, two dose levels (1.5 mg and 6 mg every 4 weeks [Q4W]) are being assessed over 36 weeks to evaluate the efficacy of RO6867461 compared to 0.3 mg ranibizumab monotherapy in treatment-naive patients with DME. Study BP29647 is evaluating the efficacy of RO6867461 over 36 weeks at dose levels of 1.5 mg (Q4W) and 6 mg (Q4W and every 8 weeks [Q8W]) compared to 0.5 mg ranibizumab monotherapy in treatment-naive patients and anti-VEGF–incomplete responder patients with nAMD.

Refer to the RO6867461 Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

As a result of the chronic, progressive nature of nAMD, frequent injections of currently available therapies over extended periods (e.g., monthly or bimonthly injections) are recommended. However, in routine clinical practice, such frequent office visits may not be practical or possible for all patients. Real-world data suggest many patients are under-treated with current therapies, leading to suboptimal outcomes (Cohen et al. 2013;

Finger et al. 2013; Holz et al. 2015). In addition, a significant burden is placed on patients and their caregivers, as well as treating physicians and the healthcare system. A less frequent treatment administration schedule (e.g., every 3 or 4 months) that would provide visual acuity outcomes comparable to clinical trial results with frequent anti-VEGF monotherapy would therefore represent an important advance on currently available therapies, and would address the high unmet medical need for a more feasible treatment approach in nAMD patients.

RO6867461 binds to Ang-2, as well as to all isoforms of VEGF-A. Nonclinical data suggest the potential of adjunctive Ang-2 inhibition for both additional efficacy and prolonged duration of anti-leakage action (Cheung et al. 2014; von Leithner et al. 2014; Heier 2016; Regula et al. 2016). This study will assess whether RO6867461 has the potential for administration at 12-week or 16-week intervals in further, larger scale studies of treatment-naive patients with nAMD. The study features four initial injections of the 6-mg dose followed by monthly assessment visits and fixed injections either every 12 weeks (Q12W) or every 16 weeks (Q16W). The extended initiation phase will allow patients to continue with frequent dosing during the “gain” phase of their treatment, aiming to maximize visual outcomes. The less frequent dosing thereafter is expected to, on average, at least maintain these initial gains. Only the 6-mg dose of RO6867461 will be utilized in this study to ensure sufficient VEGF-A and Ang-2 inhibition to permit less frequent dosing (Hutton-Smith et al. 2016). Patients will undergo monthly assessments throughout the study, with those patients intended for Q16W dosing undergoing a disease activity assessment at Week 24. Patients with anatomic or functional signs of disease activity at this timepoint will receive Q12W rather than Q16W dosing, in order to minimize the risk of under-treatment.

There are limited clinical efficacy evaluations with anti-Ang-2 approaches in patients with retinal disease. In the Phase I study (BP28936), RO6867461 was well tolerated up to the highest dose tested of 6 mg in previously treated patients with nAMD. No dose-limiting events (DLEs) or unexpected ocular adverse events were observed, and no systemic, drug-related serious adverse events or severe adverse events were reported. In addition, pharmacodynamic (PD) activity was observed both in terms of anatomical changes and improvements in visual acuity.

Ongoing review of masked safety data from the two ongoing Phase II studies (Study BP29647 in nAMD and Study BP30099 in DME) indicates that the side effects are consistent with the safety profile observed in the Phase I study in nAMD, as well as the adverse events which are associated with an IVT procedure or natural progression of the respective diseases. To date, no unexpected safety signals have been identified.

Nonclinical toxicology studies did not reveal any adverse effects that require specific warnings and precautions that are different from those applicable to any anti-VEGF agents currently used in clinical practice for the treatment of nAMD.

This study is designed to evaluate the duration of efficacy response to 6 mg RO6867461 administered at 12- or 16-week intervals as assessed by the mean change from baseline BCVA at Week 40 using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts in patients with nAMD. Secondary endpoints will include further BCVA evaluations and anatomical PD imaging measures relevant to the mechanism of action of RO6867461. In addition, safety and pharmacokinetics will be evaluated in patients receiving up to seven doses of RO6867461.

Taken together, the nonclinical data, the results from the Phase I study in nAMD, and the ongoing masked safety assessment in the Phase II studies in nAMD and DME disease indications, as well as the unmet need for less frequent dosing, support initiation of this Phase II study assessing the duration of efficacy, safety, and PK response to RO6867461 in patients with nAMD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of RO6867461 administered at 12- and 16-week intervals in patients with nAMD. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of RO6867461 on visual acuity when administered at 12- and 16-week intervals	• Mean change from baseline BCVA at Week 40 using the ETDRS-like charts
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of RO6867461 on additional visual acuity outcomes	• Mean change from baseline BCVA over time using the ETDRS-like charts • Proportion of patients gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters from baseline BCVA over time • Proportion of patients avoiding loss of ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters from baseline BCVA over time • Proportion of patients with BCVA of 20/40 or better over time • Proportion of patients with BCVA of 20/200 or worse over time
• To evaluate the efficacy of RO6867461 on anatomic outcome measures using SD-OCT	• Mean change from baseline in CFT over time • Mean change from baseline in mean CST (1 mm diameter) over time • Proportion of patients with intraretinal fluid, subretinal fluid, cysts, or pigment epithelial detachment over time
• To evaluate the efficacy of RO6867461 on anatomic outcome measures using FFA	• Mean change from baseline in total area of CNV at Week 40 and Week 52 • Mean change from baseline in total area of CNV component at Week 40 and Week 52 • Mean change from baseline in total area of leakage at Week 40 and Week 52
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To investigate the incidence of disease activity at Week 24	• Proportion of patients with disease activity at Week 24
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of multiple IVT doses of RO6867461 at 12- and 16-week intervals	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events • Other safety data, including but not limited to, reasons for withdrawal from study, laboratory data, concomitant medications, vital signs, and physical examination results will be listed and summarized descriptively

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic/ Pharmacodynamic Objectives	Corresponding Endpoints
• To assess the systemic PK profile of RO6867461	• Plasma concentration of RO6867461 at specified timepoints
• To evaluate the RO6867461, ranibizumab, free VEGF-A, and Ang-2 profile in aqueous humor	• Relationship between aqueous humor RO6867461 concentrations or PK parameters and free VEGF-A and Ang-2 concentrations • Relationship between aqueous humor ranibizumab concentrations or PK parameters and free VEGF-A and Ang-2 concentrations • Time course of free VEGF-A and Ang-2 concentrations in aqueous humor
Immunogenicity Objective	**Corresponding Endpoints**
• To investigate the formation of plasma anti-RO6867461 antibodies	• Incidence of ADAs during the study
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To explore levels of potential biomarkers of angiogenesis and inflammation in aqueous humor at baseline and at additional timepoints to assess their response to RO6867461	• Relationship between aqueous humor concentration of potential biomarkers with primary and secondary endpoints

ADA = anti-drug antibody; Ang-2 = angiopoietin-2; BCVA = best corrected visual acuity; CFT = central foveal thickness; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FFA = fundus fluorescein angiography; IVT = intravitreal; PK = pharmacokinetic; SD-OCT = spectral domain optical coherence tomography; VEGF-A = vascular endothelial growth factor A.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study Design

This is a Phase II, multicenter, randomized, active comparator-controlled, subject and outcome-assessor masked, parallel group, 52-week study to investigate the efficacy, safety, and pharmacokinetics of RO6867461 administered at 12- and 16-week intervals in treatment-naive patients with nAMD. Approximately 75 patients will be enrolled and randomized in a 2:2:1 ratio to one of three treatment arms:

- Arm A (Q12W): 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 12 weeks up to Week 48 (injections at Weeks 24, 36, and 48; 3 injections)
- Arm B (Q16W): 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 16 weeks up to Week 48 (injections at Weeks 28 and 44; 2 injections)

  A protocol-defined assessment of disease activity at Week 24 requires Arm B patients with active disease (see criteria below) to switch to a 12-weekly dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.
- Arm C (comparator arm): 0.5 mg ranibizumab IVT every 4 weeks for 48 weeks (13 injections)

Only one eye will be chosen as the study eye.

