**Official Title:** **A MULTIPLE-CENTER, MULTIPLE-DOSE, 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 DIABETIC MACULAR EDEMA**

**NCT Number:** NCT02699450

**Document Date:** Protocol Version 3: 18-August-2016

## PROTOCOL

| | |
|---|---|
| **TITLE:** | **A MULTIPLE-CENTER, MULTIPLE-DOSE, 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 DIABETIC MACULAR EDEMA** |
| **PROTOCOL NUMBER:** | BP30099 |
| **VERSION:** | *3* |
| **EUDRACT NUMBER:** | NA |
| **IND NUMBER:** | 119,225 |
| **TEST PRODUCT:** | RO6867461 |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | See electronic date stamp below. |

## FINAL PROTOCOL APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | Company Signatory | 18-Aug-2016 16:24:31 |

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF APPENDICES

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A MULTIPLE-CENTER, MULTIPLE-DOSE, 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 DIABETIC MACULAR EDEMA** |
| **PROTOCOL NUMBER:** | BP30099 |
| **VERSION:** | 1 |
| **EUDRACT NUMBER:** | NA |
| **IND NUMBER:** | 119,225 |
| **TEST PRODUCT:** | RO6867461 |
| **PHASE:** | II |
| **INDICATION:** | Diabetic macular edema (DME) |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

---

**OBJECTIVES**

**Primary Objective**

The primary objective of this study is:

To evaluate the efficacy of RO6867461 compared with the active comparator in *treatment naïve* patients with center-involving diabetic macular edema (CI-DME)

**Secondary Objectives**

The secondary objectives for 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 and anatomical outcomes informing on the mechanism of action of RO6867461
- To investigate the formation of plasma anti-RO6867461 antibodies
- To explore the duration of effect of RO6867461

**Exploratory Objectives**

The exploratory objectives for this study are as follows:

- *To explore the predictive effect of previous IVT anti-VEGF treatment on efficacy of RO6867461*
- *To evaluate the efficacy and safety of RO6867461 compared with the active comparator in patients with CI-DME with previous IVT anti-VEGF treatment.*
- [redacted]
- [redacted]
- To evaluate improvement in diabetic retinopathy (DR) severity score

**STUDY DESIGN**

This is a multiple-center, multiple-dose, randomized, active comparator–controlled, double-masked, three parallel group, *36*-week study in patients with CI-DME.

The three groups of this study are as follows:

- Arm A: 0.3 mg ranibizumab IVT
- Arm B: 1.5 mg RO6867461 IVT
- Arm C: 6 mg RO6867461 IVT

Only one eye will be selected as the study eye. Where both eyes meet all eligibility criteria, the eye with the worse BCVA will be defined as the study eye. Where both eyes meet all eligibility criteria and have the same BCVA letter score at Day 1, study eye selection is at the investigator's discretion.

**NUMBER OF PATIENTS**

*Up to 210 patients will be randomized.*

Approximately 150 *treatment-naïve patients and approximately 60* patients *who have been previously treated with IVT anti-VEGF will* be enrolled in the study.

Approximately 50 *treatment-naïve* patients will be randomized on each arm (1:1:1 randomization scheme) *and approximately 30 patients previously treated with IVT anti-VEGF will be randomized into arms A and C.*

**TARGET POPULATION**

Male and female patients of ≥18 years of age with CI-DME.

**INCLUSION/EXCLUSION CRITERIA**

**Inclusion Criteria**

Patients must meet the following criteria for study entry:

**Ocular criteria for study eye:**

- Macular edema associated with DR defined as macular thickening by spectral domain optical coherence tomography (SD-OCT) involving the center of the macula: central subfield thickness (CST) of≥325 μm with Spectralis (Heidelberg) at screening (where Spectralis is not available, the following devices and CST thresholds are acceptable: CST≥315 μm for Cirrus, CST≥315 μm for Topcon, CST≥295 μm for Optovue).
- Decreased visual acuity attributable primarily to DME, with best corrected visual acuity (BCVA) letter score of 73–24 letters (inclusive) on Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts (20/40–20/320 Snellen equivalent) on Day 1
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

**General criteria:**

- Diagnosis of diabetes mellitus (DM; Type 1 or Type 2), as defined by the World Health Organization and/or American Diabetes Association
- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to ICH and local regulations.
- Age ≥18 years
- For women who are not postmenopausal (i.e. ≥12 months of non-therapy-induced amenorrhea, confirmed by FSH, if not on hormone replacement) 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 4 weeks after last dose.

Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the

patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception;

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.

- For men: agreement to use a barrier method of contraception during the treatment period for at least 4 weeks after the last dose of study drug
- Patients must be willing not to participate in any other clinical trial including an investigational medical 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:**

- *Any signs of high-risk PDR defined as:*
  - *any vitreous or pre-retinal hemorrhage*
  - *NVE ≥ 1/2 disc area within an area equivalent to the standard mydriatic ETDRS 7-field on clinical examination*
  - *NVD ≥1/3 disc area on clinical examination*
- Any IVT anti-VEGF treatment *within 3 months prior* to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- *Any IVT or periocular corticosteroid treatment within 3months prior to Day 1. Any history of Iluvien or Ozurdex implants prior to Day 1 will not be permitted*
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure [IOP] ≥25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions in the study eye:**

- History of rubeosis
- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision (e.g., age-related macular degeneration, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- *Any current ocular condition for which, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, non-retinal condition)*
- Any active ocular infection on Day 1
- Any active intraocular inflammation (grade trace or above) on Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment within 7 days prior to Day 1
- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 needs to be controlled by antihypertensive medication, the patient *should be taking the same* medication continuously for at least 1 month prior to Day 1.
- Patients with glycosylated hemoglobin HbA1c > 12% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with an IMP in the 3 months prior to Day 1

**LENGTH OF STUDY**

The total duration of the study will be up to *40* weeks (from screening through study completion) for each enrolled patient as follows:

- Screening: up to 4 weeks
- Baseline: Day 1
- Study treatment administration *period*: from Day 1 to Week 2*0*
- *Observational period: From Week 20 up to Week 36*
- *Safety follow up call: During the observational period and 7 days after ranibizumab administration*

**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**

The safety outcome measures for this study are as follows:

- Any relevant safety observations derived from BCVA (modified ETDRS charts), slit-lamp examination, dilated binocular indirect high-magnification ophthalmoscopy, 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

**PHARMACOKINETIC OUTCOME MEASURES**

**Plasma Levels of RO6867461**

Plasma concentrations will be measured by a validated ELISA method. The pharmacokinetic (PK) analysis is described in the statistical methods section in the protocol. Samples may also be analyzed for ranibizumab by an appropriate assay.

[redacted]

**EFFICACY AND PHARMACODYNAMIC OUTCOME MEASURES**

*The primary analysis population will be treatment naïve patients. Additional analyses may be performed in the overall population and in patients previously treated with IVT anti-VEGF.*

The primary efficacy outcome measure for this study is the mean change *in BCVA (ETDRS letters)* from baseline at Week 24 *in treatment-naïve patients.*

The secondary efficacy outcome measures for this study include functional (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 24
- Proportion of patients with BCVA ≥ 69 letters (20/40 or better) at Week 24
- Proportion of patients with BCVA ≥ 84 letters (20/20 or better) at Week 24

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 24
- Mean change from baseline in mean CST (1 mm diameter) at Week 24
- Proportion of patients with resolution of subretinal and intraretinal fluid at Week 24

Anatomic outcome measures by fundus fluorescein angiography (FFA)

- Proportion of patients with resolution of leakage at the macula at Week 24
- Change from baseline in the size of the foveal avascular zone at Week 24

Plasma PD biomarker outcome measure

- Change in plasma levels of VEGF and Ang-2

**EXPLORATORY OUTCOME MEASURES**

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

*BCVA:*

- *Difference in mean BCVA change from baseline between the treatment-naïve patients and patients with previous IVT anti-VEGF (differential effect of RO6867461)*
- *Proportion of patients with BCVA ≥ 69 letters (20/40 or better) over time*
- *Proportion of patients with BCVA ≥84 letters (20/20 or better) over time*

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

*Durability-related exploratory outcome measures:*

- *Time to increase of CST by ≥50µm and/or loss of ≥ 5 letters of BCVA due to DME compared to values at Week 20*
- *Time to treatment with 0.3 mg ranibizumab after Week 20*

[redacted]

**BIOMARKER/GENOTYPING SAMPLE COLLECTION**

**Mandatory Biomarkers Samples**

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

**Clinical Genotyping Samples**

A mandatory whole blood sample will be taken for DNA extraction from every patient. The DNA may be used to study genes related to DME, DR, and angiogenesis (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 other mandatory blood samples. This specimen will be destroyed up to 2 years after the final closure of the clinical database.

[redacted]

## INVESTIGATIONAL MEDICINAL PRODUCT(S)

**Test Product: RO6867461**

Vials of sterile, colorless to brownish, preservative-free solution of RO6867461 (120 mg/mL) for IVT administration of either 1.5 mg or 6 mg dose every 4 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.

A volume of 50 μL will be administered by IVT injection for all study drugs tested in this study.

**Comparator: ranibizumab**

Ranibizumab (nominal content 0.3 mg/0.05 mL) required for completion of this study will be provided by the Sponsor as a solution formulated at 6 mg/mL and supplied as a single-use vial.

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

## PROCEDURES

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

**Screening**

Patients with CI-DME 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 females of childbearing potential, and safety laboratory parameters. A predefined set of imaging criteria for eligibility will be confirmed by a Central Reading Center before enrollment.

**Treatment Period**

On Day 1, baseline assessments will be conducted on the eligible patients, according to the SoA. Patients will receive their first IVT injection of either RO6867461 or comparator therapy according to the randomization schedule and following established standard procedures. Patients will return to the eye clinic *every 4 weeks* for study *drug* administration and assessments as outlined in the SoA.

A post-treatment administration check of study eye will be performed for each patient immediately after study treatment administration by testing finger count vision, hand motion, and light perception, as appropriate. On the day of dosing, IOP will be monitored at 30 minutes post-administration in the study eye, using either Goldmann tonometry or Tono-pen, and if IOP ≥30 mmHg in the study eye, 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.

[redacted]

***Observational* Period**

Patients will return *for evaluation every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1 ), the patients will receive a single dose of 0.3 mg ranibizumab, exit the study, and receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

## STATISTICAL METHODS

**PRIMARY ANALYSIS**

The primary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

The primary efficacy variable is the BCVA change from baseline to Week 24. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM)

model.

**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., 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 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.

[redacted]

**SAMPLE SIZE JUSTIFICATION**

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline *at* Week 24 *in the treatment-naïve patients*. Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 *treatment-naïve* patients randomized to Arm A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides approximately 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

*Approximately 60 previously IVT anti-VEGF treated patients will be enrolled in addition for exploratory analyses.*

**INTERIM ANALYSES**

Two efficacy interim analyses *to inform about possible future development options for RO6867461 are foreseen. They will not* influence the study conduct. One *interim efficacy analysis is foreseen after* approximately 28 *treatment-naïve* patients in each arm have completed the Week 24 visit, and one when approximately all patients have completed the Week 24 visit.

*A safety analysis will be performed if safety issues have been identified during ongoing review of the masked data.*

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

**OTHER CONSIDERATIONS**

NA

**LIST OF PROHIBITED MEDICATIONS**

**Concomitant Therapy**

Patients who use maintenance therapy other than those required to treat DME should continue its use.

PRP is permitted in either eye, if clinically indicated *for the treatment of proliferative diabetic retinopathy or retinal holes or tears post randomization*.

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

**Prohibited Therapy**

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

- Concurrent use of systemic anti-VEGF agents
- Concurrent use of IVT anti-VEGF therapy in the fellow eye within 7 days preceding or following the study eye treatment
- Concurrent use of IVT or subtenon corticosteroids in study eye, except as required to treat adverse events

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **ADA** | anti-drug antibody |
| **AMD** | age-related macular degeneration |
| **Ang-1** | angiopoietin- 1 |
| **Ang-2** | angiopoietin-2 |
| **aPTT** | activated partial thromboplastin time |
| **AST** | aspartate aminotransferase |
| **AUC** | area under the concentration-time curve |
| **$AUC_{0\text{-}inf}$** | area under the concentration-time curve from time 0 to infinity |
| **$AUC_{0\text{-}\tau}$** | area under the concentration–time curve during one dosing interval |
| **BCVA** | best corrected visual acuity |
| **bFGF** | basic fibroblast growth factor |
| **BP** | blood pressure |
| **BRB** | blood-retinal barrier |
| **CI** | center involvement |
| **CI-DME** | center-involving DME |
| **CL** | clearance |
| **CL/F** | apparent clearance |
| **CNV** | choroidal neovascularization |
| **$C_{max}$** | maximum concentration observed |
| **CRP** | C-reactive protein |
| **CSME** | clinically significant macular edema |
| **CST** | central subfield thickness |
| **DBP** | diastolic blood pressure |
| **DLE** | dose-limiting event |
| **DM** | diabetes mellitus |
| **DME** | diabetic macular edema |
| **DR** | diabetic retinopathy |
| **EC** | Ethics Committee |
| **eCRF** | electronic Case Report Form |
| **EDC** | electronic data capture |
| **EDI** | enhanced depth imaging |
| **ESF** | Eligibility Screening Form |
| **ETDRS** | Early Treatment Diabetic Retinopathy Study |
| **E.U.** | European Union |

| Abbreviation | Definition |
|---|---|
| **Fab** | fragment antibody binding |
| **FDA** | U.S. Food and Drug Administration |
| **FFA** | fundus fluorescein angiography |
| **FP** | fundus photography |
| **FSH** | follicle-stimulating hormone |
| **GCP** | Good Clinical Practice |
| **GLP** | Good Laboratory Practice |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **ICH** | International Conference on Harmonisation |
| **IMC** | Internal Monitoring Committee |
| **IMP** | investigational medicinal product |
| **IND** | Investigational New Drug (application) |
| **IOP** | intraocular pressure |
| **IRB** | Institutional Review Board |
| **IVT** | intravitreal |
| **IxRS** | interactive (voice/web) response system |
| **LPLO** | last patient last observation |
| **mAb** | monoclonal antibody |
| **MAD** | multiple ascending dose |
| **MMRM** | Mixed Model for Repeated Measurement |
| **NOAEL** | no observed adverse effect level |
| *NVD* | *neovascularization of the optic disc* |
| *NVE* | *neovascularization elsewhere* |
| **OTC** | over the counter |
| **PD** | pharmacodynamic |
| **PDGF** | platelet-derived growth factor |
| **PDR** | proliferative diabetic retinopathy |
| **PI** | Principal Investigator |
| **PK** | pharmacokinetic |
| **PLGF** | placenta growth factor |
| **PRP** | panretinal photocoagulation |
| **QT** | QT interval |
| **QTc** | QT corrected for heart rate |
| [redacted] | [redacted] |
| **SAD** | single ascending dose |
| **SAE** | serious adverse event |
| **SBP** | systolic blood pressure |

| Abbreviation | Definition |
|---|---|
| **SD-OCT** | spectral domain optical coherence tomography |
| **SoA** | Schedule of Assessments |
| **SoC** | standard of care |
| **$t_{1/2}$** | half-life |
| **$t_{max}$** | time to maximum concentration |
| **ULN** | upper limit of normal |
| **V** | volume |
| **VA** | visual acuity |
| **VEGF** | vascular endothelial growth factor |
| **VEGF-A** | vascular endothelial growth factor A |
| **VEGFR** | vascular endothelial growth factor receptor |

# 1. BACKGROUND AND RATIONALE

## 1.1 BACKGROUND ON DISEASE

Diabetes affects 382 million people worldwide, and its prevalence is expected to grow to 592 million by 2035 (International Diabetes Federation 2013). Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have sudden and debilitating impact on visual acuity (VA). DME is defined as retinal thickening within 2 disc diameters of the center of the macula (Albert and Jakobiec 2000) and is the major cause of central vision loss in patients with diabetes (Resnikoff et al. 2004). DME occurs in approximately 14% of patients with diabetes and can be found in both Type 1 and Type 2 patients (Girach and Lund-Andersen 2007). DME can develop at any stage of DR, but it occurs more frequently as the duration of diabetes and the severity of DR increase.

