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: SAP Version 2: 31-July-2017

STATISTICAL ANALYSIS PLAN

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
STUDY DRUG:	RO687461
VERSION NUMBER:	2.0
IND NUMBER:	119225
EUDRACT NUMBER:	N/A
SPONSOR:	F. Hoffmann-La Roche Ltd.
PLAN PREPARED BY:	[redacted]
DATE FINAL:	July 31 2017

TABLE OF CONTENTS

LIST OF TABLES

Background

This Statistical Analysis Plan (SAP) documents the statistical methods for summarizing and analyzing the efficacy and safety data from study BP30099. The main purpose of this SAP is to describe the data handling rules, derivation rules, and statistical analysis methods.

1. 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.

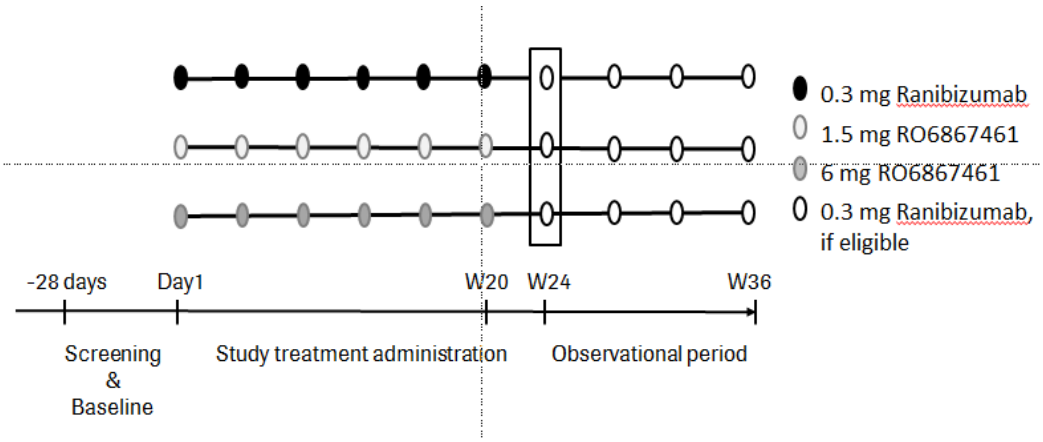
The three groups of this study are as follows (see Figure 1):

- 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, 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.

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 0), 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.

1.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is described in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

1.2 OUTCOME MEASURES

1.2.1 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

1.2.2 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]

1.2.3 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.

1.2.3.1 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.

1.2.3.2 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

Table 1 Description of Secondary Outcome Measures

Secondary EndPoint	Detailed Definition	Variable names used by central reading center
Foveal Center Point thickness (Central Foveal Thickness)	Thickness from Inner Limiting Membrane to the Retinal Pigment Epithelial at the horizontal slice closest to the center of the fovea	OCTCentralRetinalThickness1-3
mean CST	Mean thickness from Inner Limiting Membrane to the Retinal Pigment Epithelial over the 1 mm central subfield	OCTCentralSubfieldThickness1-3
intra-retinal fluid (IRF)	Presence of fluid within the retina	OCTIntraRetinalFluid
sub-retinal fluid SRF)	Presence of fluid between the retina and the retinal pigment epithelium	OCTSubretinalFluidThicknessNotPresent
Resolution of leakage at the macula	Resolution of fluorescein leakage at the macula	FAMaculaMELeakageArea1-3 or FAMaculaMELeakage
Size of the foveal avascular zone	Size of the foveal avascular zone (FAZ) by FFA	FAMaculaFAZArea1-3 FAMaculaFAZAreaIB1-3

1.2.3.3 Pharmacodynamic Biomarker Outcome Measure

Plasma PD biomarker outcome measure for this study is as follows:

- Change in plasma levels of VEGF and Ang-2

1.2.4 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 in 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]

1.3 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 α 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.

1.4 ANALYSIS TIMING

The primary analysis will be performed at the end of the study, after the last patient has completed Week 24 final visit.

2. STUDY CONDUCT

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.

