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

NCT Number: NCT05151731

Document Date: Protocol Amendment Version 3: 23-Apr-2023

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7200220 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	BP43445
VERSION:	3
EUDRACT NUMBER:	2021-00326756-16
IND NUMBER:	125644
TEST PRODUCT:	RO7200220
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 13-Sep-2021
DATE AMENDED	Version 2: 01-Jul-2022 Version 3: See electronic signature and date stamp on the final page of this document

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE MASKED, ACTIVE COMPARATOR-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RO7200220 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	BP43445
VERSION NUMBER:	3
EUDRACT NUMBER:	2021-003756-16
IND NUMBER:	125644
TEST PRODUCT:	R07200220
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol BP44345 Version 2 has been amended to reflect the changes that have been outlined in the [redacted]
Changes to the protocol, along with a rationale for each change, are summarized below.

- **Sections 2.2.3 (Clinical Studies on RO7200220)** [redacted]

  Information of the [redacted] in two Phase II studies has been added.

- **Section 5.2 (Exclusion Criteria)**
  - Exclusion criterion #26: Patients with [redacted]
  - Exclusion criterion #30: Clarification added that patients [redacted]

- **Section 6.5.1 (Rescue Medicine and SOC treatment)**

  Clarification has been added to be further consistent with Section 7.

- **Section 7.1 (Discontinuation of Study Treatment)**

  It has been specified that participants [redacted]

- **Section 8.2 (Safety Assessment)**

  Overall safety measures for assessment of [redacted] have been added. Further recommendation about additional [redacted] have been added.

- **Section 8.9.2 (Assessment during Treatment)**

  Information that at each study visit, a careful assessment for [redacted] should be done.

- **Section 8.9.5 (Assessments at the Occurrence of a [redacted])**

  It has been clarified which additional assessments are recommended in case of a [redacted] Further recommendation about additional [redacted] have been added.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in the font *Book Antiqua italics*. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	Anterior chamber
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AH	Aqueous humor
AUC	Area under the concentration-time curve
BCVA	Best corrected visual acuity
BP	Blood pressure
CI-DME	Center-involving diabetic macular edema
CSR	Clinical study report
CST	Central subfield thickness
CRC	Central reading center
DLE	Dose limiting event
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
[redacted]	
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
ETTV	Early treatment termination visit
E.U.	European Union
FcRn	Neonatal Fc receptor
FFA	Fundus fluorescein angiography
FP	Fundus photography
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c (glycosylated hemoglobin)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin

IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IOI	Intraocular inflammation
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
IxRS	Interactive voice and web response system
LPLO	Last participant, last observation
MCP-1	Monocyte chemotactic protein-1
MMRM	Mixed Model for Repeated Measurements
nAMD	Neovascular age-related macular degeneration
NSAESI	Non-serious adverse event of special interest
OCT-A	Optical coherence tomography angiography
PD	Pharmacodynamic
PK	Pharmacokinetic
QT	QT interval
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q8W	Every 8 weeks
RBR	Research Biosample Repository
SAE	Serious adverse event
SD-OCT	Spectral domain optical coherence tomography
SmPC	Summary of Product Characteristic
SoA	Schedule of activities
SoC	Standard of Care
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected unexpected serious adverse reaction
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
U.S.	United States
UME	Uveitic macular edema
UWF	Ultra-wide-field
VEGF	Vascular endothelial growth factor
VA	Visual acuity
VH	Vitreous humor
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 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 ADMINISTERED INTRAVITREALLY IN PATIENTS WITH DIABETIC MACULAR EDEMA**
SHORT TITLE	**PHASE II STUDY TO INVESTIGATE RO7200220 IN DIABETIC MACULAR EDEMA**
PROTOCOL NUMBER:	BP43445
VERSION:	3
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 patients with conditions such as DR, diabetic macular edema (DM)E, neovascular age-related macular degeneration (nAMD), uveitis, uveitic macular edema (UME), 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.

[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 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	• 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 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 patients 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 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, 4-parallel group, study in participants with 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 be up to 76 weeks.

The study will evaluate the effects of RO7200220 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 (PD) of RO7200220 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 four groups of this study will be:

- Arm A: 0.25 mg RO7200220 IVT Q8W
- Arm B: 1.0 mg RO7200220 IVT Q8W
- Arm C: 1.0 mg RO7200220 IVT Q4W
- Arm D: 0.5 mg Ranibizumab IVT Q4W (active-control arm)

Participants will be randomized 1:1:1:1 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, or on Day 1 and every 8th week (Q8W) for a total of 6 injections.

A sham procedure will be administered to participants in the Q8W arms (Arms A and B) 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 results 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 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 *anti*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 is 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 ([redacted], 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 *(noninfectious or infectious uveitis of any type)*

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 90 to 100 participants randomized per arm, the total number of participants will be approximately 360 to 400 (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 BP43445.

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 the 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

During the treatment period of the study (i.e. up to Week 44) anti-VEGF IVT treatment with SoC must be instituted if any of the following criteria due to worsening of the underlying disease (DME) or due to lack of efficacy are observed:

- [redacted]

Note: Rescue therapy can additionally be instituted at any time at the discretion of the Investigator.

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 each RO7200220 arms, and the differences to the control arm 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

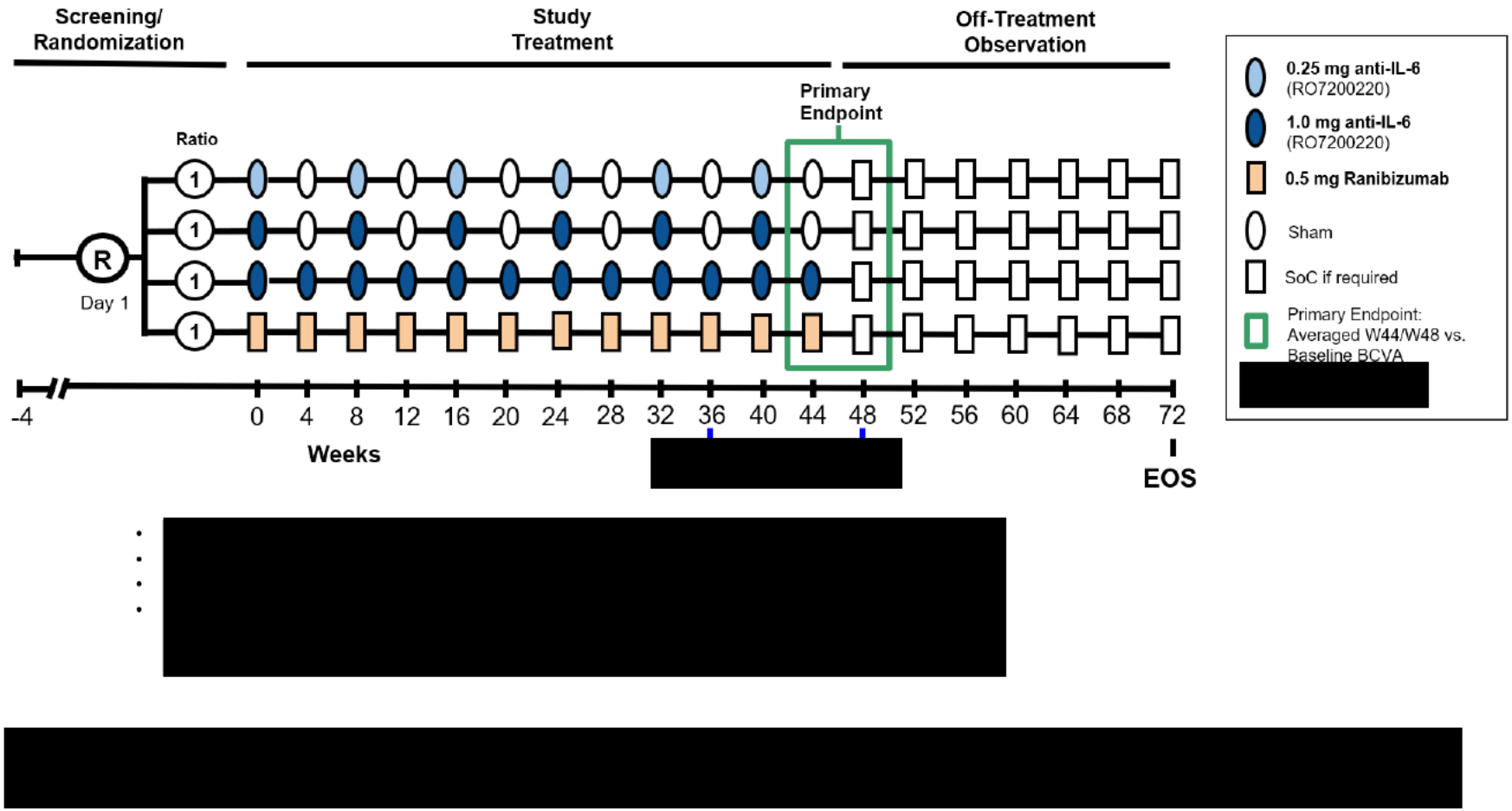
Approximately 60-65 treatment naïve participants will be enrolled in each arm to ensure that approximately 55 treatment naïve participants will be evaluable at Week 48 for the primary efficacy outcome of mean change in BCVA from baseline to Weeks 44/48.