The total duration of the study for each patient will be up to 56 weeks, divided as follows:

- Screening: up to 4 weeks prior to or on the same day as randomization
- Randomization: Day 1
- Study Treatment Administration: from Day 1 to Week 48
- Final Visit: Week 52

Patients will undergo a screening examination within 4 weeks of study treatment administration. The screening and Week 1/Day 1 (randomization) visit may occur as a combined visit if all assessments *(with the exception of informed consent)* are *completed* within 48 hours. *Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.* Where screening and randomization are combined, assessments listed for both visits only need to be conducted once. During screening (or the combined screening/Day 1 visit), the patient's eligibility will be assessed, including a central review of fundus photography (FP), spectral domain optical coherence tomography (SD-OCT), and fundus fluorescein angiography (FFA) to ensure that CNV secondary to AMD meets the predefined ocular criteria in the study.

Patients who were deemed ineligible based on screening results for any of the following reasons will be allowed to be re-screened:

- Uncontrolled blood pressure
- Administrative reason (e.g., unable to schedule Day 1 within 28 days from the screening visit)
- Not meeting eligibility criteria for the study eye (in the event the patient might be eligible to participate for the second eye after the initial screening period)

At re-screening, all screening visit assessments will be performed (except for FFA imaging collection), provided the Central Reading Center-eligible FFA images were taken within 4 weeks before the new Day 1 visit (randomization).

On Day 1, eligible patients will receive their first IVT administration of either RO6867461 or ranibizumab according to the randomization schedule described above and following established standard administration procedures. Patients will return to the eye clinic 7 days after their first IVT administration and then every 4 weeks for study treatment administration and assessments as outlined in the schedule of activities (Appendix 1). Sham IVT administration will be delivered to patients randomized to Arms A and B to maintain masking throughout the study period.

All patients will be assessed for disease activity at Week 24. Patients randomized to Arm B who have active disease at Week 24 (see criteria below) will switch to the Q12W dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.

Determination of active disease will be made if any of the following criteria are met (also see Section 4.5.5.4):

- Increase in central $subfield$ thickness (CST of >50 μm on Spectralis® OCT compared to average CST over last 2 visits (Weeks 16 and 20)

  Or

- Increase in CST of ≥ 75 μm compared to lowest CST recorded at either Week 16 or Week 20

  Or

- Decrease of at least 5 letters of BCVA compared with average BCVA over last 2 visits (Weeks 16 and 20) due to nAMD disease activity

  Or

- Decrease of ≥ 10 letters of BCVA compared to highest BCVA recorded at either Week 16 or Week 20 due to nAMD disease activity

  Or

- Presence of new macular hemorrhage due to nAMD activity

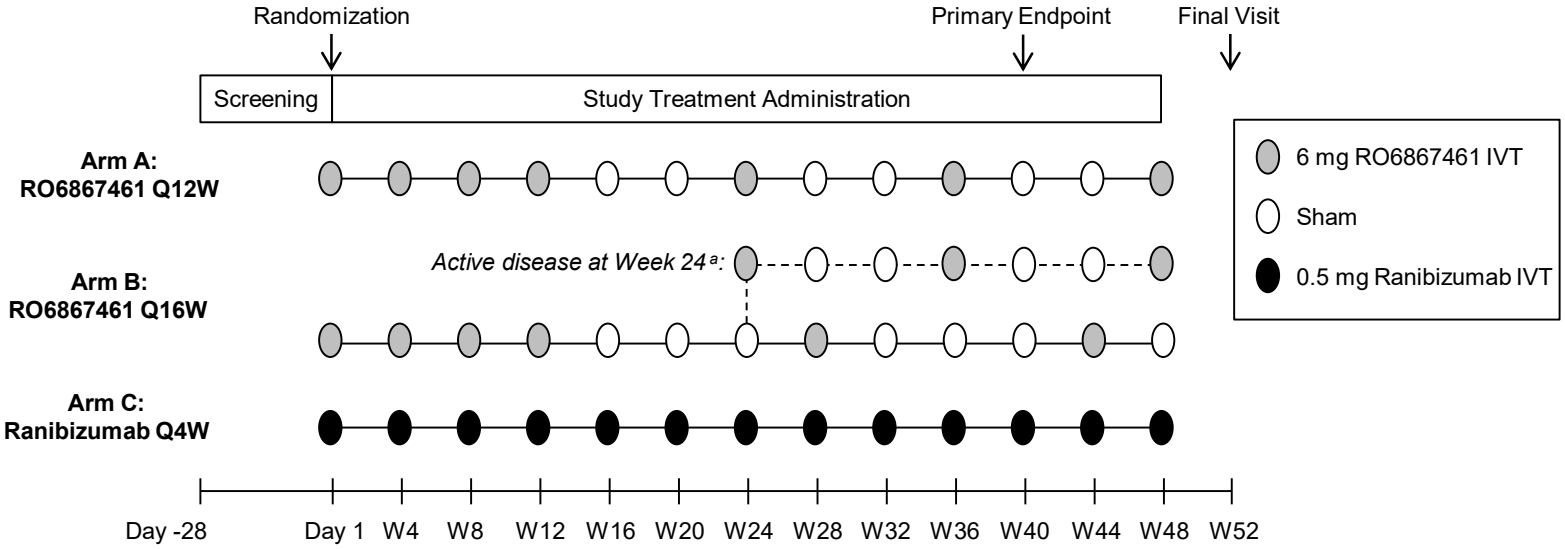
If, in the opinion of the investigator, there is significant nAMD disease activity at Week 24 that requires immediate treatment, but does not meet the above criteria, the Medical Monitor should be contacted. In such cases, following approval by the Sponsor, patients randomized to Arm B will receive 6 mg RO6867461 at Week 24 and stay on repeated 12-weekly treatments at Weeks 36 and 48.

Patients who are withdrawn from the study early but have not withdrawn consent should return for an early termination visit 28 (+7) days following the last study treatment for assessments as well as monitoring of all adverse events.

Patients will return for a final visit at Week 52. After the final visit, adverse events should be followed up as outlined in Section 5.6. Assessments performed in case of an unscheduled visit(s) are at the discretion of the investigator.

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

Figure 1 Study Schema



IVT = intravitreal; Q4W = every 4 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; W = week.

[a] All patients will be assessed for disease activity at Week 24. Patients in Arm B who are assessed with active disease at Week 24 will switch to RO6867461 Q12W dosing regimen for the remainder of the study.

3.1.2 Internal Monitoring Committee

The unmasked Roche Internal Monitoring Committee (IMC) will be responsible for the review of interim data in the event of an interim analysis for efficacy and/or for safety (see Section 6.9). The IMC will evaluate both safety and efficacy data in the instance where assessment of benefit-risk is warranted. These analyses will take place at predefined timepoints or on an ad-hoc basis.

The IMC consists of a selected subset of Roche representatives including a Statistician, Safety Science Representative, Clinical Science Representative, and Clinical Pharmacology Representatives. The IMC members participating in a given interim analysis will be kept to the minimum required to address the objective of that interim analysis. Additional Roche representatives may be involved to produce/process the unmasked listing/data to be analyzed by the IMC.

Full details regarding the IMC will be provided separately in the IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur 52 weeks after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 18−19 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Dose and Schedule

The RO6867461 dose (6 mg) selected for this study in patients with nAMD is based on both nonclinical and clinical studies. The Phase I first-in-human study (BP28936) evaluated the safety and tolerability of single and multiple administrations of doses ranging from 0.5 mg to 6 mg RO6867461. The selection of these doses was based on nonclinical findings and absolute IVT doses administered in the toxicology studies. The nonclinical 6-month Good Laboratory Practice (GLP) toxicity study tested RO6867461 up to the 3-mg dose level, seven times Q4W IVT. Due to the approximately 2-fold lower vitreous humor volume in cynomolgus monkey as compared to humans, a 3-mg dose administered to monkeys achieves similar IVT initial concentrations to the 6-mg dose in humans.

