Official Title:	**A MULTIPLE-CENTER, MULTIPLE-DOSE AND REGIMEN, RANDOMIZED, ACTIVE COMPARATOR CONTROLLED, DOUBLE-MASKED, PARALLEL GROUP, 36 WEEK STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF RO6867461 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION**
NCT Number:	**NCT02484690**
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PROTOCOL

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PROTOCOL NUMBER:	BP29647
VERSION:	3
EUDRACT NUMBER:	N/A
IND NUMBER:	119225
TEST PRODUCT:	RO6867461
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 13 March 2015
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Sep-2016 13:47:21

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SYNOPSIS OF PROTOCOL NUMBER BP29647

TITLE	**A MULTIPLE-CENTER, MULTIPLE-DOSE AND REGIMEN, RANDOMIZED, ACTIVE COMPARATOR CONTROLLED, DOUBLE-MASKED, PARALLEL GROUP, 36-WEEK STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF RO6867461 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	BP29647
VERSION:	3
EUDRACT NUMBER:	N/A
IND NUMBER:	119225
TEST PRODUCT:	RO6867461
PHASE:	II
INDICATION:	Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD)
SPONSOR:	**F. Hoffmann-La Roche Ltd.**

OBJECTIVES

Primary:

The primary objective of this study is as follows:

- To evaluate the efficacy of RO6867461 compared to ranibizumab monotherapy in treatment-naive and anti-vascular endothelial growth factor (VEGF)–incomplete-responder patients with CNV secondary to AMD.

Secondary:

The secondary objectives of this study are as follows:

- To assess the safety of multiple intravitreal (IVT) doses of RO6867461
- To assess systemic pharmacokinetics of RO6867461
- To investigate pharmacodynamics (PD) and anatomical outcomes informing on the mechanism of action of RO6867461
- To investigate the formation of plasma anti-RO6867461 antibodies
- To investigate 2 different RO6867461 dosing regimens

Exploratory:

The exploratory objectives of this study are as follows:

- To evaluate RO6867461 effects on plasma levels of markers of angiogenesis and inflammation
- To investigate RO6867461 concentration and, if sample volume allows, inflammatory and pro-angiogenic factors, in aqueous humor samples (optional) and vitreous (optional)
- To evaluate the effect of genetic polymorphisms in genes associated with AMD and/or involved in angiogenesis and response to RO6867461

STUDY DESIGN

Description of Study

Multiple-center, multiple-dose and regimen, randomized, active comparator controlled, double-masked, five parallel group, 36-week study in patients with CNV secondary to AMD

The five groups of this study are as follows:

- Arm A: 0.5 mg ranibizumab IVT every 4 weeks for 32 weeks (9 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm D: 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 8 weeks (i.e., on Weeks 20 and 28; 2 injections)
- Arm E: 0.5 mg ranibizumab IVT every 4 weeks up to Week 8 (3 injections), followed by 6 mg RO6867461 IVT every 4 weeks (6 injections)

The study will allow evaluation of RO6867461 in a treatment-naive patient population (comparison of Arms A, B, C, and D) and an anti-VEGF–incomplete-responder patient population that meets a predefined criterion at Week 12 (comparison between Arms A and E). Only one eye will be chosen as the study eye.

NUMBER OF PATIENTS

In the initial recruitment period, up to 271 patients with CNV secondary to AMD are expected to be enrolled in the study. Up to 45 (Arms B, C, and D) or 68 (Arms A and E) patients are expected to be randomized per arm of the study (3:2:2:2:3 randomization scheme).

An interim analysis might be conducted to adapt the recruitment up to a maximum of 343 patients in order to have approximately 80 patients in the anti-VEGF–incomplete-responder subgroup completing the study.

TARGET POPULATION

Male and female patients of ≥50 years of age with treatment–naive CNV secondary to AMD.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

Patients must meet the following criteria at study entry:

Ocular criteria for study eye:

- Treatment-naïve with CNV secondary to AMD, with subfoveal CNV or juxtafoveal CNV with a subfoveal component related to the CNV activity by *fundus fluorescein angiography (*FFA*)* or *spectral domain optical coherence tomography (*SD-OCT) (such as subretinal fluid, subretinal hyper-reflective material, evidence of leakage, or hemorrhage)
- Best corrected visual acuity (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. Proportion of patients with BCVA letter score of 73 to 69 letters inclusive (20/40 Snellen equivalent) on Day 1 will be limited to a maximum of 40% of the planned sample size
- 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 (DAs) by FFA

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

  Active CNV confirmed by FFA (evidence of leakage)

  CNV exudation confirmed by SD-OCT (presence of fluid)
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

General Criteria:

- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonization (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to the ICH and local regulations
- Age $\geq$50 years
- For women who are not postmenopausal (i.e., $\geq$12 months of non-therapy-induced amenorrhea or surgically sterile (absence of ovaries and/or uterus) agreement to remain abstinent or use combined contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and at least through Week 36.

  Examples of contraceptive methods with an expected failure rate of $<$1% per year include male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<$1% per year, barrier methods must always be supplemented with the use of a spermicide.
- Males must agree to use a barrier method of contraception starting from first treatment administration for at least 2 months post-last treatment administration.
- 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 (CSC) 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, transplasminogen 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
- 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, etc.) that, in the opinion of the Investigator, could either reduce the potential for visual improvement or require medical or surgical intervention
- Active intraocular inflammation (grade trace or above) *in the study eye*
- 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*

***General Criteria**:*

- Any major illness or major surgical procedure within one month before screening
- Patients with glycosylated hemoglobin HbA1C $>$ 7.5%
- 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 *either* 30 or more minutes 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 within 12 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
- For females of childbearing potential, a positive blood pregnancy test
- Lactating women
- Known hypersensitivity to ranibizumab, fluorescein, indocyanine green, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used
- Any other restriction accorded to the use of
- Any treatment with an IMP in the 3 months prior to Day 1

LENGTH OF STUDY

The total duration of the study for each patient will be up to 40 weeks, divided as follows:

- Screening: up to 4 weeks
- Baseline: Day 1
- Study Treatment Administration: from Day 1 to Week 32
- Final safety and efficacy period: from Week 32 to Week 36

END OF STUDY

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur 36 weeks after the last patient is enrolled.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

Adverse events

Adverse events and concomitant medications will be monitored throughout the entire study.

Vital signs

Body temperature (oral or tympanic) will be collected at the time-points indicated in the schedule of assessments (SoA).

BP and pulse rate will be performed after the patient has rested for at least 5 minutes at the time-points indicated in the SoA.

Electrocardiograms

12-lead triplicate electrocardiogram (ECG) will be performed at the time-points indicated in the SoA.

Ocular safety

Visual acuity will be assessed using best correction determined from protocol refraction (BCVA) using ETDRS-like charts, slit lamp examination, dilated binocular indirect high-magnification ophthalmoscopy, IOP, fundus photography, SD-OCT, and angiography will be performed at the time-points indicated in the SoA.

Laboratory tests

Hematology, blood chemistry, and urinalysis, listed below, will be collected at the time-points indicated in the SoA.

- Hematology: Hemoglobin, hematocrit (HCT), red blood cell 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), erythrocyte sedimentation rate (ESR)
- Coagulation (at screening only): Activated partial thromboplastin time (APTT) and prothrombin time/International Normalized Ratio (PT/INR)
- Blood chemistry: Sodium, potassium, bicarbonate, phosphate, chloride, calcium, urea, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), gamma glutamyl transferase (GGT), total protein, glucose, HbA1C (at screening and at final or early termination visits only), total cholesterol (TC), triglycerides (TG), C-reactive protein (CRP)
- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, and pH. Microscopy to be performed if abnormalities are observed and deemed necessary by the Investigator or Designee, in particular when blood or protein is positive or strong positive
- Pregnancy test: for females of childbearing potential, serum pregnancy test at screening

Anti-drug antibodies

Plasma samples will be collected at the time-points indicated in the SoA to evaluate the presence of anti-RO6867461 antibodies.

PHARMACOKINETIC OUTCOME MEASURES

Plasma levels of RO6867461

Plasma concentrations will be measured by a specific enzyme-linked immunosorbent assay (ELISA) method. The pharmacokinetic (PK) analysis is described in the statistical methods section. Samples may also be analyzed for ranibizumab.

Aqueous humor samples (optional)

Samples will be collected from patients who provide additional (optional) consent to participate in aqueous humor collection. Samples will be analyzed for RO6867461 and biomarker concentrations. Samples may also be analyzed for ranibizumab.

Unscheduled collection of vitreous samples (optional)

If elective vitrectomy surgery is medically necessary, a vitreous sample can be obtained from

the study eye from patients who provide additional (optional) consent to participate in vitreous collection for the measurement of RO6867461 and biomarker concentrations. Samples may also be analyzed for ranibizumab. A blood sample for PK measurement should be taken at the same time.

EFFICACY OUTCOME MEASURES

The primary efficacy outcome measure for this study is the mean change from baseline BCVA at Week 36 using the ETDRS-modified charts.

The secondary efficacy outcome measures for this study include BCVA and anatomical PD imaging measures relevant to the mechanism of action of RO6867461 as follows:

BCVA

- Proportion of patients gaining ≥ 15 letters from baseline BCVA at Week 36
- Proportion of patients with BCVA of 20/40 or better at Week 36
- Proportion of patients with BCVA of 20/200 or worse at Week 36

Anatomic outcome measures using SD-OCT

- Mean change from baseline in foveal center point thickness at Week 36
- Mean change from baseline in mean central subfield thickness (1 mm diameter) at Week 36
- Proportion of patients with no intraretinal fluid, subretinal fluid, cysts, or pigment epithelial detachment at Week 36

Anatomic outcome measures using FFA

- Mean change from baseline in total area of CNV at Week 36
- Mean change from baseline in total area of CNV component at Week 36
- Mean change from baseline in total area of leakage at Week 36

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study include but are not limited to the following:

- Biomarkers in plasma related to angiogenesis and inflammation
- Pro-angiogenic factors in aqueous humor and vitreous samples for patients who provide consent to participate

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BIOMARKER/GENOTYPING SAMPLE COLLECTION

Biomarkers Plasma Samples

All patients who have been enrolled in the study will have mandatory PD and exploratory biomarker plasma samples taken at the time-points indicated in the SoA. The PD and exploratory plasma samples will be collected to investigate biomarkers in plasma related to angiogenesis and inflammation.

Clinical Genotyping (CG) Samples

A mandatory whole blood sample will be taken for DNA extraction from every subject. The DNA may be used to study genes related to AMD (e.g., AMRS2. HTRA1, CFH, C3, etc.) as well as related to angiogenesis (e.g., VEGFA, VEGFR2, angiopoietin-2, angiopoietin-1 receptor [Tie-2], etc.), and the effect on the PK/PD/efficacy/safety of RO6867461. Data arising from this sample will be subject to the same confidentiality as the rest of the study. This specimen will be destroyed no later than 2 years after the final closure of the clinical database.

INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMPs will include the two study drugs as follows:

- **RO6867461:** Vials of sterile, colorless to brownish, preservative-free solution of RO6867461 (120 mg/mL), for IVT administration of either 1.5 or 6 mg dose every 4 or 8 weeks
  Placebo is provided as sterile, colorless to slightly brownish, preservative-free liquid, used only for dilution of RO6867461 drug product to the appropriate clinical dose.
- **Comparator—Ranibizumab:** Vials containing ranibizumab solution (10 mg/mL), for IVT

administration of a 0.5 mg dose every 4 weeks.