Additionally, approximately 30-35 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.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design



1.3 SCHEDULE OF ACTIVITIES

The schedule of activities is provided in Table 1.

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	Day 504	
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	Day 504	
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]	
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 Recordings														
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. If IOP ≥ 30 mmHg at [redacted] minutes post-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 patient 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. Patients 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, PD=pharmacodynamics, PK=pharmacokinetics, 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.

2. INTRODUCTION

2.1 STUDY RATIONALE

[redacted]

Besides efficacy (primary endpoint), this study will further assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of RO7200220. [redacted]
(Funatsu et al 2004), [redacted]

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

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on IL-6 and Diabetic Macular Edema

DME is defined by the accumulation of fluid within the macular area of patients with diabetic retinopathy (DR). It is a major cause of vision loss worldwide affecting predominantly the working-age population, and the most common cause of moderate to severe visual impairment in patients with DR (Resnikoff et al 2004; Cheung et al 2010).

Persistent inflammation in the retina is present from the early stages of diabetes to the sight-threatening advanced forms of DR (e.g. Simó-Servat et al 2012). Indeed, a complex milieu of dysregulated proinflammatory factors is found in the diabetic retina, which includes interleukin (IL)-6, IL-1β, IL-8, Monocyte chemotactic protein-1 and Tumor necrosis factor-α (Simó-Servat et al 2012; Valle et al 2019).

IL-6 levels in particular have been found frequently increased in ocular fluids of patients with conditions such as DR, DME, neovascular age-related macular degeneration (nAMD), uveitis, uveitic macular edema (UME), and retinal vein occlusion. In a recent meta-analysis of 18 studies with 362 cases of DR and 100 cases of DME, high intraocular levels of IL-6 were significantly correlated both with the risk of developing DR and DME (Wu et al 2019). Additionally, [redacted]

Moreover, the clinical efficacy of IVT corticosteroids (triamcinolone acetonide, dexamethasone and fluocinolone implants) in patients with DME highlights the

prominent role of inflammation in this condition (Whitcup et al 2018; Cunningham et al 2008). In addition, systemic inhibition of the IL-6 pathway (with e.g. tocilizumab or sarilumab) has been shown to be efficacious in multiple inflammatory conditions including noninfectious uveitis and UME (Ramanan et al 2020; Karkhur et al 2019; Vegas-Revenga et al 2019; Lopalco et al 2012; Sepah et al 2017).

It thus seems reasonable to assume that anti-IL-6 treatment with RO7200220 may improve functional and anatomical outcomes in DME patients, [redacted]

2.2.2 Background on RO7200220

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.

A detailed description of the chemistry, pharmacology, and safety of RO7200220 is provided in the RO72000220 Investigator's Brochure (IB).

2.2.3 Clinical Studies with RO7200220

[redacted]

No apparent pattern of clinically significant abnormalities in ECG, vital sign or laboratory safety parameters were observed.

[redacted]

Up to a dose of [redacted] RO7200220 displayed a favorable safety profile, with no serious adverse events (SAEs) related to study drug, and no unexpected safety findings observed. [redacted]

For more details see the RO7200220 IB.

[redacted]

2.2.4 Choice of Comparator

Ranibizumab is an approved anti-VEGF treatment in patients with DR with or without DME. It demonstrated efficacy in controlled randomized clinical studies. In the United States, monthly dosing of 0.3 mg IVT ranibizumab is the approved treatment regimen based on data from the clinical studies RIDE and RISE (Nguyen et al 2012). In territories outside of the United States, including the European Union, the approved treatment regimen is 3 monthly doses of 0.5 mg followed by as-needed (pro-re-nata) 0.5 mg IVT injections.

RIDE and RISE evaluated monthly IVT injections of 0.3 and 0.5 mg ranibizumab over a period of 24 months. The results indicated that both the 0.3 and 0.5 mg doses show a similar benefit in the management of DME, as well as the underlying DR, and both doses were generally well-tolerated. A meta-analysis conducted on systemic AEs associated with anti-VEGF IVT use (including ranibizumab, bevacizumab and aflibercept), suggested that anti-VEGF treatments do not increase the risk of systemic AEs (studies included different anti-VEGFs, different doses and regimens) (Thulliez et al 2018).

[redacted]

For more information on ranibizumab, please refer to the Lucentis® EU Summary of Product Characteristic (SmPC).

2.3 BENEFIT/RISK ASSESSMENT

Previous non-clinical and clinical studies

[redacted]

Of note, an assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the benefit/risk assessment of this study protocol including, but not limited to, the patient population under study and study treatment being evaluated. On the basis of that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and the risk mitigation measures provided in the study protocol are considered adequate.

COVID-19 vaccine given to a trial participant has no anticipated study treatment-vaccine interaction and does not require advice on timing of the vaccine or the implementation of any other risk mitigation activities. COVID-19 vaccine should be considered as a concomitant medication.

Careful monitoring of safety parameters, routine clinical ocular examinations, and well-defined participants characteristics will be implemented to ensure participant safety *(see Section 8.2)*.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7200220 is provided in the RO7200220 IB.

[redacted]

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 2.

Table 2 Objectives and Endpoints

Primary Objective	Primary Endpoint
• To investigate the effect of RO7200220 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	• 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 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 patients 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 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

Exploratory Objectives	Exploratory Endpoints
[redacted]	

4. STUDY DESIGN

4.1 OVERALL DESIGN

STUDY DESIGN

This is a multicenter, multiple-dose, randomized, active comparator-controlled, double-masked, 4-parallel group, Phase II study in participants with 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 be up to 76 weeks.

The study will evaluate the effects of RO7200220 on visual function and retinal structure by assessing changes from baseline in 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 will be evaluated.

Participants will be carefully monitored for potential ocular 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.

A schematic of the study design is shown in Section 1.1. An overview of the scientific rationale for the study design is provided in Section 4.2.

Treatment Groups and Duration

The four groups of this study will be:

- Arm A: 0.25 mg RO7200220 IVT Q8W
- Arm B: 1.0 mg RO7200220 IVT Q8W
- Arm C: 1.0 mg RO7200220 IVT Q4W
- Arm D: 0.5 mg Ranibizumab IVT Q4W (active-control arm)

Participants will be randomized 1:1:1:1 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, or on Day 1 and every 8th week (Q8W) for a total of 6 injections.

A sham procedure will be administered to participants in the Q8W arms (Arms A and B) at applicable visits to maintain masking between treatment arms (see Section 1.3).

Off-treatment observational period

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.1 Length of the 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.

4.1.1.1 Communication Strategy

Not applicable.

4.1.2 Administrative Structure

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 (Appendix 1).

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]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

The study will be conducted in adult male and female participants over 18 years of age with diabetes mellitus (Type 1 and Type 2) and center-involving macular edema associated with DR as well as vision loss due to the DME. The primary aim is to evaluate the efficacy of RO7200220 compared with the active comparator in treatment-naïve patients with CI-DME. Inclusion of previously anti-VEGF and/or IVT corticosteroid treated patients will allow the exploratory evaluation if these populations respond differently to treatment with RO7200220.

4.2.2 Rationale for Control Group

The control group will receive anti-VEGF treatment in the form of 0.5 mg IVT ranibizumab Q4W as active-comparator control (see Section 2.2.4 for details).

[redacted]

[redacted]

a. [redacted]

b. [redacted]

c. [redacted]

[redacted]

4.2.4 Rationale for Blood Biomarker Assessments

Both protein and genetic biomarkers may be analyzed as exploratory analysis to improve the understanding of the participants' response to RO7200220.

[redacted]

4.3 JUSTIFICATION FOR DOSE

[redacted]

[redacted]

Preliminary signals of functional and anatomical improvements (BCVA/CST) were seen across all dose-groups.

The doses of 0.25 mg Q8W, 1.0 mg Q8W and 1.0 mg Q4W RO7200220 administered for up to 44 weeks were selected, because

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

[redacted]

See Section 4.2.2 for the rational of the ranibizumab dose.

Further details are provided in the Lucentis® EU SmPC and the RO7200220 IB.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study, including the End-of-Study (EOS) visit. The end of the study is defined as the date when the last participant, last observation (LPLO) occurs. LPLO is expected to occur at the EOS visit 4 weeks after the last participant has received SoC treatment in the off-treatment observation period, or at Week 72 latest.

5. STUDY POPULATION

The study population consists of male and female participants of ≥ 18 years of age with DM (Type 1 or Type 2) and CI-DME who fulfill all of the inclusion criteria and none of the exclusion criteria.

The study population rationale is provided in Section 4.2.1.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

One month is equivalent to a duration of 4 weeks (28 days).

5.1 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 5
   - 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 of at least one highly effective contraception method that results 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.