The dose of 6 mg RO6867461 was selected as the highest feasible dose of RO6867461 in the Phase I study in nAMD, as well as in the two ongoing Phase II studies (one in nAMD and one in DME). It represents an anti-VEGF dose equivalent to a 2-mg ranibizumab dose, which was shown to be safe in a large clinical trial (Busbee et al. 2013). The Phase I study did not reveal a safety signal following 3 monthly IVT doses of up to 6 mg RO6867461 (n=6) in patients with nAMD. RO6867461 was well tolerated in

23 patients up to 4 weeks after the last of 1–3 IVT administrations of up to the 6-mg dose level.

The two ongoing Phase II studies are evaluating two dose levels (1.5 mg and 6 mg) of RO6867461 at different dosing schedules (Q4W for Study BP30099; Q4W and Q8W for Study BP29647) in nAMD and DME disease indications. Of note, the Phase I study used a 60-mg/mL formulation as the highest concentration, translating to a 50- and 100-μL injection volume for the 3 mg and 6 mg RO6867461 doses, respectively. However, the formulation for the present study, similar to the ongoing Phase II studies, utilizes a 120-mg/mL concentration, which translates to a 50-μL injection volume for the 6-mg RO6867461 dose.

Systemic exposure observed in patients following IVT administration is lower as compared to exposures observed in the cynomolgus monkey GLP toxicity study (refer to the RO6867461 Investigator's Brochure).

The nonclinical and clinical data suggest that the 6-mg RO6867461 dose is safe and well tolerated. The current study will assess the clinical outcomes of less frequent dosing following four initial monthly injections of RO6867461. As the durability of effect is expected to increase with higher doses (Hutton-Smith et al. 2016), the 6-mg dose has been selected for this study. RO6867461 will be delivered according to one of two dosing regimens following treatment initiation with four monthly injections. Patients randomized to Arm A will then receive injections of RO6867461 Q12W, while patients in Arm B will receive injections of RO6867461 Q16W. Based on a protocol-specified assessment of nAMD disease activity at Week 24 (see Section 4.5.5.4), patients in Arm B with active disease will receive an injection of RO6867461 at that visit, and then subsequently at 12-week intervals until end of study. Patients in Arm B who do not exhibit active nAMD will receive 16-weekly injections until the end of the study.

3.3.2 Rationale for Patient Population

This study will be conducted in patients with treatment-naive nAMD who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (see Section 4.1.1 and Section 4.1.2).

3.3.3 Rationale for Control Group

The proposed study includes an anti-VEGF arm instead of a placebo arm, as anti-VEGF therapy is a well-established standard of care in the target population and placebo is no longer an ethically acceptable comparator. Ranibizumab was the first approved treatment demonstrating improvement of mean BCVA in patients with nAMD (Brown et al. 2006; Rosenfeld et al. 2006). These data led to the U.S. approval of ranibizumab 0.5 mg monthly for the treatment of nAMD in 2006. Since then, no approved treatment has demonstrated superiority over ranibizumab 0.5 mg monthly, and therefore it is an appropriate comparator for this study.

3.3.4 Rationale for Optional Aqueous Humor Assessments

nAMD is a heterogeneous disease, and VEGF-A and Ang-2 expression has been shown to vary among patients (Hera et al. 2005), as well as other mediators of angiogenesis and inflammation. Levels of VEGF-A and Ang-2 in the aqueous humor are believed to resemble concentrations in vitreous humor and possibly in the retina. The primary mode of action of RO6867461 is to decrease the free ocular concentrations of VEGF-A and Ang-2. Thus, the assessment of free concentrations of VEGF-A and Ang-2 in aqueous humor provides information about the time course of VEGF-A and Ang-2 suppression, which is the basis for the duration of drug effect. Moreover, aqueous humor contains several angiogenic and inflammatory factors that may be important for the disease progression or response to therapy (Muether et al. 2013; Rezar-Dreindl et al. 2016). Thus, assessment of these molecules that have potential to serve as biomarkers of angiogenesis and inflammation may help with understanding prognostic factors and predictors of response to treatment in nAMD.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 75 treatment-naive patients with nAMD are expected to be enrolled and randomized in this study in the United States.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Ocular Criteria for Study Eye

- Treatment-naive CNV secondary to AMD (nAMD)
- Subfoveal CNV or *juxtafoveal CNV with a subfoveal component related to the CNV activity by FFA or SD-OCT (as evidenced by subretinal fluid, subretinal hyper-reflective material, evidence of leakage, or hemorrhage)*
- CNV lesion of all types (predominantly classic, minimally classic, or occult) with:

  Total lesion size (including blood, atrophy, fibrosis, and neovascularization) of ≤6 disc areas by FFA

  And

  CNV component area of ≥50% of total lesion size by FFA

  And

  Active CNV confirmed by FFA (evidence of leakage)

  And

  CNV exudation confirmed by SD-OCT (presence of fluid)
- BCVA letter score of 73 to 24 letters (inclusive) on ETDRS-like charts (20/40 to 20/320 Snellen equivalent) *on Day 1*
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

General Criteria

- Signed Informed Consent Form
- Age $\geq$50 years *on Day 1*
- Ability to comply with the study protocol, in the investigator's judgment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<$1% per year during the treatment period and for at least 28 days after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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 acceptable methods of contraception.
- Patients must be willing not to participate in any other clinical trial including an investigational medicinal product (IMP) or device up to completion of the current study

4.1.2 Exclusion Criteria

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

Ocular Criteria for Study Eye

- CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis
- Central serous chorioretinopathy at screening
- Retinal pigment epithelial tear involving the macula
- On FFA

  Subretinal hemorrhage of $>$50% of the total lesion area and/or that involves the fovea

  Fibrosis or atrophy of $>$50% of the total lesion area and/or that involves the fovea
- Any prior or concomitant treatment for CNV including (but not restricted to) IVT treatment (steroids, anti-VEGF, tissue plasminogen activator, ocriplasmin, C_3F_8 gas, air), periocular pharmacological intervention, argon LASER photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or surgical intervention

- Cataract surgery within 3 months of baseline assessments *(Day 1)*
- Any other intraocular surgery (pars plana vitrectomy, glaucoma surgery, corneal transplant, radiotherapy)
- Prior IVT treatment (including anti-VEGF medication) except for management of cataract complication with steroid IVT treatment
- Prior periocular pharmacological intervention for other retinal diseases

Concurrent Ocular Conditions

- Any concurrent intraocular condition *in the study eye* (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the course of the study
- Active intraocular inflammation (grade trace or above) *in the study eye* *on Day 1 (prior to randomization)*
- Current vitreous hemorrhage *in the study eye*
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure [IOP] $\geq$25 mmHg despite treatment with anti-glaucoma medication) *in the study eye*
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia *in the study eye*
- History of idiopathic or autoimmune-associated uveitis *in either eye*
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis *in either eye* *on Day 1 (prior to randomization)*

General Criteria

- Any major illness or major surgical procedure within 1 month before screening
- Uncontrolled blood pressure ([BP] defined as systolic $>$180 mmHg and/or diastolic $>$100 mmHg while patient at rest). 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 BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 30 days prior to Day 1.
- Stroke or myocardial infarction within 3 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated 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 treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Known hypersensitivity to ranibizumab, fluorescein, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used
- Treatment with investigational therapy within 3 months prior to initiation of study treatment

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

After written informed consent has been obtained, all patients will receive a screening number assigned through the Interactive Voice and Web Response System (IxRS). A patient must satisfy all eligibility criteria (see Section 4.1.1 and Section 4.1.2) prior to randomization.

Patients will be randomized on the same day the study treatment is to be initiated (Day 1 visit). After randomization and at each visit with study treatment administration (i.e., including Day 1) the IxRS will assign the appropriate study treatment kit to be used.