Thickening of the basement membrane and reduction in the number of pericytes are believed to lead to increased permeability and incompetence of the retinal vasculature. Hypoxia produced by this mechanism is postulated to stimulate the production of vascular endothelial growth factor (VEGF). In addition, the compromise of the blood-retinal barrier leads to the leakage of plasma constituents into the surrounding retina, with subsequent retinal edema (Antonetti et al. 1999). In addition to VEGF, other inflammatory and angiogenic cytokine levels are also elevated in DME and proliferative diabetic retinopathy (PDR) (Aiello et al. 1994; Gardner et al. 2002).

The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that macular laser photocoagulation reduced the risk of moderate vision loss by 50% (from 24% to 12% 3 years after initiation of treatment). However, few patients experience improvement in vision following laser alone for DME and persistent and recurrent macular edema is common (ETDRS Report No. 9 1991).

Over the past few years, the use of anti-VEGF therapy to treat DME has improved visual outcomes. Existing therapies include ranibizumab and aflibercept [EYLEA®]. Although anti-VEGF therapies have markedly improved the management of these patients and established a new efficacy paradigm in visual gain, a significant percentage of patients do not achieve clinically meaningful improvements in vision; furthermore, these therapies do not sufficiently improve macular vascular perfusion or target all DME-associated sequelae. Due to its novel mode of action, it is anticipated that RO6867461 will improve efficacy over existing anti-VEGF therapies.

Angiopoietin-1 (Ang-1) and Ang-2 are of key importance in the homeostasis of the vascular compartment, functioning as ligands of the Tie-2 receptor tyrosine kinase that is expressed on endothelial cells (Davis et al. 1996; Maisonpierre et al. 1997; Fiedler et al. 2003). Ang-1 is a homeostatic factor that stabilizes the mature vasculature by promoting recruitment of pericytes and smooth muscle cells. In contrast, Ang-2 acts as an antagonist of Tie-2 by blocking Ang-1-dependent Tie-2 activation (Davis et al. 1996;

Maisonpierre et al. 1997; Fiedler et al. 2003). Ang-2 acts as a destabilization factor and, under the influence of other angiogenic factors such as VEGF-A, renders the vasculature more plastic and amenable to endothelial barrier breakdown and sprouting. Ang-2 is also upregulated by VEGF and other pro-angiogenic factors.

## 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 endothelial cell permeability in vitro. In addition, their vitreous concentrations were shown to be significantly upregulated in patients with DR. (Park et al. 2014; Rangasamy et al. 2011) 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, and result in further improvement of visual and anatomic outcomes in patients with DME.

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 (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 choroidal neovascularization (CNV). Also see the *RO6867461 Investigator's Brochure* for details on nonclinical and clinical studies.

### 1.2.1 Previous Non-Clinical 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).

In the absence of a suitable model of DME, pharmacological evaluation in vivo focused on well characterized models of choroidal vessel edema and neovascularization. These evaluations demonstrated that RO6867461 reduces the formation of neovessels, 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* Version 4).

[redacted]

In a 2-month Good Laboratory Practice (GLP) study in cynomolgus monkeys, ocular and extra-ocular findings occurred following three IVT injections of the highest 3 and 6 mg/eye/dose. 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.

In both studies, findings generally correlated with the systemic presence of anti-drug antibodies (ADAs) against RO6867461 and exposure loss in the serum of animals. In addition, immunohistochemistry confirmed the presence of immune-complex deposits in RO6867461-treated animals with ocular and extra-ocular findings (in the 3-month study). Therefore, these effects were consistent with an immune-mediated response to a humanized antibody like RO6867461 in non-human primates.

RO6867461 did not induce any neurological (CNS) findings or effects on heart rate/electrocardiogram 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 CNV secondary to age-related macular degeneration (AMD) has been completed (Study 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).

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

A multicenter, double-masked, Phase II study to investigate the safety, tolerability, pharmacokinetics, and efficacy of RO6867461 administered IVT in patients with CNV secondary to AMD is ongoing (Study BP29647 – AVENUE, *clinicaltrials.gov: NCT02484690*). In Study BP29647, treatment-naive patients are randomized to receive either ranibizumab 0.5 mg every 4 weeks or 1.5 or 6 mg RO6867461 every 4 or 8 weeks

for 32 weeks. *To date, side effects observed in patients enrolled in Study BP29647 (masked data) are consistent with the safety profile observed in the completed BP28936 study described above.* No other data are yet available.

No clinical data are yet available for RO6867461 in patients with DME.

#### 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 (see Table 1). No deaths and no dose-limiting events (DLEs) were reported.

In the Phase I study (BP28936), one serious adverse event was reported, which was non-ocular, and was considered unrelated to the study drug by the Principal Investigator. One patient from the 3 mg dose group of Part A was withdrawn from the study because of a diagnosis of coronary heart disease, which was considered unrelated to study drug by the Investigator (see *RO6867461 Investigator's Brochure* Version 4 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 | 20 | 10 | 4 |
| 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.

[redacted]

[redacted]

### 1.2.2.3 Functional and Anatomical Pharmacodynamics

Higher BCVA was observed in patients treated with RO6867461 compared to baseline in the Phase I study. In the SAD part, a median 7 letter (range: 0 to 18; n = 11) higher BCVA was observed on Day 28 as compared to baseline across all patients. In the MAD part, after the first, second, and third administration of 6 mg RO6867461, a median BCVA increase from baseline of −0.5, 3, and 7.5 letters, respectively, was observed, while no change in BCVA was seen with the 3 mg RO6867461.

The changes in BCVA were associated with a reduction in central subfield thickness (CST). A median change from baseline of −42 μm in CST on Day 28 pooled for all dose levels was observed in Part A. For the patients treated with 3 mg RO6867461 in Part B, a median change from baseline of −13.5 μm, −25.0 μm, and −9.0 μm at 28 days after the first, second, and third drug administration, respectively, was observed. Patients in the 6 mg RO6867461 in Part B showed a consistent and durable reduction in CST, with an overall magnitude comparable to Part A. The CST median change from baseline was −79.5 μm, −86 μm, and −117 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).

## 1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

There are limited clinical evaluations with anti-Ang-2 approaches in patients with DME. The Phase I RO6867461 study, which included a small number of patients with CNV secondary to AMD, 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 based on Phase I data is therefore favorable and justifies evaluation of RO6867461 efficacy as compared with SoC therapy in patients with DME.

Nonclinical toxicology studies (see 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 DME.

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 patients with center-involving DME (CI-DME). This study is designed to evaluate the effects of RO6867461 on visual function and retinal structure by assessing changes from baseline in BCVA (ETDRS letters) and anatomy (imaging procedures), respectively. In addition, the safety, tolerability, and pharmacokinetics will be evaluated in patients receiving up to 6 doses of RO6867461.

Patients who will be enrolled in the 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 Section 4.4.2. Treatment will be administered as necessary for any concurrent medical events.

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 OBJECTIVE

The primary objective of this study is:

- To evaluate the efficacy of RO6867461 compared with the active comparator in *treatment naïve* patients with CI-DME.

## 2.2 SECONDARY OBJECTIVES

The secondary objectives for 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 explore the duration of effect of RO6867461

## 2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- *To explore the predictive effect of previous IVT anti-VEGF treatment on efficacy of RO6867461*
- *To evaluate the efficacy and safety of RO6867461 compared with the active comparator in patients with CI-DME with previous IVT anti-VEGF treatment.*
- [redacted]

- [redacted]
- To evaluate improvement in DR severity score

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a multiple-center, multiple-dose, randomized, active comparator–controlled, double-masked, three parallel group, *36*-week study in patients with CI-DME.

### 3.1.1 Overview of the Study Design

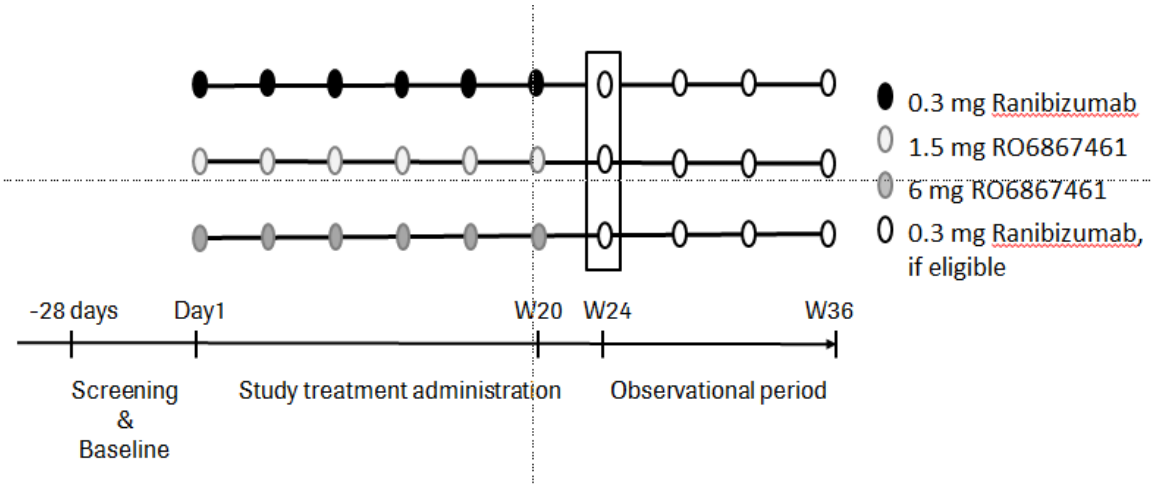
The three groups of this study are as follows (see Figure 1):

- Arm A: 0.3 mg ranibizumab IVT
- Arm B: 1.5 mg RO6867461 IVT
- Arm C: 6 mg RO6867461 IVT

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab, and exit the study. They will receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

Only one eye will be selected as the study eye (see Section 4.3.1).

**Figure 1 Study Design**




Q4W = every 4 weeks.

The total duration of the study for each patient will be up to *40* weeks, divided as follows (see Figure 1):

- Screening: *U*p to 4 weeks
- Baseline: Day 1
- Study treatment administration *period*: *F*rom Day 1 to Week *20*
- *Observational period*: *From Week 20* up to Week *36*
- *Safety follow up call: During the observational period and 7 days after ranibizumab administration*

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 the Schedule of Assessments (SoA; see Appendix 1), are completed.

If a site has an unexpected issue (e.g., the interactive voice and web response system (IxRS) is not able to assign the study kit), 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

*Up to 210 patients will be randomized.* Approximately 150 *treatment-naïve patients and approximately 60* patients *who have been previously treated with IVT anti-VEGF* will be enrolled in the study. Approximately 50 *treatment-naïve* patients will be randomized

*into* each arm (1:1:1 randomization scheme) *and approximately 30 patients previously treated with IVT anti-VEGF will be randomized into arms A and C.*

### 3.1.3 Internal Monitoring Committee

A Roche Internal Monitoring Committee (IMC) will be responsible in the event of an interim analysis of efficacy for operational/administrative/study related purposes and/or for safety data monitoring. Two efficacy analyses are foreseen, one after approximately 28 *treatment naïve* patients in each treatment arm have completed the Week 24 visit, and one when approximately all patients have completed the Week 24 visit. A safety analysis may be performed if safety issues have been identified during ongoing review of the masked data.

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. The IMC Chair may provide members from other functions access to the unmasked reports or data. 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 DME.

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

### 3.2.1 Rationale for Dosage Selection

The first-in-human study (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 molar binding equivalent anti-VEGF dose to the 0.5 mg ranibizumab dose (approved ranibizumab dose for most indications and in most countries) due to the 3-fold higher molecular weight of the IgG antibody, RO6867461, as compared with 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; Dhoot et al. 2015). 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, 7 times every 4 weeks, intravitreally. Due to the approximately 2-fold lower vitreous humor volume in cynomolgus monkey as compared with humans, a 3-mg dose administered to monkeys achieves similar IVT initial concentrations as compared with humans.

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

Taken together, the nonclinical and clinical data suggest that the selected doses of 1.5 mg and 6 mg RO6867461 administered every 4 weeks were safe and tolerated and allow a further testing in a *Phase II* study. The same doses were selected for the ongoing Phase II study in patients with CNV secondary to AMD.

### 3.2.2 Rationale for Study Population

This study will be conducted in patients with vision loss due to DME who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (see Section 4.2.1 and Section 4.2.2).

*Both treatment naïve DME patients and prior IVT anti-VEGF treated DME patients will be included. The aim is to evaluate the efficacy of RO6867461 compared with the active comparator in treatment naïve patients with CI-DME. Inclusion of treatment naïve and previously anti-VEGF treated patients will enable the exploratory evaluation of the predictive effect of previous IVT anti-VEGF treatment on efficacy of RO6867461.*

### 3.2.3 Rationale for Control Group

This study is an interventional superiority study aiming to evaluate the efficacy of RO6867461, as compared with standard of care anti-VEGF therapy in patients with DME. Anti-VEGF therapy is a well-established SoC in patients with DME, and placebo, sham injection, or macular laser are no longer an ethically acceptable alternative given the improvements in visual and anatomic outcomes associated with anti-VEGF treatment.

Ranibizumab is an approved treatment in patients with DME and has demonstrated improvement of VA in the target population in controlled, randomized clinical studies.

Controlled, randomized clinical studies in patients with DME led to the approval of ranibizumab 0.3 mg monthly or 0.5 mg pro re nata after vision is stable for 3 consecutive monthly doses in the United States and rest of the world, respectively (Mitchell et al. 2011; Nguyen et al. 2012).

Therefore, we selected the ranibizumab 0.3 mg every 4 weeks approved regimen as an optimal active comparator for a superior efficacy design in the target population for this study conducted in the United States.

### 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 DR (Goldberg 2009; Kaul et al. 2010) and DME. Moreover, some genetic polymorphisms in genes involved in the mechanism of action of RO6867461, such as VEGF and VEGFR, have been described in the literature as associated with DR (Churchill et al. 2008) and with response to anti-VEGF therapy (Hermann et al. 2014).

Therefore, both genetic markers and protein biomarkers of pathways involved in these processes may be analyzed to improve the understanding of the patient's response to RO6867461 treatment. [redacted]

Genetic polymorphisms associated with DR and DME and related to angiogenesis such as VEGFA, Ang-2, and VEGFR 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 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: Clearance (CL) and volume (V)

  Secondary parameters: Maximum concentration observed ($C_{max}$), area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), $AUC_{0\text{-}\tau}$, time to maximum concentration ($t_{max}$), $t_{1/2}$

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

  [redacted]

### 3.3.3 Efficacy and Pharmacodynamic Outcome Measures

*The primary analysis population will be treatment naïve patients. Additional analyses may be performed in the overall population and in patients previously treated with IVT anti-VEGF.*

#### 3.3.3.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the mean change *in BCVA (ETDRS letters)* from baseline at Week 24 *in treatment-naïve patients*.

### 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 ≥15 letters from baseline BCVA at Week 24
- Proportion of patients with BCVA ≥69 letters (20/40 or better) at Week 24
- Proportion of patients with BCVA ≥84 letters (20/20 or better) at Week 24

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 24
- Mean change from baseline in mean CST (1 mm diameter) at Week 24
- Proportion of patients with resolution of subretinal and intraretinal fluid at Week 24

Anatomic outcome measures by FFA:

- Proportion of patients with resolution of leakage at the macula at Week 24
- Change from baseline in the size of the foveal avascular zone at Week 24

### 3.3.3.3 Pharmacodynamic Biomarker Outcome Measure

Plasma PD biomarker outcome measure for this study is 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:

*BCVA:*

- *Difference in mean BCVA change from baseline between the treatment-naïve patients and patients with previous IVT anti-VEGF (differential effect of RO6867461)*
- *Proportion of patients with BCVA 69 letters (20/40 or better) over time*
- *Proportion of patients with BCVA ≥ 84 letters (20/20 or better) over time*

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

*Durability-related exploratory outcome measures:*

- *Time to increase of CST by ≥50µm and/or loss of ≥ 5 letters of BCVA due to DME compared to values at Week 20*
- *Time to treatment with 0.3 mg ranibizumab after Week 20*

[redacted]

[redacted]

[redacted]

# 4. MATERIALS AND METHODS

## 4.1 CENTERS

This is a multicenter study to be conducted in the United States. Additional site(s) in the United States 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

### 4.2.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

**Ocular criteria for study eye:**

- Macular edema associated with DR defined as macular thickening by spectral domain optical coherence tomography (SD-OCT) involving the center of the macula: CST of≥325 µm with Spectralis (Heidelberg) at screening (where Spectralis is not available, the following devices and CST thresholds are acceptable: CST≥315 µm for Cirrus, CST≥315 µm for Topcon, CST≥295 µm for Optovue)
- Decreased VA attributable primarily to DME, with BCVA letter score of 73–24 letters (inclusive) on ETDRS-like charts (20/40–20/320 Snellen equivalent) on Day 1
- Clear ocular media and adequate pupillary dilatation to allow acquisition of good quality retinal images to confirm diagnosis

**General criteria:**

- Diagnosis of diabetes mellitus (DM; Type 1 or Type 2), as defined by the World Health Organization and/or American Diabetes Association
- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to ICH and local regulations.