5.2 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 *anti*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-IL6 or anti-IL6-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 is 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., [redacted], 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 *(noninfectious or infectious uveitis of any type)*

Criteria for fellow (non-study) eye:

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

5.3 LIFESTYLE CONSIDERATIONS

There are no study-specific restrictions to meals and dietary requirements.

Participants may experience temporary visual disturbances after an IVT injection and the associated eye examinations. Participants should be advised not to drive or use machinery until visual function has recovered sufficiently.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to study treatment. Screen failures should be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Participants who do not meet the criteria for participation in this study (screen failure) may be re-screened at the discretion of the Investigator. Eligible participants could be re-screened up to 3 times (i.e. up to a total of 4 screenings) if required.

In order to re-screen a participant after the end of the *initial* 28-day screening window, all inclusion and exclusion criteria should be re-evaluated and all screening assessments repeated. Note: If a participant will be re-screened within *the 28-day* window, fundus photography (FP) and FFA need to be repeated only if they were performed more than 14 days before the new screening date.

If the originally chosen eye does not meet eligibility criteria, the second eye may be evaluated within the initial *28-day* screening period. If the second eye meets the eligibility criteria, then the participant would retain the same screening number and would not be considered screen-failed.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using clinical database and/or Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) approved newspaper/radio/social-media advertisements prior to consenting to take part in this study.

6. TREATMENTS

Study treatment is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

The IMPs for this study are RO7200220 and ranibizumab 0.5 mg; with RO7200220 and ranibizumab administered each at a constant volume of 50 μL IVT in the specified single study eye.

All IMPs required for completion of this study will be provided by the Sponsor. Study drug will be administered at the study center by qualified treatment administrator (see the Procedures Manual for study administration procedures).

Cases of accidental overdose or medication error along with any associated AEs, should be reported as described in Section 5.2 of Appendix 2.

6.1 TREATMENTS ADMINISTERED

RO7200220 will be administered to the participants on Day 1 and every 4th week (Q4W), for a total of 12 injections for Arm C, or every 8th week (Q8W) for a total of 6 injections in Arm A and B each. Ranibizumab 0.5 mg will be administered to the participants of Arm D 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 Q8W Arms (Arms A and B) at applicable visits to maintain masking between treatment arms.

Participants enrolled under Version 1 of this protocol and who have consented to this version of the protocol will be handled as follows:

[redacted]

[redacted]

[redacted]

[redacted]

Table 3 summarizes the treatments administered. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Note: During the off-treatment observation period IVT anti-VEGF may be administered as SoC per discretion of the Investigator for those patients who show disease recurrence as defined in Section 6.5.1.2. Ranibizumab administered in this context is not considered an IMP. Additionally, ranibizumab administered as rescue treatment, or as per discretion of the Investigator, is not considered an IMP (see Section 6.5.1).

Please see the Lucentis® EU SmPC for more details on ranibizumab (Lucentis®). For RO7200220, please see the RO7200220 IB and the pharmacy manual for RO200220 for more details.

Table 3 Summary of Treatments Administered

Study Treatment Name:	RO7200220 (Drug Product)	RO7200220 (Diluent)	Ranibizumab	SHAM
Dose Formulation:	[redacted]	[redacted]	Ranibizumab is provided in a single-use 0.5 mL prefilled syringe (buffered using a L-histidine-HCl solution (pH 5.5) containing trehalose, polysorbate 20, and water.	No dose
IMP and NIMP	IMP	N/A (diluent)	IMP	N/A
Concentration	100 mg/mL	0 mg/mL	10 mg/mL	N/A
Dose:	0.25 mg in Arm A; 1.0 mg in Arms B and C	Only used for dilution	0.5 mg in Arm D	No dose
Route of Administration:	IVT injection	Only used for dilution	IVT injection	The sham is a procedure that mimics an IVT injection and involves the blunt end of an empty syringe (without a needle) being pressed against the anesthetized eye.
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	RO7200220 Drug Product will be provided in vials. Each vial will be labeled as required per country requirement.	RO7200220 Diluent will be provided in vials. Each vial will be labeled as required per country requirement.	Ranibizumab will be provided in prefilled syringes. Each syringe will be labeled as required per country requirement.	Sham treatments will be provided as empty vials in cartons. Each vial will be labelled as required per country requirement.
Manufacturer	Genentech	Genentech	Genentech or Novartis	N/A

Legend: IMP=investigational medicinal product; NIMP = non-investigational medicinal product; IVT=intravitreal; N/A = Not applicable

6.1.1 Medical Devices

The Sponsor-manufactured medical devices (or devices manufactured for the Sponsor by a third party) provided for use in this study are relating to pre-filled syringes with ranibizumab.

The Investigator must report all medical device incidents to the Sponsor throughout the study (see Section 8.3.9).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized staff.

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the pharmacy manual for RO7200220 and as per the Lucentis® EU SmPC for the comparator (i.e. ranibizumab).

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.

The Investigator, Institution, or the Head of the Medical Institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the RO7200220 IB, or the Lucentis® EU SmPC for ranibizumab for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

6.3.1 Method of Treatment Assignment and Masking

After written informed consent has been obtained, all participants will receive a screening number assigned through the interactive voice and web response system (IxRS).

A participant must meet all eligibility criteria (see Section 5.1 and Section 5.2) at the screening or Day 1 visit prior to randomization and first study treatment (see Section 8.9). As part of the screening process, FP, FFA, and SD-OCT will be transferred to the CRC, and the images will be evaluated to provide an objective, masked assessment of certain eligibility criteria.

After all participant eligibility requirements are confirmed on Day 1 visit, the site personnel will contact the IxRS for assignment of a participant identification number (a separate number from the screening number).

Participants will be randomized on the same day the study treatment is to be initiated (Day 1 visit).

Note: 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.

Randomization will be stratified for the factors below:

- Baseline BCVA ETDRS letter score assessed on Day 1 (categories: ≤ 38 letters; > 38 to <64; ≥ 64).
- IVT anti-VEGF and/or periocular/IVT corticosteroids treatment naïve participants vs. previously treated participants (Note: treatment naïve and previously treated participants as defined in Section 5.2).

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 1:1:1:1 ratio to one of the four 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=60-65 for treatment naïve and approximately n=30-35 for previously treated participants.

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

[redacted]

6.3.4 Masking

6.3.4.1 Masked Roles

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study, and both are required to be present at each scheduled study visit where study treatment is administered.

Principal Investigator

The Principal Investigator who will be a retina specialist (or the equivalent in ex-U.S. countries) must be in a masked role as he or she has to oversee the whole trial conduct at his or her site and must be masked to participants' treatment assignment. In addition, the Principal Investigator can assume any other masked role for which he or she qualifies except for BCVA examiner tasks.

Assessor Physician

At least one investigator who will be a retina specialist (or the equivalent in ex-U.S. countries) will be designated as the assessor physician. He or she will be masked to participants' treatment assignments and will evaluate all pre-treatment assessments, as well as all assessments performed at screening, Day 7, Week 48, throughout the off-treatment observation period and at the EOS or early treatment termination visit (ETTV). The assessor physician will also evaluate the causality of all AEs reported by the treatment administrator. If qualified, this role can take on any other masked role tasks except tasks performed by the BCVA examiner.

Photographer(s) and OCT Technician(s)

If qualified, the photographers and OCT technicians can share any other masked role tasks except tasks performed by the BCVA examiner.

Study Coordinator(s)

If qualified, the study coordinator(s) can share any other masked role tasks except tasks performed by the BCVA examiner.

BCVA Examiner

The BCVA examiner will be masked to both the assigned treatment arm and the location (right vs. left) of the study eye. The BCVA examiner will have no access to participants' medical charts or the VA scores from a participant's previous visits and may have access only to a participant's refraction data from previous visits. The BCVA examiner is not allowed to perform any other task involving direct participant care.

Phlebotomist

The phlebotomist's tasks can be performed by a qualified masked or unmasked role individual except for BCVA examiner role.

Note: Vital signs and ECG assessments can also be done by a qualified masked or unmasked role, except for the BCVA examiner role.

6.3.4.2 Unmasked Roles

Treatment Administrator

At least one investigator will be designated as the treatment administrator and will be unmasked to the participants' treatment assignment.

The study treatment administrator must be an ophthalmologist, and ideally a retina specialist. It is the PI's responsibility to ensure that the treatment administrator ophthalmologist is suitably qualified to safely perform the IVT injection procedure, is able to manage any adverse events that may occur following the IVT procedure, and is [redacted]

The treatment administrator(s) performing the study treatment administration (RO720220, ranibizumab, or sham) will also perform the post-treatment administration vision testing (finger-counting and, if applicable, hand movement and/or light perception tests) and will treat AEs that occur during or shortly after the study treatment administration. The person in this role, however, will not evaluate the causality of AEs, which is the responsibility of the masked assessor physician(s). The treatment administrator can also perform post-treatment IOP measurements, [redacted]

In addition, the qualifying treatment administrator can assist with and perform the screening and Day 1 visit assessments. The treatment administrator must not be involved in any other aspect of the study and must not divulge treatment assignment to anyone.