Randomization will be stratified for baseline BCVA ETDRS letter score assessed on Day 1 (55 letters or better vs. 54 letters or worse).

Randomization with fixed permuted blocks will be used to obtain an approximate 2:2:1 ratio between the different arms within each stratum.

4.2.2 Masking

This is a patient- and outcome assessor (BCVA and Central Reading Center)-masked study. The intent of this design allows for a single investigator per site to be present at a given visit to fulfill the masking requirements of this study.

At a site level:

- *Patients and BCVA examiners will be masked to treatment assignment. BCVA examiners will also be masked to study eye (see Section 4.5.5.1). All other site personnel that do not have a role in drug preparation and/or treatment delivery should be masked to study eye drug assignment.*
- *The investigator administrating the patient's treatment (RO6867461, comparator ranibizumab, or sham) and/or pharmacist/designated personnel responsible for drug preparation will be unmasked to treatment assignment.*

The number of unmasked study personnel should be limited to ensure the integrity of this masked study. All roles for each study staff member should be clearly documented in the site delegation log. The delegation log must be signed by the Principal Investigator. Unmasked personnel cannot switch to a masked role, but masked

personnel can switch to an unmasked role. Any change should be documented in the delegation log.

At a study level:

The Central Reading Center personnel, study vendors, and the Sponsor *(with the exception of a point person[s] to support unmasked site personnel and IMC members in the case of an optional interim analysis; Section 3.1.2 and Section 6.9)* and its agents will be masked to study eye drug assignment.

For biosamples:

To maintain the masked design of the study, blood samples collected at timepoints specified in the schedule of activities (Appendix 1) will also be taken from all patients receiving ranibizumab per the RO6867461 schedule. The samples from these patients may or may not be analyzed. Unmasking for independent analysis of the relevant biosamples during the conduct of the study will be performed according the Sponsor's internal standard procedures in place to ensure integrity of the data. The number of Roche representative(s) and delegates unmasked will be kept to the minimum required to address the objective of the biosample analysis.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are RO6867461 and ranibizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 RO6867461

RO6867461 Drug Product (120 mg/mL) will be provided as a sterile, colorless to brownish liquid and contains no preservatives. Each single-use, 2-mL vial with a nominal 0.5-mL fill contains 60 mg (nominal) of RO6867461 formulated as a 120-mg/mL in L-histidine/HCl buffer solution (approximately pH 6.0) containing sodium chloride, sucrose, and polysorbate 20.

RO6867461 Drug Product required for completion of this study will be provided by the Sponsor.

RO6867461 Drug Product packaging will be overseen by the Roche clinical trial supplies department and bear labels with the identification required by local law, the protocol number, drug identification, and strength.

The packaging and labeling of RO6867461 Drug Product will be in accordance with Roche standard and local regulations.

RO6867461 Drug Product must be stored according to the details on the product label and the information provided in the Pharmacy Manual.

Upon arrival of the masked investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

For further details, see the RO6867461 Investigator's Brochure.

4.3.1.2 Ranibizumab

Ranibizumab (nominal content 0.5 mg/0.05 mL) required for completion of this study will be provided by the Sponsor as a solution formulated at 10 mg/mL, and supplied as a single-use 2-mL vial.

Ranibizumab packaging will be overseen by the Roche clinical trial supplies department and bear labels with the identification required by local law, the protocol number, drug identification, and strength.

The packaging and labeling of ranibizumab will be in accordance with Roche standard and local regulations.

Ranibizumab must be stored according to the details on the product label and the information provided in the Pharmacy Manual.

Upon arrival of the masked investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

4.3.1.3 Sham

A sham administration is a procedure that mimics an IVT administration of study drug, except that the blunt end of an empty syringe is pressed against an anesthetized eye instead of a needle attached to a study drug-filled syringe (see Appendix 3). Empty boxes identical to the other study treatment boxes will be supplied for sham administration.

Upon arrival of the masked material at the site, site personnel should check sham boxes for damage and verify proper identity and quantity, and report any deviations or product complaints to the monitor upon discovery.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 RO6867461, Ranibizumab, and Sham

Patients will be given a 50-μL IVT injection of RO6867461 or ranibizumab into the study eye, or a sham administration, according to the randomization schedule as described below (also see Section 3.1.1 and Figure 1).

- Arm A (Q12W): 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 12 weeks up to Week 48 (injections at Weeks 24, 36, and 48; 3 injections)
- Arm B (Q16W): 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 16 weeks up to Week 48 (injections at Weeks 28 and 44; 2 injections)
- Arm C (comparator arm): 0.5 mg ranibizumab IVT every 4 weeks for 48 weeks (13 injections)

Only one eye will be chosen as the study eye.

A protocol-defined assessment of disease activity at Week 24 requires patients in Arm B with active disease (see criteria in Section 4.5.5.4) to switch to a 12-weekly dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.

Sham IVT administration will be delivered to patients to maintain subject masking throughout the study period. In Arm A, sham IVT administrations will occur at Weeks 16, 20, 28, 32, 40, and 44. In Arm B, sham IVT administrations will occur at Weeks 16, 20, 24, 32, 36, 40, and 48, or at Weeks 16, 20, 28, 32, 40, and 44, the latter if the dosing regimen was switched to the 12-weekly schedule.

The Pharmacist responsible for dispensing the study treatment, or designated personnel, will prepare the correct study treatment (RO6867461, ranibizumab, or sham) as assigned by the IxRS.

Detailed stepwise instructions for the preparation of RO6867461, ranibizumab, or sham for administration, and mandatory materials to be used will be provided by the Sponsor, and are detailed in the Pharmacy Manual. Pre- and post-treatment administration procedures as well as instructions for performing the IVT and sham administrations are provided in Appendix 3.

A specified filter needle must be used for each dose preparation of RO6867461 or ranibizumab as per the instructions provided in the Pharmacy Manual. All materials to prepare and administer study treatments will be provided by the Sponsor and no other material than provided should be used.

Vials of RO6867461 Drug Product and vials of ranibizumab (active comparator) are for single-use only (one injection preparation per patient per eye). Vials used for 1 patient

must not be used for any other patient. Partially used vials, leftover RO6867461 Drug Product or ranibizumab vials, as well as administration material, must not be re-used.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO6867461 and ranibizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or at the central depot. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Sham Boxes Accountability

Empty sham boxes will be provided by the Sponsor. The investigational site will acknowledge receipt of the sham boxes to confirm the shipment condition. Any damaged shipments will be replaced.

The investigator is responsible for the control of all study treatments including sham. The same accountability requirements and activities apply for sham boxes as for IMPs (see Section 4.3.3).

4.3.5 Post-Trial Access to RO6867461

Currently, the Sponsor does not have any plans to provide RO6867461 or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing RO6867461 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications and pre- and post-treatment administration medications used by a patient from 7 days prior to initiation of study drug to the final study visit/early termination visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.4.1 Permitted Therapy

Patients who use maintenance therapy other than those required to treat nAMD should continue their use (see Section 4.4.3 regarding treatment of nAMD in the fellow eye).

The decision to administer antimicrobial drops before and after the IVT administration is at the discretion of the investigator. Where antimicrobials are administered, it must be recorded on the concomitant medication forms of the eCRF.

4.4.2 Prohibited Therapy

At the discretion of the investigator, patients may continue to receive all medications and standard treatments administered for other conditions except in the following instances:

- Concurrent use of systemic anti-VEGF agents
- Concurrent use of IVT or subtenon corticosteroids in the study eye, except as required to treat adverse events
- Concurrent use of photocoagulation or photodynamic therapy with verteporfin in the study eye

4.4.3 CNV Secondary to AMD in the Fellow Eye

Should nAMD emerge or recur and require treatment in the fellow eye during the study period, the patient may receive approved anti-VEGF standard of care treatment.

When treatment in the fellow eye is scheduled on the same day as a study visit, all study assessments should be completed before treating the fellow eye.

