Official Title: A Randomized, Double-Masked, 48-Week, Parallel-Group, Placebo-Controlled, Proof-of-Concept Study to Investigate the Efficacy and Safety of RG7774 in Patients With Diabetes Mellitus Type 1 or Type 2 With Treatment-Naive Diabetic Retinopathy

NCT Number: NCT04265261

Document Date: Protocol Version 5: 4-June-2021

PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-MASKED, 48-WEEK, PARALLEL-GROUP, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF RG7774 IN PATIENTS WITH DIABETES MELLITUS TYPE 1 OR TYPE 2 WITH TREATMENT-NAÏVE DIABETIC RETINOPATHY**
PROTOCOL NUMBER:	BP41321
VERSION:	5
EUDRACT NUMBER:	2019-002067-10
IND NUMBER:	138,284
TEST PRODUCT:	RG7774
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 14 November 2019
DATE AMENDED:	Version 2: 17 December 2019 Version 3: 13 November 2020 Version 4: 03 February 2021 Version 5: See electronic stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
04-Jun-2021 13:01:12	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, DOUBLE-MASKED, 48-WEEK, PARALLEL-GROUP, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF RG7774 IN PATIENTS WITH DIABETES MELLITUS TYPE 1 OR TYPE 2 WITH TREATMENT-NAÏVE DIABETIC RETINOPATHY**
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TEST PRODUCT:	RG7774
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 5
RATIONALE

Protocol BP41321 has been amended to optimize enrolment and execution of the study, by modifying some entry criteria and reducing the length of the visits. Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3 (tables 1 and 2) has been modified to reduce the number of assessments and thus the duration of the visits as follows:
    - Removal of patient-reported outcome questionnaires (i.e., the National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25] and the Low Luminance Questionnaire [LLQ])
    - Removal of the optional UWF-FP assessments
    - Visual Field assessment made optional
    - The two post-dose pharmacokinetic (PK) samples have been made optional
    - Perform Pelli-Robson and low luminance visual acuity (LLVA) assessments only in the study eye
    - Additional Pelli-Robson assessment at Week-4 visit
    - Perform LLVA assessment only at visits on Day 1, at Week 36, and in case of early termination
- To reflect the changes in Section 1.3, Table 3 (Section 3 Objectives and Endpoints), Sections 8.1.2.3 (Low-Luminance Visual Acuity), 8.1.2.4 (Contrast Sensitivity), 8.1.2.5 (Visual Fields [Optional]), 8.2.1 (Ocular Examination), and Table 7 (Section 9.4.2 Efficacy Analyses) have been updated; Section 8.1.2.1 (Patient-Reported Outcomes), Appendix 8 (National Eye Institute Visual Functioning Questionnaire - 25 [NEI VFQ-25]), and Appendix 9 (Low Luminance Questionnaire [LLQ]) have been removed.
- Entry criteria (Sections 5.1 and 5.2) have been modified to facilitate enrolment in the trial by:
    - Adding an additional rescreening for inclusion criterion 3
    - Increasing the permitted HbA1c level from 10% to 12% (inclusion criterion 9)
    - Excluding recruitment of participants who had periocular pharmacological intervention (exclusion criterion 1)
    - Allowing recruitment of participants who were enrolled in other previous retinal/ ocular clinical trials, in specific circumstances (exclusion criteria 9 and 10)
    - Allowing enrolment of participants with no active HBV, HCV (exclusion criterion 22 and Appendix 4 Clinical Laboratory Tests)

    - Allowing recruitment of participants who had COVID-19 more than 30 days prior to screening (exclusion criterion 24)
    - Allowing the principal investigator decide on abuse of alcohol/ substances considering the results of the test and the medical history of the participant (exclusion criterion 26)
- In addition, a new screening may be performed for those patients who failed screening according to outdated inclusion/ exclusion criteria from the previous versions of the protocol that have been changed in the current version (Section 5.4).
- Section 8.2.4 has been updated to clarify that evaluation for the ECG results as normal/ abnormal should be based on the report obtained by the central laboratory to avoid potential errors in the interpretation of the results.
- Section 8.2.6 has been updated with clarification on the rationale and background for implementation of the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire.
- Section 9.4.2 has been updated to reflect that a careful consideration of missing data treatment will be discussed in an external technical document. Moreover, the exact solution to assess the robustness of efficacy estimates in the presence of missing data will be discussed thoroughly in the aforementioned technical document.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *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
AE	Adverse event
AESI	Adverse event of special interest
AMD	Age-related macular degeneration
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASNV	Anterior segment neovascularization
AST	Aspartate aminotransferase
AUC	Area under the curve
BCVA	Best corrected visual acuity
BCRP	Breast cancer resistance protein
BM	Biomarker
BP	Blood pressure
BUN	Blood urea nitrogen
CB2	Cannabinoid 2
CB2R-TE	CB2 receptor Target Engagement
CBD	Cannabinoid
Cmax	Maximum concentration
CNR2	*CB2 receptor*
CNS	*Central nervous system*
COA	Clinical outcome assessments
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CS	Contrast sensitivity
CSR	Clinical study report
C-SSRS	*Columbia-Suicide Severity Rating Scale*
CST	*Central Subfield Thickness*
CYP	Cytochrome P450
DDI	Drug-drug interaction
DM	Diabetes mellitus
DME	Diabetic macular edema
DNA	Deoxyribonucleic acid
DR	Diabetic retinopathy
DRSS	DR severity score
EC	Ethics committee

Abbreviation	Definition
ECG	Electrocardiogram
eCOA	*Electronic clinical outcome assessment*
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European economic area
EFD	*Embryofetal development*
EIH	Entry-into-human
ETDRS	Early treatment diabetic retinopathy study
EU	European commission
FDA	Food and drug administration
FE	Food effect
FFA	Fundus fluorescein angiography
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony stimulating factor
GEE	Generalized estimating equations
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HBV	*Hepatitis B virus*
HCV	Hepatitis C *virus*
HDL	High-density lipoproteins
HDPE	High-density polyethylene
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International *Council for Harmonisation*
IEC	Independent ethics committee
IFNγ	*Interferon gamma*
IL	Interleukin
IMC	Internal monitoring committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
IND	Investigational new drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
ITT	*Intent-to-treat*
IUD	Intrauterine device

Abbreviation	Definition
IVT	*Intravitreal*
IxRS	Interactive (voice/web) response system
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LDL	Low-density lipoproteins
LLVA	Low luminance visual acuity
LPLO	Last participant last observation
LPS	Lipopolysaccharide
MD	Mean deviation
MAD	Multiple-ascending doses
NGS	*Next-generation sequencing*
NIMP	*Non-investigational medicinal product*
NOAEL	No-observed-adverse-effect level
NPDR	Non-proliferative DR
OTC	Over-the-counter
PD	Pharmacodynamic
PDR	Proliferative DR
PEMA	*Patient Engagement Mobile Application*
PK	Pharmacokinetic
PRO	Patient-reported outcome (also refers to participants)
PT	Prothrombin time
qCSF	*Quantitative contrast sensitivity function*
QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBR	Research biosample repository
RNA	Ribonucleic acid
RR	RR interval
RVO	Retinal vein occlusion
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Standard automated perimetry
SD-OCT	Spectral domain optical coherence tomography
sICAM1	*Soluble Intercellular Adhesion Molecule 1*

Abbreviation	Definition
SMT	*Study Management Team*
SNP	*Single nucleotide polymorphism*
SoA	Schedule of activities
SOC	Scientific oversight committee
SUSAR	*Suspected unexpected serious adverse reactions*
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
USPI	US product information
VEGF	Vascular endothelial growth factor
VA	Visual acuity
VF	Visual fields
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-MASKED, 48-WEEK, PARALLEL-GROUP, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF RG7774 IN PATIENTS WITH DIABETES MELLITUS TYPE 1 OR TYPE 2 WITH TREATMENT-NAÏVE DIABETIC RETINOPATHY**
SHORT TITLE	**Double-masked, Placebo-controlled, Phase II Study to investigate Efficacy and Safety of RG7774 in Patients with Treatment-Naïve Diabetic Retinopathy**
PROTOCOL NUMBER:	BP41321
VERSION:	5
TEST PRODUCT:	RG7774
PHASE:	II

RATIONALE

RG7774 is a synthetic small molecule, highly selective and potent cannabinoid 2 (CB2) receptor agonist intended for the oral treatment of diabetic retinopathy (DR). Activation of CB2 receptor by RG7774 has shown to produce anti-inflammatory effects in the eye consequently preserving endothelial barrier function. The principle aim of study BP41321 is to assess the safety, tolerability and the effect of oral administration of RG7774 on the severity of DR in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and good vision. The secondary objectives are to further evaluate the potential of RG7774 to prevent progression of DR and to assess the effect of RG7774 on best-corrected visual acuity (BCVA).

Study BP41321 builds upon experiences gained in a healthy volunteer entry into human study (EIH, BP40387), as well as the itraconazole drug-drug interaction (DDI) study (BP41274). The study results from the current study BP41321 will be used to support further clinical development of RG7774.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Assess the effect of RG7774 on the severity of DR.	• Proportion of participants with ≥ 2 step improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity score (DRSS) from baseline at Week 36 measured in the study eye.
• Evaluate the safety and tolerability of RG7774.	• Frequency and severity of adverse events.

Objectives and Endpoints cont.

• **Secondary**	
• Assess the effect of RG7774 on progression to vision-threatening DR.	• Incidence of anterior segment neovascularization (ASNV), new proliferative diabetic retinopathy (PDR), new diabetic macular edema (DME), and pre-existing DME requiring intervention.
• Assess the effect of RG7774 on visual acuity.	• Change from baseline in best corrected visual acuity (BCVA) at Week 36 in the study eye.

Study Design

This is a phase II, multi-center, randomized, three-parallel-group, placebo-controlled, double-masked, proof-of-concept study. Participants will receive RG7774 or placebo for up to 36 weeks. Participants will be randomized in equal proportions to one of the following treatment groups:

- **Group A**: placebo oral once daily (QD)
- **Group B**: 30 mg RG7774 oral QD
- **Group C**: 200 mg RG7774 oral QD

Randomization will take place at the Day 1 visit prior to study treatment administration and after the assessments confirming eligibility of the participant. Randomization to the different treatment groups will be stratified on Day 1 using the following imaging features from screening:

- DRSS 47 vs. DRSS 53.
- Presence vs. absence of diabetic macular edema (DME).
- Unilateral vs. bilateral moderately severe to severe NPDR.

The stratification factors will be assessed by a central reading center, based on information obtained at the screening visit. Safety assessments will be performed at every site visit. To ensure an adequate safety follow-up also between site visits, participants will receive phone calls from the site every 4 weeks (when no site visit is scheduled), during which participants will be asked for AEs and any changed or new concomitant medication.

Participants should not change their existing stable treatment for diabetes mellitus (DM) and its consequences during the study unless it is required for the treatment of an adverse event (AE) or as a result of potential DDI. If participants during the course of the study were to develop any disease-related events:

(i) Worsening of DME (when DME present at baseline) requiring treatment at the discretion of the Investigator or if any of the following criteria applies, e.g.:

- Loss of ≥10 letters in BCVA as compared to baseline due to DME, or,
- Loss of ≥ 5 letters in BCVA as compared to previous visit due to DME, or,
- Increase in Central Subfield Thickness (CST) ≥ 100 μm as compared to previous visit due to DME.

(ii) Incident DME or PDR (not present at baseline) requiring treatment.

(iii) Anterior Segment Neovascularization (ASNV).

then participants may receive rescue treatment for any eye at the Investigator's discretion with any of the permitted therapies. Treatment with RG7774 or placebo (as applicable) should continue. In this situation, a reduced number of assessments will be performed for both eyes if

the study eye receives rescue treatment. If the eye that receives rescue treatment is the non-study eye, the non-study eye will undergo the reduced schedule of assessments, while the study eye will undergo the full schedule of assessments. This schedule will continue for all remaining visits up to and including Week 36 visit. All participants will have the safety follow-up and Week 48 visit.

Investigational medicinal products (IMPs) for this study are RG7774 and placebo. Film-coated tablets will be provided by the Sponsor to achieve the doses of 30mg or 200 mg. Participants will have study treatment self-administered orally QD until the visit at Week 36, or earlier if discontinued. A 12-week observational, off-treatment period will follow until the last visit of the study, at Week 48.

Approved anti-vascular endothelial growth factor (VEGF) and/ or approved steroids (in cases where rescue therapy is needed) are considered non-investigational medicinal products (NIMPs).

Length of Study

The total duration of the study for each participant will be up to 52 weeks divided as follows:

- Screening (from Day −28 to Day −7).
- Day 1 (1 day).
- Study treatment period with fixed dose (36 weeks).
- Safety and efficacy follow-up period / washout period (28 days after last dose: Week 40 visit).
- Long-term follow-up period (8 weeks: from Week 40 visit to Week 48 visit).

End of Study

The end of study is defined as last visit of the last participant. The last participant last observation (LPLO) is expected to occur 48 weeks after the last participant is enrolled. Participants are considered to have completed the study if they have completed all the assessments as required in this protocol.

Data Monitoring Committee:

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the Sponsor's Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) will be documented in an appropriate charter.

PARTICIPANT POPULATION

Participants of this study are adult patients with DM type 1 or type 2, with treatment-naïve moderately severe to severe NPDR, good vision, with or without DME who are not expected to require DME treatment for the duration of the study, fulfill all inclusion criteria and do not meet any exclusion criteria.

INCLUSION/ EXCLUSION CRITERIA

Patients who failed screening due to inclusion/exclusion criteria in the previous versions of the protocol that have been changed in the current version (e.g., HbA1c, serology) can be rescreened.

Only one eye will be selected as the study eye. If both eyes are eligible, the eye with DRSS 53 will be the study eye. If both eyes are eligible and have equal DRSS, the right eye will be defined as the study eye.

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to International *Council for Harmonisation* and local regulations.

Age / Gender

2. Male and female patients of at least 18 years of age.

Ocular Criteria for study eye:

3. Patients with treatment-naïve, moderately severe to severe NPDR defined as ETDRS DRSS 47 or 53. NPDR will be evaluated at the site based on e.g. the 4:2:1 rule evident on clinical examination and on digital imaging. Confirmation of DRSS 47 or 53 by the central reading center is required. *Note: One rescreening for this criterion is permitted for participants who score DRSS 43 at the screening visit. Rescreening should be scheduled at least 16 weeks (approximately 4 months) after the initial screening visit.*
4. Patients are eligible with and without DME in either eye, defined as the presence of signs in the macula such as: swelling, leakage, exudates, cystoid changes and fluid. In addition, Central Subfield Thickness (CST) on SD-OCT needs to be ≥ 300µm to confirm diagnosis of DME. The presence of DME will be confirmed at screening by the central reading center.
5. If present, DME has to be treatment-naïve and not expected to require treatment during the duration of the study in the opinion of the investigator at screening and Day 1.
6. BCVA score at screening of at least 70 letters in study eyes without DME and at least 75 letters in case DME is present, using ETDRS visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/40 or better - or 20/32 or better).
7. Clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images.