2.1 RANDOMIZATION

After written informed consent has been obtained, all patients will receive a screening number assigned through the Interactive Voice and Web Response System (IxRS). After all patient eligibility requirements are confirmed on Day 1 visit the site personnel will contact the IxRS for assignment of a patient identification number (a separate number from the screening number).

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. Randomization will be stratified for the three factors 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)

2.2 INDEPENDENT REVIEW FACILITY

A Roche internal monitoring committee (IMC) will be responsible in the event of an interim analysis for sample size evaluation, operational/administrative purposes, and/or for safety data monitoring. For other objectives, the IMC will review the safety data and will be responsible for evaluating efficacy data for instance where assessment of benefit-risk is warranted. These analyses will take place at pre-defined time points or on an ad-hoc basis.

The IMC consists of a selected subset of Roche representatives including a biostatistician, safety representative, clinical science representative, clinical pharmacology representative, and pharmacometrician. The IMC members participating in a given interim analysis will be kept to the minimum required to address the objective of that interim analysis. Additional Roche Representatives might be involved to produce/process the unmasked listing/data to be analyzed by the IMC.

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

2.3 DATA MONITORING

An IMC will review safety data, and may review efficacy data to assess benefit-risk.

3. STATISTICAL METHODS

3.1 ANALYSIS POPULATIONS

The following analysis populations will be defined: “Efficacy, Pharmacokinetic, and Pharmacodynamic Population” and safety population.

3.1.1 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.

3.1.2 Efficacy, Pharmacokinetic, and Pharmacodynamic Population

All randomized patients (Intent to Treat, ITT) will be included in the efficacy, PK, and PD analysis population. Patients who receive study drug in the study eye different that to which they were randomized will be included in the group to which they were randomized. Separate ITT populations for the treatment-naïve and previously anti-VEGF-treated patients will be defined.

3.2 ANALYSIS OF STUDY CONDUCT

The number of patients who are enrolled, discontinued, and completed the study as well as the major protocol violations will be summarized. Demographic and baseline characteristics will be summarized with descriptive statistics by previous anti-VEGF treatment status.

3.3 ANALYSIS 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 arm and previous anti-VEGF treatment status using frequency tables and summary statistics providing means, medians, standard deviations, first and third quartiles, and extreme values.

3.4 GENERAL CONSIDERATIONS

3.4.1 Visit Windows

Visit windowing will be performed for this study with nominal visits/assessments falling outside of allowable protocol-defined visit windows, being reassigned to an appropriate visit for use in analyses.

If multiple valid (non-missing) values for a variable are recorded in the same visit window, one record will be selected for summary/analysis of the data by the following priority:

- The originally scheduled visit assessment

- The assessment closest to the target/planned assessment day.

If scheduled assessments were grouped into multiple visits, the assessments will be assigned to a single visit provided all assessments fall within the same visit window.

Note that unscheduled visits could potentially be included in summaries and analyses following the application of these visit assignment rules.

Assessments that fall outside of the protocol-defined visit windows will be assigned to the closest target visit.

Unless otherwise specified, all analyses and summaries involving visit, will use visits assigned after visit windowing has been performed.

3.4.2 Baseline

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

3.5 EFFICACY ANALYSIS

The List of Planned Outputs (LoPO) contains the full list of reports for the efficacy analysis.

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, primary efficacy analyses will be repeated in all randomized patients (see 3.5.3).

3.5.1 Primary Efficacy Endpoint

The primary efficacy variable is the study eye BCVA change from baseline at Week 24. The primary efficacy analysis will be performed using a Linear Mixed Effects Model for Repeated Measurements (MMRM) model. The model will include the categorical covariates of treatment group, categorical visit, and visit by treatment group interaction term, randomization stratification factors, and a continuous covariate of baseline BCVA. An unstructured covariance will be used to account for within-patient correlation (General Linear Model), but another variance-covariance structure such as AR(1) + random patient effect may be selected in case of convergence issues. The primary statistical test will aim to test the null hypothesis:

H_0: There is no difference between either of the RO6867461arms (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 vs.

H_A: Arm B or C is different from arm A.

The model-based estimate of the difference between each of the treatment groups (Arms B and C) and the control group (Arm A) at Week 24, together with 80% confidence interval and corresponding p-value will be reported as the primary

efficacy measures. The mean and 80% 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 comparisons. Tests for arms B vs A and C vs A will be carried out at one-sided 10% alpha.