When anti-VEGF therapy is recommended and ranibizumab warranted, every effort should be made to treat with ranibizumab. This treatment will be provided by the Sponsor as long as the patient remains in the study. When provided by the Sponsor, it will be in the commercial formulation for ranibizumab labelled for investigational use only (dispatched by IxRS). *Treatment with commercial supplies of ranibizumab may be reimbursed at the discretion and approval of the Sponsor.*

Treatment with other approved anti-VEGF therapies may be provided by the site. However, commercial supplies *of other approved anti-VEGF treatments* will not be reimbursed by the Sponsor.

Standard of care treatment after the early termination visit or final visit will not be supplied by the Sponsor.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

At timepoints when several assessments coincide, the following sequence is suggested, at the discretion of the investigator. The order can be adjusted to optimize site personnel and patient's time management, except where explicitly stated as mandatory (i.e., text in italics):

- Vital signs
- Blood sampling: At visits where FFA is performed, blood sampling and angiography can be performed from the same venous cannula. *Blood samples must be collected before angiography*.
- Ocular assessments and imaging

  BCVA: *BCVA must be conducted before pupil dilation.* At screening and Day 1 visits, BCVA can be performed before vital signs and blood sampling to avoid unnecessary investigations in those patients who may be a screen failure as a result of BCVA letter score.

  Slitlamp examination

  Pupil dilation

  SD-OCT

  FP (+infrared reflectance)

  FFA

  Dilated binocular indirect high-magnification ophthalmoscopy

  IOP: *mandatory to be performed after all imaging assessments, and the same method should be used throughout the study period*
- Aqueous humor sampling (optional)

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations and pretreatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria, including Central Reading Center confirmation of eligibility for a predefined set of imaging criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

An Eligibility Screening Form documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator and kept at the investigational site.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit and within the screening period (other than reported to treat an adverse event as defined in Section 5.3.1) will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A physical examination will include body weight and height at screening, and should cover head and neck including lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems, and others as applicable.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

4.5.5 Disease-Specific Assessments

Unless otherwise noted in schedule of activities (Appendix 1), all ocular assessments should be performed for both eyes.

4.5.5.1 Best Corrected Visual Acuity

BCVA at a starting test distance of 4 meters will be measured prior to dilating eyes by a trained and certified visual acuity (VA) examiner masked to study eye treatment assignment.

BCVA will be measured using the set of three Precision Vision™ or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R). A VA Procedure Manual will be

provided to the investigators. VA examiner and VA examination room certifications will be obtained before any VA examinations are performed.

The BCVA examiner will be masked to the study eye and treatment assignment and will perform the refraction and BCVA assessments (e.g., VA Specification Manual). The BCVA examiner will also be masked to the BCVA letter scores of a patient's previous visits and may only know patient refraction data from previous visits.

4.5.5.2 Additional Ocular Assessments

Additional ocular assessments to be performed during the study include the following:

- Slitlamp examination (scales for grading flare/cells and vitreous hemorrhage density are detailed in Appendix 2)
- Dilated binocular indirect high-magnification ophthalmoscopy
- IOP

  The method of IOP measurement used for a patient must remain consistent throughout the study. *IOP measurement of both eyes is to be performed after all imaging.*

  At study treatment visits, IOP pressure is to be conducted prior to study treatment administration and 30 (±15) minutes post-treatment administration in the study eye, and if IOP ≥30 mmHg, IOP should be re-assessed 30 (±15) minutes later. If IOP continues to be elevated, treatment should be undertaken at the discretion of the investigator.

- Finger count vision assessment

  In the study eye, a post-treatment optic nerve head perfusion will be assessed for each patient immediately after study treatment administration (maximum within 15 minutes after treatment administration) by testing finger count vision, hand motion, or light perception as appropriate.

4.5.5.3 Ocular Imaging

The Central Reading Center will provide sites with the Central Reading Center Manual and training materials for study-mandated ocular imaging. Before study images are obtained, site personnel and imaging systems (where applicable) will be certified by the reading center as specified in the Central Reading Center Manual. All study subject ocular images will be obtained only by trained and Central Reading Center certified personnel on certified/registered equipment at the study sites. A copy of all study subject ocular images will be transferred to the central reading center for storage and for independent analysis, including for confirmation of eligibility of defined image-related criteria.

Ocular images to be obtained and a copy transferred to the Central Reading Center, according to specifications provided in the Central Reading Center Manual, include the following:

- Fundus photography (FP)
- Fundus fluorescein angiography (FFA)
- Spectral domain optical coherence tomography (SD-OCT)
- Optional optical coherence tomography angiography (OCT-A; to be conducted at sites with OCT-A capability)

For FFA and FP, images of both eyes should be acquired and forwarded to the Central Reading Center.

For SD-OCT and optional OCT-A, images of $the\ study\ eye\ and$ fellow eyes should be captured and forwarded to the Central Reading Center at the screening, Week 24, Week 40, and Week 52 or early termination visits. At all other visits, only the study eye images need to be acquired and forwarded to the Central Reading Center.

At visits where FFA is performed, blood sampling and angiography can be performed from the same venous cannula. Blood samples must be collected before angiography.

SD-OCT will be performed at the study sites by trained and Central Reading Center-certified personnel on a Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany), equipped with TrueTrack™ Active Eye Tracking, AutoRescan™, and enhanced depth imaging (EDI). All devices used in the study will be registered with the Central Reading Center. Scans will be acquired and a copy transferred to the Central Reading Center according specifications provided in the separate Central Reading Center Manual. The Heidelberg Eye Explorer (HEYEX) software will be used to review the images at the study site.

4.5.5.4 Week 24 Assessment of Disease Activity

All patients will be assessed for disease activity at Week 24. Patients randomized to Arm B who have active disease at Week 24 (see criteria below) will switch to the Q12W dosing regimen of 6 mg RO6867461 for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48.

Determination of active disease will be made if any of the following criteria are met:

- Increase in CST of >50 μm on Spectralis OCT compared to average CST over last 2 visits (Weeks 16 and 20)

  Or

- Increase in CST of ≥ 75 μm compared to lowest CST recorded at either Week 16 or Week 20

  Or

- Decrease of at least 5 letters of BCVA compared with average BCVA over last 2 visits (Weeks 16 and 20), due to nAMD disease activity

  Or

- Decrease of $\geq$ 10 letters of BCVA compared to highest BCVA recorded at either Week 16 or Week 20 due to nAMD disease activity

  Or

- Presence of new macular hemorrhage due to nAMD activity

If, in the opinion of the investigator, there is significant nAMD disease activity at Week 24 that requires immediate treatment, but does not meet the above criteria, the Medical Monitor should be contacted. In such cases, following approval by the Sponsor, patients randomized to Arm B will receive 6 mg RO6867461 at Week 24 and stay on repeated 12-weekly treatments at Weeks 36 and 48.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: hemoglobin, hematocrit (HCT), RBC count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet count, total and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils in absolute numbers)
- Chemistry panel (serum or plasma): sodium, potassium, bicarbonate, phosphate, chloride, calcium, urea, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT)
- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time/international normalized ratio (PT/INR)
- Pregnancy test

  All women of childbearing potential will have a urine pregnancy test within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Plasma samples for assessment of ADAs to RO6867461 through use of a validated method

  Samples may or may not be analyzed for ranibizumab. Samples must be taken prior to administration of study drug at visits where study drug is administered.

- Plasma samples for RO6867461 PK analysis through use of a validated method

  Samples may or may not be analyzed for ranibizumab. Samples must be taken prior to administration of study drug at visits where study drug is administered.

- Whole blood sample for DNA extraction

  The sample may be used to study genes related to AMD (e.g., AMRS2. HTRA1, CFH, C3) and angiogenesis pathways (e.g., VEGF-A, VEGFR2, Ang-2, Tie-2), and the effect on the PK/PD/efficacy/safety of RO6867461.