- Age ≥ 18 years
- For women who are not postmenopausal (i.e. ≥ 12 months of non–therapy-induced amenorrhea, confirmed by FSH, if not on hormone replacement) 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 4 weeks after last dose.

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  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.
- For men: agreement to use a barrier method of contraception during the treatment period for at least 4 weeks after the last dose of study drug
- Patients must be willing not to participate in any other clinical trial including an investigational medical 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:**

- *Any signs of high-risk* PDR *defined as:*
  - *any vitreous or pre-retinal hemorrhage*
  - *NVE ≥1/2 disc area within an area equivalent to the standard mydriatic ETDRS 7- field on clinical examination*
  - *NVD ≥ 1/3 disc area on clinical examination*
- Any IVT anti-VEGF treatment *within 3 months* prior to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- *Any IVT or periocular corticosteroid treatment within 3months prior to Day 1, . Any history of Iluvien or Ozurdex implants prior to Day 1 will not be permitted*
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery

- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions in the study eye:**

- History of rubeosis
- Any current or history of ocular disease other than DME that may confound assessment of the macula or affect central vision (e.g., AMD, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- *Any current ocular condition for which, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, non-retinal condition)*
- Any active ocular infection *on* Day 1
- Any active intraocular inflammation (grade trace or above) *on* Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment within 7 days prior to Day 1
- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 needs to be controlled by antihypertensive medication, the patient *should be taking the same* medication continuously for at least 1 month prior to Day 1.
- Patients with glycosylated hemoglobin HbA1c >*12*% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study

- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with 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 (see Section 4.2.1 and Section 4.2.2) at the screening or Day 1 visit (as defined for each individual criterion in Section 4.2 and below) prior to randomization and first study treatment (see Section 4.6.7.1). As part of the screening process, FP, FFA, 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.

Only one eye will be selected as the study eye. See Section 4.6.7.1 for details.

After all patient eligibility requirements are confirmed on Day 1 visit (see Section 4.2), including:

- Baseline BCVA letter score of 73 to 24 letters (inclusive) in the study eye
- Absence of active intraocular inflammation in the 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).

*Treatment naïve p*atients will be randomized in a 1:1:1 ratio to one of the arms *A, B and C, respectively. Patients previously treated with IVT anti-VEGF will be randomized in a 1:1 ratio to arms A and C.*:

- Arm A: 0.3 mg ranibizumab IVT
- Arm B: 1.5 mg RO6867461 IVT

- Arm C: 6 mg RO6867461 IVT

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab and exit the study. They will receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

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., Day 1 *through week 20*), the IxRS will assign the appropriate study treatment kit to be used.

Randomization will be stratified for the factor below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (64 letters or better vs. 63 letters or worse)
- Previous Macular Laser treatment (Yes/No)
- *Previous IVT anti-VEGF treatment in study eye (Yes/No)*

Randomization with fixed permuted blocks will be used to obtain an approximate *equal allocation* ratio between the different arms within each stratum.

#### 4.3.1.1 *Criteria for Treatment with Ranibizumab during Observational Period*

*At each visit following the last dose of study treatment (week 20 visit), BCVA will be assessed and SD-OCT imaging will be performed (except for week 26 visit).*

*BCVA and CST values obtained at week 24 will be compared to those obtained at visit week 20. BCVA and CST values obtained at weeks 28, 32 and 36 will be compared to those of week 24.*

*If the patient meets both of the following criteria the patient should receive a single dose of 0.3 mg ranibizumab and will exit the study:*

- *CST increased by ≥ 50 µm*
- *BCVA decreased by ≥ 5 letters due to DME*

### 4.3.2 Treatment Administration Procedure

Study drug will be administered IVT. The procedures are detailed in Appendix 3 and the Pharmacy Manual. *Ranibizumab during the observational period should* be *administered as* per *local practice.*

At the discretion of the investigator, the sites may use either propacaine- or tetracaine-based ophthalmic drops, subconjunctival injection of lidocaine or lidocaine gel. 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.

*Patients, study site personnel (with the exception of the pharmacist or designated personnel), BCVA examiners, vendors, Central Reading Center personnel, and the Sponsor and its agents (with the exception of drug accountability monitors and as defined in Section 4.3.3) will be masked to study drug assignment.*

There *should* be a minimum of two investigators per site to fulfill the masking requirements of this study. At least one investigator will be designated as the assessor physician who will be masked to patients' study drug 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 *could* be unmasked to patients' study drug assignment and will administer study treatment (RO6867461, ranibizumab).

*If only one investigator is available due to limited staffing resources, study drug administration can also be done by the assessing physician. In that case the treatment administrator physician(s) must not be involved in any aspects of un-masked study drug preparation. The preparation of the study drug must be done by trained staff under strict sterile condition. Detailed instructions for preparation are available in the pharmacy manual.*

The Principal Investigator must be masked to the patient's treatment assignment. All roles for each study staff member should be clearly documented in the site delegation log. The delegation log should be signed by the Principal Investigator. *An unmasked personnel cannot switch to a masked role, but a masked personnel can switch to an unmasked role. Any change should 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 drug* administration must not divulge study drug assignment to anyone.

*T*he number of unmasked study personnel *should be limited* to ensure the integrity of this masked study. There *should* 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 the Sponsor.

For the duration of the study, the patient study drug 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 treatment administrator physician performing the injection of study drug may also perform *other assessments, including* the post-injection 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 study drug 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 displays for the IMC meeting.*Other Roche Study Management Team members will remain masked throughout the study.

### 4.3.4 *Emergency Unmasking*

*If complete unmasking is necessary for patient management (e.g., in the case of a serious adverse event), the investigator will be able to share the treatment code with the masked study personnel. Treatment codes should not be shared except in emergency situations. The Investigator should document all details and provide an explanation for any premature complete unmasking (e.g., accidental unmasking of non-Investigator study personnel or unmasking due to serious adverse events).*

*Sponsor might become unmasked to study drug 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 *drug* includes IVT injections of RO6867461 and active comparator ranibizumab.

### 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 *RO6867461 Investigator's Brochure*.

#### 4.4.1.2 Ranibizumab Active Comparator

Ranibizumab (nominal content 0.3 mg/0.05 mL) required *as comparator in* this study will be provided by the Sponsor as a solution formulated at 6 mg/mL and supplied as a single-use 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.

#### 4.4.1.3 *Ranibizumab during Observational Period*

*Ranibizumab will be provided by the Sponsor via the IxRS. Proper drug accountability will be performed by the site.*

### 4.4.2 Dosage, Administration, and Compliance

#### 4.4.2.1 RO6867461 and Ranibizumab

Patients will be given 50 μL IVT injection of RO6867461 or ranibizumab into the study eye according the randomization schedule as described in the Overview of Study Design (see Section 3.1.1).

- Arm A: 0.3 mg ranibizumab IVT
- Arm B: 1.5 mg RO6867461 IVT
- Arm C: 6 mg RO6867461 IVT

The pharmacist or designee responsible for dispensing *study drug* will prepare the correct *study drug* (RO6867461 *or* ranibizumab), where applicable, as assigned by IxRS. A fixed volume of 50 μL will be injected for all study drugs and doses.

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 | 0.3 mg | NA | 50 µL |

NA = not applicable; IVT = intravitreal.

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

A specified filter needle must be used for each dose preparation of RO6867461 or ranibizumab per the instructions provided in the Pharmacy Manual. All materials to dilute/prepare and administer *study drug* 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, leftover 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] or 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 drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

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

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

IMPs will either be disposed of 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 investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product 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, destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity kit numbers of investigational products destroyed
- Quantity of investigational products 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 Drug Inventory Log.

### 4.4.4 Post-Trial Access to RO6867461

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

## 4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter (OTC) drugs, approved dietary and herbal supplements, nutritional supplements used by a patient from within 30 days of study screening until the follow-up visit. Patients who use maintenance therapy other than those required to treat DME should continue its use.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

### 4.5.1 Permitted Therapy

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).

PRP is permitted in either eye, if clinically indicated *for the treatment of proliferative diabetic retinopathy or retinal holes or tears post randomization*. PRP should be recorded on the Adverse Event eCRF in the event it qualifies for worsening of DR, as defined in Section 5.3.5.9.

### 4.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF.

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 anti-VEGF therapy for the fellow eye within 7 days preceding or following the study eye treatment
- Concurrent use of IVT or subtenon corticosteroids in study eye, except as required to treat adverse events

### 4.5.3 Emergent/Recurrent Diabetic Macular Edema in the Fellow Eye

Should DME emerge or recur and require treatment in the fellow eye during the study period, the patient may receive anti-VEGF SoC treatment. Fellow eye treatment, if required, must be administered at least 7 days preceding or following the study eye treatment.

[redacted]

## 4.6 STUDY ASSESSMENTS

All examinations listed below will be performed according to the SoAs outlined in Appendix 1.

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, definitely, 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.Optional IOP measurement at screening (with Tono-pen)

  Pupil dilation

  7-field or wide-field color FP

  Enhanced depth imaging (EDI) SD-OCT

  7-field or wide-field FFA

  Slit-lamp examination

  Dilated binocular indirect high-magnification ophthalmoscopy

  IOP (*mandatory to be performed after all imaging assessments*). The method of IOP measurement (either Goldmann tonometer or Tono-pen) used *should be recorded in the source document -and* must remain the same throughout the study.

[redacted]

Imaging assessments (FP, EDI SD-OCT, FFA) will be performed for study eye only, except at screening where either eye has a potential to meet all eligibility criteria.

### 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, and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to the

screening visit *and within the screening period (other than reported as 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 timepoints indicated in the SoA (see Appendix 1). Physical examination will include body weight at screening and either final or early termination visit and height at screening.

The 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 Systemic Medical History 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 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 timepoints specified in the SoA (see 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, by 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 or borderline.

#### 4.6.1.4 Electrocardiograms

Triplicate 12-lead ECG (i.e., three useful ECGs without artifacts) will be collected at the timepoints specified in SoA. To minimize variability, it is important that patient be in a resting position for at least 10 minutes prior to the 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 timepoints 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 by 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.

Central Reading Center will transfer the relevant ECG characteristics (including heart rate, PQ [PR], QRS, QT, T, and U abnormalities; and RR, QTcB, and QTcF will be derived) and overall interpretation directly to the Sponsor. Overall ECG interpretation will be documented on the eCRF by investigators or designees.

#### 4.6.1.5 Laboratory Assessments

Laboratory safety tests shall be collected at timepoints specified in the SoA, Details on sampling and procedures will be provided in supporting central and/or local Laboratory Manual.

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.

**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 | 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), 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, in particular when blood or protein is positive or strong positive. |
| Hormone panel (at screening only) | For females, FSH and estradiol. |
| Pregnancy test (at screening only) | For females of childbearing potential, serum or plasma pregnancy test. |

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 [redacted] 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.

This specimen will be destroyed once all results have been obtained.

#### 4.6.1.6 Anti-Drug Antibody Assessments

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

Blood samples will be obtained for measurement of anti-RO6867461 antibodies by a validated ELISA. Samples from patients receiving ranibizumab will be taken per the RO6867461 schedule to maintain the double-masked design of the study but will not be analyzed for ADA.

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 at the latest 2 years after the final closure of the database and finalization of the bioanalytical reports.

[redacted]

#### 4.6.2.1 Blood Samples

Blood samples for determination of plasma concentrations of RO6867461 will be collected at the timepoints specified in the SoA (see Appendix 1).

Plasma concentrations of RO6867461 will be measured by a specific validated ELISA. Samples may also be analyzed for ranibizumab by an appropriate assay.

[redacted]

[redacted]

[redacted]

### 4.6.3 Clinical Genotyping Sample

A mandatory whole blood sample will be taken for DNA extraction from every patient. The DNA may be used to study genes related to DME, DR, and angiogenesis (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 other mandatory blood samples. This specimen will be destroyed up to 2 years after the final closure of the clinical database.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 4.6.5 Disease-Specific Assessments

Except when noted otherwise (e.g., see SoA [Appendix 1] and below), 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 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.

The following ocular imaging assessments will be obtained for the study eye only, except at screening where either eye has a potential to meet all eligibility criteria, and will be forwarded to the Central Reading Center:

- 7-field or wide-field color FP
- EDI SD-OCT
- 7-field FFA or wide-field FFA
- *At study visit when different imaging assessments coincide, they should be obtained on the same day.*

#### 4.6.5.1 Ocular Safety Assessments

Ocular assessments will be performed as detailed in the SoA (see Appendix 1):

- BCVA using the ETDRS-like charts (see Section 4.6.5.2); performed prior to dilating eyes
- Slit-lamp examination (scales for grading flare/cells and vitreous hemorrhage density are detailed in Appendix 2)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Retinal imaging: FP (including but not limited to DR severity grading), SD-OCT, and FFA. Images will be forwarded to the Central Reading Center for grading and storage.
- 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. The method of IOP measurement (either Goldmann tonometry or Tono-pen) used must remain the same throughout the study.
- Assessment of ocular perfusion performed as soon as possible, but not later than 15 minutes post-treatment by using finger counting, hand movement, or light perception, as appropriate

#### 4.6.5.2 Efficacy and Pharmacodynamic Assessments

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

Additional PD sampling (e.g., where unscheduled PK sample is collected) and functional or imaging assessments can be performed at unscheduled visits at the discretion of the investigator (Section 4.6.7.5).

##### 4.6.5.2.1 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 drug arm assignment.

BCVA will be measured by using the set of three Precision Vision™ or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R). A VA 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 study eye and *treatment assignment and will only perform the refraction and BCVA assessment (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 the patient's refraction data from previous visits. The BCVA examiner is not allowed to perform any other tasks involving direct patient care.*

#### 4.6.5.2.2 Fundus Photography

Seven-field or wide-field FP will be performed at the study sites by trained and Central Reading Center-certified personnel. Where both 7-field and wide-field devices are available, wide-field FP should be performed. It is mandatory that the same device is used for the entire duration of the study.

FP images might include red-free, color, and infra-red, as further specified in the Central Reading Center Manual.

#### 4.6.5.2.3 Enhanced Depth Imaging Spectral Domain Optical Coherence Tomography

Enhanced Depth Imaging 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. Where Spectralis is not available at an investigational site, Cirrus, Topcon, or Optovue are acceptable devices. It is mandatory that the same device is used for the entire duration of the study.

Images should be acquired and transferred to the Central Reading Center according to specifications provided in the separate Central Reading Center Manual.

#### 4.6.5.2.4 Fundus Fluorescein Angiography

Seven-field FFA (30 degree field of view) or wide-field FFA (e.g., Optos, Spectralis) will be performed at all the study sites by trained and Central Reading Center-certified personnel. Where both devices are available, wide-field FFA should be performed. It is mandatory that the same device is used for the entire duration of the study.

Images should be acquired and transferred to the Central Reading Center according to specifications provided in the Central Reading Center Manual.

#### 4.6.5.2.5 Plasma Pharmacodynamic Biomarkers

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

- Change from baseline in plasma levels of VEGF and Ang-2

Any residual material from PD biomarker 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 samples will be destroyed up to 2 years after the final closure of the database and all intended data have been verified.

[redacted]

### 4.6.6 Amount of Blood to be Collected throughout the Study

Throughout the study, a total of approximately 185 mL of blood will be drawn from each patient, to perform clinical laboratory assessments, determine plasma concentrations and perform genetic and PD/exploratory assessments.