General Criteria:

8. Diagnosis of DM type 1 or type 2, as defined by the World Health Organization and/or American Diabetes Association, and:

   (i) Current regular use of insulin or other injectable drugs for the treatment of DM

   and/or

   (ii) Current regular use of oral anti-hyperglycemic agents for the treatment of DM
9. HbA1c $\leq 12\%$.
10. Allowed existing medication regimens for DM and associated conditions should be stable for at least 6 weeks before screening, with the intent to remain stable throughout the study. One rescreening for this criterion is permitted.
11. Patient is willing to refrain from non-topical cannabinoid (CBD) use (e.g., over-the-counter [OTC] CBD oil) for the entire duration of the study.

Sex and Contraception/Barrier Requirements:

12. Male and/or female participants

    Pregnancy of a female participant and fathering of a child by a male participant should be avoided during participation in this study. The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or 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) 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).
- Women of childbearing potential (WOCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use of two contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 4 weeks after the final dose of RG7774 or placebo.

    Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion/ ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method.
  - Have a negative pregnancy test (urine) at screening.

b) Male Participants

During the treatment period and for at least 90 days after the final dose of study treatment, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use barrier contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with a partner who is a WOCBP.

  With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating sperm.

Other:

13. In the Investigator's opinion, the subject is deemed appropriate for participation in the study, capable of following the study schedule of assessments and complying with the study restrictions and participation in the study or discontinuation of prohibited medication will not pose undue risks to the participant.

Exclusion Criteria

Participants are not eligible if any of the following criteria apply:

Ocular criteria for study eye:

1. Prior treatment for DR or other retinal diseases with *any* approved therapy, including but not limited to intravitreal steroids, intravitreal anti-VEGF, light therapy, *periocular pharmacological intervention,* and laser (e.g., focal, grid, micropulse, or pan-retinal).
   Note: Focal laser in the retinal periphery due to other reasons than DR (e.g., due to retinal hole or tear) at least *12 weeks* prior to screening is permitted. One rescreening for this criterion is permitted.
2. Intraocular surgery less than *12 weeks* prior to screening. One rescreening for this criterion is permitted.
3. Aphakia or implantation of intraocular lens outside of the capsular bag.
4. History of vitreoretinal surgery.
5. Uncontrolled glaucoma (e.g., visual field loss or defined as intraocular pressure [IOP] ≥ 25 mmHg despite treatment with anti-glaucoma medication). One rescreening for this criterion is permitted.
6. Amblyopia.
7. Any history of idiopathic or immune-mediated uveitis in either eye
8. Any concurrent intraocular condition (e.g., age-related macular degeneration [AMD], retinal vein occlusion [RVO], retinal detachment, dense cataract, epiretinal membrane with traction, or vitreomacular traction, etc.) that in the opinion of the Investigator could reduce the potential for improvement, require medical surgical intervention or may confound the visual and functional assessment and interpretation of study results.
9. *Criteria for participation in previous ocular clinical trials for the study eye:*
   - *Participation in a clinical trial for an ocular disease involving an investigational device (e.g., implant, laser), gene therapy or cell-based therapy.*
   - *Participation in a clinical trial for a retinal disease with pharmacological intervention receiving active investigational treatment.*
   - *Participation in a clinical trial for ocular non-retinal diseases with pharmacological intervention receiving active investigational treatment within 12 weeks or 5 half-lives (whichever is longer) prior to screening. One rescreening for this criterion is permitted.*

Ocular criteria for non-study eye:

10. *Criteria for participation in previous ocular clinical trials for the non-study eye:*
    - *Participation in a clinical trial for an ocular disease involving an investigational device, gene therapy, or cell-based therapy. Note: Laser treatment is permitted.*
    - *Participation in a clinical trial for ocular diseases with pharmacological intervention receiving active investigational treatment within 2 weeks or 5 half-lives (whichever is longer) prior to screening. One rescreening for this criterion is permitted.*

Concurrent ocular conditions in either eye:

11. Any active ocular infection. One rescreening for this criterion is permitted.
12. Any active intraocular inflammation. One rescreening for this criterion is permitted.

General Criteria:

13. Previous systemic use of anti-VEGF drugs within *24 weeks* prior to screening. One rescreening for this criterion is permitted.
14. Complications of DM such as end-stage renal disease or liver disease.
15. Currently untreated DM or previously untreated patients who initiated oral or injectable anti-diabetic medication within *12 weeks* prior to screening. One rescreening for this criterion is permitted.
16. Uncontrolled blood pressure ([BP] defined as systolic >180 mmHg and/or diastolic >100 mmHg while patient at rest). If a patient's initial reading exceeds these values, a second reading may be taken either 30 or more minutes later on the same day, or on another day during the screening period. If the BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 6 weeks prior to screening. One rescreening for this criterion is permitted.
17. Confirmed (e.g., 2 consecutive measurements) clinically significant abnormality on ECG at screening. That includes but is not limited to a QTcF > 450 ms for male participants and QTcF > 470 ms for female participants, absence of dominating sinus rhythm, AV-block II or III. Additional examples of clinically significant abnormalities detected by ECG or otherwise related to abnormal cardiac function are cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death, and atrial fibrillation.
18. History of coagulopathies, bleeding disorders or blood dyscrasias.
19. History of concurrent cardio-vascular disease not considered well controlled by the Investigator.
20. Risk of suicidal behavior in the opinion of the Investigator or as evidenced by a "yes" to questions 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) taken at screening, or any suicide attempt in the last 5 years.
21. Positive serology results for HIV-1 *and* HIV-2. *Positive results for hepatitis B virus (HBV) and hepatitis C virus (HCV) are exclusionary only if the disease is confirmed to be active and/ or the patient is receiving treatment.*
22. Any major illness or major surgical procedure within *4 weeks* before screening. One rescreening for this criterion is permitted.
23. History of or currently active other diseases, viral and/or bacterial infections, metabolic dysfunction, physical examination finding, malignancies not considered cured, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated the use of the investigational medicinal drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator.
    Note: *Participants with symptoms or signs of acute or long SARS-CoV-2 infection or asymptomatic disease (positive test without symptoms) within 30 days of screening will be excluded from the study. One rescreening for this criterion is permitted.*
24. Known hypersensitivity to any of the excipients of the drug used, fluorescein dye or dilating eye drops.
25. Alcohol and/or substance abuse/dependence during the last 12 months*, assessed by the investigator considering the results of the tests and the medical history, in consultation with the Sponsor, if required*. One rescreening for this criterion is permitted.

26. Use of non-topical CBD (including OTC CBD oil) within $12\ weeks$ prior to screening. One rescreening for this criterion is permitted.
27. Use of prohibited medications within 2 weeks prior to screening, or 5 half-lives (whichever is longer). One rescreening for this criterion is permitted.
28. Use of systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the $24\text{-}week$ period prior to screening or likely need to be used. One rescreening for this criterion is permitted.
29. Participation in a clinical study involving an investigational $medicinal$ product or device with exit from that study
    - within 60 days prior to screening, or
    - within less than 5 half-lives between last exposure to study treatment in the previous study and screening for the present study

    (whichever is longer). One rescreening for this criterion is permitted.
30. Blood donation or loss of blood $>$ 500 mL within $12\ weeks$ prior to screening. One rescreening for this criterion is permitted.

NUMBER OF PARTICIPANTS

A total of 135 participants are expected to be enrolled in this study and will be randomized 1:1:1 to the three groups (45 participants per group). Based on Fisher's exact test, assuming the proportion of participants with $\geq$ 2 step improvement in the ETDRS DRSS to be 15% for placebo and 40% to 45% under active treatment, 40 participants completing the study per group provide between 74% and 88% power based on a 2-sided significance level of 0.1. Allowing for about 10% of the participants randomized to not complete the study and hence not have an assessment of the primary endpoint at week 36, a total of 135 participants (45 participants per group) was selected to obtain 120 completers. If the rate of participants not completing the study is larger than 10%, the sample size may be increased beyond 135 participants with the aim of achieving approximately 45 completers per group.

CONCOMITANT MEDICATIONS

Permitted Therapy

Participants should not change their existing stable treatment for DM and its consequences during the study, unless it is required for the treatment of an AE or as a result of potential DDI. Potential DDI arising from co-administration of other drugs have been investigated in healthy volunteers only. Therefore, changed or new concomitant medication in general should be limited to the medical need of the participant and the medical judgement of the investigator, in consultation with the Sponsor.

The Investigator should be aware of the potential for DDI when prescribing concomitant medications which are inhibitors or inducers of CYP3A and/or CYP2C19, or are substrates of CYP3A, OCT2, MATE1, MATE2-K, P-gp, and/or BCRP and should carefully monitor the tolerability and safety of RG7774. The Sponsor has included two visits to monitor if there is a need to adjust the dose of warfarin, if applicable.

Therapies permitted for either eye in case of incidence or progression of DME/DR are:

- Laser (grid or focal) and/or approved anti-VEGF (except brolucizumab, if applicable), and/ or approved steroids in case of worsening DME which requires treatment for participants presenting with DME at baseline.

- Laser (grid or focal) and/or approved anti-VEGF (except brolucizumab, if applicable), and/ or approved steroids in case of incident DME requiring treatment
- Laser (pan-retinal), vitrectomy and/or approved anti-VEGF (except brolucizumab, if applicable) in case of incident PDR.

The administration of these permitted therapies will not automatically result in treatment discontinuation and participants should continue in the study as described.

Prohibited Therapy

Systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) are prohibited within $24\ weeks$ prior to baseline and during the study.

Systemic Medications Prohibited due to Effects Related to Cytochrome P450 Enzymes

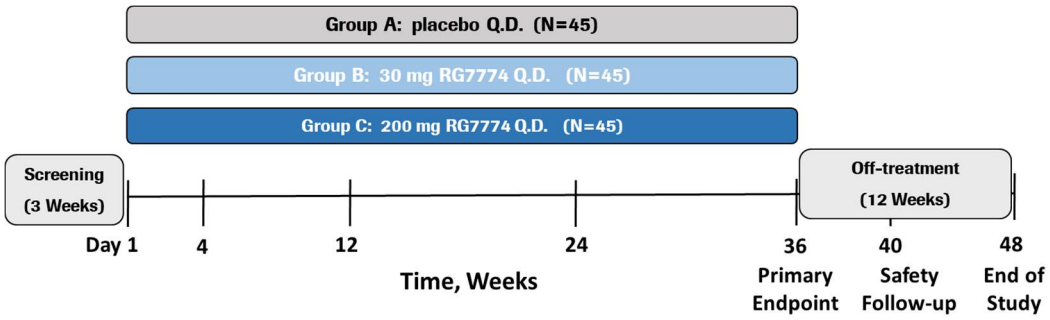
- Strong inhibitors of CYP3A including, but not limited to, grapefruit and the following drugs: e.g., ketoconazole, itraconazole, ritonavir, voriconazole, clarithromycin.
- Moderate inhibitors of CYP3A including but not limited to the following drugs: e.g., erythromycin, ciprofloxacin, cimetidine.
- Strong and moderate inducers of CYP3A including but not limited to the following drugs: e.g. rifampicin, carbamazepine, phenytoin, St. John`s wort, bosentan and modafinil.
- Strong inhibitors of CYP2C19 including but not limited to the following drugs: e.g., fluconazole, fluoxetine, fluvoxamine, and ticlopidine.
- Strong and moderate inducers of CYP2C19 including but not limited to the following drugs: e.g., rifampicin, ritonavir, efavirenz, phenytoin, and enzalutamide.

The above list of medications is not comprehensive. The Investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with the study treatment. In addition, the Investigator should contact the study team if questions arise regarding medications not listed above.

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



The primary endpoint will be assessed at Week 36. An additional observational, off-treatment period of 12 weeks will follow the last treatment administration at Week 36, until the final visit at Week 48.

1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 (Main Table) and Table 2 (Reduced Assessments).

Table 1 Schedule of Activities – Main Table

	Week	Screening	Week 1			Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Warfarin follow-up	Week 40 Safety follow-up[1,2]	Week 48	Early Termination[1] (<14d after last site visit)	Early Termination[2] (>=14d after last site visit)
	Day	D-28 to D-7	Day 1[3]	Day 7[4]	Day 7	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 259 or earlier[4]	Day 280	Day 336		
	Visit Window		none	-1/+ 3 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	-1/+ 3 days	+/- 7 days	+/- 7 days		
Category	Assessments	Site Visit	Site Visit	Site Visit	Phone Call[5]	Site Visit	Phone Call[5]	Site Visit	Phone Call[5]	Phone Call[5]	Site Visit	Phone Call[5]	Phone Call[5]	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit
	Informed Consent	x																	
	Inclusion/Exclusion criteria	x	x																
	Pregnancy Test[6]	x																	
Medical and clinical history	Demography	x																	
	Medical History	x																	
	Previous and Concomitant Treatments / Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Physical Examination	x[7]	x					x			x			x[7]		x[7]		x[7]	x[7]
	Anthropometric Measurements[7a]		x											x		x		x	x
	Vital Signs	x	x			x		x			x			x		x		x	x
	Triplicate ECG-12 lead[9]	x	x			x		x			x			x		x		x	x
Laboratory analylsis	Hematology	x				x		x			x			x		x		x	x
	Blood Chemistry	x	x[12]			x		x			x			x		x		x	x
	Coagulation	x		x		x		x			x			x	x	x	x	x	x
	Viral Serology	x																	
	Lipids	x				x		x			x			x		x		x	x
	Thyroid Hormones	x				x		x			x			x		x		x	x
	FSH[10]	x																	
	HbA1c[11]	x				x		x			x			x		x	x	x	x
	Urinalysis	x				x		x			x			x		x		x	x
	Drug of abuse/Alcohol urine test	x				x		x			x			x				x	x
	C-SSRS (Form "At Baseline")	x																	
	C-SSRS (Form "Since Last Visit")[8]		x			x		x			x			x		x		x	x
	Randomization		x																

Table 1 Schedule of Activities – Main Table (cont.)

	Week	Screening	Week 1			Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Warfarin follow-up	Week 40 Safety follow-up[1,2]	Week 48	Early Termination[1] (<14d after last site visit)	Early Termination[2] (>=14d after last site visit)
	Day	D-28 to D-7	Day 1[3]	Day 7[4]	Day 7	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 259 or earlier[4]	Day 280	Day 336		
	Visit Window		none	-1/+ 3 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	-1/+ 3 days	+/- 7 days	+/- 7 days		
Category	Assessments	Site Visit	Site Visit	Site Visit	Phone Call[5]	Site Visit	Phone Call[5]	Site Visit	Phone Call[5]	Phone Call[5]	Site Visit	Phone Call[5]	Phone Call[5]	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit	Site Visit
Sample collection	PK Sample[13]		x[13]	x		x[13]		x			x			x[13]	x				x
	PD Biomarker Sample, plasma	x	x			x		x			x			x					x
	[redacted]																	x	x
																		x	x
Ophthalmologic examinations	IOP	x	x			x		x			x			x		x		x	x
	BCVA	x	x			x		x			x			x		x	x	x	x
	LLVA[15]		x											x					x
	Contrast Sensitivity (pelli-robson)[15]		x			x		x			x			x					x
	Contrast Sensitivity (qCSF)[16]		x			x		x			x			x					x
	Visual Field (SAP) (optional)[15,17]		x					x			x			x					x
	Slit Lamp	x	x			x		x			x			x		x		x	x
	Indirect Ophthalmoscopy	x	x			x		x			x			x		x		x	x
	Fundus Photography (7F-FP)	x	x			x		x			x			x			x		x
	Fluorescein angiography (7F or UWF)[18a]	x												x[18b]				x[18b]	x[18b]
	SD-OCT	x	x			x		x			x			x			x	x	x
Study medication	Dispensing and/or return of study medication		x			x		x			x			x				x	x
	RG7774 / placebo[19]		x																
	Adverse Events[20]	x																	
Apps	PEMA[21]	x																	

Table 1 Schedule of Activities – Main Table (cont.)