3.5.2 Secondary Efficacy Endpoints

For all key secondary endpoints measured on a continuous scale, a MMRM model described in section 3.5.1 will be used. Nominal p-value will be reported without correction for multiple comparisons.

Binary key secondary endpoints will be analyzed using Generalized Estimating Equations (GEE) with a binomial distribution, logit link function for odds ratios and identity link for risk differences, and unstructured covariance. In case of convergence issues, AR(1) covariance structure will be used. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction term. Least squares means on the probability scale for each treatment arm with the corresponding 80% confidence intervals and odds ratios relative to the control arm will be computed.

Data transformation (e.g., logarithmic transformation) may be applied as appropriate. Other statistical models and additional analyses may also be performed as appropriate. Fisher's exact test may be used for binary endpoints in case GEE models do not converge.

In addition, the influence of baseline parameters on the primary endpoint will be evaluated as covariates in the linear model and in subgroup analysis as appropriate (see 4.4.5).

3.5.3 Exploratory Efficacy Endpoints

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 will be computed.

Effect modification will be tested in the overall (treatment-naïve and previously treated combined) ITT population by adding a previous IVT anti-VEGF treatment status and a treatment arm by visit by previous IVT anti-VEGF treatment status interaction terms to the Linear model described in section 3.5.1. The treatment arm by visit by previous IVT anti-VEGF treatment status interaction term will be tested at a 10% significance level.

3.5.4 Sensitivity Analyses

Effects of prognostic factors on the BCVA change from baseline will be investigated using the MMRM model described in section 3.5.1. The measurement at BL (baseline) of each of the following variables may be used as covariates in the model:

- Age

3.5.5 Subgroup Analyses

For the sub-group analysis the MMRM for change from baseline in BCVA will be used in the following subgroups defined at baseline:

- Previous macular laser treatment (from eCRF)
- Gender
- BCVA strata (64 letters or better vs. 63 letters or worse, from eCRF).
- BCVA Categories at BL (20/40 or better, 20/200 or better),

The sub-group analyses will be performed separately in each sub-group.

3.6 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population. The LoPO contains the full list of reports for safety analyses.

3.6.1 Adverse Events

The original terms recorded on the eCRF by the Investigators for adverse events will be standardized by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level, including separate exploratory analyses of ATE events (Appendix 3).

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

3.6.2 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 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.

3.6.2.1 Standard Reference Ranges and Transformation of Data

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

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Given that the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

3.6.2.2 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.

3.6.3 Vital Signs

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

3.6.4 ECG Data Analysis

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

3.6.5 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, except for treatment arm A.

3.6.6 Ocular Assessments

Results of the following ocular assessments will be summarized by time point for the study eye using descriptive summaries: BCVA (also for the non-study eye), IOP (also for the non-study eye), and changes from baseline in these measurements will be tabulated.

3.6.7 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, separated into ocular and non-ocular categories.

3.6.8 Exposure to Study Medication

The following extent to study medication will be summarized by treatment arm:

- Duration of treatment, to be calculated as first day to last day to masked study medication
- Relative extent of exposure as number of given intravitreal injections divided by number of planned intravitreal injections of masked study medication during the treatment duration of a patient.

3.7 MISSING DATA

An analysis of the sensitivity of the assumptions on missing values may be performed for the primary efficacy variable.

The primary analysis assumes that the data are missing at random (MAR).

As a sensitivity analysis the LOCF imputation will be used in the analysis of the primary endpoint.

3.8 INTERIM ANALYSES

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.

List of interim analysis outputs is described in the interim LoPO document.

APPENDIX 1

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 Harmonization (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 post ovulation 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 time points 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 enrolment.

