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

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

Statistical Analysis Plan V1.0 for Protocol BP29647.

	Name	Signature	Date
Author:	[redacted]	[redacted]	14FEB2017
Position:	Statistical Scientist		
Company:	F. Hoffmann-La Roche Ltd.		

	Name	Signature	Date
Approved By:	[redacted]		FEB2017
Position:			
Company:	F. Hoffmann-La Roche Ltd.		

STATISTICAL ANALYSIS PLAN

TITLE:	**A MULTIPLE-CENTER, MULTIPLE-DOSE AND REGIMEN, RANDOMIZED, ACTIVE COMPARATOR CONTROLLED, DOUBLE-MASKED, PARALLEL GROUP, 36 WEEK STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF RO6867461 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGERELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	BP29647
STUDY DRUG:	RO687461
VERSION NUMBER:	1.0
IND NUMBER:	119225
EUDRACT NUMBER:	N/A
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted]
DATE FINAL:	13 February 2017

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Approved By:	[redacted]	[redacted]	14 FEB2017
Position:			
Company:	F. Hoffmann-La Roche Ltd.		

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1. BACKGROUND

This Statistical Analysis Plan (SAP) documents the statistical methods for summarizing and analyzing the efficacy and safety data from study BP29647. The main purpose of this SAP is to describe the data handling rules, derivation rules, and statistical analysis methods.

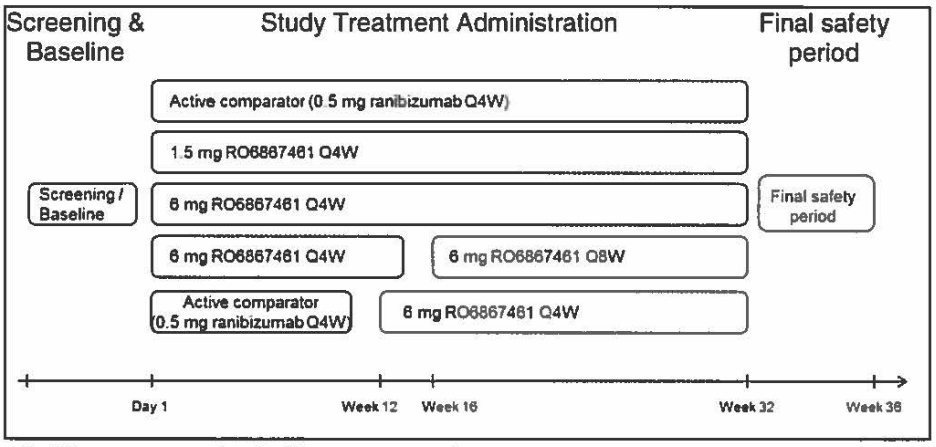
2. STUDY DESIGN

This is a multiple-center, multiple-dose and regimen, randomized, active comparator controlled, double-masked, five parallel groups, 36-week study in patients with subfoveal CNV secondary to AMD. The study design is shown in Figure 1 Study Design.

The five groups of this study are as follows.

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

Figure 1 Study Design



Q4W = every 4 weeks; Q8W = every 8 weeks

These treatment arms have been chosen to compare the treatments in a treatment-naïve population and in an anti-VEGF–incomplete-responder population. For the treatment-naïve population the arms B and C will be compared with the reference arm A. For the anti-VEGF incomplete responder population, a subgroup of arm E will be compared to a similar subgroup of arm A.

2.1 PROTOCOL SYNOPSIS

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

2.2 OUTCOME MEASURES

For efficacy analyses only measurements in the study eye are used; except where explicitly stated.

For safety analyses events and measurements in both eyes will be included in the analyses, except for imaging.