Any residual material from PK and ADA samples may be used for additional exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of the study or compound-related assays after the mentioned intended uses. Exploratory biomarker profiling may include, but will not be limited to, analysis of biomarkers of angiogenesis (including, but not limited to, Ang-1, Tie-2, VEGFR, PDGF) and inflammation (including, but not limited to, IL-1b, IL-6, autotaxin).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis and immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- The whole blood samples for DNA extraction will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.7 Optional Aqueous Humor Samples

Aqueous humor samples will be collected from all patients who provide additional consent to participate. Where the patient consents to aqueous humor sampling, all efforts should be made to collect a baseline aqueous humor sample on Day 1 (predose). The schedule of activities (Appendix 1) provides guidance on recommended visits at which aqueous humor samples should be taken; however, (unscheduled) sampling could be performed at other or additional planned visits at the discretion of the investigator in agreement with the participating patient.

The aqueous humor sample (0.1 mL) should be collected by a qualified physician after all predose assessments have been completed, using an aseptic procedure and sterile field and according to local guidelines.

Aqueous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for ranibizumab concentrations. Remaining samples may be analyzed for VEGF and Ang-2 concentrations, and possibly other biomarkers of angiogenesis (including, but not limited to, Ang-1, Tie-2, VEGFR, PDGF) and inflammation (including, but not limited to, IL-1b, IL-6, autotaxin). Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.8 Optional Unscheduled Collection of Vitreous Humor Samples

Elective vitrectomy surgery is not allowed in the study eye during study participation; however, if the surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. Approximately 0.5 mL of undiluted vitreous humor should be collected using an aseptic procedure and sterile field and according to local guidelines and shipped to the Sponsor. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor.

Vitreous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for ranibizumab concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations, and possibly other biomarkers.

The Sponsor should be contacted prior to performing any vitrectomy surgeries in the study eye. Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.5.9 Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition

- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO6867461 or diseases:

- Leftover whole blood samples (see Section 4.5.6)
- Leftover optional aqueous humor samples (see Section 4.5.7)
- Leftover optional vitreous humor samples (see Section 4.5.8)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.9.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study CR39521 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study CR39521.

4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Patients who are withdrawn from the study early but have not withdrawn consent should return for an early termination visit 28 (+7) days following the last study treatment. Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Drop in BCVA by ≥30 letters if considered to be adverse and related to study treatment in the study eye (compared with the last assessment of visual acuity prior to the most recent treatment) and lasting for more than 1 hour
- Endophthalmitis in the study eye
- Severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis; see the definition of intraocular inflammation in Section 5.3.5 and grading scales for assessment in Appendix 2)
- Retinal detachment in the study eye

- Vitreous hemorrhage that will preclude examination of macula and retinal imaging in the study eye
- Surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with IVT injection of anti-infectives or laser or retinal cryopexy with gas) to prevent permanent loss of sight

Patients who discontinue study treatment prematurely will be asked to return to the clinic for an early termination visit as outlined in the schedule of activities (Appendix 1). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients will not be followed up as part of the study for any reason after consent has been withdrawn.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

RO6867461 is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with RO6867461 in completed and ongoing studies.

In the BP28936 first-in-human study, no safety signals for the drug RO6867461 were observed for up to 3 monthly administrations of the highest dose tested in this study (cutoff: ≥4 weeks after last patient last dose of the multiple-dose part). The majority of adverse events were of mild and moderate intensity. No deaths occurred during the study period and no premature withdrawals from the study as a result of serious adverse events were reported.

To date, no identified important safety risks for the drug RO6867461 have been observed in the development program of RO6867461. Although there was a low rate of arterial thromboembolic events (ATEs) observed in clinical trials with anti-VEGF agents administered IVT, there is a potential risk of ATEs following IVT use of VEGF inhibitors, including RO6867461. IVT injections have also been associated with serious adverse reactions related to the injection procedure, including endophthalmitis, rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts. For additional details on the risks associated with RO6867461, see Section 5.1.1 and refer to the RO6867461 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Patients will undergo safety monitoring, including adverse event monitoring and regular ophthalmological monitoring (ocular safety panel and SD-OCT assessments) during the study, and the nature, frequency, and severity of adverse events will be assessed. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with RO6867461

5.1.1.1 Important Identified Risks

To date, no identified risks for RO6867461 have been observed.

5.1.1.2 Potential Important Systemic Risks for anti-VEGF Agents

Results from nonclinical studies did not reveal any adverse effects that require specific warnings and precautions that are different from those applicable to any anti-VEGF agents currently used in clinical practice for the treatment of nAMD. Based on previous experience with ranibizumab, important potential risks of RO6867461 include ATEs and immunogenicity to RO6867461.

5.1.1.3 Injection Procedure-Related Risks

IVT injections have been associated with serious adverse reactions related to the injection procedure, including endophthalmitis, rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts. Serious adverse reactions related to the injection procedure have occurred in <0.1% of IVT injections of ranibizumab (Lucentis® U.S. Package Insert).

Proper aseptic injection technique should always be used when administering RO6867461. In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

5.1.1.4 Risk of Increased Intraocular Pressure

Increases in IOP have been noted while being treated with repeated IVT injections of anti-VEGF agents, both immediately post-injection (within 60 minutes), as well as pre-injection IOP increases during the duration of studies with monthly treatment administration. Monitoring of IOP prior to and following IVT injection with RO6867461 will be implemented in the Phase II studies. Appropriate management of IOP increases should be initiated as necessary.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 2.

Table 2 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Endophthalmitis or severe ocular inflammation (endophthalmitis, 4+ anterior chamber cell/flare or 4+ vitritis; see Section 5.3.5 and Appendix 2 for intraocular inflammation grading scales)	• Discontinue study treatment.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events (systemic and ocular) and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study (i.e., regular ophthalmological monitoring and SD-OCT assessments).

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; see Section 5.3.3); the event

itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

*Non-serious or serious a*dverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Sight-threatening adverse events

  An adverse event *is* considered to be sight threatening *and* should be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; or reporting instructions) if it meets one or more of the following criteria:

  – It causes a decrease of ≥30 letters in BCVA (compared with the last assessment of VA prior to the most recent treatment) lasting more than 1 hour

  – It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with IVT injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight

- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis; see the definitions of intraocular inflammation in Section 5.3.5 and grading scales for assessment in Appendix 2)
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as angiographies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study treatment.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale in Table 3 *will be used* for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

For the purposes of reporting events of infection and inflammation of the eye, the following terms and definitions should be used.

- Iritis: the presence of inflammatory cells in the anterior chamber

  The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.

- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

Note: Trace benign, aqueous pigmented cells visible on slitlamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an adverse event.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), as a serious adverse event or an adverse event of special interest not considered serious (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History and Baseline Conditions eCRFs.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Age-Related Macular Degeneration

Medical occurrences or symptoms of deterioration that are anticipated as part of AMD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of AMD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated AMD").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

- Hospitalization for a preexisting condition, provided that the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event.

Any study drug overdose or incorrect administration of study treatment should be noted on the study drug administration form (eCRF).

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of RO6867461 are available.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor	[redacted], M.B.B.S.
Mobile Telephone No. (primary):	[redacted]
Telephone No.:	[redacted]

Alternate Medical Monitor Contact Information for All Sites

Medical Monitor:	[redacted], M.D.
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >28 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest immediately reportable to the Sponsor, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study treatment), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- RO6867461 Investigator's Brochure
- Ranibizumab U.S. Prescribing Information

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

The IMC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor RO6867461 will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The focus of this trial is estimation rather than hypothesis testing. The sample size was determined largely based on logistical considerations. Assuming a common standard deviation for BCVA change from baseline of 13.5 letters, the distance from the difference of the means between RO6867461 ($n = 30$) and ranibizumab ($n = 15$) to the 80% two-sided confidence interval bounds is estimated to be 5.5 letters.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are enrolled, discontinued, and completed the study will be summarized as well as the major protocol violations. Demographic and other baseline characteristics will be summarized with descriptive statistics.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographics, baseline characteristics (including ocular assessments, patient disposition, and medical history), and all baseline laboratory values will be summarized descriptively by treatment group using frequency tables and summary statistics providing means, medians, standard deviations, first and third quartiles, and extreme values.