### 4.6.7 Timing of Study Assessments

#### 4.6.7.1 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 for enrolled patient and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and pretreatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria, including Central Reading Center confirmation of eligibility for a predefined set of imaging criteria, and defined list of Day 1 assessments (see below). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

Only one eye will be selected as the study eye. Where both eyes meet all eligibility criteria, the eye with worse BCVA will be defined as the study eye. Where both eyes meet all eligibility criteria and have the same BCVA letter score at Day 1, study eye selection is at the investigator's discretion.

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 examination within 4 weeks before study drug administration. The list of screening procedures is outlined in the SoA (see Appendix 1)

After the screening visit, ocular images of both eyes will be forwarded as soon as possible to the Central Reading Center for those patients who meet all non-ocular eligibility criteria (eligibility for safety labs, ECG, and pregnancy test, where appropriate, might be pending). The Central Reading Center will assess the image data submitted and confirm eligibility for study eye imaging criteria. Confirmation of eligibility by the Central Reading Center for the study eye imaging criteria is required.

On Day 1 prior to enrollment, all patient eligibility requirements are reviewed, and relevant eligibility criteria (Section 4.2) are confirmed, including but not limited to the following criteria:

- Baseline BCVA letter score of 73 to 24 letters (inclusive) in the study eye

- Absence of active intraocular inflammation in the study eye
- Absence of febrile illness within one week prior to Day 1,

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 reasons (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. *If patients meet criteria upon re-screening, they will receive a new screening number and will be treated as a new patient.*

*For each patient, if one eye does not meet eligibility criteria, then the second eye may be evaluated within the initial screening period. If the second eye meets the eligibility criteria, then the patient would retain the same screening number and would not be screened-failed.*

#### 4.6.7.2 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 SoAs (see Appendix 1).

Patients will receive their first IVT injection of either RO6867461 or comparator therapy into the study eye according to the randomization schedule and following established standard procedures. Patients will return to the eye clinic for study drug administration (every 4 weeks) and assessments as outlined in the SoA.

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for*

*a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab and exit the study. They willreceive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

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

On the day of *IVT administration of either study drug or ranibizumab*, IOP will be monitored prior to and at 30 minutes post-injection, and if IOP is ≥ 30 mmHg in the study eye, IOP should be re-assessed at 1 hour post-administration. Patients will be discharged at the discretion of the investigator.

[redacted]

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

#### 4.6.7.3 Assessments at Early Termination Visit

Patients who are withdrawn from the study *during the study drug administration period* but have not withdrawn consent should return for an early termination visit 28 (+7) days following the last study drug administration 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.

Patients could receive SoC treatment for DME after all assessments are completed at the 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.

#### 4.6.7.4 Assessments at Final Visit

Patients will return *to the investigational site every 4 weeks up to week 36 during observation period after* their final *dose of study drug at week 20.*

*If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab, exit the study, and receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

[redacted]

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

#### 4.6.7.5 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 a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug 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's non-compliance

#### 4.7.1.1 Discontinuation from Study Drug

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

- Pregnancy
- Drop in BCVA by ≥30 letters if considered to be adverse and related to study drug treatment in the study eye (compared with the last assessment of VA prior to the most recent treatment) and lasting more than 1 hour
- Endophthalmitis in the study eye

- Severe intraocular inflammation (i.e., 4+anterior chamber cell/flare or 4+vitritis; see the definitions of intraocular inflammation in Section 5.3.5 and grading scales for assessment in Appendix 2.
- 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 drug prematurely will be asked to return to the clinic for an early termination visit (as defined in Section 4.6.7.3) and will undergo assessments as outlined in the SoA. The primary reason for premature study drug 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 the consent has been withdrawn (see Section 4.6.7.3).

### 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 GCP

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events (systemic and ocular), *non-serious adverse events of special interest*; 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 GCP, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8 and 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 drug or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study drug (e.g., screening invasive procedures such as angiographies)

### 5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (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 adverse event recorded on the eCRF.

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

### 5.1.3 *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.*
- *The Safety Science Responsible for the program is accountable for determining the non-serious Adverse Events of Special Interest (AESI) for a protocol.*

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

An adverse event 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 2).
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight.

## 5.2 SAFETY PLAN

Based on the first-in-human Study BP28936 and ongoing Phase 2 Study BP29647, there have been no safety signals. The majority of adverse events were of mild and moderate intensity. No deaths occurred during the study period, and no premature withdrawals from the study as a result of serious adverse events were reported.

To 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, FP, and SD-OCT assessments), adverse event 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 adverse events (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 Section 5.4–5.6.

For each adverse event 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 adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

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

After initiation of study drug through the final visit, all adverse events, regardless of relationship to study drug, will be reported.

After *the final visit and/or subsequent follow-up phone call, as applicable,* investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6)

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

**Table 3 Adverse Event Severity Grading Scale**

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

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

### 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 adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

### 5.3.5 Procedures for Recording Adverse Events

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

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

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

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

  Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an adverse event. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Diagnosis versus Signs and Symptoms

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

#### 5.3.5.2 Adverse Events Occurring Secondary to Other Events

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

#### 5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity 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 adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

#### 5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study drug (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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with 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 adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should 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 adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study drug (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 adverse event.

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

Observations of the same clinically significant vital sign abnormality from visit to visit should 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 adverse event, the occurrence of either of the following:

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

#### 5.3.5.7 Deaths

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

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 General Medical History and Baseline Conditions eCRF.

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

#### 5.3.5.9 Worsening of Diabetic Macular Edema or Diabetic Retinopathy

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

#### 5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be serious adverse events:

- 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 adverse event.

#### 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 adverse event, unless it results in untoward medical effects.

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

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills 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 drug:

- Serious adverse events
- *non-serious adverse events of special interest*
- Sight-threatening adverse events
- 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 IRB/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 monitors contact details are listed in the "Protocol Administrative and Contact Information & List of Investigators."

### 5.4.2 Reporting Requirements for Serious Adverse Events Non-Serious Adverse Events of Special Interest, *and Sight-Threatening Adverse Events*

For reports of serious adverse events, *non-serious adverse events of special interest* , and sight-threatening adverse events (see Sections 5.1.2 and 5.1.3), investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the Serious Adverse Event Responsible within 24 hours.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the last dose of study drug. 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.

#### 5.4.3.2 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).

#### 5.4.3.3 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 considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. 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 5.4.3.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, *non-serious adverse events of special interest*, sight-threatening adverse events, 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 (as defined in Section 5.3.1). However, the Sponsor should be notified if the investigator becomes aware of any death, any other serious adverse event, *or sight-threatening adverse events 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 and sight-threatening 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 Investigator's Brochure
- 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 the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

## 6.1 DETERMINATION OF SAMPLE SIZE

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline at Week 24 in the *treatment-naïve patients*. Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 *treatment-naïve* patients randomized to Arms A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

*Approximately 60 previously IVT anti-VEGF treated patients will be enrolled in addition for exploratory analyses.*

## 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 drug, whether prematurely withdrawn from the study or not, will be included in the safety analysis. Patients will be grouped according to the *actual* treatment *received*.

### 6.3.2 Efficacy, Pharmacokinetic, and Pharmacodynamic Analysis Population

All patients who have received at least one dose of the study drug will be included in the efficacy, PK, and PD analysis population, with patients grouped according to the treatment assigned at randomization.

## 6.4 DEFINITION OF BASELINE

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

## 6.5 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.

## 6.6 SAFETY ANALYSES

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

### 6.6.1 Adverse Events

The original terms recorded on the eCRF by the investigator for adverse events will be standardized by the Sponsor.

Adverse events will be summarized by mapped term and appropriate thesaurus level.

### 6.6.2 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 by 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.

#### 6.6.2.1 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. Since 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.

#### 6.6.2.2 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.

### 6.6.3 Vital Signs

Vital sign 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.

### 6.6.4 Electrocardiogram 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.

### 6.6.5 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.

### 6.6.6 Ocular Assessments

Results of the following ocular assessments will be summarized by timepoint using descriptive summaries: BCVA, IOP, slit-lamp examination, indirect ophthalmoscopy,

FFA, FP, SD-OCT, and changes from baseline in these measurements will be tabulated. The presence of intraocular inflammation (see the definitions of intraocular inflammation in Section 5.3.5) and vitreous hemorrhage, as determined from the slit-lamp examination, will be tabulated by grade (according to grading scales for flare/cells and vitreous hemorrhage density; see Appendix 2).

### 6.6.7 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.

## 6.7 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized *treatment-naïve* patients, with patients grouped according to the treatment assigned at randomization. *Patients with previous IVT anti-VEGF will be analyzed separately. Unless there is strong evidence for RO6867461 effect modification by previous IVT anti-VEGF, analyses will be repeated in all randomized patients.*

### 6.7.1 Primary Efficacy Endpoint

The primary efficacy variable is the BCVA change from baseline at Week 24. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance will be used to account for within-patient correlation, but another variance-covariance structure 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 and C) and the control group (Arm A) for mean BCVA change from baseline at Week 24 *in the treatment-naïve patient population* . The model-based estimate of the difference between each of the treatment group (Arms B and C) and the control group (Arm A) at Week 24, together with 95% confidence and corresponding p-value will be reported as the primary efficacy measures in this population. The mean and 95% CI within each treatment group and for the difference between RO6867461 treatment groups (Arms B and C) and the control group (Arm A) at the other time points will also be reported. There will be no formal correction for multiple testing.

### 6.7.2 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% CI 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.

*Time to event endpoints will be tested with a two-sided stratified log rank test using the randomization stratification factors BCVA ETDRS letter score (64 letters or better vs. 63 letters or worse) and previous macular laser treatment as strata. Kaplan Meier curves will be displayed, and median time to event estimates and confidence limits of them will be computed.*

*Effect modification will be tested by adding a previous IVT anti-VEGF treatment status, treatment arm by visit interaction, and a treatment arm by visit by previous IVT anti-VEGF treatment status interaction terms to the above MMRM model. The treatment arm by visit by previous IVT anti-VEGF treatment status interaction term will be tested at a 10% type I error rate.*

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.

[redacted]

## 6.9 PHARMACOKINETIC ANALYSES

A non-linear mixed effects modeling approach (with NONMEM software [Beal and Sheiner 1998]) will be used to analyze the concentration-time data of RO6867461. Population and individual primary PK parameters (i.e., clearances and volumes) will be estimated, and the influence of various covariates (e.g., gender, body weight, 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.

## 6.10 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.

## 6.11 INTERIM ANALYSES

Two efficacy analyses to inform about possible future development options for RO6867461 are foreseen. They will not influence the study conduct. One interim efficacy analysis is foreseen after approximately 28 *treatment-naïve patients* in each treatment have completed the Week 24 visit and another one when approximately all patients have completed their Week 24 visit. A safety analysis will be performed if safety issues have been identified during ongoing review of the masked data.

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 and reading center 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 on line 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 Principal Investigator 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 Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

## 8. ETHICAL CONSIDERATIONS

### 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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 European Union (E.U.)/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

### 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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 Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements,

policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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).

# 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 in the United States 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 storage of laboratory samples (e.g., anti-RO6867461 antibody samples) prior to being shipped to Sponsor or its designee for analysis. Central reading will be used for ECG interpretation, and for ocular imaging analyses (FP, FFAs, SD-OCT). Data will be recorded by an EDC system using eCRFs (Section 7.2) or 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.

## 10. REFERENCES


Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480–7.

Albert DM, Jakobiec FA. Principles and Practice of Ophthalmology. 2nd ed. Philadelphia: WB Saunders Co, 2000.

Antonetti DA, Lieth E, Barber AJ, et al. Molecular mechanisms of vascular permeability in diabetic retinopathy. Semin Ophthalmol 1999;14:240–8.

Beal S, Sheiner L, editors. NONMEM users guides, NONMEM projects group. University of California, San Francisco. 1998.

Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmol 2013;120:1046–56.

[redacted]

Churchill AJ, Carter JG, Ramsden C, et al. VEGF polymorphisms are associated with severity of diabetic retinopathy. Invest Ophthalmol Vis Sci 2008;49:3611–6.

Davis S, Aldrich TH, Jones PF, et al. Isolation of angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning. Cell 1996;87:1161–9.

Dhoot DS, Pieramici DJ, Nasir M, et al. Residual edema evaluation with ranibizumab 0.5 mg and 2 mg formulations for diabetic macular edema (REEF study). Eye 2015;29:534-41.

Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report Number 9. Ophthalmol 1991;98(5 Suppl):766–85.

Fiedler U, Krissl T, Koidl S, et al. Angiopoietin-1 and angipoietin-2 share the same binding domains in the Tie-2 receptor involving the first Ig like loop and the epidermal growth factor-like repeats. J Biol Chem 2003;278:1721–7.

Gardner TW, Antonetti DA, Barber AJ, et al. Diabetic retinopathy: more than meets the eye. Surv Ophthalmol 2002;47(Suppl 2):S253–62.

Girach A, Lund-Andersen H. Diabetic macular oedema: a clinical overview. Int J Clin Pract 2007;61:88–97.

Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. J Clin Endocrinol Metab 2009;94:3171–82.

Hermann MM, van Asten F, Muether PS, et al. Polymorphisms in vascular endothelial growth factor receptor 2 are associated with better response rates to ranibizumab treatment in age-related macular degeneration. Ophthalmology 2014;121:905–10.

International Diabetes Federation (IDF). IDF Diabetes Atlas, 6th ed. 2013 [cited 06 October 2015]. Available from: www.idf.org/diabetesatlas

*Investigator's Brochure RO6867461, version 4, November 2015.*

Kaul K, Hodgkinson A, Tarr JM, et al. Is inflammation a common retinal-renal-nerve pathogenic link in diabetes? Curr Diabetes Rev. 2010;6:294–303.

[redacted]

Maisonpierre PC, Suri C, Jones PF, et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Science 1997;277:55–60.

Mitchell P, Banello F, Schmidt-Erfurth U, et al. The RESTORE study. Ophthalmol 2011;118:615–25.

Nguyen QD, Brown D, Marcus DM, et al. Ranibizumab for diabetic macular edema. Ophthalmol 2012;119:789–801.

Park SW, Yun JH, Kim JH, et al. Angiopoietin 2 induces pericyte apoptosis via $\alpha 3\beta 1$ integrin signaling in diabetic retinopathy. Diabetes 2014;63:93057–68.

Rangasamy S, Srinivasan R, Maestas J, et al. A potential role for angiopoietin 2 in the regulation of the blood–retinal barrier in diabetic retinopathy. IOVS 2011; 52:3784–91.

Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–51.

Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.