2.2.1 Primary Efficacy Outcome Measures

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

2.2.2 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 in BCVA at Week 36
- Proportion of patients with BCVA of 20/40 or better at Week 36
- Proportion of patients with BCVA of 20/200 or worse at Week 36

Anatomic outcome measures by SD-OCT:

- Mean change from baseline in foveal center point thickness at Week 36
- Mean change from baseline in mean CST (1 mm diameter) at Week 36
- Proportion of patients with no intraretinal fluid, subretinal fluid, cysts, or pigment epithelial detachment at Week 36 (dry retina definition No1)

Anatomic outcome measures by FFA:

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

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory outcome measures for this study are the following:

- Proportion of patients gaining 5 or more, 10 or more, and 30 or more letters in BCVA on ETDRS charts over time
- Proportion of patients losing 5 or more, 10 or more, 15 or more, and 30 or more letters in BCVA on ETDRS charts over time

- Proportion of patients with resolution of RAP and PCV (ICGA) over time

Combined dry retina outcome measures:

- Proportion of patients with absence of IRF, SRF and cysts – all by SD-OCT, and leakage by FFA at Weeks 12, 24 and 36 (dry retina definition No2)
- Proportion of patients with absence of IRF, SRF, cysts and PED - all by SD-OCT at Weeks 12, 24 and 36 (dry retina definition No3)

Individual dry retina outcome measures:

- Proportion of patients with absence of IRF (by SD-OCT) over time
- Proportion of patients with absence of SRF (by SD-OCT) over time
- Proportion of patients with absence of cysts (by SD-OCT) over time
- Proportion of patients with absence of PED (by SD-OCT) over time
- Proportion of patients with absence of leakage (by FFA) over time

Table 1 Description of Secondary Outcome Measures

Secondary Endpoint	Detailed Definition	Variable names used by central reading center (and combinations therefore for certain endpoints)
foveal center point thickness	Thickness from Inner Limiting Membrane to the Retinal Pigment Epithelial at the horizontal slice closest to the center of the fovea	OCTcentralretinalthickness (SDTM variables : CENT RET THICK R1-3)
mean CST	Mean thickness from Inner Limiting Membrane to the Retinal Pigment Epithelial over the 1 mm central subfield	OCTCentralSubfieldThickness (SDTM variables: CENT SUBFIELD THICK ILM-RPE R1-3)
intra-retinal fluid (IRF)	Presence of fluid within the retina	OCTIntraRetinalFluid (SDTM variable: INTRARETINAL FLUID)
cysts	Presence of cystoid space (fluid) in the retina	OCTCystoidSpaces (SDTM variable: CYSTOID SPACES)
sub-retinal fluid SRF)	Presence of fluid between the retina and the retinal pigment epithelium	OCTSubretinalFluidThicknessNotPresent (derived from SDTM variable: Subret Fluid Thick)
pigment epithelial detachment (PED)	Presence of a detachment of the pigment epithelium from the Bruch's membrane Dry retina Definition 1:	OCTPigmentEpithelialDefectThickness (SDTM variables: PED THICK R1-3)
area of CNV	Total area of CNV lesion	FATotalLesionSizeMM (SDTM variables: FA TOTAL LESION SIZE R1-3)
area of CNV component	Total area of CVN membrane	FAArea (SDTM variable: FA CNV SIZE R1-3)
total area of	**Total area of fluorescein**	**FALeakage (SDTM variable:** FA

leakage	**leakage**	LEAKAGE R1-3)

- Biomarkers in plasma related to angiogenesis and inflammation: Ang-1, Tie-2, VEGFR, PLGF, bFGF, PDGF, IL-1b, IL-6, eotaxin, autotaxin
- Pro-angiogenic factors in aqueous humor and vitreous samples for patients who provide additional consent to participate.

2.2.4 Pharmacokinetic Efficacy Outcome Measures

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

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

  Primary parameters: CL and V

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

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

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

2.2.5 Pharmacodynamic Biomarker Outcome Measures

Plasma biomarker outcome measures for this study are as follows:

- Change in plasma levels of VEGF and Ang-2

2.2.6 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- 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
- Other safety biomarkers

2.3 DETERMINATION OF SAMPLE SIZE

2.3.1 Sample Size and Power for Treatment-Naive Population Evaluation

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

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

2.3.2 Sample Size and Power for anti-VEGF-Incomplete-Responder Population Evaluation

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

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

2.4 ANALYSIS TIMING

The primary analysis will be performed at the end of the study, after the last patient has completed Week 36 final visit.