1. If participants discontinue or withdraw from the study treatment prematurely, the participants should complete the Early Termination visit and attend the Follow-up visit normally done at the end of the study, 4 weeks after the last dose of study medication. If the discontinuation or withdrawal happens less than 14 days after a site visit, participants will have a reduced number of assessments.
2. If participants discontinue or withdraw from the study treatment prematurely, the participants should complete the Early Termination visit and attend the Follow-up visit normally done at the end of the study, 4 weeks after the last dose of study medication. If the discontinuation or withdrawal happens 14 days or more after a site visit, participants will have a full assessment.
3. The details of the specific order of assessments can be found in the Study Procedures Manual, which must be adhered to.
4. Visits exclusively for participants on warfarin to monitor potential need for dose adjustment of warfarin. The visits will happen 7 days after the first dose of RG7774/ placebo (at Day 7) and 7 days after the last dose of RG7774/ placebo (typically on Week 37, or earlier in case of discontinuing the study prematurely).
5. Telephone interview to assess for any clinically significant symptoms and/or new/ changed medication.
6. Screening urine pregnancy test for women of child-bearing potential (WOCBP) prior to first dose of RG7774 or placebo. Additional pregnancy tests can be performed anytime during the study at the discretion of the Investigator.
7. Full physical examination as per protocol.

7a. Height and weight will be recorded at the Day 1 visit only. Only weight will be measured at the Week 36 or Early Termination visits.

8. To be administered by masked site staff prior to any other visit assessments being performed on that day. If required, the questionnaires can be administered via telephone one business day prior to the visit. Confirmation that there are no changes should be obtained on the day of the site visit.
9. ECG (12-lead) will be obtained pre-dose on Day 1. All ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.
10. Hormonal panel for postmenopausal women only.
11. HbA1c measurement is obtained from the same sample as hematology, except for Week 48.
12. Blood chemistry at Day 1 will only be analyzed for C-reactive protein (CRP).

Table 1 Schedule of Activities – Main Table (cont.)

13. *One PK sample to be collected at all visits prior to study treatment administration.* At visits Day 1, Day 28*,* and Day 252 two *additional* post-dose samples *may be collected optionally. The two samples should be obtained*, at 1-3 hours, and 3-5 hours post-dose, respectively. Timing between the two post-dose samples should be *approximately* 2 hours.
14. [redacted]
15. *Study eye only.*
16. qCSF to be performed only if the site has the capabilities to perform this assessment.
17. *Optional* Visual Field assessments *should* be performed in study eye only *when* the site has the capabilities to perform this assessment.

18a. Only one FFA modality will be performed in each patient: *ultra-widefield*-FFA will be performed preferentially, if the site has the capabilities to perform this assessment. If not available, 7F-FFA will be performed.

18b. Fluorescein Angiography assessments not to be done more often than every *12 weeks*.

19. Study medication will be administered to participants directly in the study clinic on the day of site visit. The participant has to avoid taking medication before going to the site on the day of site visit.
20. Adverse event collection will be done throughout the full length of the study.
21. Patient Engagement App (PEMA) will be used at discretion of the participant, if applicable, throughout the full length of the study (no time restriction on Day 1).

Table 2 Schedule of Activities – Reduced Assessments as from the Time of Rescue Treatment and up to and including Week 36

	Assessments in case of rescue treatment
Previous and Concomitant Treatments / Medications	x
Physical Examination	x
Vital Signs	x
Triplicate ECG-12 lead	x
Hematology	x
Blood Chemistry	x
Coagulation	x
Lipids	x
HbA1c	x
Urinalysis	x
TSH	x
C-SSRS (Form "Since Last Visit")	x
PK Sample	x
IOP	x
BCVA	x
Slit Lamp	x
Indirect Ophthalmoscopy	x
Fundus Photography (7F-FP)	x
SD-OCT	x
Dispensing and/or return of study medication	x
RG7774 / placebo	x
Adverse Events	x
Optional Aqueous Humor sample[1]	x

Optional aqueous humor sample collection to be performed prior to the intravitreal rescue treatment in participants who give additional consent.

Reduced assessments (see Table 2) will be performed for all participants undergoing rescue therapy as indicated in Section 6.5.3. This applies to both eyes if the study eye receives rescue treatment. If the eye that receives rescue treatment is the non-study eye, the non-study eye will undergo the reduced schedule of assessments, while the study eye will undergo the full schedule of assessments. This schedule will continue for all remaining visits up to and including week 36 visit (see Section 8.10.3 for further details).

2. INTRODUCTION

2.1 STUDY RATIONALE

The endocannabinoid system has been involved in the pathology of diabetes mellitus (DM) and its complications, including diabetic retinopathy (DR) (Behl et al. 2016, Gruden et al. 2016). RG7774 (also referred to as RO6868847) is a synthetic small molecule that is a potent cannabinoid 2 (CB2) receptor agonist, with high selectivity for CB2 versus CB1 receptors, as shown by pharmacological data and by the lack of psychotropic effects of central CB1 receptor activation at the doses tested to date in humans. RG7774 is being developed for patients suffering from DR.

The primary objective of the current study BP41321 is to assess the safety, tolerability and the effect of oral administration of RG7774 on the severity of DR in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and good vision.

The secondary objectives are to further evaluate the potential of RG7774 to prevent progression of DR, as determined by the incidence of sight-threatening events (e.g., diabetic macular edema [DME] or proliferative diabetic retinopathy [PDR]), and to assess the effect of RG7774 on best-corrected visual acuity (BCVA).

Results from nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies and the outcomes of the healthy volunteer entry-in-human single-ascending dose (SAD), multiple-ascending-dose (MAD), food-effect (FE) study (EIH, BP40387), as well as the itraconazole drug-drug interaction (DDI) study (BP41274) have been considered in the development of protocol BP41321.

The study results from the current study BP41321 will be used to support further clinical development of RG7774.

2.2 BACKGROUND

2.2.1 Background on Disease

DR is a consequence of DM, and affects approximately one third of type 1 and type 2 diabetic patients. The pathological mechanisms induced by sustained, increased levels of blood glucose include oxidative stress, inflammation, vascular dysfunction and neurodegeneration (Fong et al. 2004). In the retina, Müller cells, microglia, and endothelial cells produce chemokines that induce leukostasis, diapedesis, influx of monocytes into the retina, and increased production of cytokines including VEGF, tumor necrosis factor-α (TNF-α), interleukin (IL)-1b, IL-6, metalloproteinase, and angiopoietin-2. These inflammatory mediators are involved in the breakdown of endothelial cell-cell junctions forming the blood-retinal barrier seen in DR.

Increasing evidence points to a role of inflammation in DR, contributing to retinal vascular permeability and neovascularization (reviewed in Mesquida et al. 2019).

Beyond the vascular pathology, inflammation may also contribute to retinal neurodegeneration (Semeraro et al. 2019).

DR is a serious condition that, if left untreated, can progress to vision-threatening stages and ultimately blindness. The severe sequelae of DR, proliferative DR (PDR) and DME, are treated with laser photocoagulation, intravitreal (IVT) injections of anti-vascular endothelial growth factor (VEGF), steroids and/or vitrectomy (Lee et al. 2015; Schmidt-Erfurth et al. 2017; Wong et al. 2018). Moderately severe to severe NPDR that has not yet led to these sequelae is rarely treated with laser, as photocoagulation is destructive and associated with peripheral visual field defects and possible vision loss. Anti-VEGF injections have shown benefits in slowing down and improving DR with or without DME and in the absence of PDR (Ip et al. 2012; Boyer 2019), however they are rarely used. Reasons may include concerns about the potential risks of injecting eyes of patients with no visual acuity decline and the significant treatment burden of anti-VEGF therapy, aggravated when bilateral treatment is required.

RG7774, by its proposed anti-inflammatory mode of action and convenient oral administration, can be an option to treat patients with unilateral or bilateral moderately severe to severe NPDR with good vision for whom anti-VEGF IVT is usually deferred in clinical practice.

2.2.2 RG7774

Many studies have shown that cannabinoids can suppress the production of cytokines in innate and adaptive immune responses, both in animal models and in human cell cultures (Klein 2005). Their suppression of pro-inflammatory cytokines and chemokines production indicates that these cannabinoids, specifically CB2 receptor agonists, may have anti-inflammatory effects and could therefore be used for the treatment of chronic inflammatory diseases such as DR. In fact, activation of CB2 receptors by reducing inflammatory, oxidative and fibrotic processes has shown beneficial effects in a wide range of inflammatory diseases including Crohn's Disease, arthritis, myocardial infarction and others (Maurya and Velmurugan 2018).

RG7774 is a highly selective CB2 receptor agonist intended for the oral treatment of DR. CB2 receptor is mainly expressed in immune cells, including microglia in the retina. Activation of CB2 by RG7774 has been shown to produce anti-inflammatory effects in the eye, by inhibiting leukocyte adhesion and microglia activation, decreasing vascular permeability, and consequently preserving endothelial barrier function.

The high selectivity of RG7774 for the CB2 receptor (greater than 10,000-fold) makes psychotropic effects by central CB1 receptor activation or the risk of an increased suicide rate via central CB1 receptor inhibition (Topol et al. 2010) highly unlikely. Current data suggest that RG7774 displays the highest selectivity compared with publicly $known$ CB2 receptor agonists (Soethoudt et al. 2017).

A detailed description of the chemistry, pharmacology, efficacy and safety of RG7774 is provided in the Investigator's Brochure.

2.2.2.1 Previous Clinical Studies

RG7774 has been studied in a Phase I entry- into-human (EIH) study in healthy participants (Study BP40387; 129 participants). This was a single-center study consisting of a SAD part, a FE part, a multiple-ascending-dose (MAD) part, a fourth part to investigate the effects of RG7774 on CYP2B6 and CYP2C8 activity and a fifth part to investigate the inhibitory effects of RG7774 on multiple drug transporters using metformin and atorvastatin as probe substrates in healthy participants.

In Part 1 (SAD), single oral doses of 0.75 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg RG7774 or placebo were administered under fasting conditions, with 4 participants per dose group for the 3 mg group (3 active and 1 placebo) and with 12 participants (9 active and 3 placebo) for the highest dose. The dose groups in between had 8 participants (6 active and 2 placebo) per group. The starting dose of 0.75 mg was administered to 5 participants (3 active and 2 placebo) due to the sentinel dosing.

In Part 2 (FE), 8 participants received a single oral dose of 100 mg RG7774 once after an overnight fast of at least 10 hours and once within 30 minutes after starting a high-calorie, high-fat breakfast.

In Part 3 (MAD), multiple oral doses of 6 mg, 20 mg, 60 mg, 200 mg, and 300 mg RG7774 or placebo were administered in the fasted state for 14 days, with 8 participants per cohort (6 on active and 2 placebo).

In Part 4 (DDI), the effect of multiple oral doses of 300 mg RG7774 given once daily for 14 consecutive days, on the pharmacokinetics of three different drug-metabolizing *Cytochrome P450 (*CYP*)* enzymes, namely midazolam (CYP3A), bupropion (CYP2B6) and repaglinide (CYP2C8) was explored in 17 healthy participants.

In Part 5 (transporter DDI), the effect of a single oral dose of 300 mg RG7774, on the pharmacokinetics of metformin (OCT2, MATE1, MATE2-K) and atorvastatin (OATP1B1, P-gp, BCRP) was studied in 18 healthy participants.

Study BP41274 investigated the effect of multiple oral doses of itraconazole, a strong CYP3A inhibitor, on the plasma pharmacokinetics of RG7774 in 16 healthy participants. Overall, 122 healthy participants have received RG7774. Detailed information on the effects of RG7774 in humans is described in the Investigator's Brochure.

No clinical data are yet available for RG7774 in patients with NPDR.

2.3 BENEFIT/RISK ASSESSMENT

The development program of RG7774 is designed to offer a treatment option for patients with NPDR, for whom both photocoagulation and IVT anti-VEGF therapy are commonly deferred in current practice.

Oral dosing is the preferred route of administration for patients with NPDR in order to achieve systemic and bilateral retinal exposure. Systemic exposure will target leukocytes to prevent attachment to vascular endothelial cells in the retina and other tissues, while retinal exposure will activate CB2 receptors in the microglia target cells. Furthermore, systemic exposure may influence additional complications of DM, such as diabetic nephropathy, which was shown to be ameliorated in the same nonclinical models as those used for the retinal microglia analysis (Zoja et al. 2016).

The non-clinical safety package completed to date in rats and cynomolgus monkeys showed an overall benign safety profile of RG7774, without any adverse findings up to the highest tested doses. [redacted]

No cardiovascular effects were detected in monkeys after single and repeated dosing up to the highest tested dose. At the same time, embryofetal development (EFD) dose-range findings studies in rat and rabbit did not show any indication of teratogenicity up to the highest tested dose.

The high selectivity of RG7774 towards CB2 vs. the CB1 receptor translated into no adverse findings consistent with cannabinoid-related side effects (i.e., hypolocomotion, catalepsy and hypothermia) up to the highest achieved exposures. This confirmed the results obtained *in vitro* when assessing the selectivity of RG7774 in 78 receptors and ion channels in which RG7774 demonstrated excellent selectivity for CB2 receptor. In functional cellular assays, no activity of RG7774 was detected at 15-lipoxygenase, MAGL, diacylglycerol lipase, or FAAH enzymes of the endocannabinoid pathway.

Clinical experience is currently limited to Study BP40387 (EIH study) and Study BP41274 (Itraconazole DDI study) in healthy participants. Across clinical trials, the administration of RG7774 has been found to be safe and very well tolerated for doses of RG7774 up to (and including) 300 mg once daily for 2 weeks and no pattern of adverse events (AEs) possibly characteristic for the use of RG7774 in humans has emerged to date. There was one serious adverse event (SAE) [redacted]

To ensure the safety of all participants during the conduct of the current study BP41321, several safety assessments have been included: e.g., regular ophthalmological monitoring and imaging assessments, AE monitoring (systemic and ophthalmologic), vital signs (systolic BP, diastolic BP, ECG and pulse rate), warfarin (INR) monitoring for dose adjustments and other laboratory safety tests. In months for which no site visit is scheduled, participants will be interviewed via telephone call to assess for any clinically significant symptoms and/ or new medication.