Treatment Period

On Day 1, baseline assessments will be conducted on the eligible patients, according to the SoA. Patients will receive their first IVT 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, 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 α 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

Appendix 2

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,j]	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
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,n]		x													
Anti-Drug Antibody[a,r]		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 when 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

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

d Performed prior to pupil dilation

[redacted]

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

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

[redacted]

j [redacted] Baseline assessments

k 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]

[redacted]

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

n

o Optional at Day 1

The interval between two administrations of study drug needs to be at least 21 days

p when this visit becomes the final visit

q if pre-specified criteria are met

r if patient receives ranibizumab at that visit

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

t 7 days after 0.3 mg ranibizumab administration

u (+/- 3 days)

Appendix 3

Definition of ATE

ATE events are non-fatal stroke, non-fatal myocardial infarction, or vascular death (including deaths of unknown cause). They are defined as the following MedDRA terms/baskets:

Myocardial infarction

SMQ Broad | Myocardial infarction (SMQ)
PT | Coronary arterial stent insertion
PT | Coronary artery bypass
PT | Coronary endarterectomy
PT | Coronary revascularisation

Non-myocardial arterial thromboembolic events (ATEs)

SMQ Narrow | Haemorrhagic cerebrovascular conditions
SMQ Narrow | Ischaemic cerebrovascular conditions
PT | Amaurosis
PT | Amaurosis fugax
PT | Aortic bypass
PT | Aortic embolus
PT | Aortic surgery
PT | Aortic thrombosis
PT | Aortogram abnormal
PT | Arterectomy
PT | Arterectomy with graft replacement
PT | Arterial bypass operation
PT | Arterial graft
PT | Arterial occlusive disease
PT | Arterial stent insertion
PT | Arterial therapeutic procedure
PT | Arterial thrombosis
PT | Arteriogram abnormal
PT | Arteriogram carotid abnormal
PT | Atherectomy
PT | Blindness transient
PT | Carotid angioplasty
PT | Cerebral hypoperfusion
PT | Coeliac artery occlusion
PT | Embolia cutis medicamentosa
PT | Embolism
PT | Embolism arterial
PT | Endarterectomy
PT | Femoral artery embolism
PT | Femoral artery occlusion
PT | Hepatic artery embolism
PT | Hepatic artery occlusion
PT | Hepatic artery thrombosis
PT | Hypothenar hammer syndrome

PT | Iliac artery embolism
PT | Iliac artery occlusion
PT | Intra-aortic balloon placement
PT | Intraoperative cerebral artery occlusion
PT | Leriche syndrome
PT | Mesenteric arteriosclerosis
PT | Mesenteric artery embolism
PT | Mesenteric artery stenosis
PT | Mesenteric artery stent insertion
PT | Mesenteric artery thrombosis
PT | Microembolism
PT | Penile artery occlusion
PT | Percutaneous coronary intervention
PT | Peripheral arterial occlusive disease
PT | Peripheral arterial reocclusion
PT | Peripheral artery angioplasty
PT | Peripheral artery bypass
PT | Peripheral artery stent insertion
PT | Peripheral artery thrombosis
PT | Peripheral embolism
PT | Peripheral endarterectomy
PT | Popliteal artery entrapment syndrome
PT | Pulmonary artery therapeutic procedure
PT | Pulmonary artery thrombosis
PT | Pulmonary endarterectomy
PT | Renal artery angioplasty
PT | Renal artery occlusion
PT | Renal artery thrombosis
PT | Renal embolism
PT | Splenic embolism
PT | Stress cardiomyopathy
PT | Subclavian artery embolism
PT | Subclavian artery occlusion
PT | Subclavian artery thrombosis
PT | Superior mesenteric artery syndrome
PT | Thromboembolectomy
PT | Thrombotic microangiopathy
PT | Thrombotic thrombocytopenic purpura
PT | Truncus coeliacus thrombosis
PT | Visual acuity reduced transiently

Venous thromboembolism

PT | Axillary vein thrombosis
PT | Budd-Chiari syndrome
PT | Catheterisation venous
PT | Cavernous sinus thrombosis
PT | Central venous catheterisation
PT | Cerebral venous thrombosis
PT | Compression stockings application
PT | Deep vein thrombosis

