Official Title: A Phase II, Multicenter, Randomized, Double Masked, Active Comparator-Controlled Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO7200220 in Combination With Ranibizumab Administered Intravitreally in Patients With Diabetic Macular Edema

NCT Number: NCT05151744

Document Date: Statistical Analysis Plan Version 3: 21-May-2024

STATISTICAL ANALYSIS PLAN (SAP)

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7200220 IN COMBINATION WITH RANIBIZUMAB ADMINISTERED INTRAVITREALLY IN PATIENTS WITH DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	BP43464
SAP VERSION:	3
EUDRACT NUMBER:	2021-004390-31
IND NUMBER:	125644
TEST PRODUCT:	RO7200220 in combination with ranibizumab
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted] PhD
DATE FINAL:	See electronic signature and date stamp

STATISTICAL ANALYSIS PLAN, VERSION 3:
RATIONAL

The Statistical Analysis Plan has been amended to reflect changes in the primary estimand and sensitivity analyses. [redacted] This original definition of the primary estimand is moved to a sensitivity analysis in this new Statistical Analysis Plan version and the primary estimand intercurrent events are redefined with definitions which are more restrictive.

Section 4.4.1 Primary Efficacy Estimand
The definition of the intercurrent events are modified.

Section 4.4.1.2 Sensitivity Analysis
An additional sensitivity analysis is added where the primary estimand is defined as in Statistical Analysis Plan versions 1 and 2.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse events
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
Ang-2	angiopoietin-2 (protein)
Anti-VEGF	anti-vascular endothelial growth factor
APTC	Anti-Platelet Trialists' Collaboration
BCVA	best-corrected visual acuity
BM	Bruch's membrane
CDE	(China) Center for Drug Evaluation
CFP	color fundus photograph
CI	confidence interval
CMH	Cochran Mantel-Haenszel
CNV	choroidal neovascularization
CRC	central reading center
CSR	clinical study report
CST	central subfield thickness
EC	Ethics Committee
ETDRS	early treatment diabetic retinopathy study
FFA	fundus fluorescein angiography
iDCC	independent Data Coordinating Center
IMC	Internal Monitoring Committee
ICGA	indocyanine green angiography
ILM	internal limiting membrane
IOI	intraocular inflammation
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IVT	intravitreal
IxRS	interactive voice or web-based response system
LLD	low-luminance deficit
LPLV	last participant, last visit
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
nAMD	neovascular age-related macular degeneration

NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	optical coherence tomography
OCT-A	optical coherence tomography-angiography
PD	pharmacodynamic
PED	pigment epithelial detachment
PK	pharmacokinetic
PTI	personalized treatment interval
Q12W	every 12 weeks
Q16W	every 16 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RPE	retinal pigment epithelium
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
U.S.	United States
VA	visual acuity
VEGF	vascular endothelial growth factor

1. BACKGROUND

This proof-of-concept Phase II study seeks [redacted] Besides efficacy (primary endpoint), it will further assess its safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD). [redacted]

The analyses specified in this document supersede the analysis plan described in the study protocols.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

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

2.2 DETERMINATION OF SAMPLE SIZE

Approximately 60 treatment-naïve participants will be enrolled in each arm to ensure that approximately 55 treatment-naïve participants will be evaluable at Week 48 for the primary efficacy outcome. [redacted]

Additionally, approximately 30 previously treated participants will be enrolled in each arm to ensure that approximately 25 previously treated participants will be evaluable at Week 48 for the primary efficacy outcome. This number is considered sufficient to assess the difference between the treatment and control arms in the change in CST from baseline to Week 48. [redacted]

Approximately 180 participants will be enrolled in this study.

Not all participants recruited will be evaluable at Week 48 because protocol version 1 stipulated participants would have their last treatment visit at Week 20, compared to Week 44 in Protocol Version 2 (signed July 2022). At the time of implementation of Protocol Version 2 (October 2022), some participants had already entered the off-treatment observation stage of the trial under Protocol Version 1.

2.3 ANALYSIS TIMING

The primary analysis will be performed when all participants have either completed the study treatment phase until Week 48 or have discontinued from the study prior to Week 48, and all data collected prior to the primary LPLV are in the database and have been cleaned and verified. At the time of the primary analysis, the study will be ongoing as participants continue in the off-treatment observation phase after completing the treatment phase. Results of the primary analyses, summarized by treatment group, may be reported to the public before completion of the study. Participants and masked study site personnel will remain masked to individual treatment assignment until the study is completed, the database is locked, and the study analyses are final.

The final analysis will be performed when all participants either have completed the study until Week 72 or have discontinued early from the study, all data from the enrollment phase are in the database and have been cleaned and verified.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Using a stratified permuted block randomization method, participants are randomized in a 1:1 ratio so that approximately 90 participants are randomized to each of the two arms

- Arm A: 1.0 mg RO7200220 IVT Q4W and ranibizumab 0.5 mg IVT Q4W
- Arm B: 0.5 mg ranibizumab IVT Q4W (active-control arm).

Randomization is stratified by baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, as assessed on Day 1 (categories: $\leq$ 38 letters; > 38 to <64; $\geq$ 64) and prior IVT anti-VEGF/corticosteroid therapy (IVT anti-VEGF and/or periocular/IVT corticosteroids treatment-naïve participants vs. previously treated participants). Randomization will be performed through an IxRS (Interactive Voice/Web Response System) and the first study treatment will be administered on the same day as randomization (i.e., at the Day 1 visit).

Randomization will be used to obtain an approximate equal allocation ratio between the different arms within each stratum. All participants will be randomized in a 1:1 ratio to one of the two arms. Limits will be placed on the number of treatment-naïve and previously treated participants to ensure the planned distribution of participants in these two populations, i.e. per treatment arm approximately n=60 for treatment-naïve and approximately n=30 for previously treated participants.

After randomization and at each visit with study treatment administration (i.e., Day 1 until Week 44), the IxRS will assign the appropriate study treatment kit to be used.