To ensure the safety of study participants and staff and minimize their risk of COVID-19, appropriate trial- and site-specific COVID-19 risk mitigation measures will be implemented as required per local and site regulations.

Based on current evidence, a favorable benefit-risk balance is envisaged for RG7774 and - given its systemic activity and non-invasive route of administration - RG7774 could encourage initiation of treatment of patients with NPDR who, in current practice, are not receiving immediate ophthalmologic treatment. Additionally, the expected benefits of improving the severity of DR and/or halting progression to PDR or DME would reduce the need for future intravitreal administration.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RG7774 is provided in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Assess the effect of RG7774 on the severity of DR.	• Proportion of participants with ≥ 2 step improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity score (DRSS) from baseline at Week 36 measured in the study eye.
• Evaluate the safety and tolerability of RG7774.	• Frequency and severity of adverse events.
Secondary	
• Assess the effect of RG7774 on progression to vision-threatening DR.	• Incidence of anterior segment neovascularization (ASNV), new PDR, new DME, and pre-existing DME requiring intervention.
• Assess the effect of RG7774 on visual acuity.	• Change from baseline in BCVA at Week 36 in the study eye.
Exploratory	
• Assess the effect of RG7774 on DR worsening.	• Proportion of participants with ≥ 2 step worsening in ETDRS DRSS from baseline at Week 36 measured in the study eye
• Assess the effect of RG7774 on DR severity at a participant level.	• Proportion of participants with ≥ 3 step improvement in ETDRS DRSS from baseline at post-baseline visits measured in both eyes • Proportion of participants with ≥ 3 step worsening from baseline at post-baseline visits measured in both eyes.

Table 3 Objectives and Endpoints (cont.)

Objectives	Endpoints
Exploratory	
• Assess the durability of the effect of RG7774 on DR.	• Proportion of participants with either a stable (± 1 step change), worsened (>1 step increase) or improved (>1 step decrease) DRSS between Week 36 and Week 48.
• Assess the efficacy of RG7774 on visual acuity and anatomical outcome measures using spectral domain optical coherence tomography (SD-OCT) among eyes with DME at baseline.	• Change from baseline in participants with DME at baseline in: – BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at post-baseline visits. – Central subfield thickness on SD-OCT over time at post-baseline visits. • Proportion of participants with absence of signs of DME and normalized *Central Subfield Thickness (*CST*)* at post-baseline visits.
• Assess the effect of RG7774 on visual function.	• Change from baseline in Contrast Sensitivity at post-baseline visits in *the study eye (Pelli-Robson, qCSF) or in both eyes (qCSF).* • Change from baseline in *low luminance visual acuity (*LLVA*)* at *Week 36* visit in *the study* eye.
• Assess the effect of RG7774 on visual field*s*.	• Change from baseline in mean threshold at post-baseline visits. • Change from baseline in point-by-point Standard Automated Perimetry at post-baseline visits.
• Assess systemic pharmacokinetics and exposure-response/safety relationships of RG7774 (and its metabolite[s] as appropriate).	• PK parameters of RG7774 (and its metabolite[s] as appropriate) in plasma and (if applicable) in optional aqueous humor.

Table 3 Objectives and Endpoints (cont.)

Objectives	Endpoints
Exploratory	
• Explore the effect of RG7774 on markers of kidney function.	• [redacted]
• Explore potential effects of RG7774 on glycemic status.	• Change from baseline in blood levels of HbA1c.
• Assess the effect of RG7774 on systemic biomarkers of inflammation and disease in peripheral blood.	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• To contribute to the development and/ or evaluation of advanced analytics tool (artificial intelligence based tool) for the assessment of clinically relevant features	• Performance of the advanced analytic tools

4. STUDY DESIGN

4.1 OVERALL DESIGN

An overview of the study design is provided in Section 1.2.

This is a phase II, multi-center, randomized, three parallel-group, placebo-controlled, double-masked, proof-of-concept study in treatment-naïve participants with moderately severe to severe NPDR and good vision. Participants will receive RG7774 or placebo for up to 36 weeks. Participants will be randomized in equal proportions to one of the treatment groups listed in Section 4.1.1.

Randomization will take place at the Day 1 visit prior to study treatment administration and after the assessments confirming eligibility of the participant. Starting at the Day 1 visit, randomized participants will have study treatment self-administered orally once daily until the visit at Week 36 or earlier if discontinued (see Section 7). A 12-week observational, off-treatment period will follow until the last visit of the study, at Week 48. Randomization to the different treatment groups will be stratified on Day 1 based on the following imaging features from screening:

- DR severity score (DRSS) 47 vs. DRSS 53.
- Presence vs. absence of DME.
- Unilateral vs. bilateral moderately severe to severe NPDR.

The stratification factors will be assessed by a central reading center, based on information obtained at the screening visit. Safety assessments will be performed at every site visit. To ensure an adequate safety follow-up also between site visits, participants will receive phone calls from the site every 4 weeks when no site visit is scheduled), during which participants will be asked for AEs and any changed or new concomitant medication.

4.1.1 Treatment Groups

Treatment naïve participants will be randomized in a 1:1:1 ratio to one of the groups A, B and C respectively, for a treatment period of 36 weeks (see Figure 1).

- **Group A**: placebo oral once daily (QD)
- **Group B**: 30 mg RG7774 oral QD
- **Group C**: 200 mg RG7774 oral QD

4.1.2 Length of the Study

The total duration of the study for each participant will be up to 52 weeks divided as follows:

- Screening (from Day −28 to Day −7)
- Day 1 (1 day)
- Study treatment period with fixed dose (36 weeks).
- Safety and efficacy follow-up period / washout period (28 days after last dose, week 40 visit).
- Long-term follow-up period (8 weeks: from Week 40 visit to Week 48 visit).

4.1.3 Administrative Structure

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the Sponsor's Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) will be documented in an appropriate charter (see Appendix 1, Section 3.3).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

To allow for an unbiased evaluation of RG7774 as a treatment for participants with moderately severe to severe NPDR and good vision, a multi-center, randomized, three parallel-group, placebo-controlled, double-masked trial design was selected.

4.2.1 Rationale for Study Population

This study will be conducted in participants with NPDR who meet all of the inclusion criteria and do not meet any of the exclusion criteria for this protocol (see Sections 5.1 and 5.2).

Treatment of all forms of DR with and without DME is approved for anti-VEGF in the United States (ranibizumab [Lucentis®] US product information [USPI], aflibercept [Eylea®] USPI). Nevertheless, treatment initiation (with laser or anti-VEGF therapy) even in DR patients with DME was shown to be deferred for at least 1 year in a majority of patients, despite the potential to improve their DR severity (Ip et al. 2012; Brown et al. 2015, Willis et al. 2017). While patients with NPDR have no well-defined visual impairment, their underlying retinal pathology is progressive. Moderately severe to severe NPDR, if left untreated, may progress to vision-threatening disease in about 41% of patients within 1 year (Boyer 2019).

Based on the above identified unmet medical need, the current Phase II Study BP41321 will recruit treatment-naïve patients with T1/T2 DM as defined by the World Health Organization and/or American Diabetes Association, with glycated hemoglobin (HbA1c) of $\leq 12\%$. More specifically:

- Patients presenting a clinical diagnosis of NPDR (DRSS 47 or 53 in the study eye). The more advanced stages of NPDR (i.e., DRSS 47 and 53) are associated with an increased risk of developing sight threatening complications of DR, comprising PDR, and/or DME, amongst others.
- Patients with and without DME will be eligible for the study. Since there is limited information on the effect of DME on DRSS progression, this patient population is also included as it is likely that an improvement in DRSS will benefit both patients with and without DME.
- Eligible patients will present a BCVA score of at least 70 letters (at least 75 letters if DME is present) in the study eye, using Early Treatment Diabetic

Retinopathy Study (ETDRS) visual acuity (VA) testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/40 or better – 20/32 for DME). Including this VA limit will ensure reduced probability of requirement for rescue therapy.

To ensure the study results will be representative of the target population, the number of participants with DME will be capped to 50%.

4.2.2 Rationale for Control Group

The control group in this study will receive placebo. Using placebo as study comparator allows an unbiased evaluation of the magnitude of any treatment effects. In addition, current practice for a relevant proportion of NPDR patients is observation.

4.2.3 Rationale for Primary Endpoint Assessment and Study Duration

The primary endpoint will be the proportion of participants with a ≥ 2-step improvement from baseline in ETDRS DRSS measured in the study eye at 36 weeks.

The ETDRS DRSS is a well-established scale, with step changes that are associated with different risks of long-term vision loss (Nair et al. 2016). In addition, it has already been accepted by the US regulatory agency for the label approval of ranibizumab and aflibercept (ranibizumab USPI, aflibercept USPI).

Due to the systemic administration of RG7774, the primary endpoint will be supported by additional analysis at a participant level (sum of both eyes), including the response of non-study eyes with NPDR of DRSS categories 35, 43, 47 or 53 at baseline.

The evaluation at 36 weeks is considered an appropriate time point to evaluate the primary variable, as previous results in the same population have shown significant improvements as of Week 24, with treatment effects increasing up to 52 weeks (Boyer 2019).

An exploratory efficacy endpoint will be obtained 12 weeks after the last dose of the study treatment with the objective of exploring the durability of RG7774 on DRSS change, as previous trials have shown that DRSS improvements may not be maintained once treatment has stopped (Sun et al. 2019).

4.2.4 Rationale for Response Definition and Study Eye Selection

The primary endpoint will be the proportion of participants with a ≥ 2-step improvement from baseline in ETDRS DRSS at 36 weeks, measured in the study eye. At any time, new ASNV, new PDR, new DME and pre-existing DME requiring intervention (see permitted therapies Section 6.5.1), occurring in the study eye will classify a participant as a non-responder for the primary analysis, as all these events imply progression of the disease.

Since RG7774 is an oral treatment with expected bilateral effects, the Sponsor will evaluate an in-patient (sum of both eyes) DRSS improvement of ≥ 3 steps in participants with two eligible eyes. At any time, new ASNV, new PDR, new DME and pre-existing DME requiring intervention (see permitted therapies Section 6.5.1), occurring in either eye, classifies a participant as a non-responder. An additional analysis will be conducted for each baseline DRSS level 35 and 43 in the non-study eye to allow for further characterization of RG7774 effects.

In cases where both eyes are eligible, the study eye will be the one with DRSS score of 53. The risk of progression of the disease is higher in eyes with DRSS 53, meaning this population is the one with the higher unmet need (Ip et al. 2015; ETDRS report 1991). If both eyes have the same DR score, then the right eye will be selected as the study eye.

4.2.5 Rationale for Exploratory Endpoints

The primary endpoint is based on anatomic changes measured in color fundus images. The most commonly accepted measure of visual function, i.e. change in BCVA, is not expected to vary to a large extent in this population, with already good vision at baseline. Therefore, several additional measures of visual function will be explored in this study, including amongst others:

- Contrast sensitivity: Previous studies have shown an inverse association between contrast sensitivity and severity of DR (Gella et al. 2017; Ip et al. 2017). Contrast sensitivity will be assessed using Pelli-Robson charts and the quantitative Contrast Sensitivity Function (qCSF) testing on the Manifold Contrast Vision Meter (Adaptive Sensory Technology, San Diego, CA, USA).

- Visual fields: There is evidence that visual fields (VF) dysfunction is capable of distinguishing different stages of DR (Joltikov et al. 2017) and that VF show progressive decline over time (Hellgren et al. 2014). In addition, VF deficits can be detected prior to other DR alterations, suggesting it can be a measure of early retinal neurodegeneration (Hellgren et al 2014). In the present study, VF *is an optional assessment that* will be measured using Standard Automated Perimetry (SAP) and analyzed by a VF Reading Centre.

Optional aqueous humor samples will be collected from participants who require intravitreal rescue treatment with any of the permitted therapies (see Section 6.5.1) and who give additional consent. The samples will be analyzed with an aim to further understand the ocular PK of RG7774. Single (Krohne et al. 2012) and multiple (Campochiaro et al. 2013) aqueous humor sampling has previously been instrumental in the understanding of ocular PK.

[redacted]

[redacted]

4.3 JUSTIFICATION FOR DOSE

The exploration of the doses of 30 mg and 200 mg RG7774 QD over 9 months in this Phase II study is supported by a favorable benefit-risk assessment based on the benign safety profile observed in the chronic GLP repeat-dose toxicity studies up to the highest tested doses, the safety and tolerability profiles observed in Study BP40387 and the safety monitoring in place in this study. These results will then help guide the optimum dose selection for Phase III studies.

As of 30th September 2019, in the entry-into-human study (Study BP40387) and the itraconazole DDI study (Study BP41274) a total of 75 healthy participants have received single oral doses of RG7774 ranging from 0.75 mg to 300 mg, and a further 47 healthy participants have received multiple oral doses ranging from 6 mg to 300 mg once-daily for 2 weeks. RG7774 was safe and well tolerated at all investigated doses. In Part 4 (CYP induction DDI) of the amended EIH study one SAE (asymptomatic, abnormal T-wave morphology with tachycardia) was reported (see Section 2.3). This occurred at the highest tested dose in Phase I of 300 mg of RG7774 administered once-daily for 2 weeks.

The dose selection for BP41321 was based in the results of study BP40387, as well as in several criteria, including preclinical information, CB2 receptor Target Engagement (CB2R-TE) and LPS assay:

- Data obtained in preclinical animal models suggest that the predicted pharmacological active dose range in human lies between doses of 0.22 and 42 mg per day. Assuming good translatability of this data to the clinic, the two selected doses of 30 mg and 200 mg will have pharmacological effects.
- [redacted]

[redacted]

- [redacted]

Further details are provided in the IB (including for Table 4).

Table 4 Estimated Margins of Safety for Phase II Dose

	Mean $C_{max,ss}$ (ng/mL) M/F	**Mean $AUC_{tau,ss}$ (h.ng/mL) M/F**
26-week Rat Study (GLP) NOAEL 300 mg/kg (M), 60 mg/kg (F)	22,400/27,000	189,000/193,000
39-week Cynomolgus Monkey Study (GLP) NOAEL 300 mg/kg (M/F)	7,850/8,020	82,500/103,000
Predicted Exposure in Humans at 30 mg	352	3,780
Predicted Exposure in Humans at 200 mg	2,150	24,000
Exposure Multiples (30 mg) * Rat Cyno	> 64 > 22	50 > 21
Exposure Multiples (200 mg) * Rat Cyno	> 10 > 3	> 7 > 3

* Exposure multiples calculated based on lowest NOAEL exposure

4.4 END OF STUDY DEFINITION

The end of study is defined as last visit of the last participant. The last participant last observation (LPLO) is expected to occur 48 weeks after the last participant is enrolled.

Participants are considered to have completed the study if they have completed all the assessments as required in this protocol.

5. STUDY POPULATION

Participants of this study are adult patients with DM type 1 or type 2, with treatment-naïve moderately severe to severe NPDR, good vision, with or without DME who are not

expected to require DME treatment for the duration of the study, fulfill all inclusion criteria and do not meet any exclusion criteria.

Patients who failed screening due to inclusion/exclusion criteria in the previous versions of the protocol that have been changed in the current version (e.g., HbA1c, serology) can be rescreened (see Section 5.4).