3. STUDY CONDUCT

3.1 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).

Patients will be randomized in a 3:2:2:2:3 ratio to one of the study treatment arms A, B, C, D or E (see 2 for details):

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

Randomization will be stratified for the two factors below:

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

3.2 INTERNAL REVIEW COMMITTEE

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.

3.3 DATA MONITORING

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

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

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

4.1.1 Efficacy, Pharmacokinetic, and Pharmacodynamic Population

All randomized patients 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.

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

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

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

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

4.1.1.3 Population C: Anti-VEGF-Incomplete Responder Population

The primary anti-VEGF-incomplete responder population is defined as sub-population of population B consisting of

- Population C: Patients in population B with BCVA $\leq$ 68 at Week 12 with at least one letter improvement relative to baseline.

Additional exploratory anti-VEGF-incomplete responder populations are defined as

- Population C1: Patients in population B with improvement of less than 15 letters at Week 12
- Population C2: Patients in population B without dry retina at Week 12 (dry retina definition No 2)

4.1.2 Safety Population

All patients who have received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis for this population. Patients who receive study drug in the study eye different from which they were randomized to will be included into the group to which their treatment profile match best.

4.2 ANALYSIS OF 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 baseline characteristics will be summarized with descriptive statistics. The analysis will be performed for populations A and C.

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

4.4 GENERAL CONSIDERATIONS

4.4.1 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 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.

4.4.2 Baseline

For the evaluation in the treatment-naive population, the baseline measurement is the latest non-missing observation before the first dose of study medication. For the evaluation in the anti-VEGF–incomplete-responder population, the baseline is the observation from Study Week 12. If the week 12 observation is missing, the patient will not be included in the incomplete responder population. For patients who did not receive any study medication, baseline will be set as the last available assessment before and including day 1.

4.5 EFFICACY ANALYSIS

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

4.5.1 Primary Efficacy Endpoint

4.5.1.1 Evaluation in the Treatment-Naive Population

For the evaluation of efficacy in the treatment-naïve population, all patients in Population A will be used.

The primary efficacy variable is the BCVA change from baseline to Week 36. The primary efficacy analysis will be performed using a Mixed Model for Repeated Measurement (MMRM) model. The model will include the categorical covariates of randomization stratification indicator for presence of RAP or PCV, treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA. An unstructured variance-covariance model will be used to account for within-patient correlation, but another variance-covariance structure, such as AR(1), may be used in case of convergence issues.

In case of a significant departure from the normality assumptions required for the MMRM, a nonparametric Mann-Whitney *U* test will be used to compare change from baseline between treatment arms at given visits.

The primary statistical tests will test the null hypotheses:

H_0: no difference between each of the treatment group (Arms B, C, or D) and the control group (Arm A), in mean BCVA change from baseline to Week 36 vs.

H_A: Arms B, C or D means are different from Arm A mean.

The model-based estimate of the difference between each of the treatment group (Arms B, C, and D) and the control group (Arm A) at Week 36, together with 95% confidence intervals and corresponding p-value will be reported as the primary efficacy measures in this population.

The mean and 95% confidence interval (CI) within each treatment group and for the difference in change from baseline between RO6867461 treatment groups (Arms B, C, and D) and the control group (Arm A) at the other time-points will also be reported. There will be no formal correction for multiple comparisons.

For the primary endpoints, a statistically significant difference at week 36 between any of the treatment Arms B, C, or D and Arm A will be concluded if the corresponding unadjusted 2-sided p-value is below 0.2.

4.5.1.2 Evaluation in the anti-VEGF Incomplete Responder Population C

For the evaluation of efficacy in the anti-VEGF–incomplete-responder all patients in the population C will be used.

The primary efficacy variable is BCVA change from Week 12 to Week 36. The primary efficacy analysis will be performed using a MMRM model described in section 4.5.1.1.

The model-based estimate of the difference in change from baseline between the treatment group (Arm E) and the control group (Arm A) means at Week 36, together with 95% Confidence and corresponding p-value will be reported as the primary efficacy measure in this population.