[redacted]

3.2 INDEPENDENT REVIEW FACILITY

All ocular images are obtained by trained and certified site personnel at the study sites and forwarded to CRCs (Central Reading Centers), for independent analysis and storage. As part of the screening process, the CRCs evaluate ultra-wide field [UWF] color fundus photographs ([UWF]-FPs), ultra-wide field fundus fluorescein angiographies ([UWF]-FFAs), and SD-OCT images to provide an objective, masked assessment of participant eligibility. During the study treatment period, the CRCs provide a masked evaluation of all ocular images including (UWF)-FP, (UWF)-FFA, SD-OCT or, and optional OCT angiography (OCT-A). The data resulting from this masked review of ocular images are forwarded to the Sponsor.

3.3 DATA MONITORING

A Roche Internal Monitoring Committee (IMC) will be responsible for the unmasked interim analysis of efficacy for operational/administrative/study related purposes and for safety data monitoring.

The IMC consists of selected Roche representatives including Data Scientist, Safety Representative, and a Clinical Science Representative. The IMC members participating in each meeting will be kept to the minimum required to address the objective of that meeting. The IMC Chair may provide members from other functions access to the

unmasked reports or data. Additional Roche representatives might be involved to produce/process the unmasked listing/data to be analyzed by the IMC.

The organization of the IMC meetings is described in the IMC Agreement.

3.3.1 Safety IMC meetings

[redacted]

The unmasked IMC members that perform regular safety reviews are not part of the RO7200220 project (that is, not part of the Study Management Team, Clinical Expert Team, or Project Management Team for Study BP43464 and the overall project relating to test product RO7200220).

3.3.2 Efficacy IMC meetings

Efficacy interim analyses to inform possible future development options are foreseen. They will not influence the conduct of this study. [redacted] Furthermore, the sponsor may perform further interim analyses, as outlined in Section 4.8.

Each interim analysis, will be performed and interpreted by members of the IMC and appropriate project and management personnel, who would then review aggregate results by treatment arm and by patient. Access to treatment assignment information will follow the Sponsor's standard procedures.

3.3.3 Communication plan for unmasked data monitoring

[redacted]

[redacted]

[redacted]

[redacted]

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Population	Description
Treatment-naïve Intent-to-treat	All randomized participants that are IVT anti-VEGF or periocular/IVT corticosteroids treatment-naïve as defined in the exclusion criteria 9 and 10 in the Protocol will be included in the treatment-naïve intent-to-treat population. Participants will be grouped according to the treatment assigned at randomization. These participants will be selected algorithmically depending on specific values in the database.

Population	Description
Previously treated Intent-to-treat	All randomized participants that are IVT anti-VEGF or periocular/IVT corticosteroids previously treated participants as defined in the exclusion criteria 9 and 10 in the Protocol will be included in the previously treated intent-to-treat population. Participants will be grouped according to the treatment assigned at randomization. These participants will be selected algorithmically depending on specific values in the database.
Overall Intent-to-treat	All randomized participants will be included in the overall intent-to-treat population. Participants will be grouped according to the treatment assigned at randomization. These participants will be selected algorithmically depending on specific values in the database.
Per protocol	If a significant number of Protocol Deviations are observed, a per protocol population may be used, and will include all participants who have received the full number of planned administrations of study treatment (12) in the treatment period. Participants will be excluded from this per-protocol analysis set if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure. Participants will be grouped according to the treatment assigned at randomization. These participants will be identified algorithmically using the clinical database combined with a subjective review of whether protocol deviations are significant or data are unavailable or incomplete.
Safety	All participants randomized to study treatment and who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis. Participants will be grouped according to the actual treatment received. These participants will be identified algorithmically using the clinical database.

Population	Description
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. [redacted]
Immunogenicity	Participants who had at least one pre-dose or at least one post-dose ADA assessment will be included and analyzed according to the treatment they actually received or were allocated to receive. [redacted] and reported descriptively via subgroup analyses. These participants will be identified algorithmically using the clinical database.
[redacted]	[redacted]

ADA = anti-drug antibody, [redacted] IL=interleukin; IVT=Intravitreal, Q4W=every 4 weeks, Q8W=every 8 weeks, PK=Pharmacokinetics, VEGF=Vascular endothelial growth factor

4.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be based on the overall Intent-to-treat population.

The number of participants randomized will be tabulated by country, site, and treatment arm. Participants disposition (the number of participants randomized, treated, and completing until the primary endpoint timing, as well as the end of study) will be tabulated by treatment arm. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized. Eligibility criteria deviations and other major protocol deviations will be summarized by treatment arm. The impact of COVID-19 will be assessed by including major protocol deviations

related to COVID-19 and by summarizing COVID-19 related intercurrent events by treatment arm as necessary.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race/ethnicity and region, and baseline disease characteristics (such as baseline BCVA, baseline DR severity score, ocular assessments, and medical history) will be summarized by treatment as assigned for the treatment-naïve Intent-to-treat population, previously treated Intent-to-treat population, and the overall Intent-to-treat population using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment group for the safety-evaluable population.

Baseline is defined as the last available measurement obtained on or prior to randomization. Missing baseline assessments will not be imputed.

4.4 EFFICACY ANALYSIS

Efficacy analyses will be based on the treatment-naïve Intent-to-treat, previously treated Intent-to-treat, and overall Intent-to-treat populations unless otherwise defined by estimands.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, as assessed on Day 1 (categories: ≤ 38 letters; >38 to <64; ≥ 64) and prior IVT anti-VEGF/corticosteroid therapy (IVT anti-VEGF and/or periocular/IVT corticosteroids treatment-naïve participants vs. previously treated participants).

The stratification factors will be used as recorded in the clinical database and any significant differences to the stratification factors recorded in the IxRS will be noted.

Pairwise comparisons will be performed between the 0.5 mg Ranibizumab IVT Q4W arm (Arm B) and 1.0 mg RO7200220 IVT Q4W and ranibizumab 0.5 mg IVT Q4W (Arm A).

Continuous outcomes will be analyzed using a mixed model for repeated measures (MMRM). Binary endpoints will be analyzed using stratified estimation for binomial

proportions. The estimates and confidence intervals (CIs) will be provided for the mean (for continuous variables) or proportion (for binary variables) for each of the arms and for the difference in means or proportions between pairwise comparisons of the 0.5 mg Ranibizumab IVT Q4W arm (Arm B) and the RO7200220 and ranibizumab arm (Arm A).