The double-masked design is achieved through strict independence of the pharmacist (or designated personnel) and Investigators who are preparing and administering study treatment, from the assessing Investigators and remaining site personnel.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

- **Sham:** Sham IVT administration will be delivered to patients in Arm D at Weeks 16, 24, and 32 to maintain double-masking throughout the study period.

PROCEDURES

Detailed SoAs and procedures are tabulated in Appendix 1 and Appendix 2 of the protocol.

Screening

Treatment-naive patients with CNV secondary to AMD who are willing to participate in the study and have given informed consent will undergo a thorough screening examination within 4 weeks of study treatment administration. The screening procedures as outlined in the SoA will include review of inclusion and exclusion criteria, medical history, physical examination, assessment of vital signs and ECG, serum pregnancy test for female of childbearing potential, and safety laboratory parameters. Imaging criteria for eligibility will be confirmed by a Central Reading Center before enrolment.

Treatment period

On Day 1, baseline assessments will be conducted on the eligible patients, according to the SoA. Patients will receive their first IVT administration of either RO6867461 or comparator therapy according to the randomization schedule and following established standard procedures. Patients will return to the eye clinic for study treatment administration (every 4 weeks) and assessments as outlined in the SoA. Patients will be administered the same study treatment throughout the study period, except for the patients randomized to Arms D and E:

- Patients in Arm D will receive sham administrations on Weeks 16, 24, and 32 to maintain the double-masking throughout the every 8 weeks (Q8W) regimen period.
- Patients in Arm E will initially receive 3 injections of ranibizumab followed by 6 injections of RO6867461.

A post-treatment administration check of study eye will be performed for each patient immediately after treatment administration, by testing finger count vision, or hand motion and light perception. On the day of dosing, IOP will be monitored at 30 minutes post-treatment administration in the study eye, and if IOP $\geq$30 mmHg, IOP should be re-assessed at 1 hour post-treatment administration. If IOP continues to be elevated, treatment should be undertaken at the discretion of the Investigator.

Final period

Patients will return for final visits with assessments as outlined in the SoA 4 weeks after the last study treatment administration.

STATISTICAL METHODS

SAFETY ANALYSES

All patients who receive at least one administration of the study treatment will be included in the safety analysis. The safety data, including adverse events, reasons for withdrawal from study, laboratory data, concomitant medications, vital signs, and physical examination results will be listed and summarized descriptively.

As appropriate, listings, summary tables, and graphs (subject plot and/or mean plots) will be provided for safety and tolerability assessments.

Anti-RO6867461 antibody results (positive/negative) will be listed.

General adverse events will be listed and summarized by body system and preferred term using MedDRA. Ophthalmologic adverse events will be listed and summarized.

For laboratory data subject listings will be presented with abnormalities flagged.

PHARMACOKINETIC ANALYSES

A nonlinear mixed effects modeling approach (with NONMEM software) will be used to analyze the concentration-time data of RO6867461. Population and individual primary PK parameters (i.e., clearance and volumes) will be estimated and the influence of various covariates (e.g., gender, body weight, etc.) on these parameters will be investigated. The data collected in this study may be pooled with data collected in the previous Phase I study as appropriate to build a PK model. Secondary PK parameters such as area under the concentration-time curve (AUC) and maximum plasma concentration observed (C_{max}) will be derived from the individual post-hoc predictions. The results of this analysis will be reported in a separate document from the clinical study report.

PHARMACODYNAMIC ANALYSES

Individual and mean PD data and parameters will be presented by listings and descriptive summary statistics including means, geometric means, medians, ranges, standard deviations, and coefficients of variation.

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 using a meta-analysis approach by integrating data from this study and ranibizumab clinical data.

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.

SAMPLE SIZE JUSTIFICATION

Sample size and power for treatment-naive population evaluation

The sample size is based on the primary efficacy outcome of BCVA mean change from baseline to Week 36. Each RO6867461 dose or dose regimen group (Arms B, C, and D) will be compared to the control group (Arm A).

The power calculation is based on 68 patients randomized to Arm A, and 45 randomized to each of Arms B, C, and D, with drop-out rate of 10%. Assuming a standard deviation of 13.5 letters, this sample size would provide approximately 80% power to detect a true difference of 5.9 letters at the one-sided α level of 10%. The minimum detectable difference would be approximately 3.5 letters.

Sample size and power for anti-VEGF–incomplete-responder population evaluation

The sample size is based on the primary efficacy outcome of BCVA mean change from Week 12 to Week 36 in the subset of anti-VEGF–incomplete-responders, between Arm A and Arm E.

The power calculation is based on 68 patients randomized to both Arms A and E, with 65% meeting the criteria for inclusion in anti-VEGF–incomplete-responder subgroup and a drop-out rate of 10%. Assuming a standard deviation of 9.7 letters, this sample size would provide around 80% power to detect a true difference of 4.7 letters at the one-sided α level of 10%. The minimum detectable difference would be approximately 2.7 letters.

PRIMARY ENDPOINT ANALYSIS

Evaluation in the treatment naive population: The primary efficacy variable is the mean BCVA change from baseline to Week 36. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model.

Evaluation in the anti-VEGF–incomplete-responder population: The primary efficacy variable is the mean BCVA change from Week 12 to Week 36. The primary efficacy analysis will be performed using a MMRM model.

INTERIM ANALYSES

An interim analysis may be conducted to allow for adapting the sample size.

An interim analysis of efficacy may be conducted for administrative reasons.

Up to two additional interim analyses may be conducted for efficacy.

OTHER CONSIDERATIONS

N/A

LIST OF PROHIBITED MEDICATIONS

Concomitant therapy

Patients who use maintenance therapy other than those required to treat *wet AMD (*wAMD*)* should continue its use.

The decision to administer antimicrobial drops before and after the IVT administration is at the discretion of the Investigator.

Excluded 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 either eye, except as required to treat adverse events
- Concurrent use of photocoagulation or photodynamic therapy with verteporfin in the study eye for neovascular AMD

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
bFGF	basic fibroblast growth factor
AST	aspartate aminotransferase
AMD	age-related macular degeneration
Ang-1	angiopoietin-1
Ang-2	angiopoietin-2
AUC	area under the concentration–time curve
BP	blood pressure
BCVA	best corrected visual acuity
CI	confidence interval
CNV	choroidal neovascularization
CSC	central serous chorioretinopathy
CST	central subfield thickness
DBP	diastolic blood pressure
DLE	dose-limiting event
DME	*diabetic macular edema*
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EDI	enhanced depth imaging
ETDRS	early treatment diabetic retinopathy study
Fab	fragment antigen binding
FAF	fundus autofluorescence
FDA	U.S. Food and Drug Administration
FFA	fundus fluorescein angiography
FP	fundus photography
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICGA	indocyanine green angiography
ICH	International Conference on Harmonisation

Abbreviation	Definition
IMC	internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
IVT	intravitreal
IxRS	interactive (voice/web) response system
LLD	low luminance deficit
LLVA	low luminance visual acuity
LPLV	last patient, last visit
LPLO	last patient, last observation
mAb	monoclonal antibody
MAD	multiple ascending dose
MMRM	mixed model for repeated measurement
NOAEL	no observed adverse effect level
PCV	polypoidal choroidal vasculopathy
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PT	prothrombin time
PLGF	placental growth factor
Q8W	every 8 weeks
QT	QT interval
QTc	corrected QT interval
RAP	retinal angiomatous proliferation
RPE	retinal pigment epithelium
SAE	serious adverse event
SAD	single ascending dose
SBP	systolic blood pressure
SD-OCT	spectral domain optical coherence tomography
SoA	Schedule of Assessments
SoC	standard of care
$t_{1/2}$	half-life
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

Abbreviation	Definition
wAMD	wet age-related macular degeneration

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD; alternative name wet AMD [wAMD]) can result in rapid and severe visual impairment and is the leading cause of blindness in people over the age of 50 years living in industrialized countries (Resnikoff et al. 2004; RO6867461 Investigator's Brochure). According to the National Eye Institute, 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 and 3.6 million in 2020 and 2030, respectively. CNV secondary to AMD is characterized by the proliferation of choroidal capillaries that penetrate Bruch's membrane in the form of choroidal neovascular membranes to migrate to the retinal pigment epithelium (RPE), causing a disruption in the outer retinal structure and function.

Existing therapies for CNV secondary to AMD include photodynamic therapy and anti-vascular endothelial growth factor (VEGF)-targeted therapies. Although anti-VEGF therapies have markedly improved the management of these patients and set a new efficacy paradigm in visual gain, they do not significantly improve vision in all patients, induce regression of neovascular membranes, or target all CNV-associated pathologies. Therefore, clinical evaluation of alternative anti-angiogenic targets or mechanisms of action are warranted to improve upon the clinical benefit of approved anti-VEGF therapies.

Angiopoietin-2 (Ang-2) is of key importance in the homeostasis of the vascular compartment, functioning as an antagonist of the Tie-2 receptor tyrosine kinase expressed on endothelial cells. Under hypoxic conditions, Ang-2 acts as a destabilization factor, rendering the vasculature more plastic and amenable to endothelial sprouting. Nonclinical studies show that Ang-2 is an important factor driving neovascular diseases, and potentially acts as a pivotal angiogenic switch in retinal vascular diseases.

1.2 BACKGROUND ON RO6867461

Nonclinical studies have shown that VEGF and Ang-2 act in concert to regulate the vasculature and cooperate to increase retinal EC permeability in vitro. In addition, their vitreous concentration was shown to be both upregulated in diabetic retinopathy, retinal vein occlusion, and, to a lesser extent, in patients with AMD. Therefore, selective neutralization of both VEGF and Ang-2 may further normalize the pathological ocular vasculature in comparison with the current standard of care (SoC), anti-VEGF therapies alone.

RO6867461 is a humanized bispecific immunoglobulin G1 (IgG_1) monoclonal antibody (mAb) that selectively binds VEGF-A and Ang-2. The VEGF-binding fragment antigen binding (Fab) binds VEGF with high affinity, comparable to other anti-VEGF treatments

(e.g., ranibizumab [Lucentis®]), and the Ang-2-binding Fab binds Ang-2, also with high affinity. In vivo pharmacological evaluations in spontaneous and induced mouse and non-human primate models of neovascularization have confirmed the beneficial effects of RO6867461 in the reduction of CNV.

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

1.2.1 Previous Nonclinical Studies

Pharmacological studies were performed in vitro and in vivo to investigate the target binding affinity, specificity, and biological activity of RO6867461. In vitro studies demonstrated that RO6867461 binds the target molecules VEGF and Ang-2 with high affinity. Mutations in the Fc region of RO6867461 abolish binding to Fcγ receptors, located on effector cells, and the neonatal Fc receptor (FcRn).

Pharmacological evaluation in vivo demonstrated that RO6867461 reduces the formation of CNV, the leakiness of existing CNV lesions, and subsequent injury to the retina due to lesion formation in a mutant mouse model of early bilateral CNV and a laser-induced model of CNV in cynomolgus monkeys (RO6867461 Investigator's Brochure)

Following single intravitreal (IVT) administration of 1.5 mg/eye RO6867461 in cynomolgus monkeys, flip-flop pharmacokinetics were observed with a strong correlation between exposure in vitreous humor, aqueous humor, and systemic circulation; with systemic bioavailability of 13%.

In a 2-month Good Laboratory Practice (GLP) study in cynomolgus monkeys, the ocular and extra-ocular findings following three IVT injections of the highest 3 and 6 mg/eye/dose were consistent with an immune-mediated response to a humanized antibody, like RO6867461, in nonhuman primates. The no-observed-adverse-effect level (NOAEL) was established at a dose of 1.5 mg/eye/dose for IVT administration.