Only one eye will be selected as the study eye. If both eyes are eligible, the eye with DRSS 53 will be the study eye. If both eyes are eligible and have equal DRSS, the right eye will be defined as the study eye.

The study population rationale is provided in Section 4.2.1.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to International *Council for Harmonisation* (ICH) and local regulations.

Age / Gender

2. Male and female patients of at least 18 years of age.

Ocular Criteria for study eye:

3. Patients with treatment-naïve, moderately severe to severe NPDR defined as ETDRS DRSS 47 or 53. NPDR will be evaluated at the site based on e.g. the 4:2:1 rule evident on clinical examination and on digital imaging. Confirmation of DRSS 47 or 53 by the central reading center is required. *Note: One rescreening for this criterion is permitted for participants who score DRSS 43 at the screening visit. Rescreening should be scheduled at least 16 weeks (approximately 4 months) after the initial screening visit.*
4. Patients are eligible with and without DME in either eye, defined as the presence of signs in the macula such as swelling, leakage, exudates, cystoid changes and fluid. In addition, Central Subfield Thickness (CST) on SD-OCT needs to be ≥ 300µm to confirm diagnosis of DME. The presence of DME will be confirmed at screening by the central reading center.
5. If present, DME has to be treatment-naïve and not expected to require treatment during the duration of the study in the opinion of the investigator at screening and Day 1.

6. BCVA score at screening of at least 70 letters in study eyes without DME and at least 75 letters in case DME is present, using ETDRS visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/40 or better - or 20/32 or better).
7. Clear ocular media and adequate pupillary dilation to allow acquisition of good quality retinal images.

General Criteria:

8. Diagnosis of DM type 1 or type 2, as defined by the World Health Organization and/or American Diabetes Association, and:

   (i) Current regular use of insulin or other injectable drugs for the treatment of DM

   and/or

   (ii) Current regular use of oral anti-hyperglycemic agents for the treatment of DM
9. HbA1c $\leq 12\%$.
10. Allowed existing medication regimens for DM and associated conditions should be stable for at least 6 weeks before screening, with the intent to remain stable throughout the study. One rescreening for this criterion is permitted.
11. Patient is willing to refrain from non-topical cannabinoid (CBD) use (e.g., over-the-counter [OTC] CBD oil) for the entire duration of the study.

Sex and Contraception/Barrier Requirements:

12. Male and/or female participants

    Pregnancy of a female participant and fathering of a child by a male participant should be avoided during participation in this study. The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or 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) Female Participants

A female is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Women of non-childbearing potential (WONCBP), as defined in Appendix 5.
- Women of childbearing potential (WOCBP), who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use of two contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 4 weeks after the final dose of RG7774 or placebo.

    Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion/ ligation, male sterilization, established proper use of

hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices (see Appendix 5). Hormonal contraceptive methods must be supplemented by a barrier method. Additionally see Section 6.5.1.

– Have a negative pregnancy test (urine) at screening.

b) Male Participants

During the treatment period and for at least 90 days after the final dose of study treatment, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use barrier contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with a partner who is a WOCBP, as defined in Section 1 of Appendix 5.

  With pregnant female partner, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
- Refrain from donating *unwashed* sperm.

Other:

13. In the investigator's opinion, the subject is deemed appropriate for participation in the study, capable of following the study schedule of assessments and complying with the study restrictions and participation in the study or discontinuation of prohibited medication will not pose undue risks to the participant.

5.2 EXCLUSION CRITERIA

Participants are not eligible if any of the following criteria apply:

Ocular criteria for study eye:

1. Prior treatment for DR or other retinal diseases with *any* approved therapy, including but not limited to intravitreal steroids, intravitreal anti-VEGF, light therapy, *periocular pharmacological intervention,* and laser (e.g., focal, grid, micropulse, or pan-retinal).

   Note: Focal laser in the retinal periphery due to other reasons than DR (e.g., due to retinal hole or tear) at least *12 weeks* prior to screening is permitted. One rescreening for this criterion is permitted.

2. Intraocular surgery less than *12 weeks* prior to screening. One rescreening for this criterion is permitted.
3. Aphakia or implantation of intraocular lens outside of the capsular bag.
4. History of vitreoretinal surgery.
5. Uncontrolled glaucoma (e.g., visual field loss or defined as intraocular pressure [IOP] ≥ 25 mmHg despite treatment with anti-glaucoma medication). One rescreening for this criterion is permitted.

6. Amblyopia.
7. Any history of idiopathic or immune-mediated uveitis in either eye.
8. Any concurrent intraocular condition (e.g., age-related macular degeneration [AMD], retinal vein occlusion [RVO], retinal detachment, dense cataract, epiretinal membrane with traction, or vitreomacular traction, etc.) that in the opinion of the Investigator could reduce the potential for improvement, require medical surgical intervention or may confound the visual and functional assessment and interpretation of study results.
9. *Criteria for participation in previous ocular clinical trials for the study eye:*
    - *Participation in a clinical trial for an ocular disease involving an investigational device (e.g., implant, laser), gene therapy, or cell-based therapy.*
    - *Participation in a clinical trial for a retinal disease with pharmacological intervention receiving active investigational treatment.*
    - *Participation in a clinical trial for ocular non-retinal diseases with pharmacological intervention receiving active investigational treatment within 12 weeks or 5 half-lives (whichever is longer) prior to screening. One rescreening for this criterion is permitted.*

Ocular criteria for non-study eye:

10. *Criteria for participation in previous ocular clinical trials for the non-study eye:*
    - *Participation in a clinical trial for an ocular disease involving an investigational device, gene therapy, or cell-based therapy. Note: Laser treatment is permitted.*
    - *Participation in a clinical trial for ocular diseases with pharmacological intervention receiving active investigational treatment within 2 weeks or 5 half-lives (whichever is longer) prior to screening. One rescreening for this criterion is permitted.*

Concurrent ocular conditions in either eye:

11. Any active ocular infection. One rescreening for this criterion is permitted.
12. Any active intraocular inflammation. One rescreening for this criterion is permitted.

General Criteria:

13. Previous systemic use of anti-VEGF drugs within *24 weeks* prior to screening. One rescreening for this criterion is permitted.
14. Complications of DM such as end-stage renal disease or liver disease.
15. Currently untreated DM or previously untreated patients who initiated oral or injectable anti-diabetic medication within *12 weeks* prior to screening. One rescreening for this criterion is permitted.
16. Uncontrolled BP (defined as systolic >180 mmHg and/or diastolic >100 mmHg while patient at rest). If a patient's initial reading exceeds these values, a second reading may be taken either 30 or more minutes later on the same day, or on another day

during the screening period. If the BP is controlled by antihypertensive medication, the patient should be taking the same medication continuously for at least 6 weeks prior to screening. One rescreening for this criterion is permitted.

17. Confirmed (e.g., 2 consecutive measurements) clinically significant abnormality on ECG at screening. That includes but is not limited to QTcF > 450 ms for male participants and QTcF > 470 ms for female participants, absence of dominating sinus rhythm, AV-block II or III. Additional examples of clinically significant abnormalities detected by ECG or otherwise related to abnormal cardiac function are cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death, and atrial fibrillation.
18. History of coagulopathies, bleeding disorders or blood dyscrasias.
19. History of concurrent cardio-vascular disease not considered well controlled by the Investigator.
20. Risk of suicidal behavior in the opinion of the Investigator or as evidenced by a "yes" to questions 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) taken at screening, or any suicide attempt in the last 5 years.
21. Positive serology results for HIV-1 *and* HIV-2. *Positive results for hepatitis B virus (HBV) and hepatitis C virus (HCV) are exclusionary only if the disease is confirmed to be active and/ or the patient is receiving treatment.*
22. Any major illness or major surgical procedure within *4 weeks* before screening. One rescreening for this criterion is permitted.
23. History of or currently active other diseases, viral and/or bacterial infections, metabolic dysfunction, physical examination finding, malignancies not considered cured, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated the use of the investigational medicinal drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator.

    Note: *Participants with symptoms or signs of acute or long SARS-CoV-2 infection or asymptomatic disease (positive test without symptoms) within 30 days of screening will be excluded from the study. One rescreening for this criterion is permitted.*
24. Known hypersensitivity to any of the excipients of the drug used, fluorescein dye or dilating eye drops.
25. Alcohol and/or substance abuse/dependence during the last 12 months*, assessed by the investigator considering the results of the tests and the medical history, in consultation with the Sponsor, if required*. One rescreening for this criterion is permitted.
26. Use of non-topical CBD (including OTC CBD oil) within *12 weeks* prior to screening. One rescreening for this criterion is permitted.

27. Use of prohibited medications within 2 weeks prior to screening, or 5 half-lives (whichever is longer) as listed in Section 6.5.2. One rescreening for this criterion is permitted.
28. Use of systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the $24\text{-}week$ period prior to screening or likely need to be used. One rescreening for this criterion is permitted.
29. Participation in a clinical study involving an investigational $medicinal$ product or device with exit from that study
    - within 60 days prior to screening, or
    - within less than 5 half-lives between last exposure to study treatment in the previous study and screening for the present study

    (whichever is longer). One rescreening for this criterion is permitted.
30. Blood donation or loss of blood $>$ 500 mL within $12\ weeks$ prior to screening. One rescreening for this criterion is permitted.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

In vitro data and clinical data suggest that RG7774 is metabolized predominantly by CYP3A and to a minor extent by CYP2C19 and thus there is a potential for drug-drug interaction with any food product that moderately or strongly inhibits or induces these enzymes. Therefore, the following food products are prohibited:

- Any nutrients known to modulate CYP3A activity (e.g., grapefruit, grapefruit juice, Seville orange) within 2 weeks prior to first study drug administration and up to follow-up
- Any nutrients known to modulate CYP2C19 activity (e.g., pungent ginger) within 2 weeks prior to first study drug administration and up to follow-up

The above list of food products is not necessarily comprehensive. The investigator should contact the Medical Monitor if questions arise regarding food products not listed above.

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.

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

Re-screening will be allowed based on eligibility criteria as specified in Sections 5.1 and 5.2. If participants meet criteria upon re-screening, they will receive a new screening

number and will be treated as a new participant. For re-screenings allowed per inclusion/exclusion criteria there is no need to repeat other assessments as long as these were performed within 28 days prior to randomization. A maximum of two re-screenings per participant will be allowed.

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

In addition, re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days after the start of screening period because of an administrative reason. In order to re-screen such a participant, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated. In this case, participants will receive a new screening number and will be treated as a new participant.

A new screening may be performed for those patients who failed screening due to inclusion/ exclusion criteria in the previous versions of the protocol that have been changed in the current version (e.g., HbA1c, serology) (see Sections 5.1 and 5.2). These patients will receive a new screening number and will need to undergo the full screening assessments.

5.5 RECRUITMENT PROCEDURES

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

All screening and pretreatment assessments must be completed and reviewed to confirm that participants meet all eligibility criteria, including Central Reading Center confirmation of eligibility for a predefined set of imaging criteria, and defined list of Day 1 assessments. 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 are willing to participate in the study and have given informed consent will undergo a thorough screening examination within 28 days prior to study treatment administration. The list of screening procedures is outlined in the SoA (see Section 1.3).

6. TREATMENTS

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

All investigational medicinal products (IMPs) required for completion of this study (RG7774 and placebo) will be provided by the Sponsor. Approved anti-VEGF, and/ or steroids (in cases where rescue therapy is needed, see Section 6.5.3) are considered non-investigational medicinal products (NIMPs).

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

6.1 TREATMENTS ADMINISTERED

The first study treatment will be self-administered on the same day as randomization. The administration of the first study treatment will happen only after eligibility has been confirmed at Day 1, based on review of applicable inclusion/ exclusion criteria (see Section 5). For confirmation of some of these criteria an ophthalmological examination with dilation may be required. Please refer to the Study Procedures Manual for further details.

The participants are required to take the study treatment QD at approximate the same time of the day (preferably with breakfast) with the exception of the days when site visits are scheduled. On days of site visits the participants should take their treatment at the clinic as additional PK samples at specific timepoints may be taken (see Section 1.3).

Table 5 summarizes the treatments administered.

Table 5 Summary of Treatments Administered

Study Treatment Name:	RG7774[1]	Placebo
IMP and NIMP	IMP	IMP
Dose Formulation:	film-coated tablet	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s):	30 mg or 100 mg	(NA)
Dose:	30 mg or 200 mg	(NA)
Route of Administration:	oral	oral
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	RG7774 will be provided in high-density polyethylene (HDPE) bottles. Each HDPE bottle will be labeled as required per country requirement.	Placebo will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.

[1] RG7774 is also called RO6868847.

All permitted rescue therapies as per Section 6.5.1 are considered NIMP and will be administered at the discretion of the investigators.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the IB and Pharmacy Manual for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study treatment packaging will be overseen by the Sponsor clinical trial 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 treatment will be in accordance with Sponsor standard and local regulations.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

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 randomization/treatment assignment schedule and the Pharmacy Manual.

The Investigator or delegate must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants randomized in the study may receive study treatment and only authorized site staff may supply study treatment. All study treatments 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 site staff.

The Investigator 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.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.2.1 Assessments to be Completed by Participant at Home

Accountability and participant compliance will be assessed by maintaining adequate study treatment dispensing records. Participants will be asked to return all used and unused drug supply containers at each mandatory site visit and at the end of treatment as a measure of compliance. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

6.3.1 Method of Treatment Assignment

After the screening visit and initial assessment of eligibility, images of both eyes will be forwarded as soon as possible to the Central Reading Center for those participants deemed eligible (eligibility for safety labs, ECG, and pregnancy test, where appropriate, might be pending). The Central Reading Center will assess the imaging data submitted and confirm eligibility based on the described criteria (see Section 5.1).

On Day 1 prior to randomization, all participants' eligibility requirements are reviewed, and eligibility criteria (See Sections 5.1 and 5.2) are re-assessed by the Investigator.

Participants will be enrolled and randomized if they meet all screening and Day 1 eligibility criteria. For each participant, if one eye does not meet eligibility criteria, then the second eye may be evaluated within the initial screening period *(see Section 5.4)*.

Once all eligibility criteria have been confirmed on Day 1, the site personnel will contact the Interactive Voice/Web Response System (IxRS) for assignment of a participant identification number (a separate number from the screening number). All participants will be centrally assigned to randomized study treatment using an IxRS. Before the study is initiated, the telephone number and call-in directions and/or the log in information & directions for the IxRS will be provided to each site. Study treatment will be dispensed at the study visits summarized in SoA. Returned study treatment should not be re-dispensed to the participants.

6.3.2 Masking

This is a double-masked study, i.e., the study participants, the Investigators, and all individuals at the investigative site and the Sponsor Study Management Team (SMT) will be masked. Participants will receive either an active or a size-matched placebo tablet or tablets. The number of tablets depends on the group that participants are randomized to. This strategy has been chosen to minimize the number of tablets administered to potentially multimedicated participants and to simplify dosing schedule.