Unmasked Assistant(s) and Pharmacist

Sites should have designated qualified unmasked assistant(s) who can, e.g., accept IMP packages, log them in IxRS, place them under correct conditions in the fridge, prepare study treatment incl. dilutions if applicable (as described in the Pharmacy manual), assemble study treatment supplies, prepare sterile field, prepare the participant's study eye for treatment, discard all injection materials (i.e., syringes and needles) immediately following study treatment, and place vial in the kit box. The qualified unmasked assistant(s) can be assigned to measure post-dose IOP. If the site uses a pharmacy, then the unmasked role is also assigned to the pharmacist who can take on IMP-related tasks as applicable per delegation of authority log. In addition, qualifying unmasked assistant(s) can assist with and perform the screening and Day 1 visit assessments.

Number of Unmasked Personnel per Site

Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. Typically, there should be no more than six unmasked personnel (e.g., treatment administering physician[s] and assisting technician[s] if applicable) at an investigative site at one time. In certain circumstances, the total number of unmasked personnel might be increased after discussion with and approval

by the Medical Monitor. If the site is using a pharmacist, then this person may be in an unmasked role in addition to the unmasked staff at the site.

Any other study assisting personnel not listed above will be in the masked roles.

6.3.4.3 Delegation Log

All roles for each study staff member should be clearly documented in the Site Delegation Log. The Site Delegation Log must be signed by the Principal Investigator.

6.3.4.4 Role Switching

Once personnel assigned to the designated unmasked role start performing that role they cannot switch to a masked role during the study. Switching from a masked role to an unmasked role may be possible and must be documented in the Delegation Log.

6.3.4.5 Study Backup Staff

Sites are strongly advised to have backup staff for key study roles. In case of an emergency (e.g., an unscheduled safety visit), participants should be seen preferably by the assessor physician. If the assessor physician is unavailable, then any clinic physician present, including the physician in the treatment administrator role, should see the participant.

6.3.4.6 Masking of Vendors, Sponsor's Agents, and Laboratory Personnel

CRC personnel, study vendors, the Sponsor, and its agents will also be masked to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfil their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, drug accountability clinical research associates, the images coordinator, IMC members and those responsible for preparing the IMC report(s).

To maintain the masked design of the study, [redacted] will be obtained from consenting participants in any treatment arm. The laboratories responsible for performing sample analyses and the Sponsor’s Bioanalytical Scientist will be unmasked to participants' treatment assignment to identify appropriate samples to be analyzed. Unmasking for analysis of the relevant biosamples during the conduct of the study will be performed by personnel outside of the study team (e.g., by the Sponsor's pharmacometrician, PK/PD Data Scientist) and according to the Sponsor’s internal standard procedures to ensure the integrity of the data. The number of Roche representative(s) and delegates who are unmasked will be kept to the minimum required to address the objective of the biosample analysis.

6.3.4.7 Participant Masking

Participants will be masked to treatment assignment during the study and until study closeout, until the Sponsor indicates that the study can be unmasked.

6.3.5 Unmasking

6.3.5.1 Single-Participant Emergency Unmasking

If unmasking is necessary for a medical emergency (e.g., in the case of a SAE for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The Investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

6.3.5.2 Single-Participant Non-Emergency Unmasking

If the investigator wants to know the identity of study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unmasking. The investigator will be able to break the treatment code by contacting the IxRS.

6.3.5.3 Single-Participant Unmasking for Health Authority Reporting Requirements

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all SUSARs (see Section 5 in Appendix 2) that are considered by the investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above) will remain masked to treatment assignment.

6.4 TREATMENT COMPLIANCE

Not applicable.

6.5 CONCOMITANT THERAPY

Treatments and procedures should be reported to the Investigator via the respective eCRF along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency) as follows:

- Any treatments pertinent to DR/DME (e.g. IVT with anti-VEGF component and/or IVT corticosteroids) used by a participant prior to Day 1 (at least for the year preceding Day 1). Concomitant treatments for the fellow-eye should be recorded until the final visit.
- SoC treatment of the study eye during the off-treatment follow up period will be reported on a separate form.

- Any other medication or vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 30 days prior to Day 1 until the final visit.
- Protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes, proparacaine, or antimicrobials [if applicable]) will not be reported.
- Selected ocular procedures (e. g. cataract surgery, macular laser) done prior to Day 1 will be reported on a separate form.
- All other procedures and therapies are not required to be recorded.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. All medications administered to manage AEs should be recorded on the Adverse Event eCRF.

6.5.1 Rescue Medicine and SOC treatment

6.5.1.1 Rescue Medicine

During the treatment period of the study (i.e. up to Week 44), anti-VEGF IVT treatment with SoC must be instituted if any of the following criteria due to worsening of the underlying disease (DME) or due to lack of efficacy are observed:

- [redacted]
-
-

Participants requiring rescue therapy will be asked to return to the study site for an early treatment termination visit (ETTV) and will then be withdrawn from the study *unless further follow-up visits are required for safety management of the participant*.

Note: Rescue therapy can additionally be instituted at any time at the discretion of the Investigator.

[redacted]

- [redacted]
- [redacted]

6.5.2 Permitted Therapy

Participants who use maintenance therapies should continue their use if not excluded per exclusion criteria.

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

Participants who use oral contraceptives (with a failure rate of < 1% per year), hormone-replacement therapy, or other maintenance therapy should continue their use (providing the regimen is stable for at least 12 weeks prior to Day 1 and expected to remain unchanged during the conduct of the study). For further details see Section 5.1.

6.5.2.1 Treatment of the Fellow Eye

At the discretion of the masked physician, randomized patients may have their fellow (non–study) eye treated with anti-VEGF therapy licensed for ocular use, if they are diagnosed with an ocular condition for which the selected anti-VEGF therapy is approved by the country regulatory agency. Consult with the region-specific anti-VEGF prescribing information for the recommended dose and frequency of treatment. The Sponsor will cover the cost of approved licensed ocular anti-VEGF therapy in accordance with local regulations. Note: Avastin (bevacizumab) is not licensed for ophthalmic use in any country; therefore, it is prohibited to be used.

If (per the masked investigator's judgment) treatment with anti-VEGF is to be given to the fellow (non-study) eye at the same visit as the study eye treatment, all study eye assessments (including study eye study treatment administration) must be completed first. If there are no safety concerns, the site may proceed with the fellow eye treatment administered by the unmasked treatment administrator to preserve masking.

Individual trays and sterile preparation must be separately prepared for each eye treatment.

Note: If the fellow eye anti-VEGF treatment is performed outside of the study visit, then a qualified physician, either in masked or unmasked role, can administer the treatment.

6.5.3 Prohibited Therapy

At the discretion of the Investigator, participants may start or continue to receive all medications and standard treatments administered for other conditions, except for those listed under the exclusion criteria (Section 5.2).

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

Participants are not allowed to participate in any other clinical study during participation in Study BP43445.

6.6 DOSE MODIFICATION, TEMPORARY INTERRUPTION AND RECHALLENGE

The dose and frequency of the study drug should not be modified.

6.6.1 Temporary Interruption

If study drug administration is temporary interrupted (participant misses *one or more* study treatment administration visits; see also Section 1.3 for visit window) the administration may resume at the next planned dosing date. A missed dose of study drug will not be made up for.

6.7 TREATMENT AFTER THE END OF THE STUDY

RO7200220 is an IMP for which safety and tolerability are under evaluation in an indication where SoC treatments are available.

The Sponsor does not intend to provide RO7200220 or other study interventions to participants after conclusion of the study or any earlier participant withdrawal.

7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants have the right to voluntarily withdraw from the study at any time for any reason.

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Section 4 of Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed see the SoA (Section 1.3).

Reasons for permanent discontinuation of study treatment (or withdrawal from the study) may include, but are not limited to, the following:

- Participant withdrawal of consent at any time.

- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.

Participants must discontinue study treatment if they experience any of the following:

- Pregnancy
- Meeting the defined criteria for receiving rescue medicine (see also Section 6.5).
- Retinal detachment or retinal tear in the study eye
- Vitreous hemorrhage that will preclude examination of the macula and obtaining adequate retinal imaging in the study eye
- Surgical intervention (i.e. vitreoretinal surgery, vitreous tap, or biopsy with IVT injection of anti-infectives or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- [redacted]
  - [redacted]

Every effort should be made to obtain information on participants who withdraw from the study but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for an ETTV (see Section 8.9.3) and *may* undergo follow-up *safety* assessments *if required* (see Section 8.9.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

For temporary interruption of study treatment see Section 6.6.1.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn. This includes the follow-up assessments.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study for safety or other reasons will not be replaced.