# Appendix 1
# Schedule of Assessments

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24[t] | Week 26[m] | Week 28[t] | Week 32[t] | Week 36[t] | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | Day 224 | Day 252 | | |
| Time Relative (h) | | 0 | 144 | 648 | 1320 | 1992 | 2664 | 3336 | 4008 | 4344 | 4680 | 5352 | 6024 | | |
| Visit Window | | | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +7 | |
| Assessments | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Eligibility | X | X[a] | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Medical History | X | X[a] | | | | | | | | | | | | | |
| Physical Examination | X | | | | | | | | X | | | | | X | |
| Anthropometric Measurements | X | | | | | | | | X | | | | | X | |
| Vital Signs[a] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG-12 lead[a] | X | | | | | | | | X | | | | | X | X |
| Hematology[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Blood Chemistry[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Urinalysis[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Coagulation[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Hormone Panel[b] | X | | | | | | | | | | | | | | |
| Pregnancy Test[b] | X | | | | | | | | | | | | | | X |
| Administration of Study Drug[c,p] | | X | | X | X | X | X | X | | | | | | | X |
| Administration of 0.3 mg ranibizumab[c] | | | | | | | | | X[r] | | X[r] | X[r] | X[r] | | |
| Safety Finger Count Vision[c,d] | | X | | X | X | X | X | X | X[s] | | X[s] | X[s] | X[s] | | X |
| IOP[a,l] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| BCVA[a,e] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Slit Lamp[a] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Indirect Ophthalmoscopy[a] | X | X[k] | X | X | X | X | X | X | X | | X | X | X | X | X |
| Fundus Photography[a,c] | X | X[k,o] | | | | | | | X | | X[q] | X[q] | X[q] | X | X |
| SD-OCT[a,c] | X | X[k] | X | X | X | X | X | X | X | | X | X | X | X | X |
| Angiography[a,c] | X | | | | | X | | | X | | X[q] | X[q] | X[q] | X | X |

# Appendix 1
# Schedule of Assessments (cont.)

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24[t] | Week 26[m] | Week 28[t] | Week 32[t] | Week 36[t] | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | Day 224 | Day 252 | | |
| Time Relative (h) | | 0 | 144 | 648 | 1320 | 1992 | 2664 | 3336 | 4008 | 4344 | 4680 | 5352 | 6024 | | |
| Visit Window | | | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +7 | |
| Assessments | | | | | | | | | | | | | | | |
| PK Sample[a] | | X | X | X | | X | | X | X | X | X[m,q] | X[m,q] | X[q] | X | X |
| PD Biomarkers Sample[a] | | X | X | X | | X | | | X | X | X[q] | X[q] | X[q] | X | X |
| Exploratory Plasma Biomarkers Sample[a] | | X | | | | X | | | X | | | | | X | X |
| Clinical Genotyping Sample[a,g,h] | | X | | | | | | | | | | | | | |
| Anti-Drug Antibody[a,f] | | X | X | X | | X | | X | X | | X[q] | X[q] | X[q] | X | X |
| [redacted] | | | | | | | | | | | | | | | |
| follow-up phone call[u] | | | | | | | | | X[s] | | X[s] | X[s] | X[s] | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Previous and Concomitant Treatments | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[a] Assessment prior to study drug or ranibizumab administration on days where treatment is administered

[b] For females only

[c] Assessment in study eye only; except at screening for imaging assessments (FP, EDI SD-OCT, FFA), where either eye has a potential to meet all eligibility criteria

[d] Finger count vision assessment asap after, and within maximum of 15 min from study drug or ranibizumab administration

[e] Performed prior to pupil dilation

[redacted]

[g] At day 1 but can be done at any other visit if the sample not collected at baseline

# Appendix 1
# Schedule of Assessments (cont.)

h Mandatory, except in countries or at investigational sites where IRB/EC does not approve

[redacted]

k Baseline assessments

l *IOP to be performed in both study and fellow eye. At visits with either study drug or ranibizumab administration the assessment post-treatment administration is in the study eye only.* If IOP ≥ 30 mmHg at 30 (±5) minutes post-treatment administration in the study eye, then IOP is measured again at 60 (±10) minutes. [redacted]

n At the discretion of the investigator abnormal values might be followed-up at an unscheduled visit

o Optional at Day 1

p *If a site has an unexpected issue, 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 administrations of study drug needs to be at least 21 days

q when this visit becomes the final visit

r *If pre-specified criteria are met*

s *If patient receives ranibizumab at that visit*

t *Visit becomes final visit when patient receives 0.3 mg ranibizumab based on meeting pre-specified criteria*

u *7 days after 0.3 mg ranibizumab administration (+/- 3 days)*

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

## GRADING SCALE FOR ANTERIOR CHAMBER FLARE OR CELLS

| Flare | |
|---|---|
| 0 | No protein is visible in the anterior chamber when viewed by an experienced observer using slit-lamp 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 slit-lamp 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 slit-lamp 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 slit-lamp beam is swept across the anterior chamber. |
| Trace | Few (1–3) cells are observed when the slit-lamp 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 slit-lamp 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 slit-lamp 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 slit-lamp 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 slit-lamp 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 2
# 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 slit-lamp examination. |
| 1+ | Retinal detail is visible; some hemorrhage is visible by ophthalmoscopy. |
| 2+ | Large retinal vessels are visible, but central retinal detail is not visible by ophthalmoscopy. |
| 3+ | Red reflex is visible, but no central retinal detail is seen posterior to the equator by ophthalmoscopy. |
| 4+ | No red reflex by ophthalmoscopy. |

## GRADING SCALE FOR VITREOUS CELLS

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

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

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

# Appendix 3
# Study Treatment Administration Procedure

## 1. PRE-INJECTION PROCEDURES

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

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

The above procedures (except where noted) will be conducted by the physician performing the IVT administration of study treatment. At the discretion of the investigator, patients will 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, $4 \times 4$ 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
- 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 wear a surgical face mask, put on gloves, 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 $4 \times 4$ 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

Physician must refrain from talking, coughing, or sneezing during the injection.

## 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, $4 \times 4$ 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 wear a surgical face mask, put on gloves, 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 $4 \times 4$ 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
- Physician must refrain from talking, coughing, or sneezing during the injection.

## 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, $4 \times 4$ 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 wear a surgical face mask, put on gloves, 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

Physician must refrain from talking, coughing, or sneezing during the injection.

## 5. INTRAVITREAL ADMINISTRATION OF STUDY TREATMENT

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

After preparing the study eye as outlined above,

- For RO6867461 or ranibizumab administration: insert the needle 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 5 for detailed post-injection procedures

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.

# AMENDMENT HISTORY FOR PROTOCOL BP30099, VERSION 3

## 1. SUBJECT: TITLE

### REASON FOR CHANGE:

The title has been updated from a 28 week to a 36 week study to reflect the changes to the protocol.

## 2. SUBJECT: PROTOCOL SYNOPSIS

### REASON FOR CHANGE:

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

## 3. SUBJECT: INCREASE OF SAMPLE SIZE

### REASON FOR CHANGE:

The text has been amended to include the recruitment of patients who have been previously treated with IVT anti-VEGF and to increase the sample size from 150 to 210 patients. The original sample size of 150 patients across the 3 arms was selected based on the primary efficacy outcome of mean change in BCVA from baseline at week 24 in treatment-naïve patients. However, it is not known if previously treated patients would benefit in the same way from RO6867461 treatment. To maintain the power of 80% to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%, 60 previously treated patients will be added to the original study sample of 150 treatment-naïve patients. These previously treated patients will be divided between the comparator arm A and the high dose RO6867461 arm C.

### SECTION 3.1.2 NUMBER OF PATIENTS

### New text:

*Up to 210 patients will be randomized.* Approximately 150 *treatment-naïve patients and approximately 60 patients who have been previously treated with IVT anti-VEGF* will be enrolled in the study. Approximately 50 *treatment-naïve* patients will be randomized ~~on~~*into* each arm (1:1:1 randomization scheme~~).~~*) and approximately 30 patients previously treated with IVT anti-VEGF will be randomized into arms A and C.*

### Old text:

Approximately 150 patients will be enrolled in the study. Approximately 50 patients will be randomized on each arm (1:1:1 randomization scheme).

## SECTION 6.1 DETERMINATION OF SAMPLE SIZE

### New text:

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline at Week 24~~.~~ *in the treatment-naïve patients.* Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 *treatment-naïve* patients randomized to Arms A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

*Approximately 60 previously IVT anti-VEGF treated patients will be enrolled in addition for exploratory analyses*

### Old text:

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline at Week 24. Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 patients randomized to Arms A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

## 4. SUBJECT: INCLUSION OF PREVIOUSLY IVT ANTI-VEGF TREATED PATIENTS

### REASON FOR CHANGE:

Inclusion of patients previously treated with IVT anti-VEGF therapy will enable the exploratory evaluation of the predictive effect of previous IVT anti-VEGF treatment on the efficacy of RO6867461. The results of these evaluations will inform late stage development and influence the design of phase 3 studies that will include previously treated patients.

## SECTION 1.3. STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

### New text:

This will be a Phase II proof-of concept study in ~~anti VEGF treatment naive~~ patients with center-involving DME (CI-DME). This study is designed to evaluate the effects of RO6867461 on visual function and retinal structure by assessing changes from baseline in BCVA (ETDRS letters) and anatomy (imaging procedures), respectively. In addition, the safety, tolerability, and pharmacokinetics will be evaluated in patients receiving up to 6 doses of RO6867461.

**Old text:**

None

**SECTION 2.1. PRIMARY OBJECTIVE,**

**New text:**

The primary objective of this study is:

- To evaluate the efficacy of RO6867461 compared with the active comparator in *treatment naïve* patients with CI-DME.

**Old text:**

The primary objective of this study is:

- To evaluate the efficacy of RO6867461 compared with the active comparator in patients with CI-DME

**SECTION 2.3. EXPLORATIVE OBJECTIVE,**

**New text:**

The exploratory objectives for this study are as follows:

- *To explore the predictive effect of previous IVT anti-VEGF treatment on efficacy of RO6867461*
- *To evaluate the efficacy and safety of RO6867461 compared with the active comparator in patients with CI-DME with previous IVT anti-VEGF treatment.*
- [redacted]
- [redacted]
- To evaluate improvement in DR severity score

**Old text:**

The exploratory objectives for this study are as follows:

- [redacted]
- [redacted]
- To evaluate improvement in DR severity score

**SECTION 3.1.3 INTERNAL MONITORING COMMITTEE,**

**New text:**

A Roche Internal Monitoring Committee (IMC) will be responsible in the event of an interim analysis of efficacy for operational/administrative/study related purposes and/or

for safety data monitoring. Two efficacy analyses are foreseen, one after approximately 28 *treatment naïve* patients in each treatment arm have completed the Week 24 visit, and one when approximately all patients have completed the Week 24 visit. A safety analysis may be performed if safety issues have been identified during ongoing review of the masked data.

**Old text:**

A Roche Internal Monitoring Committee (IMC) will be responsible in the event of an interim analysis of efficacy for operational/administrative/study related purposes and/or for safety data monitoring. Two efficacy analyses are foreseen, one after approximately 28 patients in each treatment arm have completed the Week 24 visit, and one when approximately all patients have completed the Week 24 visit. A safety analysis may be performed if safety issues have been identified during ongoing review of the masked data.

## SECTION 3.2.2. RATIONALE FOR STUDY POPULATION,

**New text:**

This study will be conducted in patients with vision loss due to DME who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (see Section 4.2.1 and Section 4.2.2).

*Both treatment naïve DME patients and prior IVT anti-VEGF treated DME patients will be included. The aim is to evaluate the efficacy of RO6867461 compared with the active comparator in treatment naïve patients with CI-DME. Inclusion of treatment naïve and previously anti-VEGF treated patients will enable the exploratory evaluation of the predictive effect of previous IVT anti-VEGF treatment on efficacy of RO6867461.*

**Old text:**

This study will be conducted in patients with vision loss due to DME who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (see Section 4.2.1 and Section 4.2.2).

## SECTION 3.2.3 RATIONALE FOR CONTROL GROUP,

**New text:**

This study is an interventional superiority study aiming to evaluate the efficacy of RO6867461, as compared with standard of care anti-VEGF therapy in ~~anti-VEGF treatment naive~~ patients with DME. Anti-VEGF therapy is a well-established SoC in patients with DME, and placebo, sham injection, or macular laser are no longer an ethically acceptable alternative given the improvements in visual and anatomic outcomes associated with anti-VEGF treatment.

**Old text:**

This study is an interventional superiority study aiming to evaluate the efficacy of RO6867461, as compared with standard of care anti-VEGF therapy in anti-VEGF treatment-naive patients with DME. Anti-VEGF therapy is a well-established SoC in patients with DME, and placebo, sham injection, or macular laser are no longer an ethically acceptable alternative given the improvements in visual and anatomic outcomes associated with anti-VEGF treatment.

## SECTION 3.3.3 EFFICACY AND PHARMACODYNAMICS OUTCOME MEASURES,

**New text:**

*The primary analysis population will be treatment naïve patients. Additional analyses may be performed in the overall population and in patients previously treated with IVT anti-VEGF.*

**Old text:**

None

## SECTION 3.3.3.1. PRIMARY EFFICACY OUTCOME MEASURE,

**New text:**

The primary efficacy outcome measure is the mean change *in BCVA (ETDRS letters)* from baseline ~~in BCVA~~ at Week 24 ~~by using the ETDRS modified charts~~*in treatment-naïve patients*.

**Old text:**

The primary efficacy outcome measure is the mean change from baseline in BCVA at Week 24 by using the ETDRS-modified charts.

## SECTION 3.3.4. EXPLORATORY OUTCOME MEASURES,

**New text:**

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

*BCVA:*

- *Difference in mean BCVA change from baseline between the treatment-naïve patients and patients with previous IVT anti-VEGF (differential effect of RO6867461)*
- *Proportion of patients with BCVA ≥69 letters (20/40 or better) over time*
- *Proportion of patients with BCVA ≥ 84 letters (20/20 or better) over time*

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

*Durability-related exploratory outcome measures:*

- *Time to increase of CST by ≥ 50µm and/or loss of ≥ 5 letters of BCVA due to DME compared to values at Week 20*
- *Time to treatment with 0.3 mg ranibizumab after Week 20*

[redacted]

**Old text:**

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

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

[redacted]

## SECTION 4.2.2. EXCLUSION CRITERIA,

### New text:

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

**Ocular criteria for study eye:**

- *Any signs of high-risk* PDR *defined as:*
    - *any vitreous or pre-retinal hemorrhage*
    - *NVE ≥ 1/2 disc area within an area equivalent to the standard mydriatic ETDRS 7- field on clinical examination*
    - *NVD ≥ 1/3 disc area on clinical examination*
- Any IVT anti-VEGF treatment *within 3 months* prior to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- *Any IVT~~,~~ or periocular corticosteroid~~, or corticosteroid implants~~ treatment- within 3months prior to Day 1,* ~~except for management~~. *Any history of* ~~complication of cataract surgery~~*Iluvien or Ozurdex implants prior to Day 1 will not be permitted*
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP≥25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions *in the study eye*:**

- History of rubeosis ~~in the study eye~~
- Any current or history of ocular disease ~~in the study eye~~ other than DME that may confound assessment of the macula or affect central vision (e.g., AMD, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- *Any current ocular condition for which, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, non-retinal condition)*
- Any active ocular infection ~~in *the study* eye at~~*on* Day 1
- Any active intraocular inflammation (grade trace or above) ~~in *the study* eye at~~*on* Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment ~~for a retinal condition~~ within 7 days prior to Day 1

- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 needs to be controlled by antihypertensive medication, the patient ~~can become eligible if~~*should be taking the same* medication ~~is taken~~ continuously for at least 1 month prior to Day 1.
- Patients with glycosylated hemoglobin HbA1c≥*12*% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with IMP in the 3 months prior to Day 1

**Old text:**

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

**Ocular criteria for study eye:**

- Any PDR
- Any IVT anti-VEGF treatment prior to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- Any IVT, periocular corticosteroid, or corticosteroid implants treatment prior to Day 1, except for management of complication of cataract surgery
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP $\geq$25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions:**

- History of rubeosis in the study eye
- Any current or history of ocular disease in the study eye other than DME that may confound assessment of the macula or affect central vision (e.g., AMD, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- Any active ocular infection in *the study* eye at Day 1
- Any active intraocular inflammation (grade trace or above) in *the study* eye at Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment for a retinal condition within 7 days prior to Day 1
- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 30 or more minutes later. If the patient's BP needs

to be controlled by antihypertensive medication, the patient can become eligible if medication is taken continuously for at least 1 month prior to Day 1.

- Patients with glycosylated hemoglobin HbA1c *>12*% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with IMP in the 3 months prior to Day 1

**SECTION 4.3.1. TREATMENT ASSIGNMENT,**

**New text:**

~~Patients~~ *Treatment naïve patients* will be randomized in a 1:1:1 ratio to one of the ~~study drug arms:~~*arms A, B and C, respectively. Patients previously treated with IVT anti-VEGF will be randomized in a 1:1 ratio to arms A and C.:*

- Arm A: 0.3 mg ranibizumab IVT ~~every 4 weeks for 24 weeks (7 injections)~~
- Arm B: 1.5 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~
- Arm C: 6 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab and*

*exit the study. They will receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

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 *through week 20*), the IxRS will assign the appropriate study treatment kit to be used.

Randomization will be stratified for the factor below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (64 letters or better vs. 63 letters or worse)
- Previous Macular Laser treatment (Yes/No)
- *Previous IVT anti-VEGF treatment in study eye (Yes/No)*

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

### Old text:

Patients will be randomized in a 1:1:1 ratio to one of the study drug arms:

- Arm A: 0.3 mg ranibizumab IVT every 4 weeks for 24 weeks (7 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24

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 factor below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (64 letters or better vs. 63 letters or worse)
- Previous Macular Laser treatment (Yes/No)

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

## SECTION 6.1. DETERMINATION OF SAMPLE SIZE,

### New text:

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline at Week 24. *in the treatment-naïve patients.* Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 *treatment-naïve* patients randomized to Arms A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

*Approximately 60 previously IVT anti-VEGF treated patients will be enrolled in addition for exploratory analyses.*

### Old text:

The sample size is based on the primary efficacy outcome of mean change in BCVA from baseline at Week 24. Each RO6867461 dose (Arms B and C) will be compared with the control group (Arm A).