In a 6-month GLP study in cynomolgus monkeys, no changes were observed following seven IVT injections every 4 weeks at the low dose of 0.5 mg/eye/dose comprising the NOAEL. Dose-dependent ocular inflammatory cell infiltration and clinical signs of ocular inflammation occurred in RO6867461-treated eyes at 1.5 or 1.5/3 mg/eye/dose IVT following the same dosing schedule. Ocular findings generally correlated with the systemic presence of anti-drug antibodies (ADAs) against RO6867461 and exposure loss in the serum of all animals. Immunohistochemistry detection of immune-complex deposits in the affected eyes of RO6867461-treated animals is currently ongoing.

RO6867461 did not induce any neurological (CNS) findings or effects on heart rate/electrocardiogram (ECG) endpoints (including QT and QTc [corrected QT interval]), respiratory rate, or body temperature in cynomolgus monkeys up to 6 months treatment.

See the RO6867461 Investigator's Brochure for details on nonclinical studies.

1.2.2 Previous Clinical Studies

A multicenter Phase I, open-label, single- and multiple-ascending-dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO6867461 administered IVT in patients with wAMD is currently ongoing (BP28936). Patients with CNV secondary to AMD previously treated with ≥ 3 administrations of anti-VEGF medications within the last 6 months were enrolled.

In Part A, single-ascending dose (SAD), single IVT doses of 0.5, 1.5, 3, or 6 mg were administered to a total of 12 patients (n = 3/dose). In Part B, multiple-ascending dose (MAD), 3 IVT doses of 3 or 6 mg were administered 4 weeks apart to a total of 12 patients (n = 6/dose). All patients in the SAD group (Part A) and the 3 mg MAD group of Part B completed the study. All patients of the 6 mg MAD group completed dosing and at least the Day 84 visit data (4 weeks after last dose) were available as of 2 January, 2015 (data cutoff date).

The plasma concentration-time profiles showed an approximately dose-proportional increase in drug plasma concentrations up to 3 mg RO6867461. There was no apparent accumulation of plasma concentration following multiple dosing of RO6867461. The estimated median apparent half-life ($t_{1/2}$) ranged from 6 to 11.3 days.

While the study was not designed to investigate efficacy of RO6867461, positive trends in best corrected visual acuity (BCVA) and mean central subfield thickness (CST) on spectral domain optical coherence tomography (SD-OCT) were observed.

Please refer to the RO6867461 Investigator's Brochure for details on Study BP28936.

A multicenter, Phase II study to investigate the safety, tolerability, pharmacokinetics, and efficacy of RO6867461 administered IVT in patients with diabetic macular edema (DME) is ongoing (Study BP30099 – BOULEVARD; clinicaltrials.gov: NCT02699450).

Ongoing review of masked safety data from the ongoing AVENUE study indicates that so far, the side effects observed in patients with choroidal neovascularization (CMV) due to age related macular degeneration (AMD) who are treated with IVT administration of RO6867461 are consistent with safety profile observed in Study BP28936; adverse events which are associated with IVT procedure; or natural progression of the disease. At present no new or unexpected safety signals have been identified in AVENUE study.

1.2.2.1 Safety and Tolerability

Single and multiple administrations of RO6867461 were well tolerated up to the highest tested dose of 6 mg single dose and 6 mg multiple dose in patients with CNV secondary to AMD (Table 1). No deaths and no dose-limiting events (DLEs) were reported.

One serious adverse event has been reported to date, which was non-ocular, and was considered unrelated to the study drug by the Principal Investigator (PI). One patient from the 3 mg dose group of Part A was withdrawn from the study because of an adverse event (see RO6867461 Investigator's Brochure for further details).

Table 1 Overall Adverse Event profile for all Patients Enrolled in Study BP28936

	0.5 mg (SAD) (n=3)	1.5 mg (SAD) (n=3)	3 mg (SAD) (n=3)	3 mg (MAD) (n=6)	6 mg (SAD) (n=3)	6 mg (MAD) (n=6)
Total number of patients with at least one AE	0	2 (67%)	3 (100%)	5 (83%)	2 (67%)	2 (33%)
Total number of events	0	5	12	19	10	3
Total number of patients with at least one:	—	—	—	—	—	—
AE with fatal outcome	0	0	0	0	0	0
Serious AE	0	1 (33%)	0	0	0	0
Related Serious AE	0	0	0	0	0	0
Related AE	0	0	1 (33%)	0	0	1 (17%)
Ocular AEs	0	1 (33%)	2 (67%)	4 (67%)	2 (67%)	1 (17%)
Ocular AEs study eye	0	0	2 (67%)	4 (67%)	2 (67%)	1 (17%)
Ocular AEs non-study eye	0	1 (33%)	2 (67%)	1 (17%)	0	1 (17%)
Sight-threatening AE	0	0	0	0	0	0

AE = adverse event; MAD = multiple-ascending dose; SAD = single-ascending dose.
Notes: Percentages are based on n.
Multiple occurrences of the same event in one individual counted only once.
6 mg MAD group incomplete (data cutoff: 2 January 2015)

1.2.2.2 Pharmacokinetics

Plasma RO6867461 concentrations were available for all patients from the SAD part of the study. As of the 2 January 2015 data cut-off, all RO6867461 plasma concentrations of the 3 mg MAD group were available and up to Day 35 of the 6 mg group.

The plasma concentration-time profiles showed an approximately dose-proportional increase in drug plasma concentrations up to 3 mg RO6867461. There was no apparent accumulation of plasma concentration following multiple dosing of RO6867461. The estimated median apparent $t_{1/2}$ ranged from 6 to 11.3 days.

1.2.2.3 Functional and Anatomical Pharmacodynamics

A positive trend for BCVA was observed in the study. In the SAD part, a median 7 letter (range: 0 to 18; n = 11) improvement on Day 28 across all patients was observed. For the patients in the MAD part, no change in mean BCVA was observed at 3 mg RO6867461. However, for patients treated with 6 mg RO6867461, a positive trend for BCVA was observed following the second and third administrations, with a median BCVA increase 28 days after the first, second, and third administration of 0.5, 3, and 7.5 letters, respectively.

The positive BCVA trend was correlated with a positive trend for a reduction in CST on SD-OCT. In Part A (SAD), a median -42 μm change from baseline, pooled for all dose levels (per-protocol population, n = 11), was observed on Day 28. For the patients in the 3 mg MAD group, a median change from baseline of -13.5 μm, –25.0 μm, and -9.0 μm change from baseline at 28 days after the first, second, and third drug administration, respectively. Patients in the 6 mg MAD group showed a consistent and durable trend for a reduction in CST, with an overall comparable magnitude as compared to the SAD group. The median CST change from baseline was -79.5 μm, -86 μm, and -126 μm at 28 days after the first, second, and third drug administration, respectively.

There was no overall apparent change in the fundus fluorescein angiography (FFA) but a single reader assessment will be carried out to ensure a consistent evaluation.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

There are limited clinical efficacy evaluations with anti-Ang-2 approaches in patients with retinal disease. The Phase I RO6867461 study, which included a small number of patients, showed good tolerability and safety profile and supportive signs of pharmacodynamic (PD) activity in a population of previously-treated patients with CNV secondary to AMD. Taken together, the overall risk-benefit assessment is therefore favorable and justifies evaluation of RO6867461 efficacy over SoC therapy in patients with CNV secondary to AMD.

Nonclinical toxicology studies (Section 1.2.1) 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 CNV secondary to AMD.

When administered locally, RO6867461 was well tolerated up to the highest dose tested of 6 mg in previously treated patients with CNV secondary to AMD. No DLEs or unexpected ocular adverse events were observed. This safety/tolerability study did not raise any flags regarding systemic safety, drug-related serious adverse events, or severe adverse events.

This will be a Phase II proof-of-concept study in treatment-naive and anti-VEGF–incomplete-responder patients with CNV secondary to AMD. This study is

designed to evaluate the effects of RO6867461 on visual function and retinal structure by assessing changes from baseline in BCVA and imaging procedures, respectively. In addition, the safety, tolerability, and pharmacokinetics will be evaluated in patients receiving up to 9 doses of RO6867461.

Patients who will be enrolled in the proposed study will fulfill the inclusion/exclusion criteria and will be monitored according to the protocol. Detailed instructions on dosage, preparation, and administration of RO6867461 are provided in the protocol, and patients will be cautioned and intensively monitored as described. Symptomatic treatment will be administered as necessary.

Patients will be carefully monitored for potential serious ocular risks associated with the IVT injection procedure and for other potential systemic effects associated with the IVT administration of VEGF inhibitors (refer to RO6867461 Investigator's Brochure) and managed as appropriate.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the efficacy of RO6867461 compared to monotherapy in treatment-naive and anti-VEGF–incomplete-responder patients with CNV secondary to AMD

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

- To assess the safety of multiple IVT doses of RO6867461
- To assess systemic pharmacokinetics of RO6867461
- To investigate pharmacodynamics and anatomical outcomes informing on the mechanism of action of RO6867461

  To investigate the formation of plasma anti-RO6867461 antibodies
- To investigate 2 different RO6867461 dosing regimens

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- To evaluate RO6867461 effects on plasma levels of markers of angiogenesis and inflammation
- To investigate RO6867461 concentration and, if sample volume allows, inflammatory and pro-angiogenic factors, in aqueous humor samples (optional) and vitreous (optional)

- To evaluate the effect of genetic polymorphisms in genes associated with AMD and/or involved in angiogenesis and response to RO6867461

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a multiple-center, multiple-dose and regimen, randomized, active comparator controlled, double-masked, five parallel group, 36-week study in patients with CNV secondary to AMD.

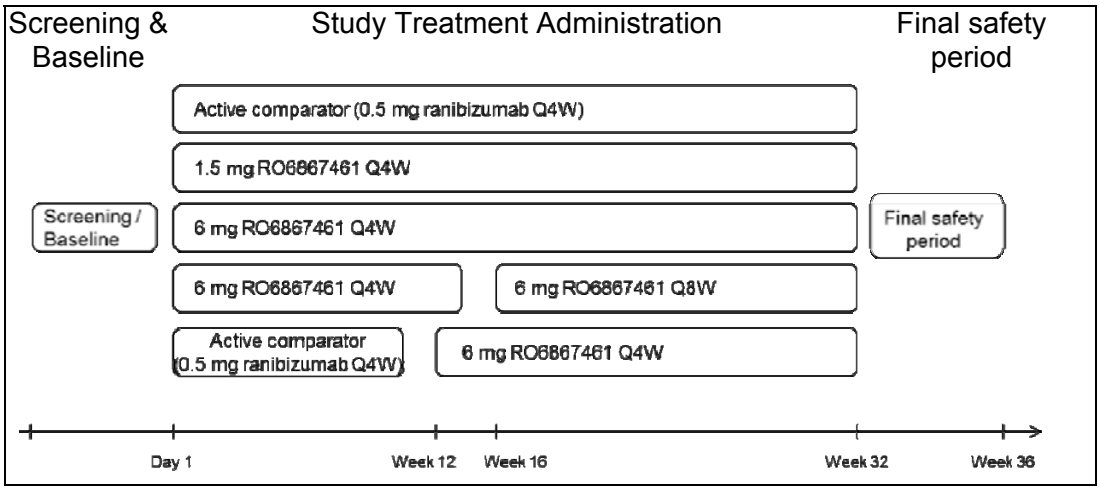
3.1.1 Overview of Study Design

The five groups of this study (Figure 1) are as follows.