For data to be collected at the time of study discontinuation and for any further evaluations that need to be completed see SoA (Section 1.3).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment *(see Section 7.1)*.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

At timepoints with multiple assessments, the following sequence is suggested; at the discretion of the Investigator, the order can be adjusted to optimize site personnel and participant's time management or to accommodate site's best practices:

1. 12-lead ECG: must be performed before blood sampling, and as early as possible
2. Vital signs
3. Blood sampling: at visits where FFA is performed; blood sampling and angiography can be performed from the same venous cannula. Blood samples must be collected before angiography.
4. Ocular assessments and imaging:
    - BCVA: At screening, BCVA can be performed before 12-lead ECG, vital signs, and blood sampling, to avoid unnecessary investigations in those participants who may be a screen failure as a result of BCVA letter score
    - IOP (may be performed after imaging assessments, see Section 8.2.6.2)
    - Slit-lamp examination
    - Dilated binocular indirect high-magnification ophthalmoscopy
    - FP
    - SD-OCT
    - OCT-A (mandatory for those sites where available)
    - FFA
5. [redacted]
6. IOP measurement

The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.1 EFFICACY ASSESSMENTS

Efficacy assessments will be performed as detailed in the SoA (Section **1.3**) and will include functional (BCVA) and imaging assessments (SD-OCT).

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (NSAESI); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; ocular safety assessments like BCVA, slit-lamp examination, binocular high-magnification ophthalmoscopy, IOP and retinal imaging, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

[redacted]

8.2.1 Physical Examinations

A physical examination will be performed by trained medical personnel at the study center.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Weight and height as outlined in the SoA (see Section 1.3) will also be recorded. The body-mass-index will be calculated form the screening measurements.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormality identified at baseline (prior to first study drug administration) should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Vital Signs

Body temperature (tympanic or oral), pulse rate, and BP will be assessed.

BP and pulse measurements should be assessed with a completely automated device, if available. When possible, the same arm should be used for all blood pressure measurements.

BP and pulse measurements should be preceded by ≥ 5 min of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Single measurements of vital signs will be taken (before blood collection for laboratory tests but after ECG collection at applicable timepoints). At the discretion of the Investigator, measurements can be repeated if the values are abnormal or borderline.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3). The full set of triplicates should be completed in less than 5 minutes using the ECG machine provided by the ECG central reading center.

To minimize variability, it is important that participants be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation, cell phones) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws. In some cases it may be appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to the ECG abnormality.

The digital ECG recordings should be transmitted immediately to the ECG central reading center for interpretation. Investigators or designees must review, sign, and date all ECG reports received back from the CRC, which will be kept as part of the

participant's permanent stud file at the site. Printouts directly from the ECG machine (not centrally reviewed) are not considered as valid ECG reports. The CRC will transfer the relevant ECG characteristics (including heart rate, PQ [PR], QRS, QT, with derived RR, and QTcF, T and U abnormalities) and overall interpretation directly to the Sponsor. Investigators or designees will document overall ECG interpretation on the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

This study will use a central laboratory for all laboratory analyses.

Normal ranges for the study laboratory parameters from the central laboratory will be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoA (Section 1.3).

The following samples will be taken for safety laboratory assessments:

- Blood
- Urine

Results of clinical laboratory testing will be received as electronically produced laboratory reports submitted directly from the central laboratory.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes (see Section 4 of Appendix 3) occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at a local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the eCRF.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at screening is considered uncertain, screening laboratory tests may be repeated to confirm eligibility.

8.2.4.1 Urine assessments

Urine pregnancy tests for WOCBP will be done at the investigational site. If positive, a serum pregnancy test will be performed. If the serum pregnancy test is positive, study treatment or SoC should not be administered.

Safety Urinalysis will be performed (see Table 1 in Appendix 4)

Urine samples will be destroyed no later than 2 years after the date of final clinical study report (CSR).

8.2.5 Medical History and Demographic Data

Medical history (general and ophthalmic) includes clinically significant diseases, reproductive status, smoking history, and any medications or vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, and nutritional supplements) used by the participant as outlined in Section 6.5.2).

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded [redacted] (Zhang et al 2018).

8.2.6 Ophthalmological Assessments

The following ocular assessments will be performed at the study sites by qualified personnel. All assessments should be performed for both eyes, except when specified for study eye only.

- BCVA
- IOP measurement
- Slit-lamp examination
- Dilated binocular indirect high-magnification ophthalmoscopy
- FP
- SD-OCT
- OCT-A (mandatory for those sites where available)
- FFA
- Safety finger counting to assess ocular perfusion after IVT

Ophthalmological assessments will be performed at timepoints as tabulated in the SoA (Section 1.3) and at the discretion of the Investigator at any other time [redacted]), if deemed appropriate.

8.2.6.1 Best Corrected Visual Acuity

Refraction and BCVA will be measured for both eyes and prior to dilating eyes by trained and certified personnel at the study sites and at each study visit. The BCVA will be measured by using the set of three Precision vision™ or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2 and R). The BCVA assessment data will be entered in the BCVA specific eCRF. The refractive error at screening will also be recorded on the eCRF.

The VA examiner will be masked to the study eye and treatment arm assignment.

A VA specifications document, procedure manual, and training materials will be provided to the study sites, and examiner certification will be obtained from a third party vendor. The VA examination room also must be certified before any VA examinations are performed.

8.2.6.2 IOP Measurement

The IOP measurements will be done at the timepoints specified in the SoA (Section 1.3). The detailed procedure and the methods of IOP measurements will be provided in the Procedures Manual.

8.2.6.3 Safety Finger Count Vision

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

8.2.6.4 Slit-Lamp Examination and Dilated Binocular Indirect High-Magnification Ophthalmoscopy

Slit-lamp biomicroscopy and dilated binocular indirect high-magnification ophthalmoscopy will be performed at each study visit for each eye. Observations will be graded as normal or abnormal. Abnormal findings will be specified as not clinically significant (NCS) or clinically significant (CS). Abnormal findings (CS and NCS) will be described. The slit-lamp biomicroscopy examination will consist of the evaluation of anterior and posterior chambers (including grading scales for anterior chamber [AC] cells or flare and for vitreous haze, vitreous cells (optional), and vitreous hemorrhage, as detailed in Appendix 6 and Appendix 7, respectively. A fluorescent dye may be applied in order to assist eye examination. All findings will be recorded on the eCRF. Further information will be provided in the Procedures Manual.

8.2.6.5 Ocular Imaging

The CRC(s) will provide sites with the CRC(s) manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software (where applicable) will be certified and validated by the CRC(s) as specified in the CRC manual. All ocular images will be obtained by

trained and certified site personnel at the study sites and forwarded to the CRC(s) for independent analysis and/or storage. Ocular imaging assessments will be done for both eyes, unless otherwise specified, at timepoints specified in the SoA (Section 1.3). It is mandatory to use the same device for each modality throughout the study.

Fundus Photography (FP)
Ultra-wide field (UWF-FP; Optos®) will preferentially be performed. Sites that do not possess UWF equipment can use other equipment, as detailed in the CRC manual.

Spectral Domain Optical Coherence Tomography (SD-OCT)
SD-OCT will be performed on a Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany), equipped with TrueTrack Active Eye Tracking, and AutoRescan. Where Spectralis is not available at an investigational site, Cirrus or Topcon are also considered acceptable devices.

Optical Coherence Tomography Angiography (OCT-A)
Optional OCT-A will be performed at the sites with OCT-A capabilities.

Fundus Fluorescein Angiography (FFA)
Ultra-wide field (UWF-FFA; Optos®) will preferentially be performed. Sites that do not possess UWF equipment can use other equipment, as detailed in the CRC manual.

8.2.7 Immunogenicity Assessments

Since RO7200220 is a humanized monoclonal antibody, there is a risk that ADAs against RO7200220 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, in particular immune-complex reactions.

[redacted] The actual date and time of each sample will be recorded in the eCRF.

If required, remaining ADA samples may also be used for assay development/validation experiments and to further characterize the immune response on an exploratory basis.

The [redacted] will be destroyed no later than 2 years after the date of the final CSR.

For details on sampling procedures see the Procedures Manual. Details on sample storage and shipment are given in the Laboratory Manual.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of AEs or SAEs can be found in Appendix 2. The non-serious adverse events of special interest (NSAESI), the sight-threatening AEs, and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs, are discussed in Sections 8.3.6, 8.3.7, and 8.3.8.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3:

- Diagnosis versus signs and symptoms
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Overdose (see also Section 8.4)
- Deaths
- Preexisting medical condition, including worsening of DME
- Worsening of disease (DME) being studied
- Hospitalization or prolonged hospitalization

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

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

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

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the final study visit (i.e. ETTV, EOS, or Week 72, whatever occurs first).

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (i.e. ETTV, EOS, or Week 72, whatever occurs first).

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, NSAESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports,

autopsy reports) in order to perform an independent medical assessment of the reported event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Immediate notification by the Investigator to the Sponsor of an SAE regardless of relationship to study drug is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate (i.e., no more than 24 hours after learning of the event) and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see Section 5 of Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Details will be available separately.

8.3.5 Pregnancy

WOCBP will be instructed to immediately inform the Investigator if they become pregnant during the study, or within 12 weeks after the last dose of study treatment, or within 12 weeks after the dose of SoC, if applicable.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5. All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-serious Adverse Events of Special Interest (immediately reportable to Roche)

Non-serious AEs of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

AEs of special interest (AESIs for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice (as defined in Section 6 of Appendix 3).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 Sight-threatening Adverse Events (immediately reportable to Roche)

Sight-threatening AEs are defined in Appendix 8.