6.4 EFFICACY ANALYSES

The primary, secondary, and exploratory efficacy analyses will be carried out in the intent-to-treat population (defined as all randomized patients), with patients grouped according to their assigned treatment.

The baseline measurement is defined as the latest non-missing observation before the first dose of study medication.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is BCVA change from baseline at Week 40. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance will be used to account for within-patient correlation, but another variance-covariance structure, such as AR(1), may be selected in case of convergence issues.

Means for RO6867461 and ranibizumab arms, difference of the means relative to ranibizumab, and the corresponding two-sided 80% confidence intervals will be computed. There will not be formal correction for multiple testing.

6.4.2 Secondary Efficacy Endpoints

Mean change from baseline BCVA over time using the ETDRS-like charts will be analyzed using the MMRM model described in Section 6.4.1.

Categorical outcomes measured repeatedly will be analyzed using Generalized Estimating Equations with a binomial distribution, logit link function, and unstructured covariance. In case of convergence issues, AR(1) covariance structure will be used. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction. Least squares means with the corresponding two-sided 80% confidence intervals and odds ratios will be computed.

6.4.3 Exploratory Efficacy Endpoint

The proportion of patients with disease activity at Week 24 will be reported with the corresponding 80% Wilson score confidence intervals by study arm.

6.5 PHARMACODYNAMIC ANALYSIS

An empirical drug-disease model of longitudinal BCVA previously developed on the ranibizumab database will be used to analyze the effect of RO6867461 on BCVA by using a meta-analysis approach.

A similar modeling approach will be used to analyze the relationship between RO6867461 exposure and BCVA. The influence of various baseline covariates on model parameters will be investigated. The PK/PD or dose/PD relationship will be

characterized. The results will be reported in a separate document from the Clinical Study Report.

6.6 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, with patients grouped according to treatment received.

The original terms recorded on the eCRF by the investigators for adverse events will be standardized by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.

Separate summaries will be prepared for systemic and ocular adverse events, with events in the study eye and non-study eye summarized separately. Serious adverse events will be summarized similarly. Adverse events leading to discontinuation from the study will be listed and tabulated.

6.7 PHARMACOKINETIC ANALYSES

A non-linear mixed effects modeling approach (with NONMEM® software [Beal and Sheiner 1998]) will be used to analyze the concentration-time data of RO6867461. Population and individual primary PK parameters (i.e., clearances and volumes) will be estimated, and the influence of various covariates (e.g., gender, body weight) on these parameters will be investigated. The data collected in this study may be pooled with data collected in the previous studies, as appropriate, to build a PK model. Secondary PK parameters such as area under the concentration–time curve (AUC) and maximum concentration observed (C_{max}) will be derived from the individual post-hoc predictions. The result of this analysis will be reported in a separate document from the Clinical Study Report.

Additional PK analyses will be conducted as appropriate.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment, with patients grouped according to treatment received.

6.9 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by the Sponsor IMC (see Section 3.1.2) and appropriate senior management personnel who will be unmasked at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data Central Reading Center data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or

patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This research study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland and may be implemented in individual countries by Roche's local affiliates. The Sponsor will perform project management, study management, monitoring, vendor management, and statistical programming. An IxRS will be used for patient screening and randomization and for management of study drug requests and shipments. A central laboratory will be used for most laboratory assessments and for storage of other laboratory samples (i.e., anti-RO6867461 antibody samples) prior to being shipped to Sponsor or its designee for analysis. Data will be recorded by an EDC system using eCRFs (Section 7.2) or forwarded to Sponsor electronically (e.g., PK data). A Central Reading Center will be used for ocular imaging analyses (FP, FFA, and SD-OCT), which will be forwarded to Sponsor electronically.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Week	Screening	Wk 1		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Early Termination [b]	Unscheduled Visit [c]
Day (Visit window)	–28 to 1 [a]	1 [a]	7 (±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	364 (±7)		
Informed consent	x [d]																	
Eligibility	x	x																
Demographic data	x																	
Medical history	x	x																
Physical examination [e]	x															x	x	
Body weight and height	x																	
Vital signs [f]	x	x																x
BCVA [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Optional OCT-A [h, i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
FFA [h]	x												x			x	x	
Fundus photography [h]	x												x				x	
Optional aqueous humour sample [j]		x							x	x	x	x				x		x
Optional vitreous humor sample [k]		If elective vitrectomy surgery is performed [k]																
Plasma PK sample [j]		x					x		x	x				x		x	x	

Appendix 1
Schedule of Activities (cont.)

Week	Screening	Wk 1		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Early Termination [b]	Unscheduled Visit [c]
Day (Visit window)	–28 to 1 [a]	1 [a]	7 (±3)	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	364 (±7)		
Plasma sample for ADAs [j]		x					x		x	x				x		x	x	
Blood hematology/ chemistry [l, m]	x [m]															x	x	x
Coagulation [m]	x [m]																	x
Whole blood sample for DNA		x [n]																
Pregnancy test [o]	x																	
Assessment of disease activity [p]									x									
IOP (post-imaging) [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IOP (pre- and post-study treatment) [r]		x		x	x	x	x	x	x	x	x	x	x	x	x			
Administration of study treatment [s]		x		x	x	x	x	x	x	x	x	x	x	x	x			
Finger count vision assessment [t]		x		x	x	x	x	x	x	x	x	x	x	x	x			
Adverse events [u]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCVA = best corrected visual acuity; FFA = fundus fluorescein angiography; HCT = hematocrit; IOP = intraocular pressure; IVT = intravitreal; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; OCT-A = optical coherence tomography angiography; PK = pharmacokinetic; SD-OCT = spectral domain optical coherence tomography; Wk = week.

Notes: There must be a minimum of 21 days between all study visits occurring from Week 4 through Week 52. Standard of care treatment for nAMD in the fellow eye may be provided by the Sponsor as long as the patient remains in the study (see Section 4.4.3). Standard of care treatment after the early termination visit or final visit will not be supplied by the Sponsor.

[a] The screening and Week 1/Day 1 (randomization) visit may occur as a combined visit if all assessments *(with the exception of informed consent)* are *completed* within 48 hours. Where screening and randomization are combined, assessments listed for both visits only need to be conducted once.

[b] Patients who are withdrawn from the study early but have not withdrawn consent should return for an early termination visit 28 (+7) days following the last study treatment.

[c] Assessments performed in case of an unscheduled visit(s) are at the discretion of the investigator.

[d] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[e] A physical examination should cover head and neck including lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems, and others as applicable. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[f] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[g] To be performed prior to other ocular assessments.

[h] The Central Reading Center will review these assessments at screening for determination of patient eligibility. At all subsequent visits, outputs from these assessments will be sent to the Central Reading Center. For SD-OCT and OCT-A, images of *the study eye and* fellow eyes should be captured and forwarded to the Central Reading Center at the screening, Week 24, Week 40, and Week 52 or early termination visits. At all other visits, only the study eye images need to be acquired and forwarded to the Central Reading Center.

[i] To be conducted at sites with OCT-A capability.

[j] Sample must be taken prior administration of study drug at visits where study drug is administered.

[k] If elective vitrectomy surgery is medically necessary and the patient consents, a vitreous sample can be obtained from the study eye. A PK blood sample (for plasma preparation) should also be collected and shipped to the Sponsor. Vitreous humor samples will be analyzed primarily for RO6867461 concentrations and may also be analyzed for ranibizumab concentrations. The remaining samples may be analyzed for VEGF and Ang-2 concentrations, and possibly other biomarkers.

Appendix 1
Schedule of Activities (cont.)

[l] Hematology includes hemoglobin, HCT, RBC count, MCV, MCH, platelet count, and total and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils in absolute numbers). Chemistry panel includes sodium, potassium, bicarbonate, phosphate, chloride, calcium, urea, creatinine, total bilirubin, ALP, AST, and ALT.