If unmasking is necessary for participant management (e.g., in case the knowledge is needed for treatment of a SAE), the Investigator will be able to break the treatment code using IxRS. Treatment codes should not be broken except in emergency situations. The Investigator should document and provide an explanation for any premature unmasking (e.g., accidental unmasking, unmasking due to a SAE). The randomization list will be made available to the individual responsible for PK sample bioanalysis and the staff at bioanalytical laboratories, to statisticians or statistical programmers and any other person considered necessary by the Sponsor's study team to assist with the decision and support the IMC and SOC (see Section 4.1.3). Also, members of the IMC and SOC, as well as any individuals who provide relevant information to the IMC for review, will be unmasked. PK data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a secure area that is not accessible by any masked SMT member.

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAE (see Section 8.3.4 and Appendix 2) that are considered by the Investigator to be related to study treatment. Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment bottle label and on the Drug Accountability Record. This individual will also record the medication number received by each participant during the study.

For drug accountability and assessment of compliance by the site, participants are requested to bring back the bottles at every site visit.

In order to increase treatment compliance, the sites are encouraged to offer the participants the option to use a Patient Engagement Mobile Application (PEMA; see Appendix 1, Section 2.1.6). PEMA is an optional service that participants can use to remind them of activities or tasks relevant to the study such as when to take their study treatment or attend clinical site visits. The application also provides study information and any study related supportive instructions. Reminders are delivered to the

participants via push notifications to encourage them to continue their participation and comply with the study.

The study site will assess adherence of the participants to the treatment at every site visit and at every phone call, as specified in the provided script (see Study Procedures Manual). Whenever a participant is, under the opinion of the investigator, not expected to comply with the treatment, the investigator is requested to encourage the study participants and to monitor closely in future visits their adherence.

No diaries will be provided as part of this study.

6.5 CONCOMITANT THERAPY

Any medication or vaccine used by a participant from 30 days prior to screening until the safety follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency) in the Previous and Concomitant Medications eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All therapy and/or medication administered to manage AEs should be recorded on the treatment section of the Adverse Event eCRF.

6.5.1 Permitted Therapy

Participants should not change their existing stable treatment for DM and its consequences during the study, unless it is required for the treatment of an AE or as a result of potential DDI. Potential DDI arising from co-administration of other drugs have been investigated in healthy volunteers only. Therefore, changed or new concomitant medication in general should be limited to the medical need of the participant and the medical judgement of the investigator, in consultation with the Sponsor.

For all concomitant medication, therapeutic drug monitoring has to be done at the judgement of the investigator to the uses and administration requirements of the product/package insert.

The Investigator should be aware of the potential for DDI when prescribing concomitant medications which are inhibitors or inducers of CYP3A and/or CYP2C19, or are substrates of CYP3A, OCT2, MATE1, MATE2-K, P-gp, and/or BCRP and should carefully monitor the tolerability, safety and efficacy of the respective medication. The Sponsor has included two visits to monitor if there is a need to adjust the dose of warfarin, if applicable (see SoA in Section 1.3 and Section 8.10.2).

Due to the observed CYP3A enzyme induction of RG7774 at doses of 200 mg and 300 mg administered once-daily, caution should be exercised when co-administrating drugs predominantly metabolized by CYP3A and/or the CYP2C9 family, including oral contraceptives or hormonal replacement therapeutics. Therefore, female participants of childbearing potential taking hormonal contraceptives must supplement with a barrier method.

Therapies permitted for either eye in case of incidence or progression of DME/DR are:

- Laser (grid or focal) and/or approved anti-VEGF (except brolucizumab, if applicable), and/ or approved steroids in case of worsening DME which requires treatment for participants presenting with DME at baseline.
- Laser (grid or focal) and/or approved anti-VEGF (except brolucizumab, if applicable), and/ or approved steroids in case of incident DME requiring treatment
- Laser (pan-retinal), vitrectomy and/or approved anti-VEGF (except brolucizumab, if applicable) in case of incident PDR.

The administration of these permitted therapies will not automatically result in treatment discontinuation and participants should continue in the study as described in Section 7.

6.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Systemic medications known to be toxic to the lens, retina or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) are prohibited within $24\ weeks$ prior to baseline and during the study.

6.5.2.1 Systemic Medications Prohibited due to Effects Related to Cytochrome P450 Enzymes

- Strong inhibitors of CYP3A including, but not limited to, the following drugs: e.g., ketoconazole, itraconazole, ritonavir, voriconazole, clarithromycin.
- Moderate inhibitors of CYP3A including but not limited to the following drugs: e.g., erythromycin, ciprofloxacin, cimetidine.
- Strong and moderate inducers of CYP3A including but not limited to the following drugs: e.g. rifampicin, carbamazepine, phenytoin, St. John`s wort, bosentan and modafinil.
- Strong inhibitors of CYP2C19 including but not limited to the following drugs: e.g., fluconazole, fluoxetine, fluvoxamine, and ticlopidine.
- Strong and moderate inducers of CYP2C19 including but not limited to the following drugs: e.g., rifampicin, ritonavir, efavirenz, phenytoin, and enzalutamide.

The above list of medications is not comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be

safely administered with the study treatment. In addition, the investigator should contact the study team if questions arise regarding medications not listed above.

6.5.3 Rescue Medicine and Follow-Up

If participants during the course of the study were to develop any disease-related events:

(i) Worsening of DME (when DME present at baseline) requiring treatment at the discretion of the Investigator or if any of the following criteria applies, e.g.:

- Loss of ≥10 letters in BCVA as compared to baseline due to DME, or,
- Loss of ≥ 5 letters in BCVA as compared to previous visit due to DME, or,
- Increase in CST ≥ 100 μm as compared to previous visit due to DME.

(ii) Incident DME or PDR (not present at baseline) requiring treatment.

(iii) Anterior-Segment Neovascularization (ASNV).

then participants may receive rescue treatment for any eye at the Investigator's discretion with any of the permitted therapies outlined in Section 6.5.1. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. Treatment with RG7774 or placebo (as applicable) should continue.

In this situation, a reduced number of assessments will be performed for both eyes if the study eye receives rescue treatment.

If the eye that receives rescue treatment is the non-study eye, the non-study eye will undergo the reduced schedule of assessments, while the study eye will undergo the full schedule of assessments.

This schedule will continue for all remaining visits (until week 36 included; see Section 1.3 and Table 2). This strategy will enable collection of relevant data in participants being treated with the permitted therapies but with a reduced burden for the participants.

6.6 DOSE MODIFICATION

There are no significant safety findings from all nonclinical and clinical data available for the doses studied in this trial at the time of writing, suggesting that dose modifications of the IMP may not be required during the study (see Sections 2.3 and Section 2.2.2).

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RG7774 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

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 whenever possible.

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Participant withdrawal of consent at any time
- Participant non-compliant to study treatment
- Pregnancy
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.

Every effort should be made to obtain information regarding the reason why participants withdraw from study treatment, including cases of non-compliance with treatment administration. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

Participants who terminate study treatment prematurely for any reason will be asked to return to the clinic for a study completion/early termination visit (see Section 8.10.3) and may undergo follow-up assessments (see Section 8.10.4), unless the participant withdrew consent. Two different sets of assessments will be available to the participants depending on the date of discontinuation relative to the last site visit (see Section 1.3).

- If the discontinuation happens within 14 days after a site visit, fewer assessments will be performed. This will avoid the unnecessary repetition of assessments whose outcomes generally do not vary in such time window.
- If the early termination visit happens more than 14 days after a site visit a complete set of assessments needs to be performed.

Please refer to Section 8.10.2 for those participants taking warfarin.

For participants who require rescue medication due to disease-related events (see Section 6.5.3 and Section 8.3.7) that are considered natural disease progression by the

Investigator, the study treatment should not be discontinued. However, if the disease-related events are not considered natural progression of the disease and thus qualify as AEs, study treatment may be discontinued upon Investigator discretion or Sponsor decision. The occurrence and type of events leading to rescue medication must be recorded.

Please refer to SoA for further details (Section 1.3) for data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed.

Participants who discontinue study treatment prematurely will not be replaced.

7.1.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator or Sponsor), an interruption should be considered. Participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified in the opinion of the Investigator. Participants can resume treatment if this has been interrupted during less than 7 days. Treatment interruption is to be recorded in eCRF.

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.

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 for other reasons will not be replaced.

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 cannot be reached 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 time-points are summarized in the Schedules of Activities (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.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or Day 1 purposes provided the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

8.1.1 Efficacy Assessments to be Completed by Participant or Clinician at Site Visits

Efficacy and PD assessments will be performed as detailed in the SoA (see Section 1.3) and will include functional and imaging assessments. All ocular assessments will be performed in both eyes unless otherwise indicated in the SoA.

The Study Procedures Manual details the suggested sequence of assessments for time points with multiple assessments.

8.1.2 Ocular Assessments and Imaging

The ocular and imaging assessments performed in this study are described below. Independent of the objectives of the present protocol, ocular images can be used in support of research aiming at the development of analytical tools.

8.1.2.1 IOP Measurement

The method of IOP measurement (either Goldmann tonometry or Tonopen) used should be recorded in the source document and must remain the same throughout the study. IOP should occur prior or after pupil dilation, but should be consistent throughout the study and recorded. If IOP measurement is done with Goldmann tonometry any fluorescein should be carefully washed-out with saline prior to imaging assessment.

If IOP is ≥ 30 mmHg, IOP measurement should be repeated.

8.1.2.2 Best Corrected Visual Acuity

BCVA will be measured by a qualified VA examiner prior to dilating pupils. 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 examiner will perform the refraction and BCVA assessment according to the Study Procedures Manual. The BCVA examiner will be masked to the study treatment assignment as well as to the previous BCVA letter scores of a participant.

8.1.2.3 Low-Luminance Visual Acuity

BCVA under low luminescence (LLVA) will be measured prior to dilating pupils. LLVA will be measured *only in the study eye* by placing a 2.0-log-unit neutral density filter (Kodak Wratten 2.0 Neutral Density Filter) over the best correction for that eye and having the participant read the normally illuminated ETDRS chart (using the set of three Precision Vision™ or Lighthouse distance acuity charts [modified ETDRS Charts 1, 2, and R]). Instructions on how to perform the assessment are provided in the Study Procedures Manual.

The LLVA examiner will be masked to the study treatment assignment as well as to the previous LLVA letter scores of a participant.

8.1.2.4 Contrast Sensitivity

Contrast Sensitivity (CS) is assessed in two ways: Pelli-Robson and qCSF.

Pelli-Robson will be performed only in the study eye. Instructions on how to perform Pelli-Robson are provided in the Study Procedures Manual.

The qCSF will be performed twice at each visit as specified in the SoA (See Section 1.3), once for the study eye and once for binocular vision. The qCSF will be performed only in sites with capabilities to perform this assessment. *Instructions* for qCSF are provided in the qCSF Procedures Manual.

The CS assessment*(s)* will be performed by a trained and qualified examiner masked to study treatment assignment and to the previous CS data of a participant.

8.1.2.5 Visual Field*s (Optional)*

Visual fields will be assessed in the study eye only, using standard automated perimetry (SAP) by a trained and certified examiner masked to study treatment assignment and to the previous VF data of a participant. Visual field assessment will be performed *optionally*. Field setting, grid choice, assessment program as well as number of assessments on respective visit days (see Section 1.3) will be detailed in the VF manual of procedures. *The participants undergoing visual field assessments should complete the assessments at all visits as specified in the SoA (See Section 1.3).*

The VF manual of procedures will also define the reliability measures (e.g., fixation errors, false positive and negative results), the indicators of field function (Mean deviation [MD], e.g., foveal threshold) and the indicators of longitudinal changes (e.g., MD change from baseline).

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

Slit-lamp biomicroscopy will be performed during the study for each eye. Observations will be graded as normal or abnormal. Abnormal findings will be specified as not clinically significant or clinically significant. Abnormal findings (*clinically significant* and *not clinically significant*) will be described. The biomicroscopy examination will consist of the evaluation of anterior and posterior chambers (including grading scales for anterior chamber cells or flare and for vitreous haze/vitreous hemorrhage, as detailed in Appendix 6 and Appendix 7) and dilated binocular indirect high-magnification ophthalmoscopy).

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 Study Procedures Manual.

8.1.2.7 Fundus Photography

Seven-field stereo color fundus photography will be performed at the study sites by trained and Central Reading Center-certified personnel. It is mandatory that the same device is used for the entire duration of the study.

FP image specifications will be detailed in the Central Reading Center Manual.

8.1.2.8 Fundus Fluorescein Angiography

Seven-field FFA (30-degree field of view) or wide-field FFA (e.g., Optos, Spectralis) will be performed at all the study sites by trained and Central Reading Center-certified

personnel. Where both devices are available then wide-field FFA should be performed only. It is mandatory that the same device is used for the entire duration of the study.

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

8.1.2.9 Spectral Domain Optical Coherence Tomography

Imaging 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, Topcon, or Optovue are acceptable devices (see Central Reading Center Manual). It is mandatory that the same device is used for the entire duration of the study. Additional specifications on data capturing, reading and data storage will be provided in the Central Reading Center Manual.

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of ocular and systemic monitoring and recording AEs, including SAEs and adverse events of special interest (AESIs); protocol specified ocular clinical assessments and measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study. In addition, telephone interviews will be performed to assess for any clinically significant symptoms and/or new medication.

8.2.1 Ocular Examination

Ocular safety assessments include data obtained from functional tests such as BCVA, visual fields *(when available)* and IOP measurement, ophthalmic investigations using slit lamp and indirect ophthalmoscopy, and ocular imaging including fundus photographs, OCT and fluorescein angiography.

8.2.2 Physical Examinations

The physical examination should cover head and neck including lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems, and others, as applicable. Height, weight, and *body mass index* will also be measured and recorded (see Section 1.3). Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

The physical exam will not include pelvic, rectal or breast exams.

Any abnormality identified at baseline should be recorded on the Medical History eCRF.

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

8.2.3 Vital Signs

Body temperature (tympanic, oral, or non-contact methods), pulse rate, and systolic and diastolic BP will be assessed. BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm and the same device should be used for all BP measurements.

BP and pulse measurements should be preceded by at least 5 minutes 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 when scheduled at the same time-point. At the discretion of the Investigator, measurements can be repeated if the values are abnormal or borderline.

8.2.4 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each time-point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, with 1 to 5 minutes apart. The average of the three readings will be used to determine ECG intervals (i.e., PR (PQ), QRS, QT, QTcF and RR). Any clinically significant ECG abnormalities should be captured on the eCRF.

To minimize variability, it is important that participants be in a resting position for $\geq$ 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) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to 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 as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. ECGs will be analyzed at a central laboratory and will be electronically captured.

QTcF (Fridericia's correction) and RR will be calculated. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal. *The interpretation of the ECG results as normal or abnormal should be based on the revised report received by the central laboratory.*

The timings of assessments may be amended or the number of assessments increased during study conduct based on emerging data in order to allow for optimal characterization of the study treatment effect profile.

8.2.5 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must 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 Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. 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 the 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.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

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 lab results at screening is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility.