Sight-threatening AEs, regardless if considered serious or non-serious, are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

The follow-up actions for sight-threatening AEs are defined in Section 8.9.5.

8.3.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable.

8.3.9 Medical Device Complaints (Including Malfunctions)

Medical devices being provided for use in this study are pre-filled syringes with ranibizumab. In order to fulfill regulatory reporting obligations worldwide, the Investigator must report all device deficiencies to the Sponsor in the form of a medical device complaint. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, and it can include malfunctions, use errors, and inadequate labeling.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 2.

8.3.9.1 Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

8.3.9.2 Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3). This applies to all participants, including those who discontinue the study treatment.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.9.3 Prompt Reporting of Medical Device Incidents to Sponsor

The Investigator must report all medical device complaints, including AEs and SAEs, to the Sponsor. The Investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event. Refer to the pharmacy manual for further details.

If the medical device results in an AE to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the electronic data capture (EDC) system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5 of Appendix 2.

8.3.9.4 Regulatory Reporting Requirements for Medical Device Incidents

The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the Head of the Medical Institution) will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.4 TREATMENT OF OVERDOSE

For this study, study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved
3. Obtain a blood sample for PK, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

8.5 PHARMACOKINETICS

Mandatory samples to evaluate concentrations of study treatment will be collected from all participants. [redacted] The date of each sample collection will be recorded in the eCRF. RO7200220 levels, and ranibizumab levels (when applicable and if deemed necessary), will be analyzed by using validated assays. [redacted]

The following samples will be taken for PK analysis:

- [redacted]
- [redacted]

For details on sampling procedures see the Procedures Manual. Details on sample storage and shipment are given in the Laboratory Manual.

Any volume of [redacted] remaining after the specified analyses may be used for additional exploratory biomarker profiling and/or identification, development and validation of assays, [redacted]. All PK samples will be destroyed no later than 2 years after the date of final CSR.

Drug concentration information that would unblind the study, will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 PHARMACODYNAMICS AND BIOMARKER ANALYSES

[redacted]

[redacted]

- [redacted]
- [redacted]

For details on sampling procedures see the Procedures Manual. Details on sample storage and shipment are given in the Laboratory Manual and Flowchart.

The following analyses will be performed:

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

[redacted]

[redacted]

[redacted]

For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.7).

8.7 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.7.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

These samples will be derived only from participants who give specific consent to participate in this optional RBR. RBR samples can be used (but not limited to) to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

8.7.2 Sample Collection

RBR samples will be derived from any residual material from [redacted]

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7200220 or diseases:

- Any leftover samples:
- [redacted]
- [redacted]

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development. For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until no longer needed or until they are exhausted. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 TIMING OF STUDY ASSESSMENTS

8.9.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and all pre-treatment assessments (related to entry criteria) must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

On Day 1 prior to enrollment, all participant eligibility requirements are reviewed and relevant eligibility criteria (see Section 5) are confirmed, including but not limited to the following criteria:

- Absence of ocular or periocular infections in the study eye
- Absence of active intraocular inflammation in the study eye

- Absence of febrile illness within 1 week prior to Day 1
- For WOCBP: Absence of pregnancy confirmed by urine pregnancy test

Screening and pre-treatment assessments will be performed as outlined in the SoA (see Section 1.3) unless otherwise specified.

Ocular images of both eyes performed at the screening visit will be forwarded as soon as possible to the CRC for those participants who meet all non-ocular eligibility criteria. The CRC will assess the image data submitted and confirm eligibility for study eye imaging criteria. Confirmation of eligibility by the CRC for the study eye imaging criteria is required before enrollment.

8.9.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified, be permitted to re-enroll in the study.

On Day 1, baseline assessments will be conducted on the eligible participants prior receiving study treatment according to the SoA (see Section 1.3).

Participants will come to the clinic for each visit and assessments as outlined in the SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration or prior receiving SoC (as applicable) should be performed prior to administration of study treatment, unless otherwise noted in the SoA (see Section 1.3).

[redacted]

In the study eye, a post-administration optic nerve head perfusion will be assessed for each participant immediately after IVT administration of study treatment or SoC by using testing finger count vision, hand motion, or light perception, as appropriate (Section 8.2.6.3).

On the days of IVT administration of the study treatment, IOP must be monitored during clinical assessment and before discharge of the participant. Note: The first IOP measurement must be taken during clinical assessment before any intervention, i.e. before IVT administration of [redacted] (Section 8.2.6.2 and Section 1.3).

Participants will be discharged at the discretion of the Investigator.

On the days without IVT administration of the study treatment or SoC, but when [redacted] is sampled, IOP must be measured before sampling. IOP measurements will be repeated [redacted] (see also Section 8.2.6.2 and Section 1.3).

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

8.9.3 Assessments at Study Treatment Completion (Week 48)/Early Treatment Termination Visit

Participants who complete the study treatment administration period (up to Week 44) as planned will return to the investigational site for the Week 48 visit assessments, as outlined in the SoA (see Section 1.3). Participants who are withdrawn from the study during the study treatment administration period but have not withdrawn consent should return for an ETTV for monitoring of all AEs (serious and non-serious), as well as for assessments specified in the ETTV as outlined in the SoA (see Section 1.3).

8.9.4 Assessments at Off-Treatment Observation Period Visits

Participants will return to the investigational site every 4 weeks up to Week 72 during the off-treatment observation period after their final dose of study drug at Week 44 for follow-up visits with assessments as outlined in the SoA (see Section 1.3) and in Section 4.1.1.

If during any of these visits the participants [redacted] for the EOS visit (see SoA in Section 1.3). If the participants meet the criteria at Week 72 they would also receive a dose of SoC and the visit would become the EOS visit.

8.9.5 Assessments at the Occurrence of a Sight-Threatening Adverse Event or Events of Intraocular Inflammation

At the occurrence of sight-threatening AEs potentially linked to IMP (see Section 8.3.7 and Appendix 8) or events of intraocular inflammation (IOI), additional assessments are recommended to be done (if not anyway required at the visit) and will be reported in the eCRF:

- [redacted]
- Blood sample for laboratory safety analyses
- [redacted]
- Ophthalmological assessments including imaging

[redacted]

[redacted]

[redacted]

9. STATISTICAL CONSIDERATIONS

The primary efficacy endpoint is change in BCVA from baseline over the average of Weeks 44/48 in treatment naïve population. The estimated changes in each RO7200220 arm and the differences to the control arm 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.

9.1 SAMPLE SIZE DETERMINATION

Approximately 60 to 65 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 to 35 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]

Between approximately 360 and 400 participants will be enrolled in this study.

9.2 SETS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 4.

Table 4 Analysis Sets

Population	Description
Treatment naïve Intent-to-treat	All randomized participants that are IVT anti-VEGF or periocular/IVT corticosteroids treatment naïve participants as defined in the exclusion criteria 9 and 10 in Section 5.2 will be included in the treatment naïve intent-to-treat population. Participants will be grouped according to the treatment assigned at randomization.

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 Section 5.2 will be included in the previously treated intent-to-treat population. Participants will be grouped according to the treatment assigned at randomization.
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.
Per protocol	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 for Q4W arms or 6 for Q8W arm if enrolled under Protocol Version 2, and 6 for Q4W arms or 3 for Q8W arms if enrolled under the Protocol Version 1) 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.
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.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one postdose 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.
[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

9.3 STATISTICAL ANALYSES

9.3.1 Demographics and Baseline Characteristics

Descriptive statistics of the demographic and baseline characteristics will be presented by treatment group and treatment population (treatment naïve population or pre-treated population).

Baseline is defined as Day 1 (where available; otherwise the last value prior to Day 1 will be taken).

9.3.2 Efficacy Analyses

The primary and secondary efficacy analyses will include all randomized participants in the treatment naïve intent-to-treat analysis population (see Section 5.2 for definition and Table 5). Analyses will also be repeated separately in the previously treated intent-to-treat population and the overall intent-to-treat population.

Table 5 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary: • BCVA change from baseline to Weeks 44/48 (treatment naive participants)	A 90% CI for the difference between each treatment arm and the control arm will be produced as well as the mean values and corresponding standard deviation for each arm. These will be estimated using a Mixed Model for Repeated Measurement (MMRM). The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA.