- Arm A: 0.5 mg ranibizumab IVT every 4 weeks for 32 weeks (9 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm D: 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 8 weeks (i.e., on Weeks 20 and 28; 2 injections)
- Arm E: 0.5 mg ranibizumab IVT every 4 weeks up to Week 8 (3 injections), followed by 6 mg RO6867461 IVT every 4 weeks (6 injections)

The study will allow evaluation of RO6867461 in a treatment-naive patient population (comparison of Arms A, B, C, and D) and an anti-VEGF–incomplete-responder patient population that meets a predefined criterion at Week 12 (comparison between Arms A and E). Only one eye will be chosen as the study eye.

Figure 1 Study Design



Q4W = every 4 weeks; Q8W = every 8 weeks

The total duration of the study for each patient will be up to 40 weeks, divided as follows:

- Screening: up to 4 weeks
- Baseline: Day 1
- Study Treatment Administration: from Day 1 to Week 32
- Final safety and efficacy period: from Week 32 to Week 36

Patients will be admitted to the investigational site on Day 1 and for subsequent scheduled visits, and will be discharged the same day after all mandatory and safety assessments as specified in Schedule of Assessments (SoA) are completed.

If a site has an unexpected issue (e.g., interactive voice and web response system [*IxRS*] *is not able to assign the study kit, or the study treatment administration cannot be done on the same day due to unavailability of the unmasked investigators at the site), the patient's study treatment may be administered within 3 working days of the scheduled treatment visit with the Medical Monitor's permission.*

The interval between two study treatment administrations needs to be at least 21 days.

3.1.2 Number of Patients

In the initial recruitment period, up to 271 patients with CNV secondary to AMD are expected to be enrolled in the study. Up to 45 (Arms B, C, and D) or 68 (Arms A and E) patients are expected to be randomized per arm of the study (3:2:2:2:3 randomization scheme) in this initial recruitment period.

The Roche Internal Monitoring Committee (IMC; see Section 3.1.3) may conduct an interim analysis at approximately 1 to 3 months before the end of the initial recruitment period to determine the proportion of patients meeting the criterion for anti-VEGF–incomplete-responder at Week 12 (Section 3.2) in Arms A and E. The IMC may recommend adapting the recruitment up to a maximum of 343 patients in order to have approximately 80 patients in the anti-VEGF–incomplete-responder subgroup completing the study. The same 3:2:2:2:3 randomization scheme will be applied in any extension recruitment period.

Further details on this possible interim analysis will be provided separately in the IMC agreement.

3.1.3 Internal Monitoring Committee

The Roche IMC will be responsible in the event of an interim analysis for sample size evaluation (Section 3.1.2), operational/administrative purposes, and/or for safety data monitoring. For other objectives, the IMC will review the safety data and will be responsible for evaluating efficacy data for instance where assessment of benefit-risk is

warranted. These analyses will take place at pre-defined time-points or on an ad-hoc basis.

The IMC consists of a selected subset of Roche representatives including Statistician, Safety Representative, Clinical Science Representative, Clinical Pharmacology Representative, and Pharmacometrician. 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 might 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 agreement.

3.1.4 End of Study

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur 36 weeks after the last patient is enrolled.

3.2 RATIONALE FOR STUDY DESIGN

A multiple center, double-masked, randomized, comparator controlled trial design was selected to allow for an unbiased evaluation of RO6867461 as a treatment for patients with CNV secondary to AMD.

The study will allow evaluation of the efficacy of RO6867461 in treatment-naive patients (including 2 dose levels and 2 dose regimens) and patients who are switched to RO6867461 treatment after 3 administrations of ranibizumab. The latter group will allow for the assessment of RO6867461 in an anti-VEGF–incomplete-responder population using a predefined criterion based on a traditional secondary efficacy outcome in the target population (Sections 3.3.3.2 and 6.6.1.2):

- Patients with BCVA ≤68 letters at Week 12

The double-masked design is achieved through the strict independence of the pharmacists (or designated personnel) and Investigators who are preparing and administering study treatment, from the assessing Investigators and remaining site personnel.

Sham administration will be delivered to patients in Arm D at Weeks 16, 24, and 32 to maintain double-masking throughout the study period.

To ensure the safety of all patients during the conduct of the study, several safety assessments have been included: e.g., regular ophthalmological monitoring (ocular safety panel and SD-OCT assessments), adverse events monitoring (systemic and ophthalmologic), vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate), and laboratory safety tests.

Optional aqueous humor samples will be collected in consenting patients with an aim to further understand the ocular pharmacokinetics of RO6867461 and assess biomarkers (see Section 4.6.2). Single (Krohne et al. 2012) and multiple (Campochiaro et al. 2013) aqueous humor sampling has been instrumental in the understanding of ocular pharmacokinetics.

3.2.1 Rationale for Dosage Selection

The 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. 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 dose of 1.5 mg RO6867461 was selected based on its equivalent anti-VEGF dose to ranibizumab due to the 3-fold higher molecular weight of the IgG antibody, RO6867461, as compared to the antibody fragment ranibizumab.

The dose of 6 mg RO6867461 was selected as the highest feasible dose of RO6867461 in the first-in-human study. 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 BP28936 did not reveal a safety signal following 3-monthly IVT doses of up to 6 mg RO6867461 ($n=6$) in patients with CNV secondary to AMD. The 6-month GLP toxicity study tested RO6867461 up to the 3 mg dose level, seven times every 4 weeks, intravitreally. 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 intravitreal initial concentrations as compared to humans. Of note, the clinical 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 and 6 mg RO6867461 doses, respectively. The formulation for the present study protocol utilizes a 120 mg/mL highest concentration, which translates to a 50 μL injection volume for the 6 mg RO6867461 dose. However, this difference in concentration injected intravitreally is covered by the higher concentration achieved in the monkey eye as discussed above.

Systemic exposure observed in patients following IVT administration is lower as compared to exposures observed in the cynomolgus monkey GLP toxicity study.

Taken together, the nonclinical and clinical data suggest that the selected doses of 1.5 and 6 mg RO6867461 administered every 4 weeks were safe and tolerated and allow a further testing in a 36-week clinical study.

3.2.2 Rationale for Study Population

This study will be conducted in patients with treatment-naive CNV secondary to AMD, who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (Section 4.2.1 and Section 4.2.2).

3.2.3 Rationale for Control Group

This study is an interventional superiority study aiming to evaluate the efficacy of RO6867461 in treatment-naive and in anti-VEGF–incomplete-responder patients. Anti-VEGF therapy is a well-established SoC in the target population, and placebo is no longer an ethically acceptable alternative.

Ranibizumab was the first approved treatment demonstrating improvement of visual acuity (VA) in patients with CNV secondary to AMD. Aflibercept demonstrated non-inferiority to ranibizumab in the target population (Heier et al. 2012; Schmidt-Erfurth et al. 2014), and is currently administered in medical practice with similar frequency as ranibizumab in many countries including the United States (Turpcu et al. 2014).

In clinical studies aimed at evaluating dosing regimens of ranibizumab, a fixed treatment regimen every 4 weeks consistently showed a BCVA improvement of 1–2 letters above an as needed regimen at 12–24 months, although the difference was either non-significant (Busbee et al. 2013) or treatment regimen were non-inferior (The CATT Research Group, 2011).

Therefore, we selected the ranibizumab every 4 week regimen as an optimal comparator control for a superior efficacy design in the target population.

3.2.4 Rationale for Biomarker Assessments

Several biochemical and biological processes such as angiogenesis, inflammation, and oxidative stress are known to play a role in the pathogenesis of AMD (The CATT Research Group, 2011; Turpcu et al. 2014). Moreover, several genetic polymorphisms have been shown to be strongly associated with AMD prevalence and progression.

Therefore, both genetic markers and protein biomarkers of pathways involved in these processes may be analyzed to improve the understanding of the patients' response to RO6867461 treatment. The molecular targets of RO6867461 (VEGF and Ang-2) will be measured in the systemic circulation and, if possible, in aqueous and vitreous humor. Other biomarkers of angiogenesis that may be measured are: angiopoietin-1 (Ang-1), vascular endothelial growth factor receptor (VEGFR), Tie-2, placental growth factor (PLGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF). Furthermore, biomarkers of inflammation and oxidative stress may be measured in plasma and, if possible, in aqueous humor.

Genetic polymorphisms associated with AMD (e.g., AMRS2, HTRA1, CFH, and C3) as well as related to angiogenesis (e.g., VEGFA, VEGFR2, Ang-2, and Tie-2) may be analyzed.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Any relevant safety observations derived from BCVA (modified early treatment diabetic retinopathy study [ETDRS] charts), slit lamp examination, dilated binocular indirect high-magnification ophthalmoscopy, intraocular pressure (IOP), fundus photography (FP), SD-OCT, and angiography
- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- Incidence of anti-RO6867461 antibodies
- ECGs
- Vital signs

3.3.2 Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are as follows:

- PK profiles and parameters derived from the nonlinear mixed effects modeling approach following IVT administration of RO6867461, including the following parameters:

  Primary parameters: CL and V

  Secondary parameters: C_{max}, AUC_{inf}, $AUC_{0-\tau}$, t_{max}, $t_{1/2}$

  Compartmental analysis to assess IVT concentrations, as appropriate (exploratory)

  RO6867461 concentrations in aqueous humor samples for patients who provide additional consent to participate (exploratory)

3.3.3 Efficacy and Pharmacodynamic Outcome Measures

For the evaluation in the treatment-naive population, the baseline measurement is the latest non-missing observation before the first dose of study medication. For the evaluation in the anti-VEGF–incomplete-responder population, the baseline is the observation from Study Week 12.

3.3.3.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measure is the mean change from baseline in BCVA at Week 36 using the ETDRS modified charts.

3.3.3.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures include functional (BCVA) and anatomical PD imaging measures relevant to the mechanism of action of RO6867461 as follows.

BCVA:

- Proportion of patients gaining $\geq$15 letters from baseline in BCVA at Week 36
- Proportion of patients with BCVA of 20/40 or better at Week 36
- Proportion of patients with BCVA of 20/200 or worse at Week 36

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 36
- Mean change from baseline in mean CST (1 mm diameter) at Week 36
- Proportion of patients with no intraretinal fluid, subretinal fluid, cysts, or pigment epithelial detachment at Week 36

Anatomic outcome measures by FFA:

- Mean change from baseline in total area of CNV at Week 36
- Mean change from baseline in total area of CNV component at Week 36
- Mean change from baseline in total area of leakage at Week 36

3.3.3.3 Pharmacodynamic Biomarker Outcome Measures

Plasma biomarker outcome measures for this study are as follows:

- Change in plasma levels of VEGF and Ang-2

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures for this study include but are not limited to the following:

- Biomarkers in plasma related to angiogenesis and inflammation, including but not limited to Ang-1, Tie-2, VEGFR, PLGF, bFGF, PDGF, IL-1b, IL-6, eotaxin, autotaxin
- Pro-angiogenic factors in aqueous humor and vitreous samples for patients who provide additional consent to participate.

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study to be conducted in the United States. Additional site(s) will be included for back-up purposes and may be activated if needed. The site Investigators will be qualified ophthalmologists/retinal specialists.

Administrative and Contact Information and List of Investigators are provided separately.

4.2 STUDY POPULATION

Patients with CNV secondary to AMD who fulfill all the inclusion criteria listed in Section 4.2.1 will be enrolled in the study. Patients meeting one or more of the conditions listed in Section 4.2.2 will be excluded from the study. Written informed consent will be obtained before initiation of any study procedure.