No formal hypothesis testing will be performed.

4.4.1 Primary Efficacy Estimand

The primary efficacy endpoint is the change from baseline in BCVA averaged over Weeks 44 and 48.

The primary estimand is defined as follows:

- Population(s):
    - Adult participants with DME, who are prior IVT anti-VEGF or periocular/IVT corticosteroids treatment-naive, as defined by the inclusion / exclusion criteria (treatment-naïve Intent-to-treat population- see Section 4.1)
- Variable:
    - Change in BCVA score from baseline averaged over Weeks 44 and 48. BCVA score is based on the ETDRS VA charts assessed at a starting distance of 4 meters.

- Intercurrent events:

Row	Intercurrent events (the first applicable event from top to bottom takes precedence)	Estimand Strategy
1	Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 6.5.3 of Protocol)	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event
2	Missed doses or discontinuation of study treatment due to adverse events (AEs) or lack of efficacy	A *treatment policy* strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
3	• third consecutive missed dose OR • discontinuation of study treatment due to reasons other than in Row 2 (e.g. COVID-19, or the rollover to new Protocol versions)	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event (the first instance of, if both occur). If more than one dose is given on a particular visit, this only counts as a single missed dose for the purposes of counting numbers of missed doses.
4	• Missed dose due to reasons other than in Row 2 (e.g. COVID-19, or the rollover to new Protocol versions)	A *treatment policy* strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
5	Death	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event.

- Population-level summary
    - Difference in adjusted mean between the RO7200220 and Ranibizumab arm (Arm A) and the 0.5 mg Ranibizumab IVT Q4W arm (Arm B).

In the case there are multiple visits within the same visit window and an intercurrent event occurs between these visits, the visits following the intercurrent event will be handled according to the type of intercurrent event as described in the Primary Efficacy Estimand. In the case where the data from the second visit is censored due to the intercurrent event handling, data from the first visit will be used towards the endpoint assessment.

4.4.1.1 Analysis Methods

The primary analysis will be performed using a MMRM. The model will include the change from baseline at Weeks 4-48 as the response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), as well as randomization stratification factors as fixed effects. Comparisons between the 0.5 mg Ranibizumab IVT Q4W arm (Arm B) and Ranibizumab arm (Arm A) will be made using a composite contrast over Weeks 44 and 48. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an AR (1) covariance structure may be fitted.

Missing data as determined by the primary efficacy estimand will be implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism. Non-standard BCVA data (defined as not conforming to the Visual Acuity Specifications from vendor Clinical Edge) will be excluded from the analyses.

4.4.1.2 Sensitivity Analysis

The following sensitivity analysis using a different handling of missing data will be performed for the primary efficacy endpoint to evaluate the robustness of the primary analysis finding:

a) Treatment policy

The estimand from the primary analysis will be modified to use a treatment policy strategy for all non-death intercurrent events for all available data.

In addition, the intercurrent event definitions and handling strategies from Statistical Analysis Plan version 1 and 2 will be used as a sensitivity analysis. These are displayed below:

Row	Intercurrent events (the first applicable event from top to bottom takes precedence)	Estimand Strategy
1	Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 6.5.3 of Protocol)	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event
2	Missed doses or discontinuation of study treatment due to adverse events (AEs) or lack of efficacy	A *treatment policy* strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
3	• 2 or more missed doses OR • at least one missed dose on Weeks 36,40,44 OR • discontinuation of study treatment due to reasons other than in Row 2 (e.g. COVID-19, or the rollover to new Protocol versions)	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event (the first instance of, if more than one ICE or missed dose). If more than one dose is given on a particular visit, this only counts as a single missed dose for the purposes of counting numbers of missed doses.
4	• 1 missed dose not on Weeks 36,40,44. due to reasons other than in Row 2 (e.g. COVID-19, or the rollover to new Protocol versions)	A *treatment policy* strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
5	Death	A *hypothetical* strategy will be applied where all values will be censored after the intercurrent event.

4.4.2 Secondary Efficacy Endpoints

A key secondary endpoint is the change from baseline in BCVA averaged over Week 44 and Week 48 in previously treated participants and the overall enrolled population. This endpoint will be analyzed using the estimand, analysis method, and sensitivity analysis as in the Primary Efficacy Endpoint (see Section 4.4.1), with population being the

previously treated Intent-to-treat and overall Intent-to-treat rather than the treatment-naïve Intent-to-treat population.

Another key secondary endpoint is the Change from baseline in Central Subfield Thickness (CST) averaged over at Weeks 44 and 48. This endpoint will be analyzed using the estimand, analysis method, and sensitivity analysis as in the Primary Efficacy Endpoint (see Section 4.4.1), with population being the previously treated Intent-to-treat, overall Intent-to-treat, and the treatment-naïve Intent-to-treat population, and the variable being the change from baseline in Central Subfield Thickness (CST) as measured by the Central Reading Center averaged over Weeks 44 and 48.

Other secondary endpoints for change in BCVA and CST at other times (in particular, the average over Weeks 20 and 24 and Weeks 32 and 36 in BCVA and Week 24 and Week 36 in CST) will be analyzed reported in a similar way. However, sensitivity analyses will not be required for these.

Change from baseline in BCVA and CST will also be reported using graphical methods. These outputs will be generated separately for the treatment-naïve Intent-to-treat, previously treated Intent-to-treat, and overall Intent-to-treat populations.

Proportions of participants gaining a particular number of letters in BCVA, reaching a particular number of letters in BCVA, reaching a specified CST level, or having absence of intraretinal fluid and subretinal fluid will be reported using tables. These outputs will be generated separately for the treatment-naïve Intent-to-treat, previously treated Intent-to-treat, and overall Intent-to-treat populations.