[m] Results from the screening samples are not required for randomization.

[n] *If whole blood sample for DNA is not taken at the assigned visit (Week 1, Day 1), this sample may be collected at any subsequent study visit where a blood draw is being performed for other purposes as specified in the schedule of activities (e.g., PK, ADA, and/or blood hematology/chemistry).*

[o] All women of childbearing potential will have a urine pregnancy test within 28 days prior to initiation of study treatment. If the urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Assessment of disease activity conducted per specified criteria outlined in Section 4.5.5.4.

[q] Assessment to be performed after all imaging assessments, and the same method should be used throughout the study period.

[r] IOP pressure is to be conducted prior to study treatment administration and 30 (±15) minutes post-treatment administration in the study eye, and if IOP ≥30 mmHg, IOP should be re-assessed 30 (±15) minutes later. If IOP continues to be elevated, treatment should be undertaken at the discretion of the investigator.

[s] Sham IVT administration will be delivered to patients to maintain subject masking throughout the study period. In Arm A, sham IVT administrations will occur at Weeks 16, 20, 28, 32, 40, and 44. In Arm B, sham IVT administrations will occur at Weeks 16, 20, 24, 32, 36, 40, and 48, or at Weeks 16, 20, 28, 32, 40 and 44, the latter if the dosing regimen was switched to the 12-weekly schedule.

[t] Finger count vision assessment should be conducted within 15 minutes of study treatment administration for the study eye only.

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 2
Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreal Hemorrhage Density, and Vitreous Cells

GRADING SCALE FOR ANTERIOR CHAMBER FLARE OR CELLS

Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein is detectable in the anterior chamber: This protein is visible only with careful scrutiny by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Slight amount of protein is detectable in the anterior chamber: the presence of protein in the anterior chamber is immediately apparent to an experienced observer using slitlamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2-3+	Moderate amount of protein is detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+ .
4+	A large amount of protein is detectable in the anterior chamber. This grade is similar to 3+ , but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It should be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
Cells	
0	No cells are seen in any optical section when a large slitlamp beam is swept across the anterior chamber.
Trace	Few (1–3) cells are observed when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells/optical section are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
3+	25–50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

Modified from: Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(5, Part 2):155–70.

Appendix 2
Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreal Hemorrhage Density, and Vitreous Cells (cont.)

GRADING SCALE FOR VITREOUS HEMORRHAGE DENSITY

None (0)	Retina is visible.
Trace	Retina is visible and red blood cells are visible only on slitlamp examination.
1+	Retinal detail is visible; some hemorrhage is visible by ophthalmoscopy.
2+	Large retinal vessels are visible, but central retinal detail is not visible by ophthalmoscopy.
3+	Red reflex is visible, but no central retinal detail is seen posterior to the equator by ophthalmoscopy.
4+	No red reflex by ophthalmoscopy.

GRADING SCALE FOR VITREOUS CELLS

Cells in Retroilluminated Field	Description	Grade
0–1	Clear	0
2–20	Few opacities	Trace
21–50	Scattered opacities	1
51–100	Moderate opacities	2
101–250	Many opacities	3
>251	Dense opacities	4

Notes: The grading will be performed using a Hruby lens.

Excerpted from: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis. Fundamentals and clinical practice. 2nd rev. ed. New York: Mosby, 1996,p. 64.

Appendix 3
Study Treatment Administration Procedure

1. PRE-INJECTION PROCEDURES

The following procedures will be used to minimize the risk of potential adverse events associated with intravitreal (IVT) injections (e.g., endophthalmitis).

Aseptic technique will be observed by clinic staff involved in the administration tray assembly, anesthetic preparation, and study treatment preparation and administration. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with IVT injections will be observed.

The above procedures (except where noted) will be conducted by the physician performing the IVT administration of study treatment. At the discretion of the investigator, patients **may** self-administer ophthalmic broad-spectrum antimicrobial drops on days prior to study treatment administration.

At the discretion of the investigator, the sites may use either ophthalmic drops or lidocaine injection for study eye anesthesia, and where possible the same method used throughout the study.

2. PROCEDURE FOR PROPACAINE- OR TETRACAINE-BASED ANESTHESIA

If using propacaine- or tetracaine-based ophthalmic drops for anesthesia, the treatment administrator physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 5% povidone iodine ophthalmic solution, ophthalmic broad-spectrum antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial), and treatment administration supplies.

- Instill two drops proparacaine- or tetracaine-based ophthalmic drops into the study eye, followed by, at the discretion of the investigator, ophthalmic antimicrobial solution.
- Wait 90 seconds.
- Instill two more drops of proparacaine- or tetracaine-based ophthalmic drops into the study eye,
- Disinfect the periocular skin and eyelid of the study eye in preparation for study treatment administration. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.

- The treatment administrator physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with proparacaine- or tetracaine-based drops and hold the swab against the planned IVT injection site for 10 seconds.
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct patient to direct gaze away from syringe prior to study treatment administration.

3. PROCEDURE FOR LIDOCAINE INJECTION-BASED ANESTHESIA

If using lidocaine injection for anesthesia, treatment administrator physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 1% lidocaine for injection, ophthalmic antimicrobial solution, and treatment administration supplies.

- Instill two drops of 0.5% proparacaine hydrochloride into the study eye, followed, at the discretion of the investigator, by drops of broad-spectrum antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial).
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The treatment administrator physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned IVT injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Inject 1% lidocaine (without epinephrine) subconjunctivally.

- Use a sterile 4 × 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct patient to direct gaze away from syringe prior to study treatment administration.

4. PROCEDURE FOR LIDOCAINE-GEL BASED ANESTHESIA

If using lidocaine-gel for anesthesia, the treatment administrator physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4 × 4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 5% povidone iodine ophthalmic solution, ophthalmic broad-spectrum antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial), and treatment administration supplies.

- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, followed at the discretion of the investigator, by two drops of ophthalmic antimicrobial solution.
- Wait 90 seconds
- Instill lidocaine gel onto the planned injection site in the study eye
- Wait 3 minutes
- Instill lidocaine gel onto the planned injection site in the study eye
- Disinfect the periocular skin and eyelid of the study eye in preparation for study treatment administration. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects
- The treatment administrator physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva
- Wait 90 seconds
- Saturate a sterile, cotton-tipped applicator with proparacaine- or tetracaine-based drops and hold the swab against the planned IVT injection site for 10 seconds
- Use a sterile 4 × 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin
- Instruct patient to direct gaze away from syringe prior to study treatment administration

Appendix 3
Study Treatment Administration Procedure (cont.)

5. INTRAVITREAL ADMINISTRATION OF STUDY TREATMENT

Study treatment must be prepared according to the detailed instructions in the Pharmacy Manual. The instructions in the Pharmacy Manual cover all steps until the syringe is ready for treatment administration.

After preparing the study eye as outlined above:

- For RO6867461 or ranibizumab administration: insert the syringe through an area 3.0 to 4.0 mm posterior to the limbus (aphakic/pseudophakic patients 3.0–3.5 mm), avoiding the horizontal meridian, and aiming toward the center of the globe. The injection volume should be delivered slowly. The needle should then be removed slowly to ensure that all drug solution is in the eye. Refer to Section 6 below for detailed post-injection procedures.
- For sham administration: the patients do not receive an actual injection. The treatment administrator physician will withdraw the tuberculin syringe plunger to the 0.1 mL mark on the syringe, then place the hub of the syringe (without the needle) against the pre-anesthesized conjunctival surface. The treatment administrator physician will then press the syringe hub firmly against the globe and then slowly depress the plunger, mimicking the action of an injection.

The injection site should be rotated at every study treatment visit.

6. POST-INJECTION PROCEDURES

At the discretion of the investigator, drops of ophthalmic antimicrobial drops could be instilled in the study eye after study treatment administration and for the days following study treatment administration.

Discard all administration materials (i.e., syringe, needles) in the sharps container.