4.2.1 Inclusion Criteria

Patients must meet the following criteria at study entry.

Ocular Criteria for Study Eye:

- Treatment-naive with CNV secondary to AMD**,** with 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)
- BCVA letter score of 73 to 24 letters (inclusive) on ETDRS-like charts (20/40 to 20/320 Snellen equivalent) on Day 1. Proportion of patients with BCVA letter score of 73 to 69 letters inclusive (20/40 Snellen equivalent) on Day 1 will be limited to a maximum of 40% of the planned sample size
- CNV lesion of all types (predominantly classic, minimally classic, or occult) with:

  Total lesion size (including blood, atrophy, fibrosis, and neovascularization) of $\leq$6 disc areas (DAs) by FFA

  CNV component area of $\geq$50% of total lesion size by FFA

  Active CNV confirmed by FFA (evidence of leakage)

  CNV exudation confirmed by SD-OCT (presence of fluid)
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

General Criteria:

- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonization (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to the ICH and local regulations
- Age $\geq$50 years

- For women who are not postmenopausal (i.e., $\geq$12 months of non-therapy–induced amenorrhea or surgically sterile (absence of ovaries and/or uterus) agreement to remain abstinent or use combined contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and at least through Week 36.

  Examples of contraceptive methods with an expected failure rate of $<$1% per year include male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $<$1% per year, barrier methods must always be supplemented with the use of a spermicide.
- Males must agree to use a barrier method of contraception starting from first treatment administration for at least 2 months post-last treatment administration
- 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

4.2.2 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 (CSC) 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, transplasminogen 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
- 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, epiretinal membrane with traction, etc.) that, in the opinion of the Investigator, could either reduce the potential for visual improvement or require medical or surgical intervention
- Active intraocular inflammation (grade trace or above) *in the study eye*
- Current vitreous hemorrhage *in the study eye*
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP $\geq$25 mmHg despite treatment with anti-glaucoma medication) *in the study eye*
- Spherical equivalent of the 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*

General Criteria:

- Any major illness or surgical procedure within one month before the screening examination
- Patients with glycosylated hemoglobin HbA1C $>$7.5%
- 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 *either* 30 or more minutes 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 within 12 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding 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
- For females of childbearing potential, a positive blood pregnancy test
- Lactating women
- Known hypersensitivity to ranibizumab, fluorescein, indocyanine green, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used
- Any other restriction accorded to the use of
- Any treatment with an IMP in the 3 months prior to Day 1

4.3 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.3.1 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 (Section 4.2.1 and Section 4.2.2) at the screening and for selected criteria at the Day 1 visit (first study treatment) prior to randomization (Section 4.6.6.1). As part of the screening process, FP, fundus autofluorescence (FAF), FFA, indocyanine green angiography (ICGA), and SD-OCT will be transferred to the central reading center, and a set of images will be evaluated to provide an objective, masked assessment of certain eligibility criteria.

After all patient eligibility requirements are confirmed on Day 1 visit, including:

- Day 1 baseline BCVA
- Absence of active intraocular inflammation on Day 1 (study eye)
- Absence of febrile illness within one week prior to Day 1,

the site personnel will contact the IxRS for assignment of a patient identification number (a separate number from the screening number).

Patients will be randomized in a 3:2:2:2:3 ratio to one of the study treatment arms:

- Arm A: 0.5 mg ranibizumab IVT every 4 weeks for 32 weeks
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 32 weeks
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 32 weeks
- Arm D: 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 8 weeks (i.e., on Weeks 20 and 28; 2 injections)
- Arm E: 0.5 mg ranibizumab IVT every 4 weeks up to Week 8 (3 injections), followed by 6 mg RO6867461 IVT every 4 weeks (6 injections)

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 the two factors below:

- Presence of retinal angiomatous proliferation (RAP) or polypoidal choroidal vasculopathy (PCV) at screening as assessed by the Reading Center (presence of vs. absence of RAP or PCV)
- Baseline BCVA ETDRS letter score assessed on Day 1 (69 letters or better vs. 68 letters or worse)

Randomization with fixed permuted blocks will be used to obtain an approximate 3:2:2:2:3 ratio between the different arms within each stratum.

4.3.2 Treatment Administration Procedure

Study drug will be administered IVT. The procedures are detailed in Appendix 4 and the Pharmacy Manual. Sham will be used per the instructions in Section 4.4.1.3.

At the discretion of the Investigator, the sites may use either propacaine- or tetracaine-based ophthalmic drops, or subconjunctival injection of lidocaine. All efforts should be made to maintain the same anesthetic procedure throughout the study for a given patient to minimize bias and the risk of unmasking.

At the discretion of the Investigator, the patient may self-administer ophthalmic broad-spectrum antimicrobial drops before and/or after study treatment administration.

4.3.3 Masking

This is a double-masked study. There must be a minimum of two Investigators per site to fulfill the masking requirements of this study. *All efforts should be made to schedule study visits* when both Investigators are present. At least one Investigator will be designated as the assessor physician who will be masked to patients' treatment assignment and will evaluate all ocular assessments. At least one other Investigator (and designated, unmasked assistant, as needed) will be designated as the treatment administrator physician who will be unmasked to patients' treatment assignment and will administer study treatment (RO6867461, comparator, or sham).

Once the designated roles are determined, *unmasked study personnel cannot switch to a masked role during the conduct of the study. Switching from a masked to an unmasked role would be possible and would be documented in the delegation log*. In the event an alternate Investigator needs to be substituted for an Investigator, that alternate physician may assume only one role (i.e., treatment administrator physician or assessor physician) for the duration of the study. The treatment administrator physician(s) performing the study treatment administration must not be involved in any other aspect of the study in any way and must not divulge treatment assignment to anyone.

Patients, study site personnel (with the exception of the treatment administrator physician[s], assistant[s], and pharmacist or designated personnel, if any), the designated assessor physician(s), Central Reading Center personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) will be masked to treatment assignment.

Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There must be no more than five unmasked personnel at an investigative site at one time. *Under certain circumstances, the total number of unmasked personnel might be increased after discussion and approval by Sponsor.* For the duration of the study, the patient treatment assignment will not be unmasked unless required for patient safety.

All study visit assessments, except those at screening, should be performed by masked site personnel only. The unmasked treatment administrator physician will perform the injection of study treatment, and may also perform the post-treatment administration vision testing (finger counting and, if applicable, hand movement and/or light perception).

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.

IMC members (see Section 3.1.3) will be unmasked at the treatment group level. The IMC agreement will also identify individuals unmasked at the individual patient level for safety analysis and for the purpose of preparing summary data display for the IMC meeting. Other Roche Study Management Team members will remain masked throughout the study.

4.3.4 Emergency Unmasking

If unmasking is necessary for patient management (e.g., in the case of a serious adverse event), the Investigator will be able to break the treatment code by contacting the IxRS system. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study treatment for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document all details and provide an explanation for any premature unmasking (e.g., accidental unmasking or unmasking due to serious adverse events).

Sponsor might become unmasked to study treatment in the event of a serious adverse event reporting.

As per health authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (see Section 5.1) that are considered by the Investigator to be related to study drug.

4.4 STUDY TREATMENT

In this protocol, study treatment includes IVT administration of study drugs (RO6867461 and active comparator ranibizumab) and sham IVT administration. The latter is used to maintain double masking on Arm D throughout the fixed every 8 weeks (Q8W) regimen period.

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 RO6867461 and Placebo

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.

Placebo will be provided with a nominal 1.0 mL fill of a sterile, colorless to slightly brownish, preservative-free liquid solution in 2 mL single-use vials, containing L-histidine/HCl buffer solution (approximately pH 6.0), sodium chloride, sucrose, and polysorbate 20 (excipient composition of the placebo is same as for RO6867461 Drug Product).

In this study, Placebo will only be used for dilution of RO6867461 Drug Product to the appropriate clinical dose. Detailed dilution instructions are provided separately in the Pharmacy Manual.

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

RO6867461 Drug Product and Placebo 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 and Placebo will be in accordance with Roche standard and local regulations.

RO6867461 Drug Product and Placebo 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 IB.

4.4.1.2 Ranibizumab (Active 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.

4.4.1.3 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 (Appendix 4). 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.

4.4.2 Dosage, Administration, and Compliance

4.4.2.1 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 in the Overview of Study Design (Section 3.1.1).

- Arm A: 0.5 mg ranibizumab IVT every 4 weeks for 32 weeks (9 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 32 weeks (9 injections)
- Arm D: 6 mg RO6867461 IVT every 4 weeks up to Week 12 (4 injections), followed by 6 mg RO6867461 IVT every 8 weeks (i.e.: on Weeks 20 and 28; 2 injections)
- Arm E: 0.5 mg ranibizumab IVT every 4 weeks up to Week 8 (3 injections), followed by 6 mg RO6867461 IVT every 4 weeks (6 injections)

Only one eye will be chosen as the study eye.

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

For the 6 mg dose, RO6867461 is administered without dilution whereas for the 1.5 mg dose, RO6867461 must be diluted with Placebo provided by the Sponsor to the appropriate dose, as described in the Pharmacy Manual.

Table 2 *Dosage Strengths and Dilution*

Drug	*Clinical Dose*	*Dilution with Placebo Required (Yes/No/NA)*	*Administered Volume for IVT treatment*
RO6867461	*1.5 mg*	*Yes*	*50 µL*
RO6867461	*6 mg*	*No*	*50 µL*
Ranibizumab	*0.5 mg*	*NA*	*50 µL*

NA =not applicable; IVT =intravitreal.

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 4*.

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 dilute/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 placebo, and vials of ranibizumab are for single-use only (one injection preparation per patient per eye). Vials used for one patient must not be used for any other patient. Partially used vials, left over RO6867461 Drug Product, placebo, or ranibizumab vials as well as administration material must not be re-used. Only provided placebo vials should be used for dilutions and dose preparation should always be performed as per the instructions in the Pharmacy Manual. Dilution procedure with placebo or concentrations to adjust the doses should not be changed without prior approval from the Sponsor.

4.4.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO6867461 [including placebo for dilution] and ranibizumab) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of the treatment under investigation. Adequate records of the receipt (e.g., Treatment Receipt Record) and dispensing (e.g.Treatment Dispensing Log) of the study treatment must be maintained. The Treatment Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study treatment was dispensed (for example patient initials and date of birth)
- The date(s) and the quantity of the study drug dispensed to the patient

- All records and treatment supplies must be available for inspection by the Roche Monitor

IMPs will either be disposed at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed and provided that adequate storage and integrity of drug has been confirmed. Written authorization must be obtained from the Sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity kit numbers of investigational products destroyed
- Quantity of investigational product[s] destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person or company who destroyed investigational products

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

4.4.4 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 (Section 4.4.3).

4.4.5 Post-Trial Access to RO6867461

RO6867461 is an IMP product which safety and tolerability is under evaluation in an indication where alternative SoC treatments are available. Patients will not be allowed access to RO6867461 after study completion.

4.5 CONCOMITANT THERAPY

4.5.1 Concomitant Therapy

Patients who use maintenance therapy other than those required to treat CNV secondary to AMD should continue its use.

Concomitant medications are any prescription drugs or over-the-counter preparations (including but not limited to vitamins) other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dye, etc.) and pre- and post-treatment administration medications (e.g., propacaine, antimicrobials, etc.) used by a patient within 7 days preceding Day 1 until conclusion of the patient's study participation (Week 36) or early termination visit. Administration of antimicrobials four times daily for 3 days before and after the IVT administration may be prescribed at the discretion of the Investigator. Where antimicrobials are administered, it must be recorded on the concomitant medication forms of the electronic Case Report Form (eCRF).