The mean and 95% confidence intervals within each treatment group and for the difference between RO6867461 treatment group and the control group change from baseline at the other time points will also be reported. There will be no formal correction for multiple comparisons.

4.5.2 Secondary Efficacy Endpoints

All analyses of secondary efficacy endpoints as defined in section 2.2.2 will be performed for population A and for population C, using their respective baseline definition (see 4.4.2).

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-values for treatment effect will be reported for all post-baseline visits without correction for multiple testing.

Binary 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, other covariance structures, such as AR(1) covariance structure, will be used.

The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and randomization stratification indicator for presence of RAP or PCV and the continuous covariate of baseline outcome measure.

Least squares means on the probability scale for each treatment arm with the corresponding 95% confidence intervals and odds ratios relative to the control arm will be computed for all post-baseline visits.

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 will be evaluated as covariates in the MMRM model and in subgroup analysis as appropriate (see Section 4.5.5).

4.5.3 Exploratory Efficacy Endpoints

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. They will be described here.

- Proportion of patients with resolution of PCV over time
- Proportion of patients with resolution of RAP over time

4.5.4 Sensitivity Analyses

Effects of prognostic factors on the BCVA change from baseline will be investigated using the MMRM model described in section 4.5.1. The measurement at BL (baseline) of each of the following variables may be used as covariates in the model:

- Age
- CNV component area, (FFAArea)
- LLD (Difference between BCVATOT for the BCVA assessment and LLVATOT for the LLVA assessment)

The sensitivity analyses will be performed separately for each covariate in populations A and C.

4.5.5 Subgroup Analyses

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

- Gender

- CNV lesion type at baseline (FACNV) CNV on FA as Classic, Classic+occult or Occult
- CNV lesion type by ICG at baseline as 3 categories: PCV, RAP or Neither
- OCT analysis: Fluid Type at baseline (by type of fluid – intraretinal. subretinal or other)
- BCVA Categories at baseline (20/40 or better vs worse than 20/40, 20/200 or better vs worse than 20/200),
- Baseline LLD quartiles or medians.

The subgroup analyses will be performed separately for each sub-group factor in populations A and C. For population C the subgroups will be defined based on the baseline defined for this population. Subgroup analyses in population C will be performed only if there are a sufficient number of patients in this population.

4.6 SAFETY ANALYSES

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

4.6.1 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 a separate summaries for ATE events (see 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.

4.6.2 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.

4.6.2.1 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. 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.

4.6.2.2 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.

4.6.3 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.

4.6.4 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.

4.6.5 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, but not for treatment arm A.

4.6.6 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.

4.6.7 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.

4.6.8 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.

4.7 MISSING DATA

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

The primary endpoint analysis using the MMRM assumes a missing at random (MAR) missing-data mechanism (i.e., the probability that missing data are dependent on other observed variables, but not on the missing data itself.)

A LOCF imputation will be applied to the primary end-point as a sensitivity analysis.

4.8 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 DRC who would then be unmasked at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

Details of the interim analyses are described in the IMC charter.

Appendix 1

SYNOPSIS OF PROTOCOL NUMBER BP29647

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

OBJECTIVES

Primary:

The primary objective of this study is as follows:

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

Secondary:

The secondary objectives of this study are as follows:

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

Exploratory:

The exploratory objectives of this study are as follows:

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

STUDY DESIGN

Description of Study

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

The five groups of this study are as follows:

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

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

NUMBER OF PATIENTS

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

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

TARGET POPULATION

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

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

Patients must meet the following criteria at study entry:

Ocular criteria for study eye:

- Treatment-naïve with CNV secondary to AMD, with subfoveal CNV or juxtafoveal CNV with a subfoveal component related to the CNV activity by *fundus fluorescein angiography* (FFA) or *spectral domain optical coherence tomography* (SD-OCT) (such as subretinal fluid, subretinal hyper-reflective material, evidence of leakage, or hemorrhage)
- Best corrected visual acuity (BCVA) letter score of 73 to 24 letters (inclusive) on Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts (20/40 to 20/320 Snellen equivalent) on Day 1. Proportion of patients with BCVA letter score of 73 to 69 letters inclusive (20/40 Snellen equivalent) on Day 1 will be limited to a maximum of 40% of the planned sample size
- CNV lesion of all types (predominantly classic, minimally classic, or occult) with:

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

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

  Active CNV confirmed by FFA (evidence of leakage)

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

General Criteria:

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

  Examples of contraceptive methods with an expected failure rate of <1% per year include male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year, barrier methods must always be supplemented with the use of a spermicide.
- Males must agree to use a barrier method of contraception starting from first treatment administration for at least 2 months post-last treatment administration.
- Patients must be willing not to participate in any other clinical trial including an investigational medicinal product (IMP) or device up to completion of the current study.

Exclusion Criteria:

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

Ocular criteria for study eye:

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

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

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

Concurrent Ocular Conditions:

- Any concurrent intraocular condition *in the study eye* (e.g., amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction, etc.) that, in the opinion of the Investigator, could either reduce the potential for visual improvement or require medical or surgical intervention
- Active intraocular inflammation (grade trace or above) *in the study eye*
- Current vitreous hemorrhage *in the study eye*
- Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure [IOP] ≥25 mmHg despite treatment with anti-glaucoma medication) *in the study eye*
- Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia *in*

the study eye

- History of idiopathic or autoimmune-associated uveitis *in either eye*
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis *in either eye*

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 major illness or major surgical procedure within one month before screening
- Patients with glycosylated hemoglobin HbA1C>7.5%
- Uncontrolled blood pressure ([BP] defined as systolic >180 mmHg and/or diastolic BP >100 mmHg while patient at rest). If a patient's initial reading exceeds these values, a second reading may be taken *either* 30 or more minutes later *on the same day, or on another day during the screening period.* If the patient's BP is controlled by antihypertensive medication, the patient should be taking *the same* medication continuously for at least 30 days prior to Day 1
- Stroke within 12 months prior to Day 1
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the Investigator
- For females of childbearing potential, a positive blood pregnancy test
- Lactating women
- Known hypersensitivity to ranibizumab, fluorescein, indocyanine green, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used
- Any other restriction accorded to the use of
- Any treatment with an IMP in the 3 months prior to Day 1

LENGTH OF STUDY

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

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

END OF STUDY

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

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

Adverse events

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

Vital signs

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

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

Electrocardiograms

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

Ocular safety

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

Laboratory tests

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

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

Anti-drug antibodies

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

PHARMACOKINETIC OUTCOME MEASURES

Plasma levels of RO6867461

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

Aqueous humor samples (optional)

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

Unscheduled collection of vitreous samples (optional)

If elective vitrectomy surgery is medically necessary, a vitreous sample can be obtained from the study eye from patients who provide additional (optional) consent to participate in vitreous collection for the measurement of RO6867461 and biomarker concentrations.

Samples may also be analyzed for ranibizumab. A blood sample for PK measurement should be taken at the same time.

EFFICACY OUTCOME MEASURES

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

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

BCVA

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

Anatomic outcome measures using SD-OCT

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

Anatomic outcome measures using FFA

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

EXPLORATORY OUTCOME MEASURES

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

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

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BIOMARKER/GENOTYPING SAMPLE COLLECTION

Biomarkers Plasma Samples

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

Clinical Genotyping (CG) Samples

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

INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMPs will include the two study drugs as follows:

- **RO6867461:** Vials of sterile, colorless to brownish, preservative-free solution of RO6867461 (120 mg/mL), for IVT administration of either 1.5 or 6 mg dose every 4 or 8 weeks
  Placebo is provided as sterile, colorless to slightly brownish, preservative-free liquid, used only for dilution of RO6867461 drug product to the appropriate clinical dose.
- **Comparator–*Ranibizumab*:** Vials containing ranibizumab solution (10 mg/mL), for IVT administration of a 0.5 mg dose every 4 weeks.