Endpoint	Statistical Analysis Methods
Secondary: • BCVA change from Baseline to Weeks 44/48 (previously treated participants and overall enrolled population) • BCVA change from Baseline to Weeks 32/36 (treatment naive participants, previously treated participants and overall enrolled population) • BCVA change from Baseline to Weeks 20/24 (treatment naive participants, previously treated participants and overall enrolled population) • BCVA over time • Anatomical outcomes (CST)	A 90% CI for the difference between each treatment arm and the control arm will be produced as well as the mean values and corresponding standard deviation for each arm. Estimates of the difference at Week 44/48, 32/36, and 20/24, and the averages over time will be estimated using MMRM. The model will include the categorical covariates of treatment group, visit, and visit by treatment group interaction and the continuous covariate of baseline BCVA/CST.
Secondary: • Proportion of participants with intraretinal and/or subretinal fluid • BCVA categories • Anatomical outcomes (presence/absence of fluid)	For binary endpoints, a bar chart with a supporting table of the raw numbers at each visit will be provided. The difference in proportions with the associated 90% CI will be provided along with plots over time.
Exploratory:	
[redacted]	

ADA=anti-drug antibody, AE=adverse event, BCVA=best corrected visual acuity, CI=Confidence interval, [redacted] DME=diabetic macular edema, [redacted] MMRM=Mixed Model for repeated measurement

Mixed model for repeated measurement (MMRM) models will be used to estimate contrasts based on the longitudinal BCVA and SD-OCT data. An unstructured covariance structure will be used to account for within-patient correlation, but another variance-covariance structure may be selected in case of convergence issues.

Appropriate assumptions will be made for missing data due to Intercurrent Events.

The model-based estimate of the difference between each treatment group and the control group at Week 44/48, together with 90% CI will be produced. The mean and 90% CI within each treatment group and for the difference between treatment groups and the control group at the other timepoints will also be reported.

9.3.3 Safety Analyses

All safety analyses will be based on the safety analysis population grouped according to the study treatment a patient received.

Safety will be assessed through descriptive summary of ocular and systemic (non-ocular) AEs, deaths, and ocular assessments. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as AEs and evaluated as part of the AE assessments (see Table 6).

Table 6 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level. Individual listings will be used, as appropriate.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual outputs with flagging of abnormal results. Summary tables of change from baseline over time will be displayed. Shifts in NCI CTCAE v5.0 grades (published on 27 November 2017) from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented using appropriate outputs. In addition, tabular summaries will be used, as appropriate.

Endpoint	Statistical Analysis Methods
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented using appropriate outputs.
BCVA, SD-OCT	Data will be presented as individual listings and descriptive summary statistics.
FFA, FP, IOP, indirect ophthalmoscopy, OCT-A, slit lamp	Data will be presented as individual listings and descriptive summary statistics where appropriate.
ADA	Incidence and titers of ADAs will be presented as individual listings and descriptive summary statistics where appropriate

ADA =anti-drug antibody, AE=adverse event, BCVA =best corrected visual acuity, ECG =electrocardiogram, eCRF=electronic case report form, FFA =fundus fluorescein angiography, FP =fundus photography, IOP =intraocular pressure, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse events, OCT-A=optical coherence tomography angiography, SD-OCT =spectral domain optical coherence tomography (-angiography).

Safety analyses will be based on the safety-evaluable population.

Verbatim descriptions of treatment-emergent AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and their incidence and severity will be summarized by treatment arm. 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. AEs will be tabulated by System Organ Class and preferred term. In addition, summaries will be generated for SAEs, deaths, AEs leading to discontinuation of study drug, AESI, and AEs judged to be related to study treatment. Separate summaries will be prepared for systemic (non-ocular) and ocular AEs.

Results of the ocular assessments will be summarized by timepoint and by eye (study vs. fellow) using descriptive summaries. In addition, changes from baseline in pre-dose IOP measurements and changes between pre-dose and post-dose IOP measurements will also be summarized.

9.3.4 Immunogenicity Analyses

The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment (Shankar et al 2014).

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after study drug administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized.

- Participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response).
- Treatment-induced ADA responses will be further categorized as either:
- Transient ADA response: defined as a) ADA negative or missing data at baseline and b) at least one post-treatment ADA-positive sample and c) only one ADA positive sample or the time between the first and last ADA-positive sample is less than 16 weeks and d) the last ADA sample is negative
- Persistent ADA response: defined as a) ADA negative or missing data at baseline and b) post-treatment ADA-positive samples over 16 weeks or more or the last ADA timepoint is positive (Shankar et al 2014)
- Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4fold greater than the titer of the baseline sample (treatment unaffected).

[redacted] and reported descriptively in a separate document from the main CSR.

9.3.5 Pharmacokinetic Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3.8 Other Analyses

Biomarker exploratory analyses, Population PK/PD analyses, may be performed and will be presented separately from the main clinical study report.

[redacted]

9.4 INTERIM ANALYSES

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

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

The interim analyses, should they occur, will be performed and interpreted by members of the IMC (see Section 4.1.2) 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.

9.5 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by country, site, and treatment arm. Patient disposition (the number of patients randomized, treated, and completing through to 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 exceptions and other major protocol deviations will be summarized by treatment arm.

10. REFERENCES

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

Chakravarthy U, Bailey C, Brown D, et al. Phase I Trial of Anti–Vascular Endothelial Growth Factor/Anti-angiopoietin 2 Bispecific Antibody RG7716 for Neovascular Age-Related Macular Degeneration. Ophthalmology Retina;2017;1:474-85

Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past, the present, and the future. Surv Ophthalmol 2008;53:139–149

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–136

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

Fauser S, Muether PS. Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. Br J Ophthalmol 2016;100(11):1494–8.

Funatsu H, Yamshita H, Noma H, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. Graefe's Archive for Clinical and Experimental Ophthalmology 2005;243:3-8

Hutton-Smith LA, Gaffney EA, Byrne HM, et al. Ocular pharmacokinetics of therapeutic antibodies given by intravitreal injection: estimation of retinal permeabilities using a 3-compartment semi-mechanistic model. Mol Pharm 2017;14(8):2690–6.

Investigator’s Brochure for RO7200220.

Investigator’s Brochure for RO7200220 Version 6 Addendum.

Karkhur S, Hasanreisoglu M, Vigil E, et al. Interleukin-6 inhibition in the management of non-infectious uveitis and beyond. J Ophthalmic Inflamm Infect. 2019;9:17

Kitazawa K, Sotozono C, Koizumi N, et al. Safety of anterior chamber paracentesis using a 30-gauge needle integrated with a specially designed disposable pipette. Br J Ophthalmol 2017;101(5):548–50.

Krohne TU, Liu Z, Holz FG, et al. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. Am J Ophthalmol 2012;154:682–6.

Lopalco G, Fabiani C, Sota J, et al. IL-6 blockade in the management of non-infectious uveitis. Clin Rheumatol 2017;36(7):1459−69. Missel PJ. Simulating intravitreal injections in anatomically accurate models for rabbit, monkey, and human eyes. Pharm Res 2012;29:3251−72.

Lucentis® EU Summary of Product Characteristics

Muether PS, Droege KM, Fauser S. Vascular endothelial growth factor suppression times in patients with diabetic macular oedema treated with ranibizumab. Br J Ophthalmol. 2014;98(2):179–81.

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

O'Neill CA, Miller PE, Christian BJ, et al. 26-Week IVT injection toxicity study with rhuFab vegf in Cynomolgus monkeys with an 8-weeek recovery. Invest Ophthalmol Vis Sci 2003;44: Abstract 3929.

Ponce R, Abad L, Amaravadi L, et al. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. Regul Toxicol Pharmacol 2009;54:164-82

Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. Lancet Rheumatol. 2020;2(3):e135-e141

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

Sahni J, Patel SS, Dugel PU, et al. Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial. Ophtalmology 2019;126:1155-70

Sahni J, Dugel PU, Patel SS, et al. Safety and Efficacy of Different Doses and Regimens of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration The AVENUE Phase 2 Randomized Clinical Trial. JAMA Ophthalmol. 2020;138:955-63

Sepah YJ, Sadiq MA, Chu DS, et al. Primary (Month-6) Outcomes of the STOP-Uveitis Study: Evaluating the Safety, Tolerability, and Efficacy of Tocilizumab in Patients With Noninfectious Uveitis. Am J Ophthalmol 2017;183:71−80.

Sepah YJ, Nguyen QD, Do DV, et al. Trends for poorer vision outcomes in nAMD and DME patients with higher aqueous humor levels of IL-6. Investigative Ophthalmology & Visual Science. 2019;59:1077

Shankar G, Arkin S, Cocea L, et al. Assesment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides – Harmonized Terminology and Tactical Recommendations. The AAPS Journal. 2014;16(4):658-673

Simó-Servat O, Hernández C, Simó R. Usefulness of the vitreous fluid analysis in the translational research of diabetic retinopathy. Mediators Inflamm 2012;2012:872978.

Thulliez M, Angoulvant D, Pisella P-J. Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitrea lAnti–Vascular Endothelial Growth Factor Medication Use. JAMA Ophthalmol. 2018;136:557-66.

Trivedi D, Denniston AK, Murray PI. Safety profile of anterior chamber paracentesis performed at the slit lamp. Clin Exp Ophthal 2011;39(8):725–8.

Valle ML, Dworshak J, Sharma A, Ibrahim AS, Al-Shabrawey M, Sharma S. Inhibition of interleukin-6 trans-signaling prevents inflammation and endothelial barrier disruption in retinal endothelial cells. Exp Eye Res 2019;178:27–36

Van der Lelij A and Rothova A. Diagnostic anterior chamber paracentesis in uveitis: a safe procedure? Br J Ophthalmol 1997;81(11):976–9.