All concomitant medications should be reported to the Investigator and recorded on the appropriate section of the eCRF.

4.5.2 Excluded Therapy

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

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

4.5.3 CNV Secondary to AMD in the Fellow Eye

Should CNV secondary to AMD emerge or recur and require treatment in the fellow eye during the study period, the patient may receive anti-VEGF SoC treatment.

When treatment in the fellow eye is scheduled on the same day than 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 may 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).*

This treatment also may be provided by the site through commercial supplies. However, commercial supplies will not be reimbursed by the sponsor.

4.6 STUDY ASSESSMENTS

All examinations listed below will be performed according to the SoA outlined in Appendix 1 and Appendix 2 .

At time-points 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)*:

- Triplicate 12-lead ECG: *mandatory to be performed as early as possible, before patient is exhausted, and before blood sampling*
- 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: At screening and Day 1 visits, BCVA can be performed before 12-lead ECG, 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.

  Low luminance visual acuity (LLVA)

  Slitlamp examination

  Pupil dilation

  SD-OCT

  FAF: *if FAF is performed after FP and/or indirect ophthalmoscopy, the subject should rest in dim light for 10 minutes between procedures*.

  FP (+infrared reflectance)

  FFA

  ICGA

  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)

4.6.1 General Safety Assessments

4.6.1.1 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 and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used

by the patient within 28 days prior to the screening visit *and within the screening period (other than reported to treat an AE as defined in Section 5.3.1)*.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded to allow association with any exploratory genetic risk factors which might be evaluated on patient genetic sample.

4.6.1.2 Physical Examinations

A physical examination will be performed at the time-points indicated in the SoA (Appendix 1 and Appendix 2). Physical examination will include body weight at screening and either final or early termination visit, and height at screening.

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.

4.6.1.3 Vital Signs

BP (SBP and DBP), pulse rate, and body temperature (tympanic or oral) will be recorded at the time-points specified in the SoA (Appendix 1).

BP and pulse rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. All measurements will be obtained from the same arm and, with the same cuff size, using an automatic instrument with a digital readout, throughout the study. To minimize variability, it is important that patient be in a resting position for at least 5 minutes prior to the evaluation. Body position should be consistently maintained for each evaluation. *At the discretion of the Investigator, measurements can be repeated if the values are abnormal.*

4.6.1.4 Electrocardiograms

Triplicate 12-lead ECG (i.e., three useful ECGs without artifacts) will be collected at the time-points specified in SoA (Appendix 1). To minimize variability, it is important that patient be in a resting position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation, mobile phones) should be minimized before and during ECG recording. Triplicate ECGs will be obtained within a 5-minute interval.

Should the time-points coincide, ECGs will be collected before any vital sign measurements or blood sampling. If an ECG is scheduled at the same time as a meal, the ECG must be obtained first.

All ECG recordings must be performed using a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements provided by the ECG Central Reading Center.

Digital ECG recording should be transmitted immediately to the ECG Central Reading Center for interpretation. Investigators or designees must review, sign, and date all ECG reports received from the Central Reading Center, which will be kept as part of the patient's permanent study file at the site.

ECG characteristics, including heart rate, QRS complex duration, and PQ (PR) and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction), QTcF (Fridericia's correction), and RR will be calculated by the Sponsor. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF by investigators or designees. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.5 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts. Laboratory safety tests shall be collected locally at time-points specified in the SoA (Appendix 1).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated to confirm eligibility. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF.

Blood and Urine Sample Collection

Blood and urine samples will be collected for the following clinical laboratory tests:

Hematology	Hemoglobin, hematocrit (HCT), red blood cell 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), erythrocyte sedimentation rate (ESR).
Coagulation (at screening only)	Activated partial thromboplastin time (aPTT) and prothrombin time/International Normalized Ratio (PT/INR).
Blood chemistry	Sodium, potassium, bicarbonate, phosphate, chloride, calcium, urea, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), gamma glutamyl transferase (GGT), total protein, glucose, HbA1C (at screening and at final or early termination visits only), total cholesterol (TC), triglycerides (TG), C-reactive protein (CRP).
Urinalysis	A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, and pH. Microscopy to be performed if abnormalities are observed and deemed necessary by the Investigator or Designee, in particular when blood or protein is positive or strong positive.
Pregnancy test	For females of childbearing potential, serum pregnancy test at screening.

Additional parameters could be assessed if judged to be clinically appropriate by the Investigator and the Scientific Responsible in order to further characterize the safety or PK/PD properties of the drug.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

4.6.1.6 Anti-Drug Antibody Assessments

Blood samples will be obtained for measurement of anti-RO6867461 antibodies by a validated enzyme-linked immunosorbent assay (ELISA).

Any residual material from 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.

This specimen will be destroyed no later than 2 years after the final closure of the clinical database.

4.6.2 Pharmacokinetic Assessments

Details on sampling procedures, sample storage, and shipment are given in the supporting documentation/Lab Manual.

Any residual material from PK samples (blood, aqueous humor, and vitreous humor 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. All PK samples will be destroyed no later than 2 years after the final closure of the clinical database.

Additional PK sampling at unscheduled visits is at the discretion of the Investigator (Section 4.6.6.5).

4.6.2.1 Blood Samples

Blood samples for determination of plasma concentrations of RO6867461 will be collected at time-points specified in the SoA (Appendix 1). *Plasma concentrations of RO6867461 will be measured by a specific validated ELISA method.*

To maintain the double-masked design of the study, blood samples will also be taken from all patients receiving ranibizumab per the RO6867461 schedule. The samples from these patients may or may not be analyzed. Plasma ranibizumab concentrations will be analyzed for patients receiving ranibizumab who also provide consent to AH sampling.

4.6.2.2 Aqueous Humor Samples (optional)

Aqueous humor samples will be collected from all patients who provide additional consent to participate. Where patient consents to aqueous humor sampling, all efforts should be made to collect a baseline aqueous humor sample on Day 1 (pre-dose). The SoA (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 pre-dose assessments have been completed, using an aseptic procedure and sterile field and according to local guidelines.

Samples will be analyzed for RO6867461 and biomarkers (Section 4.6.4.3.4), and may also be analyzed for ranibizumab. This specimen will be destroyed no later than 2 years after the final closure of the clinical database.

4.6.2.3 Unscheduled Collection of Vitreous Samples (optional)

Elective vitrectomy surgery is not allowed in the study eye during study participation; however, if the surgery is medically necessary and a vitreous sample can be obtained from the study eye, ~0.5 mL of undiluted vitreous humor should be collected according to the instructions for aqueous humor sampling and shipped to the Sponsor for measurement of RO6867461 and biomarker concentrations (Section 4.6.4.3.5), and may also be analyzed for ranibizumab. A blood sample (for plasma preparation) should also be collected and shipped to the Sponsor.

The Sponsor should be contacted prior to performing any vitrectomy surgeries in the study eye. This specimen will be destroyed no later than 2 years after the final closure of the clinical database.

4.6.3 Clinical Genotyping (CG) Sample

A mandatory whole blood sample will be taken for DNA extraction from every subject. The DNA may be used to study genes related to AMD (e.g., AMRS2. HTRA1, CFH, C3, etc.) as well as to angiogenesis pathways (e.g., VEGFA, VEGFR2, Ang-2, Tie-2, etc.), and the effect on the PK/PD/efficacy/safety of RO6867461. Data arising from this sample will be subject to the same confidentiality as the rest of the study.

This specimen will be destroyed up to 2 years after the final closure of the clinical database.

4.6.4 Disease-Specific Assessments

Except when noted otherwise (e.g., SoA), all ocular assessments should be performed for both eyes.

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, test images, and systems and software (where applicable) will be certified/validated by the reading center as specified in the Central Reading Center Manual. All ocular images will be obtained only by trained and Central Reading Center certified personnel at the study sites and forwarded to the central reading center for storage and for independent analysis including confirmation of eligibility for defined imaging criteria.

Ocular images to be obtained and forwarded to the Central Reading Center include the following:

- FP
- FAF
- SD-OCT
- FFA

- ICGA

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

For SD-OCT, FP and FAF, images of fellow eyes should only be captured and forwarded to the Central Reading Center at the Screening, and Week 36 or Early termination visits. At all other visits, only the study eye images need to be acquired and forwarded.

SD-OCT must, and where possible FAF, FFA, and ICGA should be collected using Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany), equipped with TrueTrack Active Eye Tracking, AutoRescan, and enhanced deep imaging (EDI).

4.6.4.1 Ocular Safety Assessments

Ocular assessments will be performed as detailed in the SoA (Appendix 1 and Appendix 2) and include:

- BCVA using the ETDRS-like charts (see Section 4.6.4.2); performed prior to dilating eyes.
- Slit lamp examination (scales for grading flare/cells and vitreal hemorrhage density are detailed in Appendix 3)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Retinal imaging: FP, SD-OCT and angiographies
- IOP measurement: If IOP $\geq$30 mmHg at 30 ($\pm$5) minutes post-treatment administration in the study eye, then it should be measured again at 60 ($\pm$10) minutes post-treatment administration.
- Assessment of ocular perfusion performed as soon as possible, but not later than 15 minutes post-injection, using finger counting, hand movement, or light perception as appropriate

4.6.4.2 Efficacy and Pharmacodynamic Assessments

Efficacy and PD assessments will be performed as detailed in the SoA (Appendix 1) and will include functional (BCVA), imaging assessments (SD-OCT, FFA), and plasma PD biomarkers.

Additional PD sampling, functional or imaging assessments can be performed at unscheduled visits at the discretion of the Investigator (Section 4.6.6.5).

4.6.4.2.1 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 VA examiner masked to study 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., Visual acuity 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.

4.6.4.2.2 Spectral Domain Optical Coherence Tomography

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 EDI. Images will be acquired and transferred to the Central Reading Center according specifications provided in the separate "Central Reading Center Procedures Manual". The Heidelberg Eye Explorer (HEYEX) software will be used to review the images at the study site.

4.6.4.2.3 Fundus Fluorescein and Indocyanine Green Angiographies

FFA and ICGA will be performed successively at the study sites by trained and Central Reading Center-certified personnel. Images should be acquired and transferred to the Central Reading Center according to specifications provided in the "Central Reading Center Manual".

4.6.4.2.4 Plasma Pharmacodynamic Biomarkers

Samples for plasma PD biomarkers will be taken at the time-points detailed in the SoA (Appendix 1). The following analyses will be performed:

- Change from baseline in plasma levels of VEGF and Ang-2
- Samples will be destroyed no later than 2 years after the final closure of the clinical database.

4.6.4.3 Exploratory Assessments

4.6.4.3.1 Low Luminescence Visual Acuity

On Day 1, BCVA at a starting test distance of 4 meters under low luminescence (LLVA) will be measured prior to dilating eyes by trained and certified VA examiner masked to study treatment assignment.

LLVA is mandatory at the Day 1 visit only. At the discretion of the Investigator and in agreement with the patient, LLVA (optional) can be assessed at the other time-points detailed in the SoA (Appendix 1). Participation in the optional LLVA assessment will be recorded locally and data entered in the eCRF.

LLVA will be measured by placing a 2.0-log-unit neutral density filter (Kodak Wratten 2.0 Neutral Density Filter) over the best correction for that eye and having the participant read the normally illuminated ETDRS chart (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.

4.6.4.3.2 Fundus Autofluorescence

FAF will be performed at the study sites by trained personnel at the time-points detailed in the SoA (Appendix 1). FAF may be considered as an exploratory safety assessment to monitor progression of atrophy.