If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

8.2.6 Suicidal Risk Monitoring

Even though RG7774 is not considered to be central nervous system *(CNS)*-active due to its 10,000-fold greater affinity to CB2 receptors with respect to CB1 receptors*, the FDA strongly recommends that prospective suicidal ideation and behavior assessment is carried out in all clinical trials for all drugs that are pharmacologically similar to those with potential CNS activity*. A suicidal monitoring strategy has been implemented using the Columbia-Suicide Severity Rating Scale (C-SSRS). This is a clinical-rated tool used to assess the recent suicidality of a subject (C-SSRS screening to be used at screening) as well as any new instances of suicidality (C-SSRS since last visit, to be used at subsequent visits). The C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

Participants showing suicidal behavior may be discontinued from the study at the Investigator's discretion.

8.2.7 Medical History and Demographic Data

Medical history (general and ophthalmology) includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications or vaccines (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant regularly or within 30 days prior to the screening visit.

Demographic data will include age, sex, and self‑reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. AESIs are discussed in Sections 8.3.6.

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:
  - Other AEs
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
- Preexisting medical conditions
- Lack of efficacy or worsening of the condition 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). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of their relationship to study treatment, will be reported until 28 days after the final dose of study treatment.

Post-study treatment adverse events and serious adverse events: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (28 days after the final dose of study treatment).

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 AE information at all participant evaluation time−points.

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 trial-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, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE 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 suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a 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 and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see 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

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 90 days after the final dose of study treatment

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their female partner becomes pregnant during the study or within 90 days after the final dose of study treatment.

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.

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

8.3.6 Adverse Events of Special Interest

AESIs 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).

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 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.

- Serious complications of DM, including but not limited to, amputations, ulcers, and/or DM-related surgeries

- Sight-threatening AEs: an AE is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:
  - Causes a decrease of ≥ 30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour
  - Requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas or a medication) to prevent permanent loss of sight
  - Is associated with severe intraocular inflammation (i.e., endophthalmitis, Grade 4+ anterior chamber cells/flare; see Appendix 6 for intraocular grading scales).

All of the above listed sight-threatening AEs should be reported as SAEs (see Appendix 2), listing the underlying cause (if known) of the event as the primary event term.

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Natural progression of the disease may include development of DME, worsening of DME (if present at baseline), development of ASNV or development of PDR. These events are thus not considered AEs. However, it is upon the Investigator's opinion to determine if the above events are to be considered AEs. In this case they will be reported following the usual procedure (see Appendix 2 for further details on AE reporting).

8.3.8 Management of Specific Adverse Events

This section does not apply to study BP41321.

8.4 TREATMENT OF OVERDOSE

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 Section 5 and 5.2 of Appendix 2 for further details). For RG7774 no specific information regarding treatment of overdose is currently available.

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, no further RG7774 should be administered and 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 analysis within 24 hours from the date of the final dose of study treatment, 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.

For further information see the Investigator's Brochure.

8.5 PHARMACOKINETICS

Blood samples for pharmacokinetic determination of plasma concentrations of RG7774 (and its metabolite[s] as appropriate) will be collected as specified in the Schedule of Assessments Table.

The actual date and time of the PK blood sampling needs to be precisely entered into the corresponding eCRF section.

Plasma concentrations of RG7774 will be measured by a specific and validated LC-MS/MS method. Plasma concentrations of RG7774-derived metabolite(s) may be measured (as appropriate) for exploratory metabolite(s) quantification purposes, with the use of non-validated LC-MS/MS method(s). Any residual material from blood PK samples may be used for additional exploratory biomarker profiling, identification, assay development purposes, and assay validation or compound-related assays after the mentioned intended use. All PK samples will be destroyed at the latest 5 years after the final clinical study report (CSR). Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

Additional PK sampling at unscheduled visits is allowed at the discretion of the investigator for safety purposes (see Section 8.4).

Study treatment concentration information that may unmask the study, will not be reported to investigative sites or masked personnel until the study has been unmasked.

Any changes in the timing or addition of time-points for any planned study assessments must be documented and approved by the relevant study team member and then,

archived in the Sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1 Aqueous Humor Samples (Optional)

An optional aqueous humor sample will be collected from either eye receiving intravitreal rescue treatment with the therapies permitted in Section 6.5.1 and who provide additional consent to participate. Aqueous humor samples must not be collected from monocular participants. Where participants consent to aqueous humor sampling, all efforts should be made to collect a baseline aqueous humor sample prior to the administration of rescue treatment. Unscheduled sampling could be performed at other or additional planned visits at the discretion of the Investigator in agreement with the participant.

The aqueous humor sample (0.1 mL) should be collected by a qualified physician after all other assessments have been completed but before rescue therapy is provided as per Table 2 (Section 1.3), using an aseptic procedure and sterile field and according to local guidelines.

Determination of RG7774 (and its metabolite[s], as appropriate) concentration in aqueous humor for exploratory quantification purposes may be performed with the non-validated LC-MS/MS method(s). [redacted] identification, assay development purposes, and assay validation or compound-related assays after the mentioned intended use. These specimens will be destroyed no later than 5 years after the date of final CSR.

The informed consent form will contain a separate section that addresses the use of aqueous humor samples for optional exploratory biomarker research. A separate signature will be required to document a participant's agreement to allow this sample to be taken and used for exploratory research.

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8.7 PHARMACODYNAMICS AND BIOMARKER SAMPLES

The samples may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RG7774, identifying biomarkers useful for predicting and monitoring RG7774 safety, assessing pharmacodynamic effects of RG7774, and investigating mechanism of therapy resistance. Additional markers may be measured in the case that a strong scientific rationale develops.

[redacted]

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

Unless otherwise specified below, samples (including blood, slides, extracts, etc.) will be destroyed no later than 5 years, and for genetics/ genomics samples up to 15 years, after the date of final CSR. [redacted]

[redacted]

Details on processes for collection and shipment of these samples can be found in separate sample documentation.

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8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

This section does not apply to study BP41321.

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Screening and Pre-treatment Assessments

Written or electronic (eConsent) informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms 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.

At any study visit (including screening visit), each category of assessments (i.e., sample collection, imaging procedures, PROs, etc.) is recommended to be performed following the order specified in the SoA table (see Section 1.3).

Screening and pre-treatment assessments will be performed during 21 days, Day −28 to Day −7 prior to Day 1, unless otherwise specified, to allow for sufficient time to process samples and receive external eligibility reports.

8.10.2 Assessments during Treatment

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

All assessments must be performed as per SoA (see Section 1.3).

The Sponsor has included two visits to monitor if there is a need to adjust the dose of warfarin. These visits will take place 7 days after the first dose of the study treatment (on Day 7) and 7 days after the last dose of the study treatment (i.e. at around Week 37 for participants completing the treatment period and at individually determined time-points for participants discontinuing treatment or the study prematurely). The visits are required for all participants on warfarin and will include a blood test for clinical parameters of coagulation. The Investigator will communicate the results to the participant's regular diabetologist/ endocrinologist. All participants will be managed according to the best judgment of their treating physicians as informed by current local clinical practice guidelines and the best clinical evidence for patients with DR.

See also Sections 8.1 and 8.2 for further details.

8.10.3 Assessments at Study Treatment Completion / Early Termination Visit

Participants who complete the 36-week treatment phase will be asked to return to the clinic for two visits with fewer assessments compared to the regular visits:

- A safety follow-up visit, 28 (±7) days after the final dose of study treatment (week 40 visit),
- An efficacy visit, 84 (±7) days after the final dose of study treatment (week 48 visit).

Participants who discontinue from the study treatment phase early, will have an early termination visit and be asked to return to the clinic 28 (±7) days after the final dose of study treatment for a safety follow-up visit.

- if the early termination visit occurs within 14 days of the last site visit, the list of assessments to be performed will be reduced.
- If the early termination visit happens more than 14 days after a site visit a complete set of assessments needs to be performed.

See Section 1.3 (Table 2), and Sections 8.1 and 8.2 for further details.

8.10.4 Follow-Up Assessments

After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.10.5 Assessments at Unscheduled Visits

Please see Section 1.3 for activities that are required to be performed in case of an unscheduled visit. Assessments (e.g., for safety or for PK/PD sampling purpose) performed in case of an unscheduled visit(s) are at the discretion of the investigator. Participants will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, participants will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit. Assessments performed at unscheduled safety visits are at the discretion of the investigator. It is recommended to perform ocular assessments on both eyes.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Denoted by p_k the proportion of participants with ≥ 2 step improvement in ETDRS DRSS from baseline at Week 36 measured in the study eye in treatment group k (k = 0 for placebo and k = 1, 2, for low, and high dose, respectively), the hypotheses

$$p_0 = p_k, k = 1, 2,$$

will each be tested at the two-sided 10% level. Due to the exploratory dose finding nature of the study no adjustments for multiplicity will be made. Hypothesis testing will be performed using the framework of Generalized Estimating Equations (GEE), as it takes into account repeated measures within each participant and can provide unbiased effect estimates even if the correlation structure between measures is misspecified.

9.2 SAMPLE SIZE DETERMINATION

A total of 135 participants are expected to be randomized 1:1:1 to the three groups (45 participants per group). Based on Fisher's exact test, assuming the proportion of participants with ≥ 2 step improvement in the ETDRS DRSS to be 15% for placebo and 40% to 45% under active treatment, 40 participants completing the study per group provide between 74% and 88% power based on a 2-sided significance level of 0.1. Allowing for about 10% of the participants randomized to not complete the study and hence not have an assessment of the primary endpoint at week 36, a total of 135 participants (45 participants per group) was selected to obtain 120 completers. If the rate of participants not completing the study is larger than 10%, the sample size may be increased beyond 135 participants with the aim of achieving approximately 45 completers per group.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 6.

Table 6 Analysis Populations

Population	Description
Intent-to-treat	The Intent-to-Treat (ITT) population is defined as all participants who give informed consent, are randomized, and receive at least one dose of study treatment (active or placebo). For the ITT population, data will be analyzed according to the treatment participants were randomized to. The ITT population is the primary population of interest.
Safety	The Safety population is defined as all participants who give informed consent, receive at least one dose of study medication (active or placebo) and will be grouped according to the actual treatment received. The Safety population will be used for the analyses of all safety endpoints.
Efficacy	The ITT population will be used for the analyses of all efficacy endpoints.
Pharmacokinetic	All participants in the safety population who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. 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.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographics, baseline characteristics (including subject disposition and medical history) and all baseline laboratory values will be summarized descriptively by treatment using frequency tables and summary statistics providing means, medians, standard deviations, and extreme values.

Definition of baseline: Baseline for all efficacy and safety analyses is defined as the last non-missing value recorded prior to or on the first study drug administration.

9.4.2 Efficacy Analyses

For the primary and exploratory efficacy analyses, see Table 7.

All efficacy data will be summarized by randomized treatment group and visit for the ITT population.

Participants in whom any of the events (i) to (iii) described in Section 6.5.3 occur in either eye, or participants who require rescue treatment prior to the week 36 assessment will still be considered as completing participants and will enter the analysis as non-responders at the visit at which the event occurs as well as all subsequent visits.

The primary endpoint will be analyzed using GEE with a binomial distribution using a logit link function for odds ratios and unstructured covariance. In case of convergence issues, an alternative covariance structure will be used. The model will include categorical covariates for treatment group, visit, and visit by treatment group interaction term. Also the baseline stratification factors will be added. Least squares means on the probability scale for each treatment group with the corresponding 90% confidence intervals and odds ratios relative to the placebo group will be computed for each visit. Full details of the statistical analysis will be described in a separate document prior to any unmasking of the study.

In accordance with the ITT principle, assessments at all visits will be included in the analysis. This includes any assessments made at visits while the participant is on randomized study treatment as well as any assessments made at visits after randomized study treatment has been terminated.

If visits occur as described in Section 1.3, a response assessment at week 36 will be available for all participants. Despite best efforts, there may be missing response assessments at week 36 (e.g., for participants withdrawing consent or being lost to follow-up). *The statistical methodology to deal with missing data will be described in a separate technical document prior to any unmasking of the study.*

The proposed methodology is known to render unbiased effect estimates only under the restrictive missing completely at random assumption (Liang and Zeger, 1986). Therefore, if the amount of total missing data (across patients and visits) exceeds 10% of all expected data, sensitivity *analyses* will be carried out (Molenbergs and Verbeke, 2005).

Table 7 Efficacy Statistical Analysis Methods

Endpoints	Statistical Analysis Methods
Primary	
Proportion of participants with ≥ 2 step improvement in ETDRS DRSS from baseline at Week 36 measured in the study eye.	Generalized Estimating Equations (GEE) with a binomial distribution taking into account repeated measures within each participant.
Secondary	
Incidence of ASNV, new PDR, new DME, and pre-existing DME requiring intervention.	Descriptive summaries of the number, frequency and percentage of participants experiencing the types of events.
Change from baseline in BCVA at Week 36 in the study eye.	Analysis of variance model for longitudinal data taking into account repeated measures within each participant
Exploratory	
Proportion of participants with ≥ 2 step worsening in ETDRS DRSS from baseline at Week 36 measured in the study eye.	GEE with a binomial distribution taking into account repeated measures within each participant.
Proportion of participants with ≥ 3 step improvement in ETDRS DRSS from baseline measured in both eyes at post-baseline visits.	Analysis performed in subgroup of ITT population with bilateral disease. Modeling will be similar as for the primary endpoint.
Proportion of participants with ≥ 3 step worsening in ETDRS DRSS from baseline measured in both eyes at post-baseline visits.	Analysis performed in subgroup of ITT population with bilateral disease. Modeling will be similar as for the primary endpoint.
Proportion of participants with either a stable (± 1 step change), worsened (>1 step increase) or improved (<1 step decrease) DRSS between week 36 and week 48.	Modeling will be similar as for the primary endpoint.

Table 7 Efficacy Statistical Analysis Methods (cont.)

Change from baseline in participants with DME at baseline in: • BCVA (as measured on the ETDRS chart at a starting distance of 4 meters) at post-baseline visits. • Central subfield thickness on SD-OCT at post-baseline visits. Proportion of participants with absence of signs of DME and normalized CST over time	Analysis of variance model for longitudinal data taking into account repeated measures within each participant.
Change from baseline in Contrast Sensitivity at post-baseline visits in *the study eye (Pelli-Robson, qCSF) or in both eyes (qCSF).*	Analysis of variance model for longitudinal data taking into account repeated measures within each participant.
Change from baseline in LLVA at *Week 36* visit in *the study* eye.	Analysis of variance model for longitudinal data taking into account repeated measures within each participant.
Absolute change from baseline in mean threshold and in point-by-point Standard Automated Perimetry at post-baseline visits.	Analysis of variance model for longitudinal data taking into account repeated measures within each participant.
PK parameters of RG7774 (and its metabolite(s) as appropriate) in plasma and (if applicable) in optional aqueous humor.	Descriptive summaries of the PK parameters (e.g., C_{max}, AUC, etc.)
Change from baseline in blood levels of HbA1c.	Descriptive summaries by treatment group and visit
Performance of the advanced analytic tools	Analysis of the exploratory efficacy endpoints

9.4.3 Safety Analyses

All safety analyses will be based on the safety analysis population according to the treatment assigned at randomization. A summary of key safety analyses is provided in Table 8 below.