Vegas-Revenga N, Calvo-Río V, Mesquida M, et al. Anti-IL6-Receptor Tocilizumab in Refractory and Noninfectious Uveitic Cystoid Macular Edema: Multicenter Study of 25 Patients. Am J Ophthalmol. 2019;200:85-94.

Whitcup SM, Cidlowski JA, Csaky KG, Ambati J. Pharmacology of corticosteroids for diabetic macular edema. Invest Ophthalmol Vis Sci 2018;59:1–12

Wu J, Zhong Y, Yue S, et al. Aqueous Humor Mediator and Cytokine Aberrations in Diabetic Retinopathy and Diabetic Macular Edema: A Systematic Review and Meta-Analysis. 2019; 2019: 6928524

Zhang X, Lai TYY. Baseline predictors of visual acuity outcome in patients with wet age-related macular degeneration. Biomed Res Int 2018;1−10 [cited: 18 May 2018]. Available from: https:doi.org/10.1155/2018/9640131.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices (Nrs. 1-5) and additional appendices describing grading scales and sight-threatening AEs (Nrs. 6-8) used in this study:

- Appendix 1 (for regulatory, ethical and study oversight considerations),
- Appendix 2 (for AE definitions, reporting) and
- Appendix 3 (procedures for recording Adverse Events)
- Appendix 4 (clinical laboratory tests),
- Appendix 5 (contraceptive guidance and collection of pregnancy information).
- Appendix 6 (Grading Scale for Assessment of Anterior Chamber Cells or Flare, Vitreous Cells, and Vitreous Haze
- Appendix 7 (Grading Scale for Vitreous Hemorrhage)
- Appendix 8 (Sight-threatening AEs)

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States (U.S.) or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms (ICFs), any information to be given to the participant (e.g. advertisements, diaries etc), and relevant supporting information must be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all AEs to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable, as well as Pregnant Partner Authorization Form and Infant Authorization Form) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/Independent EC (IEC) or study center.

The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

The ICFs must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant or the participant's legally authorized representative. All signed and dated ICFs must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 60 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research.

Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the Research Biosample Repository (RBR). The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent electronic case report form (eCRF).

In the event of death or loss of competence of a subject who is participating in the Research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the United States, each ICF may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's

IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP43445 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP43445. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR sample data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor’s monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the

course of the study and for one year after completion of the study (i.e., Last Patient Last Observation).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, clinical outcome assessments (COAs; paper or electronic COA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico‑technical departments involved in a clinical study.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial‑related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.3. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.1.4. Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Dissemination of Clinical Study Data

Regardless of the outcome of this study, the Sponsor is dedicated to openly provide information on the study to healthcare professionals and to the public, at scientific congresses, in clinical trial registries (e.g. www.ClinTrials.gov), and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see confidentiality in Section 1.4 of this appendix), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trial Data at: www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to first participant entry into the study, the Sponsor will identify and evaluate potential risks associated with critical trial processes and data and will implement controls for the communication, review and reporting of these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

3. ADMINISTRATIVE STRUCTURE

See Section 4.1.2.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A International Council on Harmonisation guideline for Good Clinical Practice, an **adverse event (AE)** is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, angiography) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as angiographies).

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect.**
- **Other significant events:**

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may

jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF).

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Medical Monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Medical Monitor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 below (as a guidance for assessing AE severity).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to a predefined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for AEs criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Table 1 Adverse Event Severity Grading Scale

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

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

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Assessments at the occurrence of a sight-threatening AE or events of Intraocular Inflammation are described in Section 8.9.5

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings (if available) including histopathology. New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 2 in Appendix 2)
- Non-serious Adverse events of special interest (AESI) (see Section 8.3.6)
- Sight-threatening AEs (see Section 8.3.7)
- Pregnancies (see Section 8.3.5)
- Medical device incidents (see Section 8.3.9 for details on medical device incidents).

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local Health Authority and IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/Special Situations Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of SAEs, non-serious AESI (Section 8.3.6), and sight-threatening AES (Section 8.3.7) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other SAE occurring after the end of the AE reporting period, and if the event is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  Note: In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. Special situations and AEs (non-serious) associated with special situations need to be reported to Roche within 30 calendar days. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO7200220 and ranibizumab, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with RO7200220 and ranibizumab, regardless of whether they result in an AE, should be recorded on the Adverse Event eCRF and should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- RO7200220:
  - use RO7200220 IB
- Ranibizumab:
  - use Lucentis® EU SmPC.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events (AEs) on the Adverse Event electronic case report from (eCRF). Avoid colloquialisms and abbreviations.

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

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

The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for AE reporting purposes.

- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.

- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by dilation and are not red blood cells or white blood cells or the result of any ocular disorder should not be recorded as an AE.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

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

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

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

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

4. ABNORMAL LABORATORY VALUES

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

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

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of potential severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>5\times$ ULN value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin).
- Treatment-emergent ALT or AST $>5\times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event (SAE) or a non-serious AESI (see Section 8.3.6).

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

9. WORSENING OF DISEASE (DIABETIC MACULAR EDEMA; DIABETIC RETINOPATHY) BEING STUDIED

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

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered an AE.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 below will be performed by the central laboratory with the exception of local dipstick urinalysis.

The tuberculosis (interferon gamma release assay) *and syphilis assessment* may be done locally after Sponsor's approval.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
Clinical Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, HbA1C, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urate, LDH, CRP.
Coagulation	INR, aPTT, PT.
Serology/testing for infection screening	HIV (specific tests HIV-1/2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody. Tuberculosis (interferon gamma release assay), syphilis
Lipids	Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Hormone	For women of unclear menopausal status (at the discretion of the investigator): Estradiol, follicle-stimulating hormone (FSH), in females
Pregnancy Test	All women of childbearing potential (including those who have had a tubal occlusion) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Laboratory Assessments	Parameters
Urinalysis	Specific gravity Dipstick: pH, glucose, protein and blood o If there is a clinically significant positive result *for blood or protein* (confirmed by a positive repeated sample), urine will be sent to the central laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the central laboratory, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

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

- Definition of Laboratory Abnormalities

For all laboratory parameters included in this analysis, 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 participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. 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 participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive and Barrier Guidance

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

  – Documented hysterectomy.

  – Documented bilateral salpingectomy.

  – Documented bilateral oophorectomy.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

  – A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  – Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

  – Only discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use at least one highly effective method of contraception consistently and correctly as described in Table 1 below.

Per International Council on Harmonisation M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent[a] (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to medical cause) A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[b] • Cap, diaphragm or sponge with spermicide[b]

a) Hormonal contraception may be susceptible to interaction with the investigational medicinal product (IMP), which may reduce the efficacy of the contraception method.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

- **Male Participants**

No requirements.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the Clinical Trial Pregnancy Reporting Form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an adverse event (AE) or serious AE (SAE), and should not be recorded on the Adverse Event electronic case report form

(eCRF), any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5 ABORTIONS

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryofetal toxicity should also be classified as SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant exposed to study treatment should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 6
Grading Scale for Assessment of Anterior Chamber Cells or Flare, and Vitreous Haze

Grading Scales for Anterior Chamber Cells or Flare

The SUN Working Group Grading Scale for Anterior Chamber Cells	
Grade	**Cells in Field[a]**
0	< 1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	> 50
The SUN Working Group Grading Scale for Anterior Chamber Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

SUN = Standardization of uveitis nomenclature

a: Field size is a 1 mm by 1 mm slit beam

Source: Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.

Grading Scale for Vitreous Haze

Score	Description
0	No evident vitreous haze
0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2+	Permits better visualization of the retinal vessels (compared to higher grades)
3+	Permits the observer to see the optic nerve head, but the borders are quite blurry
4+	Optic nerve head is obscured

Source: Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92(4):467-71.

Grading Scale for Vitreous Cells

Grade	Description
0	No cells
0.5+	1 - 10
1+	11 - 20
2+	21 - 30
3+	31 - 100
4+	> 100

Source: Mahendradas P, Khanna A, Kawal A, et al Quantification of inflammation in inflammatory eye diseases. IJRCI. 2014;2(S1):SR4

Appendix 7
Grading Scale for Vitreous Hemorrhage

Grading Scale for Vitreous Hemorrhage

None (0)	Retina is visible.
1+	Retinal details are visible; some hemorrhage/s are visible by ophthalmoscopy.
2+	Large retinal vessels are visible, but central retinal details are not visible by ophthalmoscopy.
3+	Red reflex is visible, but no central retinal details are seen posterior to the equator by ophthalmoscopy.
4+	No red reflex by ophthalmoscopy.

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

Appendix 8
Sight-Threatening Adverse Events

An adverse event is considered to be sight-threatening if it meets one or more of the following criteria:

- It causes a decrease of ≥30 letters in best corrected visual acuity (compared with the last assessment of VA prior to the most recent treatment) lasting more than 1 hour.
- It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- It is associated with severe intraocular inflammation (i.e., 4+anterior chamber cell/flare or 4+vitritis; see grading scales for assessment in Appendix 6.
- In the opinion of the Investigator, it may require medical intervention to prevent permanent loss of sight.

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