4.6.4.3.3 Exploratory Plasma Biomarkers

Samples for exploratory plasma biomarkers will be taken at the time-points detailed in the SoA (Appendix 1). The following exploratory analyses may be performed:

- Levels of Ang-1, Tie-2, VEGFR, PLGF, bFGF, and PDGF, but analyses may also be extended to other disease biomarkers (e.g., cytokines).

Samples will be destroyed no later than 2 years after the final closure of the clinical database and all intended data have been verified.

4.6.4.3.4 Aqueous Humor Samples (optional)

Aqueous humor samples will be analyzed primarily for RO6867461 concentrations *and may also be analyzed for ranibizumab concentrations*, as described in section 4.6.2.2; and the remaining samples may be analyzed for:

- VEGF and Ang-2 concentrations, and possibly other biomarkers

4.6.4.3.5 Vitreous Humor Samples (optional)

Vitreous humor samples will be analyzed primarily for RO6867461 concentrations *and may also be analyzed for ranibizumab concentrations*, as described in Section 4.6.2.3, and the remaining samples may be analyzed for:

- VEGF and Ang-2 concentrations, and possibly other biomarkers

The samples will be destroyed at the latest 2 years after the final closure of the database and finalization of the bioanalytical report

4.6.5 Amount of Blood to be Collected throughout the Study

Throughout the study, a total of approximately 155 mL of blood will be drawn from each subject**,** to perform clinical laboratory assessments, determine plasma concentrations and to perform PD/exploratory assessments.

4.6.6 Timing of Study Assessments

4.6.6.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms of enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment 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.

An Eligibility Screening Form (ESF) 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.

Patients who are willing to participate in the study and have given informed consent will undergo a thorough screening medical examination within 4 weeks before study treatment administration. The list of screening procedures is outlined in the SoA (Appendix 1).

After the screening visit, ocular images *(both eyes)* of the patients who meet all screening eligibility criteria (eligibility for safety labs, pregnancy test where appropriate, and ECG might be pending) as judged by the Investigator will be forwarded as soon as possible to the Central Reading Center. The Central Reading Center will assess the image data submitted and confirm eligibility for study eye imaging criteria. In the event the Central Reading Center does not confirm eligibility, the patient will not be considered for enrollment.

On Day 1 prior to enrollment, the following criteria will need to be assessed:

- Day 1 BCVA eligibility
- Absence of febrile illness in the week prior enrollment
- Absence of intraocular inflammation on Day 1 (study eye)

Patients will be enrolled if they meet all screening and Day 1 eligibility criteria.

Where febrile illness is identified within 6 days of the scheduled Day 1 visit, or on the date of the visit, the Day 1 visit must be rescheduled at the earliest 7 days after the end of the febrile illness episode and no later than 4 weeks after the screening visit.

Patients who failed screening due to:

- *Febrile illness (where "end of febrile illness + 7 days" extends beyond the 4 week screening period)*
- *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*

will be allowed to be re-screened.

4.6.6.2 Assessments during Treatment

Under no circumstances will patients who enroll in this study be permitted to be allocated a new randomization number and re-enroll in the study.

On Day 1, baseline assessments will be conducted on the eligible patients, according to the SoA (Appendix 1 and Appendix 2). Patients will receive their first IVT administration of either RO6867461 or comparator therapy according to the randomization schedule and established standard administration procedures. Patients will return to the eye clinic for study treatment administration (every 4 weeks) and assessments as outlined in the SoA. Patients will be administered the same study treatment throughout the study period, except patients randomized to Arms D and E:

- Patients in Arm D will receive sham administration on Weeks 16, 24, and 32 to maintain the double-masking throughout the Q8W regimen period.
- Patients in Arm E will initially receive 3 injections of ranibizumab followed by 6 injections of RO6867461.

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 using testing finger count vision, or hand motion or light perception as appropriate.

On the day of dosing, IOP will be monitored at 30 minutes post-treatment administration, and if IOP is $\geq$30 mmHg in the study eye, IOP should be re-assessed at 1 hour post-treatment administration. Patients will be discharged at the discretion of the Investigator.

Patients will be instructed to report any signs or symptoms of intraocular inflammation (uveitis) or endophthalmitis which may be a clinical sign and include symptoms such as pain, photophobia, redness, or reduced vision.

4.6.6.3 Assessments at Early Termination Visit

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 monitoring of all adverse events (serious and non-serious), as well as for assessments specified in the early termination visit as outlined in the SoA (Appendix 1 and Appendix 2).

Patients could receive SoC treatment for CNV secondary to AMD after all assessments are completed on early termination visit. SoC treatment after the early termination visit will not be supplied by the Sponsor.

After the early termination visit, adverse events should be followed up as outlined in Section 5.5.1 and Section 5.5.2.

4.6.6.4 Assessments at Final Visit

Patients will return for their final visit with assessments as outlined in the SoA (Appendix 1 and Appendix 2) at Week 36.

Patients can receive SoC treatment for CNV secondary to AMD after all assessments are completed on Week 36. SoC treatment after the final visit will not be supplied by the Sponsor.

After the final visit, adverse events should be followed up as outlined in Section 5.6.

4.6.6.5 Assessments at Unscheduled Visits

Assessments (e.g., for safety or for PK/PD sampling purpose) performed in case of an unscheduled visit(s) are at the discretion of the Investigator.

4.7 PATIENT WITHDRAWAL, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. Reasons for discontinuation of study treatment or 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, including worsening of the disease
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

4.7.1.1 Discontinuation from Study Drug

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+vtritis; see the definition of intraocular inflammation in Section 5.3.5 and grading scales for assessment in Appendix 3)*
- 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 (see Section 4.6.6.3) and may undergo assessments as outlined in the SoA. 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.

4.7.2 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 and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing 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 ICH guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events (AEs), including serious adverse events (SAEs) (systemic and ocular); measurement of protocol−specified safety laboratory assessments; measurement of protocol-specified vital signs (SBP, DBP), ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study (i.e., regular ophthalmological monitoring [ocular safety panel and SD-OCT assessments]).

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

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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, angiography) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- AEs 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).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any adverse event that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death).
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death).

This does not include any AE 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 AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment.
- 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 AE (rated as mild, moderate, or severe); 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 AE recorded on the eCRF.

SAEs 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).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse 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 an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6 (Abnormal Liver Function Tests).*
- *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.

5.1.4 Sight-Threatening Adverse Events (Immediately Reportable to the Sponsor)

An AE is considered to be sight threatening and serious, 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 3
- In the opinion of the Investigator, it may require medical intervention to prevent permanent loss of sight

5.2 SAFETY PLAN

Based on the BP28936 First-in-Human study, there have been no safety signals 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 AEs were of mild and moderate intensity. No deaths occurred during the study period and no premature withdrawals from the study as a result of SAEs were reported.

To ensure the safety of all patients during the conduct of the study, several safety assessments will be performed, including: regular ophthalmological monitoring (ocular safety panel and SD-OCT assessments), AE monitoring (systemic and ophthalmologic), vital signs (SBP, DBP), and laboratory safety tests.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.1.2 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 AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. AEs will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as angiographies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the final visit.

After a period of 28 days from the last dose of study treatment, Investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient-evaluation time-points. 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

Table 3 provides guidance for assessing AE 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 5.1.2).

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 or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug
- Known association of the event with the study treatment 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 AEs 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 AE 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 slit lamp examination that are caused by dilation and are not red blood cells (RBCs) or white blood cells (WBCs) or the result of any ocular disorder should not be recorded as an AE.

Only one AE 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 AEs based on signs and symptoms should be nullified and replaced by one AE 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 Occurring Secondary to Other Events

In general, AEs occurring 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. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent fracture, all three events should be reported separately on the eCRF.

All AEs 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 AE is one that extends continuously, without resolution, between patient-evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- 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
- 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 AE.

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 cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if 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 AE. 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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. Therefore, Investigators must report as an AE 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 SAE.

5.3.5.7 Deaths

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

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 only be used 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 of 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.

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 Systemic or Ocular Medical History eCRF.

A preexisting medical condition should be recorded as an AE 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 Worsening of AMD

Medical occurrences or symptoms of deterioration that are anticipated as part of AMD should be recorded as an AE 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, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious AE (per the definition of SAE in Section 5.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious AEs:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of 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 suffered an AE

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study treatment should be noted on the *Additional Observation* eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious

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).

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 treatment:

- SAEs
- *Non-serious AESI*
- Sight-threatening AEs
- Pregnancies

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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours a day 7 days a week. Medical Monitor contact details are listed in the "Protocol Administrative and Contact Information & List of Investigators".

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of child-bearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 3 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after

learning of the pregnancy. 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.

5.4.2.2 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), 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).

5.4.2.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient 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 or sight-threatening adverse events considered to be related to study treatment 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. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.4.2.

5.5.2 Sponsor Follow-Up

For serious adverse events, *non-serious adverse events of special interest and* sight-threatening adverse events 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 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days) after the last dose of study treatment). However, the Sponsor should be notified if the Investigator becomes aware of any death, other serious adverse event, *non-serious adverse events of special interest,* or sight-threatening adverse events immediately reportable to the Sponsor occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. *The event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event 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 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 I*nvestigator's* B*rochure*
- *Ranibizumab US 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

6.1.1 Sample Size and Power for Treatment-Naive Population Evaluation

The sample size for the treatment-naive population is based on the primary efficacy outcome of mean change in BCVA from baseline to Week 36. Each RO6867461 dose

or dose regimen group (Arms B, C, and D) will be compared to the control group (Arm A).

Consider 68 patients randomized to Arm A and 45 randomized to each of Arms B, C, and D, with a drop-out rate of 10%. Assuming a standard deviation of 13.5 letters, this sample size would provide approximately 80% power to detect a true difference of 5.9 letters at the one-sided α level of 10%. The minimum detectable difference would be approximately 3.5 letters.

6.1.2 Sample Size and Power for Anti-VEGF-Incomplete-Responder Population Evaluation

The sample size for anti-VEGF–incomplete-responder population is based on the primary efficacy outcome of mean change in BCVA from Week 12 to Week 36 in the subset of anti-VEGF–incomplete-responders, between Arm A and Arm E.

Consider 68 patients randomized to both Arms A and E with 65% meeting the criteria for inclusion in anti-VEGF–incomplete-responder subgroup and a drop-out rate of 10%. Assuming a standard deviation of 9.7 letters, this sample size would provide approximately 80% power to detect a true different of 4.8 letters at the one-sided α level of 10%. The minimum detectable difference would be approximately 2.8 letters. If only 50% meet the criteria for inclusion in anti-VEGF–incomplete-responder subgroup, this sample size would provide approximately 80% power to detect a true different of 5.4 letters at the one-sided α level of 10%. The minimum detectable difference would be approximately 3.3 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 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All patients who have received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.

6.3.2 Efficacy, Pharmacokinetic, and Pharmacodynamic Analysis Population

All randomized patients will be included in the efficacy, PK, and PD analysis population.

6.3.2.1 Population A: All Patient Randomized to Arms A, B, C, and D

Population A consists of all patients randomized to the treatment arms A, B, C, and D. In this population, the baseline reference is the latest non-missing observation before start of study treatment. Population A will be used for the evaluation of efficacy in the treatment-naive population.

6.3.2.2 Population B: All Patients Randomized to Arms A and E

Population B consists of all patients randomized to the treatment arms A and E. In this population, the Week 12 visit is the reference for all efficacy and PD analyses. For example, the primary endpoint is BCVA change from Week 12. A subgroup of Population B will be used for the evaluation of efficacy in the anti-VEGF–incomplete-responder population.