The double-masked design is achieved through strict independence of the pharmacist (or designated personnel) and Investigators who are preparing and administering study

treatment, from the assessing Investigators and remaining site personnel.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

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

PROCEDURES

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

Screening

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

Treatment period

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

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

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

Final period

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

STATISTICAL METHODS

SAFETY ANALYSES

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

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

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

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

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

PHARMACOKINETIC ANALYSES

A nonlinear mixed effects modeling approach (with NONMEM software) will be used to analyze the concentration-time data of RO6867461. Population and individual primary PK parameters (i.e., clearance and volumes) will be estimated and the influence of various covariates (e.g., gender, body weight, etc.) on these parameters will be investigated. The

data collected in this study may be pooled with data collected in the previous Phase I study as appropriate to build a PK model. Secondary PK parameters such as area under the concentration-time curve (AUC) and maximum plasma concentration observed (C_{max}) will be derived from the individual post-hoc predictions. The results of this analysis will be reported in a separate document from the clinical study report.

PHARMACODYNAMIC ANALYSES

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

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

A similar modeling approach will be used to analyze the relationship between RO6867461 exposure and BCVA. The influence of various baseline covariates on model parameters will be investigated. The PK/PD or dose/PD relationship will be characterized. The results will be reported in a separate document from the clinical study report.

SAMPLE SIZE JUSTIFICATION

Sample size and power for treatment-naive population evaluation

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

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

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

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

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

PRIMARY ENDPOINT ANALYSIS

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

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

INTERIM ANALYSES

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

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

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

OTHER CONSIDERATIONS

N/A

LIST OF PROHIBITED MEDICATIONS

Concomitant therapy

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

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

Excluded therapy

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

- Concurrent use of systemic anti-VEGF agents
- Concurrent use of IVT anti-VEGF therapy in the fellow eye within 7 days before or after study eye treatment
- Concurrent use of IVT or subtenon corticosteroids in either eye, except as required to treat adverse events
- Concurrent use of photocoagulation or photodynamic therapy with verteporfin in the study eye for neovascular AMD

Appendix 2
Schedule of Assessments

Week	Screening	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Termination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-3	+/-3	+/-3	-4/+3[m]	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+7	
Assessments															
Informed Consent	X														
Eligibility	X	X[a]													
Demography	X														
Medical History	X	X													
Physical Examination	X												X	X	
Anthropometric Measurements	X												X	X	
Vital Signs[a,b]	X	2[k]	X	2	2	2	x	2	2	2	2	2	X	X	X
ECG-12 lead	X												X	X	X
Hematology	X					X							X	X	X
Blood Chemistry	X					X							X	X	X
Urinalysis	X					X							X	X	X
Coagulation	X														X
Pregnancy Test	X														X

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

Week	Screening	Week 1		Week 4	Week 8	Week 12	Week 13	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 Final Visit	Early Termination Visit	Unscheduled
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 91	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252		
Visit Window			+/-3	+/-3	+/-3	+/-3	-4/+3[m]	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+7	
Assessments															
PK Sample[a]		X		X		X	X	X		X			X	X	X
PD Biomarkers Sample[a]		X		X		X	X	X		X			X	X	X
Exploratory Plasma Biomarker Sample[a]		X		X		X				X			X		
Aqueous Humor Sample (optional)[a,d,f,g]		X				X						X			X
Vitreous Humor + Blood Samples (optional)[f,h]															X
Clinical Genotyping Sample[a,i,j]		X													
Anti-Drug Antibody (ADA)[a]		X		X		X		X		X			X	X	X
Adverse Events[a]	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 drug administration on days where study treatment is administered
b Multiple assessments on a single visit day, details on timing on a separate table
c Finger count vision assessment asap after, and within maximum of 15 min from study treatment administration
d Assessment in study eye only
e Performed prior to pupil dilation
f Optional sample. Additional consent required from the patient
g Unscheduled sample could be obtained at other or additional planned visits at the discretion of the Investigator in agreement with the participating patient
h Only in case of vitrectomy surgery during the study and if vitreous sampling is feasible. A blood sample for plasma preparation should be drawn at the same time
i Mandatory, except in countries where IRB/EC does not approve.
j At Day 1 but can be done at any other visit if the sample not collected at baseline.
k Baseline assessments
l Assessment post-treatment administration in study eye only
m Relative to the previous study treatment administration date (Week 12)

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