4.4.3 Other Efficacy Endpoints

The following exploratory endpoints will be summarized using descriptive statistics by including the mean, standard deviation, median, and range for continuous endpoints, and counts and percentages for categorical endpoints, or other listings or tables as appropriate. The handling of intercurrent events (such as the censoring of data following administration of prohibited therapy in study eye) will follow that of the primary efficacy estimand, and outputs will be generated separately for the treatment-naïve Intent-to-treat, previously treated Intent-to-treat, and overall Intent-to-treat populations.

- [redacted]

- Proportion of participants with absence of DME (CST <325 µm for Spectralis SD-OCT, or <315 µm for Cirrus SD-OCT or Topcon SD-OCT) over time
- Proportion of participants with absence of intraretinal fluid and/or subretinal fluid over time

4.4.4 Subgroup Analyses

The following subgroups may be analyzed with respect to the primary efficacy endpoint using the same method as specified above for each respective endpoint. Forest plots may be presented to summarize the results. The subgroup categories may be combined if there is not enough representation of a specific subpopulation.

- Baseline BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, as assessed on Day 1 (categories: ≤ 38 letters; > 38 to <64; ≥ 64)
- Prior IVT anti-VEGF/corticosteroid therapy (IVT anti-VEGF and/or periocular/IVT corticosteroids treatment-naïve participants vs. previously treated participants)
- Prior IVT anti-VEGF with/without corticosteroid therapy (IVT anti-VEGF **with no** periocular/IVT corticosteroids previously treated participants vs. IVT anti-VEGF **with** periocular/IVT corticosteroids previously treated participants vs. IVT anti-VEGF and/or periocular/IVT corticosteroids treatment-naïve participants)
- Region (North America, rest of the world)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Age (≤65 years and > 65 years)
- Gender (female and male)
- Race (White, Black or African American, Asian, and other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- ADA (positive at some point during study vs negative at all points)

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

[redacted]

- [redacted]
- [redacted]

[redacted]

1. [redacted]
    1. [redacted];
    2. [redacted]
    3. [redacted]
2. [redacted]
3. [redacted]

[redacted]

1. [redacted]
    1. [redacted]
    2. [redacted]
2. [redacted]
3. [redacted]

PK analyses will be run on the PK population.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.4 Immunogenicity Analysis

4.5.4.1 Immunogenicity Analysis

Immunogenicity analyses will be based on the immunogenicity-analysis population as defined in Section 4.1.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted].
- [redacted].
- [redacted].
- [redacted].

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

4.5.6 Other Analyses

Biomarker exploratory analyses, Population PK/PD analyses, may be

performed and will be presented separately from the main clinical study report.

4.6 SAFETY ANALYSES

Safety analyses will be based on the safety population. No missing data shall be imputed, and no data shall be censored following intercurrent events. As defined in the safety population, participants will be grouped according to the actual treatment received. In the event that a participant received more than one type of RO7200220 dose, as not intended by protocol, they would be considered in the higher dose level.

Safety will be assessed through descriptive summary of ocular and non-ocular AEs, deaths, and ocular assessments. Clinically significant laboratory abnormalities and clinically significant vital sign and ECG abnormalities will be reported as AEs and evaluated as part of the AE assessments.

Incidence and titer of ADAs to RO7200220 during the study relative to the prevalence of anti-drug antibodies at baseline will be assessed through listings and tables. [redacted]

At the time of the primary analysis, safety summaries will be summarized based on the complete Week 48 data in the safety population. At the time of the final analysis, safety summaries will be produced based on cumulative Week 72 data in the safety population.

Baseline for safety analyses is defined as the last available measurement prior to first exposure to study drug.

4.6.1 Exposure of Study Medication

Exposure to study drug (number of study drug administrations and duration of treatment) will be summarized by treatment group for the study eye in the safety-evaluable population.

Duration of treatment is the time from first study drug (RO7200220 and/or ranibizumab) to the earlier of

- Date of study treatment completion
- The analysis cutoff date

Pre-randomization and concomitant systemic medications, ocular medications for the study eye, and ocular medications for the fellow eye will be summarized separately by treatment group.

The following exposure summaries will be presented using tables:

- The average number of doses received as well as the count of patients by doses received of RO7200220 or ranibizumab during the masked treatment period.
- The average AE observation time at each visit.
- The average number of ranibizumab doses received during the off-treatment observation period by each visit.

4.6.2 Adverse Events

All verbatim AE terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), and the incidence, severity, and seriousness will be summarized by treatment arm.

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. A treatment-emergent AE is defined as any new AE reported or any worsening of an existing condition on or after the first dose of study drug. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

Frequency tables, including participant incidence proportions by treatment arm, will be provided for the events listed below. In addition, graphical presentations will be included, as applicable. For ocular AEs, events in the study eye and fellow eye will be summarized separately.

- Ocular AEs and serious adverse events (SAEs)
- Non-ocular AEs and SAEs
- AEs leading to discontinuation of study treatment
- Treatment related ocular AEs and SAEs as determined by the Investigator
- Procedure related ocular AEs and SAEs as determined by the Investigator
- Intraocular inflammation (IOI)

- Cataract
- Elevated Intraocular Pressure (IOP)
- Infection/Endophthalmitis
- Retinal Detachment
- Retinal vascular occlusive disease

Adverse events associated with suspected or confirmed COVID-19 will also be provided.

4.6.3 Ocular Assessments

Results of the following ocular assessments will be summarized by treatment group, by timepoint, using descriptive summaries and graphical presentations (as applicable):

- intraocular pressure (IOP)
- slitlamp examination
- indirect ophthalmoscopy

Changes from baseline in pre-dose IOP measurements will be summarized. The presence of signs of IOI and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade (according to Grading Scale for Assessment of Anterior Chamber Cells or Flare, and Vitreous Haze and hemorrhage in Appendix 6 of the Protocol). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

4.6.4 Laboratory Data

Laboratory assessments will be summarized by treatment group, by timepoint, using descriptive summaries.

4.6.5 Vital Signs

Vital signs will be collected at each visit. These data can be used for interpretation of some AEs, no general summary is planned.

Incidence of abnormal laboratory findings, abnormal vital signs and electrocardiogram (ECG) parameters will be summarized descriptively.