PT | Deep vein thrombosis postoperative
PT | Embolism
PT | Embolism venous
PT | Hepatic vein occlusion
PT | Hepatic vein thrombosis
PT | Homans' sign positive
PT | Iliac vein occlusion
PT | Inferior vena cava syndrome
PT | Inferior vena caval occlusion
PT | Intracranial venous sinus thrombosis
PT | Intravenous catheter management
PT | Jugular vein thrombosis
PT | May-Thurner syndrome
PT | Mesenteric vein thrombosis
PT | Obstetrical pulmonary embolism
PT | Obstructive shock
PT | Ovarian vein thrombosis
PT | Paget-Schroetter syndrome
PT | Pelvic venous thrombosis
PT | Penile vein thrombosis
PT | Phlebectomy
PT | Phleboplasty
PT | Portal vein cavernous transformation
PT | Portal vein occlusion
PT | Portal vein thrombosis
PT | Post procedural pulmonary embolism
PT | Post thrombotic syndrome
PT | Postoperative thrombosis
PT | Postpartum venous thrombosis
PT | Pulmonary embolism
PT | Pulmonary infarction
PT | Pulmonary microemboli
PT | Pulmonary thrombosis
PT | Pulmonary vein occlusion
PT | Pulmonary veno-occlusive disease
PT | Pulmonary venous thrombosis
PT | Renal vein embolism
PT | Renal vein occlusion
PT | Renal vein thrombosis
PT | SI QIII TIII pattern
PT | Splenic vein occlusion
PT | Splenic vein thrombosis
PT | Subclavian vein thrombosis
PT | Superior sagittal sinus thrombosis
PT | Superior vena cava syndrome
PT | Thrombophlebitis
PT | Thrombophlebitis migrans
PT | Thrombophlebitis neonatal
PT | Thrombophlebitis superficial
PT | Thrombosed varicose vein
PT | Thrombosis corpora cavernosa

PT | Transverse sinus thrombosis
PT | Vascular graft
PT | Vena cava embolism
PT | Vena cava filter insertion
PT | Vena cava thrombosis
PT | Venogram abnormal
PT | Venoocclusive disease
PT | Venoocclusive liver disease
PT | Venous occlusion
PT | Venous operation
PT | Venous recanalisation
PT | Venous stent insertion
PT | Venous thrombosis
PT | Venous thrombosis in pregnancy
PT | Venous thrombosis limb
PT | Venous thrombosis neonatal

Appendix 4

Imaging Variables not listed as primary or secondary endpoints

Imaging Modality	Outcome Variable	Detailed Definition	Variable names used by central reading center
SD-OCT	Total macular volume	Cube Volume (mm3) ILM-RPE - Reader 1-3	OCTTotalMaculaVolume1-3
	Epiretinal Membrane		OCTEpiretinalMembrane
FFA	Macular perfusion and leakage		FAMaculaIschemiaArea1-3 FAMaculaIschemiaAreaIB1-3 FAMaculaIschemiaNone
	Peripheral perfusion and leakage		FANonMaculaCapillaryNonperfusionArea FANonMaculaCapillaryNonperfusionAreaIB1-3 FANonMaculaCapillaryNonperfusionNone
	Prior Macular Laser	Prior Macular Laser by FFA-Red-free present	RFPriorMacularLaser
	Prior Macular Laser	Prior Macular Laser by FFA present	FAMaculaPriorMacularLaserNone
	Prior PRP	Prior panretinal photocoagulation by FFA present	FANonMaculaPriorPRP
	Focal Edema	Macula focal leakage	FAMaculaMEFocalLeakage
	Diffuse Edema	Macula diffuse leakage	FAMaculaMEDiffuseLeakage
	Cystoid Edema	Cystoid edema	FAMaculaCystoidEdema
Fundus Color Photography	Cup/Disk Ratio		ColorCuptoDiskRatio1-3
	Diabetic retinopathy severity scale		DRSS
	Prior Macular Laser	Prior Macular Laser by FP present	ColorPriorMacularLaser
	Prior PRP	Prior panretinal photocoagulation by FP present	ColorNonMaculaPriorPRP

Baseline Ocular Characteristics

1. Cataracts - Use Medical History as source for the Baseline Ocular table.
2. Pan Retinal Photocoagulation laser - Targeted Surgeries and Procedures eCRF page
3. Peripheral Ischemia/Perfusion - Use FANonMaculaCapillaryNonperfusionNone, alongside FANonMaculaCapillaryNonperfusionArea for area size

[redacted]