Consider 50 patients randomized to Arms A, B, and C, with a drop-out rate of 10%. Assuming a standard deviation of 11 letters, this sample size provides 80% power to detect a true difference of 5 letters at the one-sided $\alpha$ level of 10%. The minimum detectable difference is approximately 3 letters.

## SECTION 6.7. EFFICACY ANALYSES,

### New text:

The primary and secondary efficacy analyses will include all randomized *treatment-naïve* patients, with patients grouped according to the treatment assigned at randomization. *Patients with previous IVT anti-VEGF will be analyzed separately. Unless there is strong evidence for RO6867461 effect modification by previous IVT anti-VEGF, analyses will be repeated in all randomized patients.*

### Old text:

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

## SECTION 6.7.1 PRIMARY EFFICACY ENDPOINT

### New text:

The primary efficacy variable is the BCVA change from baseline at Week 24. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of

treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance ~~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 and C) and the control group (Arm A) for mean BCVA change from baseline at Week 24~~.~~ *in the treatment-naïve patient population* . The model-based estimate of the difference between each of the treatment group (Arms B and C) and the control group (Arm A) at Week 24, together with 95% confidence and corresponding p-value will be reported as the primary efficacy measures in this population. The mean and 95% CI within each treatment group and for the difference between RO6867461 treatment groups (Arms B and C) and the control group (Arm A) at the other ~~timepoints~~*time points* will also be reported. There will be no formal correction for multiple testing.

**Old text:**

The primary efficacy variable is the BCVA change from baseline at Week 24. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance 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 and C) and the control group (Arm A) for mean BCVA change from baseline at Week 24. The model-based estimate of the difference between each of the treatment group (Arms B and C) and the control group (Arm A) at Week 24, together with 95% confidence and corresponding p-value will be reported as the primary efficacy measures in this population. The mean and 95% CI within each treatment group and for the difference between RO6867461 treatment groups (Arms B and C) and the control group (Arm A) at the other timepoints will also be reported. There will be no formal correction for multiple testing.

## SECTION 6.11 INTERIM ANALYSIS

**New text:**

Two efficacy analyses to inform about possible future development options for RO6867461 are foreseen. They will not influence the study conduct. ~~The first~~*One* interim efficacy analysis is foreseen after approximately 28 *treatment-naïve patients* in each treatment have completed the Week 24 visit and ~~the second~~*another* one when approximately all patients have completed their Week 24 visit. A safety analysis will be performed if safety issues have been identified during ongoing review of the masked data.

**Old text:**

Two efficacy analyses to inform about possible future development options for RO6867461 are foreseen. They will not influence the study conduct. The first interim efficacy analysis is foreseen after approximately 28 patients in each treatment have completed the Week 24 visit and the second one when approximately all patients have completed their Week 24 visit. A safety analysis will be performed if safety issues have been identified during ongoing review of the masked data.

## 5. SUBJECT: CHANGE IN STUDY DESIGN

**REASON FOR CHANGE:**

The study design was modified to enable the evaluation of whether the durability of effect is longer following treatment with RO6867461 than with ranibizumab, as measured by BCVA and SD-OCT. The original study design consisted of a fixed assessment at 8 weeks after the last dose. The new design will add an additional observational period of up to 16 weeks. During this period, once the patient meets pre-specified criteria, they will be provided with a single dose of 0.3mg of Ranibizumab, which is the current standard-of-care for DME. This approach will provide informative data for the phase 3 study design (inclusion of Q8W, Q12W, or Q16W arm).

**SECTION 3.1. DESCRIPTION OF STUDY,**

**New text:**

This is a multiple-center, multiple-dose, randomized, active comparator–controlled, double-masked, three parallel group, ~~28~~*36*-week study in patients with CI-DME.

**Old text:**

This is a multiple-center, multiple-dose, randomized, active comparator–controlled, double-masked, three parallel group, 28-week study in patients with CI-DME.

**SECTION 3.1.1. OVERVIEW OF THE STUDY DESIGN,**

**New text:**

The three groups of this study are as follows (see Figure 1):

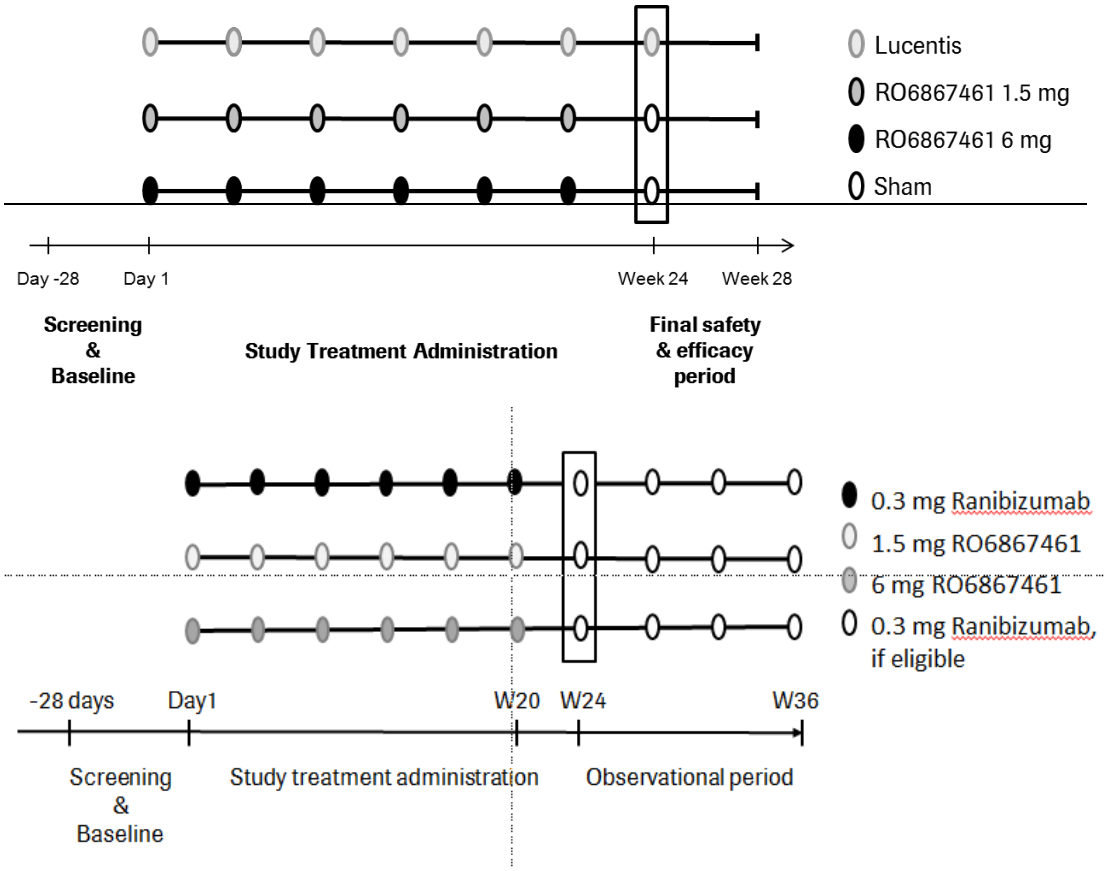
- Arm A: 0.3 mg ranibizumab IVT ~~every 4 weeks for 24 weeks (7 injections)~~
- Arm B: 1.5 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~
- Arm C: 6 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every*

*4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab, and exit the study. They will receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

Only one eye will be selected as the study eye (see Section 4.3.1).

**Figure 1 Study Design**




Q4W = every 4 weeks.

The total duration of the study for each patient will be up to ~~32~~*40* weeks, divided as follows (see ~~Figure 1~~*Figure 1*):

- Screening: ~~up~~*Up* to 4 weeks
- Baseline: Day 1
- Study treatment administration~~: from~~ *period: From* Day 1 to Week ~~24~~*20*

- ~~Final safety and efficacy~~*Observational period: From Week 20* up to Week ~~28~~*36*
- *Safety follow up call: During the observational period and 7 days after ranibizumab administration*

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 the Schedule of Assessments (SoA; see Appendix 1), are completed.

If a site has an unexpected issue (e.g., the 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 unmasked and masked 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.

**Old text:**

The three groups of this study are as follows (see Figure 1):

- Arm A: 0.3 mg ranibizumab IVT every 4 weeks for 24 weeks (7 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24

Only one eye will be selected as the study eye (see Section 4.3.1).

The total duration of the study for each patient will be up to 32 weeks, divided as follows (see Figure 1):

- Screening: up to 4 weeks
- Baseline: Day 1
- Study treatment administration: from Day 1 to Week 24
- Final safety and efficacy period: up to Week 28

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 the Schedule of Assessments (SoA; see Appendix 1), are completed.

If a site has an unexpected issue (e.g., the 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 unmasked and masked 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.

## SECTION 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 ~~28~~*36* weeks after the last patient is enrolled.

### Old text:

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur 28 weeks after the last patient is enrolled.

## SECTION 3.3.3.2. SECONDARY EFFICACY OUTCOME MEASURES,

### New text:

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 ≥15 letters from baseline BCVA at Week 24
- Proportion of patients with BCVA ≥69 letters (20/40 or better) at Week 24
- Proportion of patients with BCVA ≥84 letters (20/20 or better) at Week 24
- ~~Mean change in BCVA from baseline to Week 28~~

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 24 ~~and 28~~
- Mean change from baseline in mean CST (1 mm diameter) at Week 24 ~~and 28~~
- Proportion of patients with resolution of subretinal and intraretinal fluid at Week 24 ~~and 28~~

Anatomic outcome measures by FFA:

- Proportion of patients with resolution of leakage at the macula at Week 24
- Change from baseline in the size of the foveal avascular zone at Week 24

### Old text:

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 ≥15 letters from baseline BCVA at Week 24
- Proportion of patients with BCVA ≥69 letters (20/40 or better) at Week 24
- Proportion of patients with BCVA ≥84 letters (20/20 or better) at Week 24
- Mean change in BCVA from baseline to Week 28

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 24 and 28
- Mean change from baseline in mean CST (1 mm diameter) at Week 24 and 28
- Proportion of patients with resolution of subretinal and intraretinal fluid at Week 24 and 28

Anatomic outcome measures by FFA:

- Proportion of patients with resolution of leakage at the macula at Week 24
- Change from baseline in the size of the foveal avascular zone at Week 24

**SECTION 3.3.4 EXPLORATORY OUTCOME MEASURES,**

**New text:**

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

*BCVA:*

- *Difference in mean BCVA change from baseline between the treatment-naïve patients and patients with previous IVT anti-VEGF (differential effect of RO6867461)*
- *Proportion of patients with BCVA ≥69 letters (20/40 or better) over time*
- *Proportion of patients with BCVA ≥ 84 letters (20/20 or better) over time*

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

*Durability-related exploratory outcome measures:*

- *Time to increase of CST by ≥ 50µm and/or loss of ≥ 5 letters of BCVA due to DME compared to values at Week 20*
- *Time to treatment with 0.3 mg ranibizumab after Week 20*

[redacted]

[redacted]

**Old text:**

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

Disease-related exploratory outcome measure:

- Proportion of patients with DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24

Anatomic exploratory outcome measures:

- Change from baseline in macular perfusion and leakage by FFA at Week 12
- Change from baseline in peripheral perfusion and leakage by FFA at Week 24

[redacted]

**SECTION 4.3.1 TREATMENT ASSIGNMENT,**

**New text:**

~~Patients~~ *Treatment naïve patients* will be randomized in a 1:1:1 ratio to one of the ~~study drug arms:~~*arms A, B and C, respectively. Patients previously treated with IVT anti-VEGF will be randomized in a 1:1 ratio to arms A and C.:*

- Arm A: 0.3 mg ranibizumab IVT ~~every 4 weeks for 24 weeks (7 injections)~~
- Arm B: 1.5 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~
- Arm C: 6 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab and exit the study. They will receive a follow up phone call 7 days after the dose of*

*ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

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 *through week 20*), the IxRS will assign the appropriate study treatment kit to be used.

Randomization will be stratified for the factor below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (64 letters or better vs. 63 letters or worse)
- Previous Macular Laser treatment (Yes/No)
- *Previous IVT anti-VEGF treatment in study eye (Yes/No)*

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

### Old text:

Patients will be randomized in a 1:1:1 ratio to one of the study drug arms:

- Arm A: 0.3 mg ranibizumab IVT every 4 weeks for 24 weeks (7 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24

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 factor below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (64 letters or better vs. 63 letters or worse)
- Previous Macular Laser treatment (Yes/No)

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

## SECTION 4.3.1.1. CRITERIA FOR TREATMENT WITH RANIBIZUMAB DURING OBSERVATIONAL PERIOD,

### New text:

*At each visit following the last dose of study treatment (week 20 visit), BCVA will be assessed and SD-OCT imaging will be performed (except for week 26 visit).*

*BCVA and CST values obtained at week 24 will be compared to those obtained at visit week 20. BCVA and CST values obtained at weeks 28, 32 and 36 will be compared to those of week 24.*

*If the patient meets both of the following criteria the patient should receive a single dose of 0.3 mg ranibizumab and will exit the study~~.~~:*

- *CST increased by ≥ 50 µm*
- *BCVA decreased by ≥ 5 letters due to DME*

**Old text:**

None

**SECTION 4.4 STUDY TREATMENT,**

**New text:**

In this protocol, study ~~treatment~~*drug* includes IVT injections of ~~study drugs (~~RO6867461 and active comparator ranibizumab~~) and sham administration. The latter is used to maintain double masking on Arms B and C on Week 24 visit~~.

**Old text:**

In this protocol, study treatment includes IVT injections of study drugs (RO6867461 and active comparator ranibizumab) and sham administration. The latter is used to maintain double-masking on Arms B and C on Week 24 visit.

**SECTION 4.4.1.3 RANIBIZUMAB DURING OBSERVATIONAL PERIOD,**

**New text:**

*Ranibizumab will be provided by the Sponsor via the IxRS. Proper drug accountability will be performed by the site.*

**Old text:**

None

**SECTION 4.4.1.3 SHAM**

**New text:**

None

**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 the 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.

## SECTION 4.4.2.1. RO6867461 AND RANIBIZUMAB,

**New text:**

Patients will be given 50 µL IVT injection of RO6867461 or ranibizumab into the study eye ~~or a sham administration~~ according the randomization schedule as described in the Overview of Study Design (see Section 3.1.1.).

- Arm A: 0.3 mg ranibizumab IVT ~~every 4 weeks for 24 weeks (7 injections)~~
- Arm B: 1.5 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~
- Arm C: 6 mg RO6867461 IVT ~~every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24~~

The pharmacist or designee responsible for dispensing *study* ~~treatment~~*drug* will prepare the correct *study* ~~treatment~~*drug* (RO6867461~~,~~ *or* ranibizumab ~~or sham~~), where applicable, as assigned by IxRS. A fixed volume of 50 µL will be injected for all study drugs and doses.

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 1 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 | 0.3 mg | NA | 50 µL |

NA – not applicable; IVT – intravitreal.

Detailed stepwise instructions for the preparation of RO6867461~~,~~ *or* 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-*study* ~~treatment~~*drug* administration procedures as well as instructions for performing the IVT are provided in Appendix 4~~.~~*3*.

A specified filter needle must be used for each dose preparation of RO6867461 or ranibizumab per the instructions provided in the Pharmacy Manual. All materials to

dilute/prepare and administer *study* ~~treatment~~*drug* 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, leftover 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.

**Old text:**

Patients will be given 50 μL IVT injection of RO6867461 or ranibizumab into the study eye or a sham administration according the randomization schedule as described in the Overview of Study Design (see Section 3.1.1).

- Arm A: 0.3 mg ranibizumab IVT every 4 weeks for 24 weeks (7 injections)
- Arm B: 1.5 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24
- Arm C: 6 mg RO6867461 IVT every 4 weeks for 20 weeks (6 injections), followed by 1 sham administration at Week 24

The pharmacist or designee responsible for dispensing study treatment will prepare the correct study treatment (RO6867461, ranibizumab or sham), where applicable, as assigned by IxRS. A fixed volume of 50 μL will be injected for all study drugs and doses.

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 | 0.3 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-study treatment administration procedures as well as instructions for performing the IVT are provided in Appendix 43..