4.7 MISSING DATA

For efficacy and PK/PD/Biomarker analyses, the handling of missing data during analysis is specified in the relevant sections (Sections 4.4, 4.5)

For safety analyses, missing data will not be imputed, and no data shall be censored following intercurrent events.

4.8 INTERIM ANALYSES

Efficacy analyses to inform possible future development options are foreseen. They will not influence the conduct of this study. [redacted]

All data available from enrolled participants at the time of the clinical cutoff date associated with each interim analysis will be analyzed.

The interim analyses, should they occur, will be performed and interpreted by members of the IMC and appropriate project and management personnel, who would then be unmasked at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct [redacted] The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis.

The efficacy analyses will be performed during efficacy IMC meetings (see Section 3.3.2).

Safety parameters such as AEs (including SAE, and ocular AEs in study eye), ADAs, rescue therapy, IOI, and IOP may be summarized in these interim analyses using tables and graphs as appropriate. Efficacy parameters including BCVA, OCT-CST, and other imaging features may be analyzed in these interim analyses using tables and graphs. [redacted]

[redacted]

4.8.1 Communication of outputs summarizing masked data from the Interim Analyses

At each efficacy interim analysis, an efficacy IMC meeting will be held to facilitate this analysis. [redacted]

Summaries, statistics, and outputs may be shared with the IMC and a subset of the clinical expert and project team members of the RO7200220 project, and senior management personnel in order to inform possible future development options, as well as other internal staff for the purposes of authoring documentation for future studies. These may also be shared with other Data Monitoring Committees If potentially relevant. [redacted]. All team members across any project with whom any summaries, statistics, and outputs from the efficacy IMC meeting have been shared, shall be recorded.

Appendix 1
Protocol Synopsis

PROTOCOL TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7200220 IN COMBINATION WITH RANIBIZUMAB *ADMINISTERED* INTRAVITREALLY IN PATIENTS WITH DIABETIC MACULAR EDEMA**
SHORT TITLE	**PHASE II STUDY TO INVESTIGATE RO7200220 IN COMBINATION WITH RANIBIZUMAB IN DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	BP43464
VERSION:	2
TEST PRODUCT:	RO7200220
PHASE:	II

RATIONALE

Persistent inflammation in the retina is present from the early stages of diabetes to the sight-threatening advanced forms of diabetic retinopathy (DR). Indeed, a complex milieu of dysregulated proinflammatory factors is found in the diabetic retina, including interleukin (IL)-6, IL-1β, IL-8, monocyte chemotactic protein-1, and tumor necrosis factor-α.

IL-6 levels in particular have been found frequently increased in ocular fluids of participants with conditions such as DR, diabetic macular edema (DME), neovascular age-related macular degeneration, uveitis, uveitic macular edema, and retinal vein occlusion.

RO7200220 is a recombinant humanized immunoglobulin G2 isotype mono-clonal antibody that potently binds the cytokine IL-6. RO7200220 inhibits all known forms of IL-6 signaling (cis and trans). The antibody has specific mutations in the constant regions which reduce its affinity to neonatal Fc receptor (FcRn) to increase systemic clearance. It is intended for the treatment of retinal inflammatory diseases by intravitreal (IVT) administration.

Since anti-IL-6 treatment is addressing a different molecular pathway than anti-VEGF Standard of Care (SoC) therapy, it may be possible that a combination of RO7200220 and ranibizumab (Lucentis®) may improve vision in DME participants in an additive or even synergistic manner. In the [redacted] Besides efficacy (primary endpoint), it will further assess its safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD). [redacted]

Careful monitoring of safety parameters, routine clinical ocular examinations, and well-defined participants characteristics will be implemented to ensure participant safety.

[redacted]

Objectives And Endpoints

Primary Objective	Primary Endpoint
• To investigate the effect of RO7200220 in combination with ranibizumab on best corrected visual acuity (BCVA)	• Change from baseline in BCVA* averaged over Week *44* and Week *48* in treatment-naïve participants
Secondary Objectives	**Secondary Endpoints**
• To assess the safety and tolerability of RO7200220 in combination with ranibizumab	• Incidence, severity, and nature of adverse events (ocular and systemic) • Incidence of abnormal laboratory findings, abnormal vital signs and electrocardiogram (ECG) parameters • Incidence of abnormalities recorded in standard ophthalmological assessments (local safety and tolerability)
• To investigate the effect of RO7200220 in combination with ranibizumab on additional BCVA outcomes	• Change from baseline in BCVA averaged over Week *44* and Week *48* in previously treated participants and the overall enrolled population • *Change from baseline in BCVA averaged over Week 20 and Week 24 in treatment-naïve participants, previously treated participants, and the overall enrolled population* • *Change from baseline in BCVA averaged over Week 32 and Week 36 in treatment-naïve participants previously treated participants, and the overall enrolled population* • Change from baseline in BCVA over time • Proportion of participants gaining ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of participants avoiding a loss of ≥ 15, ≥ 10, ≥ 5, or ≥ 0 letters in BCVA from baseline over time • Proportion of participants with BCVA ≥ 69 letters (20/40 Snellen equivalent), or ≥ 84 letters (20/20 Snellen equivalent) over time • Proportion of participants with BCVA of ≤38 letters (Snellen equivalent 20/200) over time

• To investigate the effect of RO7200220 in combination with ranibizumab on anatomical outcome measures using SD-OCT	• Change from baseline in Central Subfield Thickness (CST) at Week *48* • *Change from baseline in CST at Week 36* • *Change from baseline in CST at Week 24* • Change from baseline in CST over time • Proportion of participants with absence of DME (CST <325 µm for Spectralis SD-OCT, or <315 µm for Cirrus SD-OCT or Topcon SD-OCT) over time • Proportion of participants with absence of intraretinal fluid and/or subretinal fluid over time
* All BCVA values are measured on the ETDRS chart at a starting distance of 4 meters.	

OVERALL DESIGN

Study Design

This is a multicenter, multiple-dose, randomized, active comparator-controlled, double-masked, 2-parallel group, study in participants with center-involving DME (CI-DME). Anti-VEGF and corticosteroids treatment-naïve & previously treated participants are eligible.