Table 8 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Ocular investigations and 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 listings with flagging of abnormal results. Summary and change from baseline in laboratory parameters of clinical significance will be provided.
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 by individual listings. In addition, tabular summaries will be used for raw values as well as changes from baseline.
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 in summary tables and listings.

9.4.4 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population. All pharmacokinetic parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) separately by group or cohorts.

A nonlinear mixed effects modeling approach will be used to analyze the sparse sampling dose-concentration-time data of RG7774 (and its metabolite(s) as appropriate) collected in this study. Those data collected may be pooled with data collected in previous phase I studies as appropriate to build the pharmacokinetic model. Population and individual primary pharmacokinetic parameters (e.g., apparent clearances and volumes) will be estimated and the influence of various covariates on these parameters will be investigated. Secondary PK parameters such as AUC and C_{max} will be derived from the individual post-hoc predictions. Graphical exploration of the relationship between RG7774 concentrations and DRSS, other selected clinical endpoints, biomarkers and safety endpoints may be performed. If indicated by such exploration, more formal analyses of the PK/PD relationship using non-linear mixed effects modelling method will be undertaken.

Details of the modelling analyses will be described in a Modelling and Simulation Analysis Plan. The results of this analysis will be reported in a separate document from the Clinical Study Report.

9.4.5 [redacted]

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9.5 INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim analyses for efficacy. The decision to conduct an optional interim efficacy analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by a Sponsor IMC and SOC; see Appendix 1, Section 3.3), the members of which are Sponsor study team, appropriate senior management personnel and external experts. Members of the IMC and individuals required to provide data analyses for IMC and SOC review will be unmasked at the treatment group level as well as the individual participant level, if required. Access to treatment assignment information will follow the Sponsor's standard procedures.

If warranted by masked safety data review, the IMC may also oversee unmasked safety information.

9.6 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study treatment administration and concomitant medication will be summarized and listed. The number of participants who were randomized, discontinued and completed the study will be summarized and listed.

10. REFERENCES

Aflibercept [Eylea®] USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf

Behl T, Kaur I, Kotwani A. Role of endocannabinoids in the progression of diabetic retinopathy. Diabetes Metab Res Rev. 2016;32:251-259.

Boyer DS. Treatment of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy with Intravitreal Aflibercept Injection: 52-Week Results from the Phase 3 PANORAMA Study. Invest. Ophthalmol Vis. Sci. 2019; 60(9):1731.

Brown DM, Schmidt-Erfurth U, Do DV et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 2015;122:2044-2052.

Campochiaro PA, Channa R, Berger BB, et al. Treatment of diabetic macular edema with a designed ankyrin repeat protein that binds vascular endothelial growth factor: a phase I/II study. Am J Ophthalmol 2013;155:697−704.

Early Treatment Diabetic Retinopathy Study (ETDRS) report number 12. Ophthalmology. 1991;98:823-833.

Fong DS, Aiello L, Gardner TW. Retinopathy in diabetes. Diabetes Care. 2004:27 (Suppl. 1): S84(7).

Gella L, Raman R, Pal SS. Contrast sensitivity and its determinants in people with diabetes. SN-DREAMS-II. Report No. 6. Eye (Lond). 2017;31:460-66.

Gruden G, Barutta F, Kunos G, et al. Role of endocannabinoid system in diabetes and diabetic complications. British Journal of Pharmacology. 2016;173: 1116-1127.

Hellgren KJ, Agardh E, Bengtsson B. Progression of early retinal dysfunction in diabetes over time: results of a long-term prospective clinical study. Diabetes. 2014;63:3104–3111 | DOI: 10.2337/db13-1628.

RO6868847 Investigator's Brochure.

Ip MS, Domalpally A, Hopkins JJ. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol. 2012 Sep;130(9):1145-52.

Ip MS, Domalpally A, Sun JK. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmology 2015;122:367-374.

Ip MS, Zhang J, Ehrlich JS. The Clinical Importance of Changes in Diabetic Retinopathy Severity Score. Ophthalmology. 2017 May;124(5):596-603.

Joltikov KA, de Castro VM, Davila JR, et al. Multidimensional Functional and Structural Evaluation Reveals Neuroretinal Impairment in Early Diabetic Retinopathy. Invest. Ophthalmol Vis. Sci. 2017; Sept;58: BIO277-BIO290.

Klein TW. Cannaboid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005; 5:400-11.

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.

Lee R, Wong TY, Sabanayagam C, et al. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye and Vision (2015) 2:17.

Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13-22.

Linnemann, B, Voigt W, Nobel W, et al. C-reactive protein is a strong independent predictor of death in type 2 diabetes: association with multiple facets of the metabolic syndrome. Exp Clin Endocrinol Diabetes. 2006;114(3): 127-134.

Maurya N, Velmurugan BK. Therapeutic application of cannabinoids. Chemico-Biological Interactions. 2018; 293: 77-88

Mesquida M, Drawnel F, Fauser S. The role of inflammation in diabetic eye disease. Semin Immunopathol. 2019; Jul;41(4):427-445.

Molenberghs G, Verbeke G. Simple methods, direct likelihood, and weighted generalized estimating equations. In: Molenberghs G, Verbeke G, editors. Models for Discrete Longitudinal Data. New York: Springer Series in Statistics. 2005; 489-509.

Nair P, Aiello LP, Gardner TW, et al. Report From the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop. Invest. Ophthalmol Vis. Sci. 2016;Oct 1;57(13):5127-5142.

Owsley C, McGwin G Jr, Scilley K, et al. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci. 2006;47(2):528–535.

Ranibizumab [Lucentis®] USPI
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125156s105lbl.pdf

Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al, for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237:185–222.

Semeraro F et al. Diabetic Retinopathy, a vascular and inflammatory diseases: Therapeutic implications. Diabetes Metab. 2019 Apr 18. pii: S1262-3636(19)30062-X (article in press).

Simó-Servat O, Simó R, Hernández C. Circulating Biomarkers of Diabetic Retinopathy: An Overview Based on Physiopathology. Journal of Diabetes Research. 2016; Article ID 5263798, 13 pages.

Soethoudt M, Grether U, Fingerle J, et al. Cannabinoid CB2 receptor ligand profiling reveals biased signalling and off-target activity. Nat Commun. 2017; 8:13958.

Sun JK, Wang P-W, Taylor S, et al, Durability of Diabetic Retinopathy Improvement with As-Needed Ranibizumab: open-label extension of RIDE and RISE studies. Ophthalmology 2019; 126:712-720.

Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 2010;376:517-23.

Willis JR, Chia Y, Morse LS, Rich WL, et al. Treatment patterns for diabetic macular edema in the United States: analysis of the IRIS® Registry (Intelligent Research in Sight) [abstract]. Presented at the Annual Meeting of the American Academy of Ophthalmology; New Orleans, LA. Nov 2017; 11–14.

Wong TW et al, Ophthalmology. 2018; 125(10):1608-1622.

Yao, Y, Li R, Du J, et al. Tumor necrosis factor-α and diabetic retinopathy: Review and meta-analysis. Clinica Chimica Acta. 2018;485 210-217.

Zoja C, Locatelli M, Corna D, et al. Therapy with a Selective Cannabinoid Receptor Type 2 Agonist Limits Albuminuria and Renal Injury in Mice with Type 2 Diabetic Nephropathy. Nephron. 2016;132(1):59-69.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as

- Appendix 1 (Regulatory, Ethical and Study Oversight Considerations),
- Appendix 2 (AE Definitions, Reporting) and
- Appendix 3 (Procedures of 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, and Vitreous Haze)
- Appendix 7 (Grading Scale for Vitreous Hemorrhage)

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 ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. 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 ICFs, any information to be given to the participant (e.g. advertisements, diaries etc), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any 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 adverse events (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 Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) 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 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/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.

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

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant. All signed and dated Consent Forms 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 28 days from the previous ICF signature date.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the 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 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 Consent Form 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 Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 trial 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 trial is closed. A participant's withdrawal from Study BP41321 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 BP41321. 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 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 the Sponsor's 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 Informed Consent Form (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 policy of the Sponsor 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 Roche, 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 Informed Consent Form. 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 Roche. 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., LPLO).

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 electronic CRF 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 eCRF.

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

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 eCRF 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. Clinical Outcome Assessment Data

2.1.2.2. Paper Clinical Outcome Assessment Data

Paper booklets will be used to capture COA data. The data from the questionnaires will be entered into the EDC system by site staff. All original forms on which participants records responses are source documentation as described in Section 2.1.3. of this Appendix.

2.1.3. 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, COAs (paper or eCOA), 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 trial.

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

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

2.1.4. Use of Computerized Systems

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

2.1.5. 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.

2.1.6. Patient Engagement Mobile Application

The Patient Engagement Mobile Application (PEMA) Smartphone app is an optional service that participants can opt-in to use to remind them of activities or tasks relevant to the study like when to take their study treatment or attend clinical site visits. The app also provides supportive guides to help volunteers be aware of visit procedures, study information and any study related supportive instructions. Reminders are delivered to the participants via push notifications to encourage them to continue their participation and comply with the study. The features of PEMA include the following modules:

- Information: targeted important and useful information related to study that can be accessed by participants any time throughout the duration of the study.
- Tasks: inform study participants about what they need to do via a daily to do list. Once a task has been completed, participants can mark it as done.
- Schedule: is predefined based on planned site visits according to the study schedule of assessments. Reminders related to upcoming visits are sent to participants to plan for visits and upcoming tasks.
- Achievements: are awarded to participants for completing assigned tasks or activities.
- Contacts: participants can enter site contacts details for primary investigator, study coordinator etc.

The app is available for download to smartphone devices that support iOS or Android. The app will contain study-specific information only once activated by a participant. The study coordinator will provide the participant with a secure activation code, which they can use to activate the app upon their first use. The App does not collect any participant identifiable information or clinical data. This app is intended for informational purposes only. It is not a substitute for professional medical advice. Participants should contact the study site Investigator or coordinator with any medical questions or concerns.

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.

The Sponsor shall also submit an Annual Safety Report once a year to the IEC and CAs 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

A description of this clinical trial will be available at http://www.ClinicalTrials.gov.

2.3.4. 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

3.3. INTERNAL MONITORING COMMITTEE (IMC) AND SCIENTIFIC OVERSIGHT COMMITTEE (SOC)

The IMC consists of a selected subset of the Sponsor's representatives including Statistician, Safety Representative and Clinical Science Representative. The SOC includes independent external experts with relevant experience in the field. The IMC Chair may approve other individuals to get access to the unmasked reports or unmasked participant level data if this is required for the IMC and SOC to make an assessment. Additional the Sponsor's representatives might be unmasked to produce/process the unmasked listing/data to be reviewed by the IMC and SOC. The IMC and SOC will review safety data on an ad-hoc basis. The SOC will function as a consultative body to the Sponsor, providing individual expert opinions. The Sponsor retains all decision making authority for this study. More details of the role and remit of the IMC and SOC will be described in a separate IMC and SOC agreement. Access to treatment assignment information will follow the Sponsor's standard procedures.

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 AEs 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 ICH guideline for Good Clinical Practice, an **adverse event** (AE) is any untoward medical occurrence in a participant or clinical investigation subject 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, X−ray) 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 pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though *they* may have been present before the start of the study.
- AEs 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 biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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 pre-existing 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 pre-existing 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**.
- Is sight-threatening: an AE is considered to be sight-threatening and should be reported expeditiously if it meets one or more of the following criteria:

- Causes a decrease of ≥ 30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.
- Requires surgical or medical intervention (i.e., conventional surgery, vitrectomy, vitreous tap or biopsy with IVT injection of anti-infective treatments, or laser or retinal cryopexy with gas or a medication) to prevent permanent loss of sight
- Is associated with severe intraocular inflammation (i.e., endophthalmitis, Grade 4+ anterior chamber cells/flare; see Appendix 6 for intraocular grading scales).

- **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, or development of drug dependency or drug abuse.

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 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 sponsor. 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 sponsor.

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 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 pre-defined grading 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. 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).

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

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, where applicable.
- 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.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 sponsor 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.

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 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:

- SAEs
- AESIs
- Pregnancies (see Section 8.3.5)

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 SAEs to the local Health Authority and IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 and AESIs (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1; from Day 1 to Week 36) and including the safety follow-up period of 4 weeks (from Week 36 to Week 40), 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 electronic data capture (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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 Off-Treatment Observational Period and Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other SAEs occurring during the observational off-treatment period after the end of the AE reporting period (study-treatment period + 28 days after final dose of study treatment) or after the study ends, the event should be reported if it is believed to be related to prior study treatment. The report must be 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 OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

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. 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 RG7774 and placebo, 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.
- Intentional overdose: Enter the AE term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the AE term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the AE term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the AE term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the AE term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with RG7774 and placebo 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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 AESIs 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 document for RG7774:

- Investigator's Brochure

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 AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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 AE 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 BP), 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 ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

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

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 an SAE or an AESI (see Section 8.3.6).

7. DEATHS

All deaths that occur during the protocol-specified AE 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. LACK OF EFFICACY OR WORSENING OF DIABETIC RETINOPATHY

Medical occurrences or symptoms of deterioration that are anticipated as part of diabetic retinopathy 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 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 retinopathy”).

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.

11. PATIENT-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY PATIENT)

Adverse event reports will not be derived from patient-reported outcome (PRO) data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for AEs.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory. For the local laboratory results, the results must be captured in source documentation and entered into the eCRF. Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be captured in source documentation and entered as a comment into the eCRF.

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

All study-required laboratory assessments will be performed by a central laboratory.

Laboratory Assessments	Parameters
Hematology	• Leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
Blood Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, ALT, AST, ALP, BUN, CRP, CPK, HbA1c.
Coagulation	• INR, aPTT, PT.
Viral Serology	• HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), *hepatitis B DNA* hepatitis C virus (HCV) antibody*, hepatitis C RNA*.
Lipids	• Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.
Thyroid Hormones	• Thyroid stimulating hormone (TSH)
Hormones	• Follicle-stimulating hormone (FSH; in females).
Pregnancy Test	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
Urinalysis	• Specific gravity • Albumin concentration, creatinine concentration, and ratio (albumin/creatinine). • Dipstick: pH, glucose, protein, blood, ketones, albumin. • If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the 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 (RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Other Screening Tests	• Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

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 lab tests.

In this scenario, the Sponsor's standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Sponsor's standard reference range. Certain laboratory parameters will be transformed to Sponsor'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 Sponsor's 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 Sponsor 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 Guidance and Collection of Pregnancy Information

1. DEFINITIONS

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

A woman is considered fertile following menarche and until becoming post-menopausal 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 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 highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH 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 (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ ligation **Vasectomized partner** 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 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.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3).

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

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RG7774.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **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 appropriate 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 AE or SAE, and should not be recorded on the Adverse Event 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.

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 embryo-fetal toxicity should also 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; 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 or female partner of a male 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

Reference:

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.

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

Grading Scale for Vitreous Haze

Score	Description
0	No evident vitreal 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

Reference:

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

Appendix 7
Grading Scale for Vitreous Hemorrhage

Grading Scale for Vitreous Hemorrhage

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

Reference:

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