A specified filter needle must be used for each dose preparation of RO6867461 or ranibizumab per the instructions provided in the Pharmacy Manual. All materials to dilute/prepare and administer study treatment 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, leftover 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.

## SECTION 4.4.4 SHAM BOXES ACCOUNTABILITY,

### New text:

~~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).~~

### Old text:

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).

## SECTION 4.6.7.2. ASSESSMENT DURING TREATMENT,

### New text:

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 SoAs (see Appendix 1~~ and Appendix 2~~).

Patients will receive their first IVT injection of either RO6867461 or comparator therapy into the study eye according to the randomization schedule and following established standard procedures. Patients will return to the eye clinic for study ~~treatment~~*drug* administration (every 4 weeks) and assessments as outlined in the SoA. ~~Patients will be administered the same study drug into the study eye throughout the study period; except for the patients randomized on Arms B and C, who will receive a sham administration on Week 24 to maintain the double masking.~~

*This study will consist of a treatment period (20 weeks) and an observational period (up to 16 weeks), for a total study length of up to 36 weeks. During the treatment period, the study drug will be administered to the patients on Day 1 and on every 4th week, for a total of 6 injections. During the observational period, patients will be evaluated every 4th week. If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1 the patients will receive a single dose of 0.3 mg ranibizumab and exit the study. They will receive a follow up phone call 7 days after the dose of ranibizumab to evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

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

On the day of ~~dosing~~ *IVT administration of either study drug or ranibizumab*, IOP will be monitored prior to and at 30 minutes post-injection, and if IOP is $\geq$ 30 mmHg in the study eye, IOP should be re-assessed at 1 hour post-administration ~~*(see Appendix 2)*~~. Patients will be discharged at the discretion of the investigator.

~~After the last study treatment visit (Week 24), patients~~ [redacted]

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

### Old text:

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 SoAs (see Appendix 1 and Appendix 2).

Patients will receive their first IVT injection of either RO6867461 or comparator therapy into the study eye 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 drug into the study eye throughout the study period; except for the patients randomized on Arms B and C, who will receive a sham administration on Week 24 to maintain the double-masking.

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

On the day of dosing, IOP will be monitored *prior to and* at 30 minutes post-injection, and if IOP is ≥30 mmHg in the study eye, IOP should be re-assessed at 1 hour post-administration (See Appendix 2). Patients will be discharged at the discretion of the investigator.

[redacted]

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

## SECTION 4.6.7.4 ASSESSMENT AT FINAL VISIT,

**New text:**

Patients will return ~~for~~ *to the investigational site every 4 weeks up to week 36 during observation period after* their final ~~visit with assessments as outlined in the SoA~~*dose of study drug at* ~~Week 28~~*week 20.*

~~Patients can receive SoC treatment for DME after all assessments are completed on Week 28. SoC treatment after the final visit will not be supplied by the Sponsor.~~

*If during any of these evaluations the patients meet the pre-specified criteria (see Section 4.3.1.1), the patients will receive a single dose of 0.3 mg ranibizumab, exit the study, and receive a follow up phone call 7 days after the dose of ranibizumab to*

*evaluate any potential adverse events. Otherwise, patients will exit the study once they have completed the observational visit at week 36.*

[redacted]

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

**Old text:**

Patients will return for their final visit with assessments as outlined in the SoA at Week 28.

Patients can receive SoC treatment for DME after all assessments are completed on Week 28. 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.

**SECTION 5.3.1 ADVERSE EVENT REPORTING PERIOD,**

**New text:**

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

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

After initiation of study drug *through the final visit*, all adverse events, regardless of relationship to study drug, will be reported ~~until the final visit~~.

~~After a period of 28 days from the last dose of study drug~~*After the final visit and/or subsequent follow-up phone call, as applicable,* investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6)

**Old text:**

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the final visit.

After a period of 28 days from the last dose of study drug, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6)

**SECTION 6.7.2. SECONDARY EFFICACY ENDPOINTS,**

**New text:**

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% CI 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.

~~For the duration of drug effect, the same statistical models will be used. Change from baseline to week 28 and change from week 24 to week 28 will be analyzed as appropriate.~~

*Time to event endpoints will be tested with a two-sided stratified log rank test using the randomization stratification factors BCVA ETDRS letter score (64 letters or better vs. 63 letters or worse) and previous macular laser treatment as strata. Kaplan Meier curves will be displayed, and median time to event estimates and confidence limits of them will be computed.*

*Effect modification will be tested by adding a previous IVT anti-VEGF treatment status, treatment arm by visit interaction, and a treatment arm by visit by previous IVT anti-VEGF treatment status interaction terms to the above MMRM model. The treatment arm by visit by previous IVT anti-VEGF treatment status interaction term will be tested at a 10% type I error rate.*

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.

### Old text:

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% CI 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.

For the duration of drug effect, the same statistical models will be used. Change from baseline to week 28 and change from week 24 to week 28 will be analyzed as appropriate.

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.

## SECTION APPENDIX 1, SCHEDULE OF ASSESSMENTS

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24[t] | Week 26[m] | Week 28[t] | Week 32[t] | Week 36[t] | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | Day 224 | Day 252 | | |
| Time Relative (h) | | 0 | 144 | 648 | 1320 | 1992 | 2664 | 3336 | 4008 | 4344 | 4680 | 5352 | 6024 | | |
| Visit Window | | | +/-3 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +7 | |
| Assessments | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Eligibility | X | X[a] | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Medical History | X | X[a] | | | | | | | | | | | | | |
| Physical Examination | X | | | | | | | | X | | | | | X | |
| Anthropometric Measurements | X | | | | | | | | X | | | | | X | |
| Vital Signs[a] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG-12 lead[a] | X | | | | | | | | X | | | | | X | X |
| Hematology[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Blood Chemistry[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Urinalysis[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Coagulation[a] | X | | | | | X | | | X[n] | | | | | X | X |
| Hormone Panel[b] | X | | | | | | | | | | | | | | |
| Pregnancy Test[b] | X | | | | | | | | | | | | | | X |
| Administration of Study Drug[c,p] | | X | | X | X | X | X | X | | | | | | | X |
| Administration of 0.3 mg ranibizumab[c] | | | | | | | | | X[r] | | X[r] | X[r] | X[r] | | |
| Safety Finger Count Vision[c,d] | | X | | X | X | X | X | X | X[s] | | X[s] | X[s] | X[s] | | X |
| IOP[a,l] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| BCVA[a,e] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Slit Lamp[a] | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Indirect Ophthalmoscopy[a] | X | X[k] | X | X | X | X | X | X | X | | X | X | X | X | X |
| Fundus Photography[a,c] | X | X[k,o] | | | | | | | X | | X[q] | X[q] | X[q] | X | X |
| SD-OCT[a,c] | X | X[k] | X | X | X | X | X | X | X | | X | X | X | X | X |
| Fundus Fluorescein Angiography[a,c] | X | | | | | X | | | X | | X[q] | X[q] | X[q] | X | X |

## SECTION APPENDIX 1, SCHEDULE OF ASSESSMENTS (CONT.)

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24[t] | Week 26[m] | Week 28[t] | Week 32[t] | Week 36[t] | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | Day 224 | Day 252 | | |
| Time Relative (h) | | 0 | 144 | 648 | 1320 | 1992 | 2664 | 3336 | 4008 | 4344 | 4680 | 5352 | 6024 | | |
| Visit Window | | | +/-3 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +7 | |
| Assessments | | | | | | | | | | | | | | | |
| PK Sample[a] | | X | X | X | | X | | X | X | X | X[m,q] | X[m,q] | X[q] | X | X |
| PD Biomarkers Sample[a] | | X | X | X | | X | | | X | X | X[q] | X[q] | X[q] | X | X |
| Exploratory Plasma Biomarkers Sample[a] | | X | | | | X | | | X | | | | | X | X |
| Clinical Genotyping Sample[a,g,h] | | X | | | | | | | | | | | | | |
| Anti-Drug Antibody[a,f] | | X | X | X | | X | | X | X | | X[q] | X[q] | X[q] | X | X |
| [redacted] | | | | | | | | | | | | | | | |
| Follow-Up Phone Call[u] | | | | | | | | | X[s] | | X[s] | X[s] | X[s] | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Previous and Concomitant Treatments | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[a] Assessment prior to study ~~treatment drug~~ *drug or ranibizumab* administration on days where ~~study~~ treatment is administered

[b] For females only

[c] Assessment in study eye only; except at screening for imaging assessments (FP, *EDI* SD-OCT, FFA), where either eye has a potential to meet all eligibility criteria

[d] Finger count vision assessment asap after, and within maximum of 15 min from study drug or ranibizumab administration

[e] ~~Multiple assessments on a single visit day, details on timing in Appendix 2.~~

[ef] Performed prior to pupil dilation

[■] [redacted]

gh At day 1 but can be done at any other visit if the sample not collected at baseline

hi Mandatory, except in countries or at investigational sites where IRB/EC does not approve

[redacted]

kl Baseline assessments

lm *IOP to be performed in both study and fellow eye. At visits with either study drug or ranibizumab administration the assessment post-treatment administration is in the study eye only.* If IOP ≥ 30 mmHg at 30 (±5) minutes post-treatment administration in the study eye, then IOP is measured again at 60 (±10) minutes. [redacted]

no At the discretion of the investigator abnormal values might be followed-up at an unscheduled visit ~~Only for the tests where abnormal values at Week 24 require follow up, and at the discretion of the investigator~~

op Optional at Day 1

pq *If a site has an unexpected issue, 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 administrations of study drug needs to be at least 21 days

q *when this visit becomes the final visit*

r *If pre-specified criteria are met*

s *If patient receives ranibizumab at that visit*

t *Visit becomes final visit when patient receives 0.3 mg ranibizumab based on meeting pre-specified criteria*

**Old text:**

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 26 [n] | Final Visit Week 28 | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | | |
| **Visit Window** | | | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| **Assessments** | | | | | | | | | | | | | |
| Informed Consent | x | | | | | | | | | | | | |
| Eligibility | x | x [a] | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | |
| Medical History | x | x [a] | | | | | | | | | | | |
| Physical Examination | x | | | | | | | | | | x | x | |
| Anthropometric Measurements | x | | | | | | | | | | x | x | |
| Vital Signs [a] | x | x [l] | x | x | x | x | x | x | x | x [n] | x | x | x |
| ECG-12 Lead | x | | | | | | | | | | x | x | x |
| Hematology [a] | x | | | | | x | | | x | | x [o] | x | x |
| Blood Chemistry [a] | x | | | | | x | | | x | | x [o] | x | x |
| Urinalysis [a] | x | | | | | x | | | x | | x [o] | x | x |
| Coagulation [a] | x | | | | | x | | | x | | x [o] | x | x |
| Hormone Panel [b] | x | | | | | | | | | | | | |
| Pregnancy Test [b] | x | | | | | | | | | | | | x |

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 26 [n] | Final Visit Week 28 | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | | |
| **Visit Window** | | | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| **Assessments** | | | | | | | | | | | | | |
| Administration of Study Treatment [q] | | x | | x | x | x | x | x | x or sham | | | | x |
| Safety Finger Count Vision [c,d] | | x | | x | x | x | x | x | x | | | | x |
| IOP [a,e] | x | 3 [l,m] | x | 3 [m] | 3 [m] | 3 [m] | 3 [m] | 3 [m] | 3 [m] | 2 [e,n] | x | x | x |
| BCVA [a,f] | x | x [l] | x | x | x | x | x | x | x | x [n] | x | x | x |
| Slit Lamp [a] | x | x [l] | x | x | x | x | x | x | x | x [n] | x | x | x |
| Indirect Ophthalmoscopy [a] | x | x [l] | x | x | x | x | x | x | x | | x | x | x |
| Fundus Photography [a,c] | x | x [l,p] | | | | | | | x | | x | x | x |
| SD-OCT [a,c] | x | x [l] | x | x | x | x | x | x | x | | x | x | x |
| Fundus Fluorescein Angiography [a,c] | x | | | | | x | | | x | | | x | x |

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 26 [n] | Final Visit Week 28 | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | | |
| **Visit Window** | | | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| **Assessments** | | | | | | | | | | | | | |
| PK Sample [a] | | x | x | x | | x | | x | x | x [n] | x | x | x |
| PD Biomarkers Sample [a] | | x | x | x | | x | | | x | x [n] | x | x | x |
| Exploratory Plasma Biomarkers Sample [a] | | x | | | | x | | | | | x | x | x |
| Clinical Genotyping Sample [a,h,i] | | x | | | | | | | | | | | |
| Anti-Drug Antibody [a] | | x | x | x | | x | | x | x | x [n] | x | x | x |
| [redacted] | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |

| Week | Screening | Week 1 | | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 26 [n] | Final Visit Week 28 | Early Termination Visit | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | D-28 to D-1 | Day 1 | Day 7 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 | Day 168 | Day 182 | Day 196 | | |
| **Visit Window** | | | ±3 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +7 | |
| **Assessments** | | | | | | | | | | | | | |
| Adverse Events | x | x | x | x | x | x | x | x | x | x [n] | x | x | x |
| Previous and Concomitant Treatments | x | x | x | x | x | x | x | x | x | x [n] | x | x | x |

BCVA = best corrected visual acuity; EC = Ethics Committee; FFA = fundus fluorescein angiography; FP = fundus photography; IOP = intraocular pressure; PD = pharmacodynamic; PK = pharmacokinetic; [redacted] SD-OCT = spectral domain optical coherence tomography.

[a] Assessment prior to study treatment administration on days where study treatment is administered.

[b] For females only

[c] Assessment in study eye only; except at screening for imaging assessments (FP, SD-OCT, FFA), where either eye has a potential to meet all eligibility criteria.

[d] Finger count vision assessment asap after, and within maximum of 15 min from study treatment administration.

[e] Multiple assessments on a single visit day, details on timing in Appendix 2.

[f] Performed prior to pupil dilation.

[redacted]

[h] At Day 1 but can be done at any other visit if the sample not collected at baseline.

[i] Mandatory, except in countries or at investigational sites where IRB/EC does not approve.

[redacted]

[l] Baseline assessments.

[m] Assessment post-study treatment administration in the study eye only. If IOP ≥30 mmHg at 30 (±5) minutes post-treatment administration in the study eye, then IOP is measured again at 60 (±10) minutes.

[redacted]

[o] Only for the tests where abnormal values at Week 24 require follow-up, and at the discretion of the investigator

[p] Optional at Day 1.

[q] The interval between two administrations of study treatment needs to be at least 21 days.

## SECTION APPENDIX 3 (5. INTRAVITREAL ADMINISTRATION OF STUDY TREATMENT)

### New text:

- ~~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 of 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.~~

### Old text:

- 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 of 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.

## 6. SUBJECT: INCLUSION OF LOW-RISK PDR AND MODIFICATION OF CORTICOSTERIOD EXCLUSION CRITERION

### REASON FOR CHANGE:

A large proportion of patients with DME have DR. When used as a treatment of DME, intravitreous (IVT) anti-VEGF agents reduce the risk of PDR worsening and increase the chance of improvement. Therefore low-risk PDR patients will be included, to study DR severity improvement from baseline on the ETDRS-DRSS (diabetic retinopathy severity score) at Week 24 and exit visit. As the standard of care for high-risk PDR is pan retinal photocoagulation (PRP), patients with high-risk PDR will be excluded.