Only one eye will be selected as the study eye.

This proof-of-concept study will consist of a screening/randomization period (up to 4 weeks), a treatment period (from Day 1 to Week *44*), and an observational period (from Week *44* up to Week *72*). The total study length will thus be up to *76* weeks.

The study will evaluate the effects of RO7200220 in combination with the anti-VEGF inhibitor ranibizumab (Lucentis®) on visual function and retinal structure by assessing changes from baseline in best corrected visual acuity (BCVA; ETDRS letters) and anatomical outcomes (imaging assessments), respectively. The anti-VEGF inhibitor ranibizumab (Lucentis®) will be the active comparator. In addition, the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO7200220 in combination with ranibizumab will be evaluated.

Participants will be carefully monitored for potential ocular adverse events (AEs) associated with the IVT injection procedure and for other potential ocular and systemic effects associated with the IVT administration of RO7200220 and ranibizumab, and will be managed appropriately.

Treatment Groups and Duration

The two groups of this study will be:

- Arm A: 1.0 mg RO7200220 IVT Q4W and ranibizumab 0.5 mg IVT Q4W
- Arm B: 0.5 mg ranibizumab IVT Q4W (active-control arm)

Participants will be randomized 1:1 to one of the study arms.

During the treatment period, the study drug will be administered to the participants on Day 1 and on every 4th week (Q4W), for a total of *12* injections.

A sham procedure will be administered to participants in the ranibizumab only arm at applicable visits to maintain masking between treatment arms.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

The investigational medicinal products (IMP) are RO7200220 and 0.5 mg ranibizumab administered IVT.

Length of Study

The total study length will be up to *76* weeks, divided as follows:

- Screening/randomization period: up to 4 weeks
- Treatment period: Day 1 to Week *44*
- Observational period: Week *44* up to Week *72*.

End of Study

A participant is considered to have completed the study if he/she has completed all phases of the study, including the EOS visit. The end of the study is defined as the date when the last participant, last observation (LPLO) occurs.

Data Monitoring Committee:

A Roche Internal Monitoring Committee (IMC) will be responsible for the unmasked interim analysis of efficacy for operational/administrative/study related purposes and for safety data monitoring).

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

[redacted]

PARTICIPANT POPULATION

Adult male and female participants 18 years of age *or older* with diabetes mellitus (DM, Type 1 and Type 2) and center-involving macular edema associated with DR as well as vision loss due to the DME, who fulfill all of the inclusion and none of the exclusion criteria.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to the International Council for Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the participant according to ICH and local regulations

2. Willing to allow Aqueous Humor (AH) collection

Age

3. Age ≥ 18 years, at the time of signing the informed consent

Type of Participants and Disease Characteristics

4. Diagnosis of diabetes mellitus (DM; Type 1 or Type 2), as defined by the World Health Organization and/or American Diabetes Association

Sex and Contraception guidance

5. Male and female participants with contraception requirements:

   The contraception and abstinence requirements are intended to prevent conception. The reliability of sexual abstinence for female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

   a) For female participants
   A female is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

   - Women of non-childbearing potential (WONCBP), as defined in Protocol Appendix 4
   - Women of childbearing potential (WOCBP), who:
     - Have a negative pregnancy test (urine) at Day 1 prior to study treatment.
     - Agree to remain abstinent (refrain from heterosexual intercourse) or use *at least one highly* effective contraception method that result*s* in a failure rate of < 1% per year during the treatment period and for at least 12 weeks after the final dose of study treatment or any anti-VEGF given as SoC in this study.
     - Must not donate eggs during the study

   Examples of contraceptive methods with a failure rate of < 1% per year *are given in Appendix 5.*

   b) For male participants
   No requirements

Ocular Inclusion Criteria for the Study Eye

6. Macular edema associated with DR defined as macular thickening by SD-OCT involving the center of the macula: CST of ≥ 325 μm with Spectralis® (Heidelberg Engineering, Heidelberg, Germany; where Spectralis® is not available, Cirrus or Topcon would also be acceptable with a CST threshold of ≥ 315 μm) at screening. Note: CST is not part of the eligibility reconfirmation on Day 1.
7. Decreased visual acuity (VA) attributable primarily to DME, with BCVA letter score of 73 to 19 letters (both inclusive; 20/40 – 20/400 Snellen equivalent) on ETDRS-like charts at screening.
8. Clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images to confirm diagnosis.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any major illness or major surgical procedure within 4 weeks prior to Day 1
2. Any febrile illness within 1 week prior to screening or Day 1
3. Any stroke or myocardial infarction within 24 weeks prior to Day 1
4. Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis within 24 weeks prior to Day 1 or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
5. Active malignancy within 1 year of screening except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of < 6 and a stable prostate-specific antigen (PSA) for > 1 year
6. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of either of the Investigational Medicinal Products (IMPs) or that might affect interpretation of the results of the study or renders the participant at high risk for treatment complications in the opinion of the Investigator
7. Any known hypersensitivity to any of the following compounds: fluorescein, biologic IVT agents such as Lucentis® (ranibizumab), Eylea® (aflibercept), Avastin® (bevacizumab), *Beovu® (brolucizumab),* any ingredient of the formulation used, dilating eye drops, or any anesthetics and microbial drops used
8. Evidence of HIV infection and/or positive human HIV antibodies; evidence of syphilis or tuberculosis and/or positive assay

Prior/Concomitant Therapy

9. Prior or concomitant periocular or IVT corticosteroids in the study eye:
    a. For treatment-naïve participants:
        - Received any prior or concomitant IVT corticosteroid treatment
    b. For previously treated participants:
        - Received Triamcinolone within 16 weeks prior Day 1
        - Received Ozurdex® (dexamethasone IVT implant) within 16 weeks prior Day 1
        - Used *ILUVIEN®* or Retisert®(fluocinolone acetonide IVT implant) within 3 years prior Day 1

    Note: Topical or IVT corticosteroids are allowed if required to treat AEs during the study.
10. Prior or concomitant IVT *with* anti-VEGF *component* in the study eye:
    a. For treatment-naïve participants:

- Received any prior or concomitant IVT *treatment with* anti-VEGF *component*

b. For previously treated participants:

- Received the last IVT anti-VEGF treatment *(e.g. Lucentis®, Eylea®, Avastin®)* within 8 weeks prior to Day 1 *(Note: prior Beovu®is not permitted)*
- *Received the last IVT faricimab (Vabysmo ™) treatment within 16 weeks prior to Day 1*

11. Any previous or concomitant systemic corticosteroids within 4 weeks prior to Day 1
12. Any previous or concomitant systemic anti-VEGF treatment within 24 weeks prior to Day 1
13. Any previous or concomitant use of systemic anti-IL-6 or anti-IL-6-receptor treatment, including, but not restricted to: Actemra® (tocilizumab), Plivensia™ (sirukumab), Kevzara® (sarilumab), or Enspryng® (satralizumab)
14. Any concurrent use of biologics for immune-related diseases including, but not restricted to:
    - Anti-tumor necrosis factor drugs: e.g., Enbrel® (etanercept), Humira® (adalimumab), Remicade® (Infliximab), Simponi® (golimumab), Cimzia® (certolizumab pegol);
    - Anti-IL-12: e.g., Stelara® (ustekinumab);
    - Anti-IL-1: e.g., Kineret® (anakinra), Ilaris® (canakinumab), Arcalyst® (rilonacept);
    - Anti-IL-23: e.g., Tremfya® (guselkumab);
    - Anti-IL-17, anti-IL-17A: e.g., Cosentyx® (secukinumab), Taltz® (ixekizumab)

Prior/Concurrent Clinical Study Experience

15. Participants who are currently enrolled or have participated in any other clinical study:
    - Involving brolucizumab *(Beovu®);*
    - [redacted]
    - Involving any other investigational products or devices, or in any other type of medical research with the last drug administration or invasive assessment (incl. blood drawing) ≤ 12 weeks prior to Day 1.

Diagnostic Assessments

16. Uncontrolled blood pressure (BP), defined as systolic > 180 mmHg and/or diastolic > 100 mmHg while participant at rest. If a participant's initial reading exceeds these values, a second reading may be taken either ≥ 30 minutes later on the same day or on another day during the screening period. If the participant's BP needs to be controlled by antihypertensive medication, the participant should be on stable medication for at least 1 month prior to Day 1
17. Participants with HbA1c > 12% at screening

Exclusion criteria for study eye

18. Any proliferative DR defined as:
    - Any neovascularization of the optic disc;
    - Any neovascularization elsewhere;
    - Any neovascularization of iris;
    - Any neovascularization of irido-corneal angle;
    - Vitreous or pre-retinal hemorrhage;
19. Any panretinal photocoagulation prior to Day 1
20. Macular (focal, grid, or micropulse) laser treatment prior to Day 1
21. History of vitreoretinal surgery/pars plana vitrectomy, including PDS with ranibizumab implant/explant surgery
22. Any cataract surgery within 12 weeks prior to Day 1 or any planned surgery during the study
23. History of any glaucoma surgery (Note: laser glaucoma procedures are allowed if > 12 weeks prior Day 1)

24. Uncontrolled glaucoma (e.g., progressive loss of visual fields or defined as intraocular pressure (IOP) ≥ 25 mmHg at screening despite treatment with anti-glaucoma medication)
25. History of rubeosis iridis
26. Any concurrent ocular conditions (e.g., cataract, age-related macular degeneration, macular hole, retinal vein occlusion, infectious or noninfectious uveitis, angioid streaks, histoplasmosis, active or inactive cytomegalovirus retinitis, choroidal neovascularization, infectious/non-infectious conjunctivitis, keratitis, scleritis, endophthalmitis) that, in the opinion of the Investigator, could either:
    - Require medical or surgical intervention during the study period to prevent or treat visual loss that might result from that condition; **or**
    - Likely contribute to worsening of BCVA over the study period if allowed to progress untreated; **or**
    - Preclude any visual improvement due to established structural damage.
27. Rhegmatogenous or tractional retinal detachment, pre-retinal and/or sub-macular fibrosis, vitreomacular traction, foveal hard exudates, or epiretinal membrane involving the fovea or disrupting the macular architecture, as evaluated by the Central Reading Center (CRC)
28. Actual or history of myopia > -8 diopters.
29. Any active ocular or periocular infection on Day 1.
30. Any presence of active intraocular inflammation on Day 1 (i.e., SUN criteria > 0 or NEI vitreous haze grading > 0) or any history of intraocular inflammation

Criteria for fellow (non-study) eye:

31. Non-functioning non-study eye, defined as either:
    - BCVA ≤ *23*
    - No physical presence (i.e., monocular)
    - Legally blind in the participant's relevant jurisdiction

NUMBER OF PARTICIPANTS

With approximately *105 to 115* participants randomized per arm, the total number of participants will be *approximately 210 to 230* (see also sample size description in the statistical analysis section in this synopsis).

CONCOMITANT MEDICATIONS

At the discretion of the investigator, participants may start or continue to receive all medications and standard treatments administered for other conditions, except for therapies listed under the exclusion criteria.

Participants are not allowed to participate in any other clinical study during participation in Study BP43464.

Retinal laser photocoagulation is permitted in either eye, if clinically indicated for the treatment of proliferative DR or retinal holes or tears post randomization.

Administration of macular micropulse and focal or grid laser in study eye is prohibited throughout the duration of this study.

Should DME emerge or recur and require treatment in the fellow eye during the study period, the participant may receive approved anti-VEGF SoC treatment. The Sponsor will cover the cost of approved licensed ocular anti-VEGF therapy in accordance with local regulations.

Rescue medication

Not applicable

STATISTICAL ANALYSIS

The primary efficacy outcome is mean change in BCVA from baseline over the average of Weeks *44/48* in treatment-naïve population. The estimated changes in the RO7200220 in combination with ranibizumab arm (Arm A), and the differences to the control arm (Arm B) will be presented. No formal hypothesis testing will be performed. The BCVA endpoint will also be estimated in the previously treated population and in the overall population as secondary efficacy outcomes. SD-OCT measurements of CST are a key secondary endpoint.