6.4 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 using frequency tables and summary statistics providing means, medians, standard deviations, first and third quartiles, and extreme values.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population.

6.5.1 Adverse Events

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. SAEs will be summarized similarly. Adverse events leading to discontinuation from the study will be listed and tabulated.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patient listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

6.5.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests

that include AST, ALT, and alkaline phosphatase and total bilirubin. Given that the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.5.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled “H” for high or “L” for low in Patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the patient’s baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as “HH” for very high or “LL” for very low.

6.5.3 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.5 Anti-Drug Antibody Data Analysis

The number and percentage of patients who test positive for plasma antibodies to RO6867461 at baseline and at the study visits will be tabulated.

6.5.6 Ocular Assessments

Results of the following ocular assessments will be summarized by time-point using descriptive summaries: BCVA, IOP, slit lamp examination, indirect ophthalmoscopy, FFA, ICGA, FP, SD-OCT, and FAF.

6.5.7 Concomitant Medications

The original terms recorded on the patients’ eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 EFFICACY ANALYSES

6.6.1 Primary Efficacy Endpoint

6.6.1.1 Evaluation in the Treatment-Naive Population

For the evaluation of efficacy in the treatment-naïve population, all patients in Population A will be used. Population A includes all randomized patients, with patients grouped according to the treatment assigned at randomization. For all relevant efficacy evaluation, the baseline reference will be latest non missing observation before start of study drug.

The primary efficacy variable is the BCVA change from baseline to Week 36. 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. Randomization stratification factors such as baseline BCVA ($\geq$69 letters vs. $\leq$68 letters), and presence of RAP and PCV may also be incorporated in the statistical analysis as appropriate. An unstructured covariance structure will be used to account for within-patient correlation, but another variance-covariance structure may be selected in case of convergence issues. The primary statistical test will aim to test the null hypothesis (H_0) of no difference between each of the treatment group (Arms B, C, and D) and the control group (Arm A), for mean BCVA change from baseline to Week 36. The model-based estimate of the difference between each of the treatment group (Arms B, C, and D) and the control group (Arm A) at Week 36, together with 95% Confidence and corresponding p-value will be reported as the primary efficacy measures in this population. The mean and 95% confidence interval (CI) within each treatment group and for the difference between RO6867461 treatment groups (Arms B, C, and D) and the control group (Arm A) at the other time-points will also be reported. There will not be formal correction for multiple testing.

6.6.1.2 Evaluation in the Anti-VEGF–Incomplete-Responder Population

For the evaluation of efficacy in anti-VEGF–incomplete-responder population, Population B and a subgroup of Population B will be used.

The subgroup is defined as:

- Patients with BCVA$\leq$68 Letters at Week 12

The study Week 12 visit will be considered the baseline for all efficacy evaluations for the anti-VEGF—incomplete-responder population.

The primary efficacy variable is BCVA change from Week 12 to Week 36. The primary efficacy analysis will be performed using a MMRM model. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction, and the continuous covariate of Week 12 BCVA. Other covariates including the categorical stratification factors of baseline BCVA ($\geq$69 letters vs. $\leq$68 letters) and

presence of RAP or PCV may also be incorporated as appropriate. An unstructured covariance structure will be used to account or within patient correlation, but another variance-covariance structure may be selected in case of convergence issues.

The primary statistical test will aim to test the null hypothesis (H_0) of no difference between the treatment group (Arm E) and the control group (Arm A), in terms of BCVA mean change from Week 12 to Week 36. The model-based estimate of the difference between the treatment group (Arm E) and the control group (Arm A) at Week 36, together with 95% Confidence and corresponding p-value will be reported as the primary efficacy measure in this population.

The mean and 95% CI within each treatment group and for the difference between RO6867461 treatment group and the control group at the other time-points will also be reported. There will be no formal correction for multiple testing.

6.6.2 Secondary Efficacy Endpoints

For all secondary endpoints measured on a continuous scale, the same MMRM model used for the change from baseline BCVA will be employed. Nominal p-value will be reported without correction for multiple testing.

For binary endpoints, the 95% confidence interval for the proportion of “responders” in each treatment group, the difference in response rate, as well as odds ratio will be presented. Fisher’s exact test will be used for the comparison between the two groups.

Data transformation (e.g., logarithmic transformation) may be applied as appropriate. Other statistical models and additional analyses may also be performed as appropriate.

In addition, the influence of baseline parameters may be evaluated as covariates in the MMRM model and/or in subgroup analysis as appropriate.

6.7 PHARMACODYNAMIC ANALYSES

Individual and mean PD data and parameters will be presented by listings and descriptive summary statistics including means, geometric means, medians, ranges, standard deviations, and coefficients of variation.

An empirical drug-disease model of longitudinal BCVA previously developed on the database will be used to analyze the effect of RO6867461 on BCVA using a meta-analysis approach by integrating data from this study and clinical data.

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.

6.8 PHARMACOKINETIC ANALYSES

A nonlinear mixed effects modeling approach (with NONMEM software [Beal S 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, etc.) on these parameters will be investigated. The data collected in this study may be pooled with data collected in the previous Phase I study as appropriate to build a PK model. Secondary PK parameters such as AUC and 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.

6.9 OTHER EXPLORATORY ANALYSES

Additional exploratory analyses may be performed as warranted in order to more fully understand the relationship over time between parameters and either nominal dose or concentration of RO6867461.

Exploratory analysis of ranibizumab in plasma and aqueous humor will be conducted where the data would be available.

6.10 INTERIM ANALYSES

The Sponsor may conduct one interim analysis to allow for adaption of the sample size (see Section 3.1.2) and one interim analysis of efficacy for administrative reasons.

Given the hypothesis-generating nature of this study, the Sponsor may conduct up to two additional interim analyses of efficacy. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The Clinical Study Report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed and interpreted by members of the IMC and management who would then 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. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the Investigator.

The Sponsor will produce a Data Handling Manual that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

Data for this study will be captured via an online EDC system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the PI or authorized delegate from the study staff. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

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 investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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 PI 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. Food and Drug

Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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.

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.

For sites in the United States, 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 of 1996 (HIPAA). 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 PI 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 PI 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 9.5).

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 only be disclosed to third parties 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.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other 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 one year after completion of the study (i.e., last patient last visit [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, which includes an audit trail containing a complete record of all changes to data.

It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an IRB. This board must operate in accordance with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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.

9.3 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 (FAF, FP, FFA, ICGA, and SD-OCT), which will be forwarded to Sponsor electronically.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. 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.

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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

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.

9.5 PROTOCOL AMENDMENTS

Any substantial protocol amendments will be prepared by the Sponsor. Substantial 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 any non-substantial changes, as defined by regulatory requirements.

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Appendix 1
Schedule of Assessments

Week	Screen-ing	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Term-ination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-7 [l]	+/-7 [l]	+/-7 [l]	-4/+3 [m]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7	+7	
Assessments															
Informed Consent	x														
Eligibility [a]	x	x													
Demography	x														
Medical History [a]	x	x													
Physical Examination	x												x	x	
Anthropometric Measurements	x												x	x	
Vital Signs [a]	x	x [j]	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG-12 lead	x												x	x	x
Hematology [a]	x					x							x	x	x
Blood Chemistry [a]	x					x							x	x	x
Urinalysis [a]	x					x							x	x	x
Coagulation	x														x
Pregnancy Test	x														x

Appendix 1
Schedule of Assessments (cont.)

Week	Screen-ing	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Term-ination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-7 [l]	+/-7 [l]	+/-7 [l]	-4/+3 [m]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7	+7	
Assessments															
Administration of Study Medication		x		x	x	x		x or sham	x	x or sham	x	x or sham			
Administration of Study Medication		x		x	x	x		x or sham	x	x or sham	x	x or sham			
Safety Finger Count Vision [b,c]		x		x	x	x		x	x	x	x	x			
IOP [d]	x	3 [j,k]	x	3 [k]	3 [k]	3 [k]	x	3 [k]	3 [k]	3 [k]	3 [k]	3 [k]	x	x	x
BCVA [a]	x	x [j]		x	x	x		x	x	x	x	x	x	x	x
LLVA [a]		x				x [e]							x [e]	x [e]	x
Slit Lamp [a]	x	x [j]	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmoscopy [a]	x	x [j]	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus Photography [a]	x	x [c,j]				x [c]							x	x	x
Fundus Autofluorescence [a]	x					x [c]							x	x	x
SD-OCT [a]	x	x [c,j]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Week	Screen-ing	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Term-ination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-7 [l]	+/-7 [l]	+/-7 [l]	-4/+3 [m]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7	+7	
Assessments															
Fundus Fluorescein Angioraphy [a]	x					x							x	x	x
IndoCyanine Green Angiography [a]	x					x							x	x	x
PK Sample [a]		x		x		x	x	x		x			x	x	x
PD Biomarkers Sample [a]		x		x		x	x	x		x			x	x	x
Exploratory Plasma Biomarker Sample [a]		x		x		x				x			x		x
Aqueous Humor Sample (optional) [a,c,e,f]		x						x	x			x			x
Vitreous Humor + Blood Samples (optional) [c,e,g]															x
Clinical Genotyping Sample [a,h,i]		x													
Anti-Drug Antibody (ADA) [a]		x		x		x		x		x			x	x	x

Appendix 1
Schedule of Assessments (cont.)

Week	Screen-ing	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Term-ination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-7 [l]	+/-7 [l]	+/-7 [l]	-4/+3 [m]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7 [l]	+/-7	+7	
Assessments															
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments [a]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

a Assessment prior to *treatment* administration on days where study treatment is administered.
b Finger count vision assessment asap after, and within maximum of 15 min from study treatment administration.
c Assessment in study eye only.
d Multiple assessments on a single visit day, details on timing on a separate table.
e Optional *assessment. For aqueous humor, and vitreous humor + blood samples, a*dditional consent *is* required from the patient.
f Unscheduled sample could be obtained at other or additional planned visits at the discretion of the Investigator in agreement with the participating patient.
g Only in case of vitrectomy surgery during the study and if vitreous sampling is feasible. A blood sample for plasma preparation should be drawn at the same time.
h Mandatory, except in countries where IRB/EC does not approve.
i At Day 1 but can be done at any other visit if the sample *is* not collected at baseline.
j Baseline assessments.
k Assessment post-treatment administration in study eye only.
l *The interval between two study treatment administrations needs to be at least 21 days*
m *Relative to the previous study treatment administration date (Week 12).*

Appendix 2
Schedule of Assessments Detail Table for Visits with Repeated Assessments

	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32
	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224
Scheduled Time									
Pre-dose	x	x	x	x	x	x	x	x	x
30 minutes	x	x	x	x	x	x	x	x	x
60 minutes	x	x	x	x	x	x	x	x	x

IOP = intraocular pressure.

a If IOP ≥ 30 mmHg at 30 (±5) minutes post-treatment administration in the study eye, then measure again at 60 (±10) minutes.

Appendix 3
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.

Appendix 3
Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreal Hemorrhage Density, and Vitreous Cells (cont.)

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.

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 4
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.

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, at the discretion of the Investigator, by two drops of ophthalmic antimicrobial solution.
- Wait 90 seconds.
- Instill two more drops of proparacaine- or tetracaine-based ophthalmic drops into the study eye,

Appendix 4
Study Treatment Administration Procedure (cont.)

- 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 two 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

5. INTRAVITREAL ADMINSTRATION 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 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 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.