Patients on short acting off-label IVT corticosteroids used for the treatment of DME, will be included in the study. The effect of this drug treatment lasts less than 3 months. Therefore, inclusion of patients provided the treatment > 3 months prior to day 1, will not compromise the scientific integrity of the study and may help improve recruitment. Long acting IVT corticosteroids Ozurdex and Iluvien are approved treatment for DME and patients who have been treated with these drugs will be excluded

### SECTION 4.2.2. EXCLUSION CRITERIA,

### New text:

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

**Ocular criteria for study eye:**

- *Any signs of high-risk* PDR *defined as:*
    - *any vitreous or pre-retinal hemorrhage*
    - *NVE ≥ 1/2 disc area within an area equivalent to the standard mydriatic ETDRS 7- field on clinical examination*
    - *NVD ≥ 1/3 disc area on clinical examination*
- Any IVT anti-VEGF treatment *within 3 months* prior to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- *Any IVT~~,~~ or periocular corticosteroid~~, or corticosteroid implants~~ treatment~~-~~ within 3months prior to Day 1,* ~~except for management~~. *Any history of* ~~complication of cataract surgery~~*Iluvien or Ozurdex implants prior to Day 1 will not be permitted*
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP≥ 25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions *in the study eye*:**

- History of rubeosis ~~in the study eye~~
- Any current or history of ocular disease ~~in the study eye~~ other than DME that may confound assessment of the macula or affect central vision (e.g., AMD, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- *Any current ocular condition for which, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, non-retinal condition)*
- Any active ocular infection ~~in *the study* eye at~~*on* Day 1
- Any active intraocular inflammation (grade trace or above) ~~in *the study* eye at~~*on* Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment ~~for a retinal condition~~ within 7 days prior to Day 1
- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 needs to be controlled by antihypertensive medication, the patient ~~can become eligible if~~*should be taking the same* medication ~~is taken~~ continuously for at least 1 month prior to Day 1.
- Patients with glycosylated hemoglobin HbA1c ≥ *12*% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study

- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with IMP in the 3 months prior to Day 1

**Old text:**

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

**Ocular criteria for study eye:**

- Any PDR
- Any IVT anti-VEGF treatment prior to Day 1
- Any panretinal photocoagulation (PRP) treatment prior to Day 1
- Any macular laser photocoagulation within 3 months prior to Day 1
- History of vitreoretinal surgery
- Any IVT, periocular corticosteroid, or corticosteroid implants treatment prior to Day 1, except for management of complication of cataract surgery
- Any cataract surgery or treatment for complications of cataract surgery with steroids within 3 months prior to Day 1
- History of incisional glaucoma surgery
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication)

**Concurrent ocular conditions:**

- History of rubeosis in the study eye
- Any current or history of ocular disease in the study eye other than DME that may confound assessment of the macula or affect central vision (e.g., AMD, retinal vein occlusion, uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus, pathological myopia, retinal detachment, macular traction, macular hole, significant cataract)
- Any active ocular infection in *the study* eye at Day 1
- Any active intraocular inflammation (grade trace or above) in *the study* eye at Day 1

**Characteristics for fellow eye:**

- Any anti-VEGF treatment for a retinal condition within 7 days prior to Day 1
- Any retinal condition that, in the opinion of the investigator, might require anti-VEGF treatment within 7 days from Day 1

**General criteria:**

- Any systemic anti-VEGF within 6 months prior to Day 1
- Any major illness or major surgical procedure within 1 month prior to Day 1
- Any febrile illness within 1 week prior to Day 1
- Any stroke or myocardial infarction within 12 months prior to Day 1
- 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 30 or more minutes later. If the patient's BP needs to be controlled by antihypertensive medication, the patient can become eligible if medication is taken continuously for at least 1 month prior to Day 1.
- Patients with glycosylated hemoglobin HbA1c $>12$% at screening
- Untreated diabetes mellitus or initiation of oral anti-diabetic medication or insulin within 4 months prior to Day 1 or anticipated change of anti-diabetic medications within the duration of the study
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 6 months prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- 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 IMP 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 female
- Use of systemic corticosteroids within 1 month prior to Day 1
- Any known hypersensitivity to active comparator, fluorescein, any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
- Any other restriction accorded to the use of the active comparator
- Any treatment with IMP in the 3 months prior to Day 1

## 7. SUBJECT: UPDATING PREVIOUS CLINICAL TRIALS SECTION

### REASON FOR CHANGE:

The section was updated to reflect the most recent available data of ongoing clinical trials.

### SECTION 1.2.2. PREVIOUS CLINICAL STUDIES

**New text:**

A multicenter, double-masked, Phase II study to investigate the safety, tolerability, pharmacokinetics, and efficacy of RO6867461 administered IVT in patients with CNV secondary to AMD is ongoing (Study BP29647 – AVENUE*, clinicaltrials.gov: NCT02484690*). In Study BP29647, treatment-naive patients are randomized to receive either ranibizumab 0.5 mg every 4 weeks or 1.5 or 6 mg RO6867461 every 4 or 8 weeks for 32 weeks. ~~As of 4 November 2015, 15 patients have been enrolled and no serious adverse events have been reported.~~ *To date, side effects observed in patients enrolled in Study BP29647 (masked data) are consistent with the safety profile observed in the completed BP28936 study described above.* No other data are yet available.

**Old text:**

A multicenter, double-masked, Phase II study to investigate the safety, tolerability, pharmacokinetics, and efficacy of RO6867461 administered IVT in patients with CNV secondary to AMD is ongoing (Study BP29647 – AVENUE). In Study BP29647, treatment-naive patients are randomized to receive either ranibizumab 0.5 mg every 4 weeks or 1.5 or 6 mg RO6867461 every 4 or 8 weeks for 32 weeks. As of 4 November 2015, 15 patients have been enrolled and no serious adverse events have been reported. No other data are yet available.

## 8. SUBJECT: CHANGES IN MASKING REQUIREMENTS

### REASON FOR CHANGE:

The original study design contained a sham injection at week 24 for arms B and C, which required at least two investigators (treatment administrator and assessing physician) to maintain the double-blinding. However, by changing the study design, sham injection is no longer required. Treatment can be administered by the assessing physician, as long as the investigator is not involved in any aspects of drug-preparation. All roles must be documented throughout the study. The paragraph on unmasking IMC members has been updated to be in alignment with the other ongoing RO6867461 study BP29647.The section on emergency unmasking has been added because it is a current section in the protocol template and was not included in previous versions.

## SECTION 4.3.3. MASKING

**New text:**

**Masking ~~at Investigational Site~~**

This is a double-masked study.

*Patients, study site personnel (with the exception of the pharmacist or designated personnel), BCVA examiners, vendors, Central Reading Center personnel, and the Sponsor and its agents (with the exception of drug accountability monitors and as defined in Section 4.3.3) will be masked to study drug assignment.*

There ~~must~~*should* be a minimum of two investigators per site to fulfill the masking requirements of this study. At least one investigator will be designated as the assessor physician who will be masked to patients' study drug 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~~*could* be unmasked to patients' study drug assignment and will administer study treatment (RO6867461, ranibizumab ~~or sham~~).

~~Once the designated roles are determined, the roles cannot be switched or reversed at any time during the conduct of the study.~~ *If only one investigator is available due to limited staffing resources, study drug administration can also be done by the assessing physician. In that case the treatment administrator physician(s) must not be involved in any aspects of un-masked study drug preparation. The preparation of the study drug must be done by trained staff under strict sterile condition. Detailed instructions for preparation are available in the pharmacy manual.*

The Principal Investigator must be masked to the patient's treatment assignment. All roles for each study staff member should be clearly documented in the site delegation log. The delegation log should be signed by the Principal Investigator. *An unmasked personnel cannot switch to a masked role, but a masked personnel can switch to an unmasked role. Any change should 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~~*drug* administration ~~must not be involved in any other aspect of the study in any way and~~ must not divulge study drug 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 and as defined in Section 4.3.3) will be masked to study drug assignment.~~

~~Every effort must be made to limit the~~ *The* number of unmasked study personnel *should be limited* to ensure the integrity of this masked study. There ~~must~~*should* 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 the Sponsor.

For the duration of the study, the patient study drug 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~~*performing* the injection of study drug ~~and~~ may also perform *other assessments, including* the post-injection vision testing (finger counting and, if applicable, hand movement and/or light perception).

~~**Masking at Sponsor and Delegates**~~

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 study drug group level ~~as well as at the~~ *. The IMC agreement will also identify individuals unmasked at the individual patient level*~~, if required.~~

*for safety analysis and for the purpose of preparing summary data displays for the IMC meeting.*Other Roche Study Management Team members will remain masked throughout the study.

## Old text:

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study. At least one investigator will be designated as the assessor physician who will be masked to patients' study drug 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' study drug assignment and will administer study treatment (RO6867461, ranibizumab or sham).

Once the designated roles are determined, the roles cannot be switched or reversed at any time during the conduct of the study. The Principal Investigator must be masked to the patient's treatment assignment. All roles for each study staff member should be clearly documented in the site delegation log. The delegation log should be signed by

the Principal Investigator. 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 study drug 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 and as defined in Section 4.3.3) will be masked to study drug 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 the Sponsor.

For the duration of the study, the patient study drug 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 drug and may also perform the post-injection vision testing (finger counting and, if applicable, hand movement and/or light perception).

Masking at Sponsor and Delegates

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) and others, if deemed necessary by the IMC, will be unmasked at the study drug group level as well as at the patient level, if required.

Other Roche Study Management Team members will remain masked throughout the study.

## SECTION 4.3.4. MASKING AT SPONSOR AND DELEGATES

### New text:

None, incorporated into section 4.3.3

**Old text:**

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) and others, if deemed necessary by the IMC, will be unmasked at the study drug group level as well as at the patient level, if required.

Other Roche Study Management Team members will remain masked throughout the study.

## SECTION 4.3.4 EMERGENCY UNMASKING

**New text:**

*If complete unmasking is necessary for patient management (e.g., in the case of a serious adverse event), the investigator will be able to share the treatment code with the masked study personnel. Treatment codes should not be shared except in emergency situations. The Investigator should document all details and provide an explanation for any premature complete unmasking (e.g., accidental unmasking of non-Investigator study personnel or unmasking due to serious adverse events).*

*Sponsor might become unmasked to study drug 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*

**Old text:**

None

## 9. SUBJECT: EMERGENT/RECURRENT DIABETIC MACULAR EDEMA IN THE FELLOW EYE SECTION

**REASON FOR CHANGE:**

The section has been updated to clarify that Ranibizumab will be provided by the sponsor and that other commercial supplies will not be reimbursed by the sponsor.

## SECTION 4.5.3 EMERGENT/RECURRENT DIABETIC MACULAR EDEMA IN THE FELLOW EYE

**New text:**

~~Every effort should be made to treat with ranibizumab, where~~

*When anti-VEGF therapy is recommended and ranibizumab warranted*~~. If emergent/recurrent DME in the fellow eye is treated~~*, every effort should be made to treat* with ranibizumab~~, it will~~*. This treatment can either* be provided by the Sponsor ~~as long as~~*during the* ~~patient remains~~*patient's enrollment in the study*~~. The supply of ranibizumab will~~ *or be* ~~in~~*provided by the* ~~currently available~~*site through commercial supplies. When provided by the Sponsor, it will be in the commercial* formulation for ranibizumab ~~but~~ labelled for investigational use only~~. The same process of~~ *(dispatched by IxRS), and the site will need to maintain their own* drug accountability*. Commercial supplies will* ~~apply to this supply of ranibizumab as to the study drug~~*not be reimbursed.*

**Old text:**

Should DME emerge or recur and require treatment in the fellow eye during the study period, the patient may receive anti-VEGF SoC treatment. Fellow eye treatment*, if required, must be administered at least* 7 days preceding or following the study eye treatment.

Every effort should be made to treat with ranibizumab, where anti-VEGF therapy is recommended and ranibizumab warranted. If emergent/recurrent DME in the fellow eye is treated with ranibizumab, it will be provided by the Sponsor as long as the patient remains in the study. The supply of ranibizumab will be in the currently available commercial formulation for ranibizumab but labelled for investigational use only. The same process of drug accountability will apply to this supply of ranibizumab as to the study drug.

## 10. SUBJECT: CLARIFICATION ON RE-SCREENING

**REASON FOR CHANGE:**

The text was modified to clarify the terms of when a re-screening would be permitted and the conditions under which the second eye may be evaluated within the initial screening period to become the study-eye.

## SECTION 4.6.7.1 SCREENING AND PRETREATMENT ASSESSMENTS

**New text:**

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. ~~Where it extends beyond the 4 week screening period, the patient will be allowed to be re-screened.~~

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 reasons (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. *If patients meet criteria upon re-screening, they will receive a new screening number and will be treated as a new patient.*

*For each patient, if one eye does not meet eligibility criteria, then the second eye may be evaluated within the initial screening period. If the second eye meets the eligibility criteria, then the patient would retain the same screening number and would not be screened-failed.*

**Old text:**

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. Where it extends beyond the 4 week screening period, the patient will be allowed to be re-screened.

Patients who failed screening due to uncontrolled blood pressure will be allowed to be re-screened.

## 11. SUBJECT: ADDITION OF NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

**REASON FOR CHANGE:**

In response to safety requests and the current protocol template, several safety sections have been updated to include the assessment and reporting of non-serious events of special interest (AESI).

**SECTION 5.1. SAFETY PARAMETERS AND DEFINITIONS,**

**New text:**

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events (systemic and ocular~~);~~*), non-serious adverse events of special interest;* 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.

**Old text:**

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events (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.

**SECTION 5.1.3 NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST (IMMEDIATELY REPORTABLE TO THE SPONSOR),**

**New text:**

*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* ***Error! Reference source not found.*** *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* ***Error! Reference source not found.*** *(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.*
- *The Safety Science Responsible for the program is accountable for determining the non-serious Adverse Events of Special Interest (AESI) for a protocol.*

**Old text:**

None

**SECTION 5.4. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR,**

**New text:**

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take

place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- *non-serious adverse events of special interest*
- Sight-threatening adverse events
- Pregnancies

**Old text:**

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

- Serious adverse events
- Sight-threatening adverse events
- Pregnancies

**SECTION 5.4.2 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS, NON-SERIOUS ADVERSE SECTION EVENTS OF SPECIAL INTEREST, AND SIGHT-THREATENING ADVERSE EVENTS,**

**New text:**

For reports of serious adverse events*, non-serious adverse events of special interest ,* and sight-threatening adverse events (see Sections 5.1.2 and 5.1.3), investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the Serious Adverse Event Responsible within 24 hours.

**Old text:**

For reports of serious adverse events and sight-threatening adverse events (see Sections 5.1.2 and 5.1.3), investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the Serious Adverse Event Responsible within 24 hours.

**SECTION 5.5.2. SPONSOR FOLLOW-UP,**

**New text:**

For serious adverse events*, non-serious adverse events of special interest*, sight-threatening adverse events, 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..

**Old text:**

For serious adverse events, sight-threatening adverse events, 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.

**SECTION 5.6. POST-STUDY ADVERSE EVENTS,**

**New text:**

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (*as* defined ~~as 28 days after the last dose of study drug).~~*in Section 5.3.1).* However, the Sponsor should be notified if the investigator becomes aware of any death ~~or~~*,* any other serious adverse event*, or sight-threatening adverse events 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.*

**Old text:**

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 drug). However, the Sponsor should be notified if the investigator becomes aware of any death or any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment.

**12. SUBJECT: EDITORIAL CHANGES**

**REASON FOR CHANGE:**

- alignment with protocol template
- correction of typos
- references added
- changes for general updates and clarifications
- changing of study treatment to study drug throughout the document as sham injection was removed

- Appendix 2 removed

applicable to section: glossary,

1. Background and Rationale, 1.1 Background on Disease, 1.2 Background on RO6867461, 1.2.2. Previous Clinical Studies, 1.2.2.1 Safety and Tolerability, 3.2. Rationale for Study Design, 3.2.1. Rationale for Dosage selection, 3.3.1. Safety Outcome Measures, 4.2.2. Exclusion Criteria, 4.3.2. Treatment Administration Procedure, 4.4.1.1. RO6867461 and Placebo, 4.4.1.2 Ranibizumab Active Comparator, 4.4.2.1. RO6867461 and Ranibizumab, 4.5.1 Permitted Therapy, 4.6 Study Assessments, 4.6.1.1 Medical History and demographic Data, 4.6.1.3. Vital Signs, [redacted] 4.6.5 Disease-Specific Assessments, 4.6.5.2.1. Best Corrected Visual Acuity, 4.6.7.1. Screening and Pretreatment Assessments, 4.6.7.3 Assessments at Early Termination Visit, 4.7.1 Patient Discontinuation, 4.7.1.1. Discontinuation from study Drug, 5.1.1. Adverse Events, 5.3.5.4. Abnormal Laboratory Values, 5.3.5.5. Abnormal Vital Sign Values, 5.6 Post-Study adverse Events, 5.7. Expedited Reporting to Health authorities, Investigators, Institutional Review Boards, and Ethics Committees, 6.3.1. Safety Analysis Population, 6.3.2 Efficacy, Pharmacokinetic, and Pharmacodynamics Analysis Population, 10. References, Appendix 2 Schedule of Assessment Detail Table