Interim analysis

[redacted]

Sample Size

Approximately *70 to 75* treatment-naïve participants will be enrolled in each arm *to ensure that approximately 55 treatment-naïve participants will* be evaluable *at Week 48* for the primary efficacy outcome of mean change in BCVA from baseline to Weeks *44/48*.

Additionally, approximately *35 to 40* previously treated participants will be enrolled in each arm *to ensure that approximately 25 previously treated participants will* be evaluable *at Week 48* for the primary efficacy outcome.

Table 1 Schedule of Activities

Week	Scree -ning	Week 1		Week 4	Week 8	Week 12/16/20	Week 24	Week 28/32	Week 36	Week 40/44	Week 48[o]	Week 52/56/60/64/ 68	Week 72 /EOS	Early Treatment Termination Visit[p]
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84/112/140	Day 168	Day 196/224	Day 252	Day 280/308	Day 336	Day 364/392/420/ 448/476	Day504	
Visit Window			± 3	±7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	
Informed Consent														
Main Informed Consent[a]	X													
Optional (RBR) residual samples[a]	X	X												
Study Drug Administration or SoC														
Administration of Study Treatment		X		X	X	X	X	X	X	X				
Administration of SoC [b]											X[b]	X[b]	X[b]	
Assessments														
Eligibility Criteria[c]	X	X												
Demography	X													
Medical History[c]	X	X												
Physical Examination	X										X			X
Anthropometric Measurements	X						X[d]		X[d]		X[d]			X[d]
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG-12 Lead[c]	X										X			X
Specimen sampling														
Hematology	X						X		X		X			X
Blood Chemistry	X						X		X		X			X
Blood Coagulation tests	X													
Urinalysis[c]	X						X		X		X			X
Hormone Panel[e]	X													

Week	Scree-ning	Week 1		Week 4	Week 8	Week 12/16/20	Week 24	Week 28/32	Week 36	Week 40/44	Week 48[o]	Week 52/56/60/64/68	Week 72/EOS	Early Treatment Termination Visit[p]
Day	D-28 to D-1	Day 1	Day 7	Day 28	Day 56	Day 84/112/140	Day 168	Day 196/224	Day 252	Day 280/308	Day 336	Day 364/392/420/448/476	Day504	
Visit Window			± 3	±7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	
Serology	X													
Pregnancy Test [c,e]	X	X		X	X	X	X	X	X	X	X[q]	X[q]	X[q]	
[redacted]														
Ocular Assessments														
Pre-treatment IOP (part of clinical assessment)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-treatment IOP[m] (before discharge)		X	X[k]	X	X	X	X	X	X	X	X[k,q]	X[q]	X[q]	
Finger Counting Test [j]		X		X	X	X	X	X	X	X	X[q]	X[q]	X[q]	
BCVA[c,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmoscopy[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Photography (UWF preferred)	X						X				X	X[q]	X	X
SD-OCT[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[c]		X					X				X	X[q]	X	X
Fundus Fluorescein Angiography (UWF preferred)[c]	X						X				X	X[q]	X[i]	X
Safety Assessments														
Adverse Events	←---→	←----------												----------→
Previous and Concomitant Medication	←----------													----------→

Table 1 Schedule of Activities (cont.)

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments for a visit are to be performed on the same day, except those at screening. All study visits will be scheduled relative to the date of the Day 1 visit (first study treatment).
There must be a minimum of 21 days between study treatment visits occurring from the Day 1 visit through the Week 44 visit.
If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), a participant's randomization and first study treatment may be administered within 2 business days of the Day 1 visit assessments, after consultation with the Medical Monitor. The following assessments will be repeated on the day of randomization and study treatment administration: urine pregnancy test (if applicable), slit lamp examination, indirect ophthalmoscopy, pre-treatment IOP measurements (recorded on the Day 1 electronic case report form [eCRF] and dated accordingly), and any new concomitant medications.

[a] Main Informed consent must be administered and documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment at the Day 1 visit. The Optional (RBR) Informed Consent Form for residual samples collection can be signed either at the screening or Day 1 visit prior to sample collection.

[b] [redacted]

[c] Prior to study treatment administration, when applicable.

[d] Body weight only.

[e] For female participants only. If WOCBP, serum pregnancy test at screening and urine pregnancy test at the other visits.

[f] In study eye only.

[g] [redacted]

[h] [redacted]

[i] [redacted]

[j] Finger count vision assessment in study eye up to 15 minutes after study treatment or SoC administration.

[k] [redacted]

[l] Performed prior to pupil dilation.

[m] In study eye only. *The second study drug administration can only be given once IOP has returned to normal.* If IOP ≥ 30 mmHg at [redacted] minutes *after the second study* drug administration, then IOP is measured again at 60 (±10) minutes.

[n] [redacted]

[o] The study visit at Week *48* should not occur earlier than 28 days after the last study treatment.

[p] Early Treatment Termination (ETT) Visit; If a participant discontinues study treatment prior to Week *44,* the ETT visit will be done (if consent still in place). If a decision to discontinue at Week *44* is taken, the regular Week *48* visit should be performed. Participants discontinuing from Study after Week *48* will perform the EOS visit (will be either Week *72* or earlier). Fundus Photography (UWF preferred), Fluorescein Angiography (UWF preferred) and OCT-A should be done if ETT visit ≥ 12 weeks after Day 1.

[q] [redacted]

Legend: [redacted] BCVA=best corrected visual acuity, D=Day, EC=Ethics Committee, ECG=electrocardiogram, EOS= End of study, ETT= early treatment termination, IOP=intraocular pressure, IxRS= interactive voice/web based response system; OCT-A= optical coherence tomography angiography, [redacted] RBR= Roche Research Biosample Repository, SD-OCT=spectral domain optical coherence tomography, SoC= Standard of Care; UWF=Ultra-wide field, WOCBP=women of childbearing potential.

Signature Page for Statistical Analysis Plan -
System identifier: RIM-CLIN-529764

Approval Task	[redacted] Company Signatory 21-May-2024 12:18:41 GMT+0000