Cover Page for Protocol

Sponsor name:	Exonate Ltd.
NCT number	NCT04565756
Sponsor trial ID:	PQ-110-001
Official title of study:	A Randomized, Double-Masked Vehicle-Controlled, Multiple Dose, Dose Escalation Study To Evaluate The Safety And Tolerability Of Exn407 In Subjects With Center Involved Diabetic Macular Edema Secondary To Diabetes Mellitus.
Document date:	28 January 2022

A RANDOMIZED, DOUBLE-MASKED VEHICLE-CONTROLLED, MULTIPLE DOSE, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF EXN407 IN SUBJECTS WITH CENTER INVOLVED DIABETIC MACULAR EDEMA SECONDARY TO DIABETES MELLITUS.

Protocol Number: PQ-110-001

Authors: [redacted]
Development Phase: Phase Ib/II
Document Version: Protocol Version 4.0 dated 28 January 2022
Number of Pages: 100

PROTOCOL AUTHORIZATION

Title: A Randomized, Double-Masked Vehicle-Controlled, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of EXN407 in subjects with Center Involved Diabetic Macular Edema secondary to Diabetes Mellitus.

As an Exonate Ltd. ("Sponsor") representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

[redacted]

28 January, 2022.

Date

Medical Monitor, Exonate Ltd.

INVESTIGATOR'S AGREEMENT

Title: A Randomized, Double-Masked Vehicle-Controlled, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of EXN407 in subjects with Center Involved Diabetic Macular Edema secondary to Diabetes Mellitus.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not commence without the prior written approval of a properly constituted Human Research Ethics Committee/Independent Ethics Committee (hereafter referred to as an IEC) or required Health Authority Approval. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC, except where necessary to avert an immediate hazard to the subjects.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The conduct of the study will be in accordance with the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2), annotated with any applicable country specific amendments.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

_____

Investigational Site

_____

Printed name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address And Telephone Number
[redacted] Medical Monitor (MM) / 24-hour Emergency Contact	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Exonate Ltd.

Name of Investigational Product:
EXN407

Name of Active Ingredient:
[redacted]

Protocol Number:
PQ-110-001

Title of Study:
A Randomized, Double-Masked Vehicle-Controlled, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of EXN407 in subjects with Center Involved Diabetic Macular Edema secondary to Diabetes Mellitus.

Study Center(s):
The trial will be conducted at up to 17 study centers globally.

Studied Period (Years):	**Phase of Development:**
Estimated date first subject enrolled: Oct 2020 Estimated date last subject completed: Aug 2022	Phase Ib/II

Objectives:

Primary:

- To evaluate the ocular safety and tolerability of EXN407 ophthalmic solution in subjects with diabetic macular edema (DME) secondary to diabetes mellitus

Secondary:

- *Safety:* To evaluate the systemic safety and tolerability of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus
- *Safety:* To evaluate changes in ocular functional and structural measures with the use of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus
- *Pharmacokinetics (PK):* To evaluate the systemic pharmacokinetics of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus

[redacted]

Outcome Measures:

Safety

Primary:

- Frequency and severity of ocular adverse events (AEs) in the treatment and contralateral eyes

Secondary:

- Frequency and severity of non-ocular AEs
- Changes from baseline in safety parameters, including vital sign measurements, physical examination findings, electrocardiogram (ECG), and laboratory parameters
- Changes from baseline in ophthalmic examination findings, including ophthalmoscopy

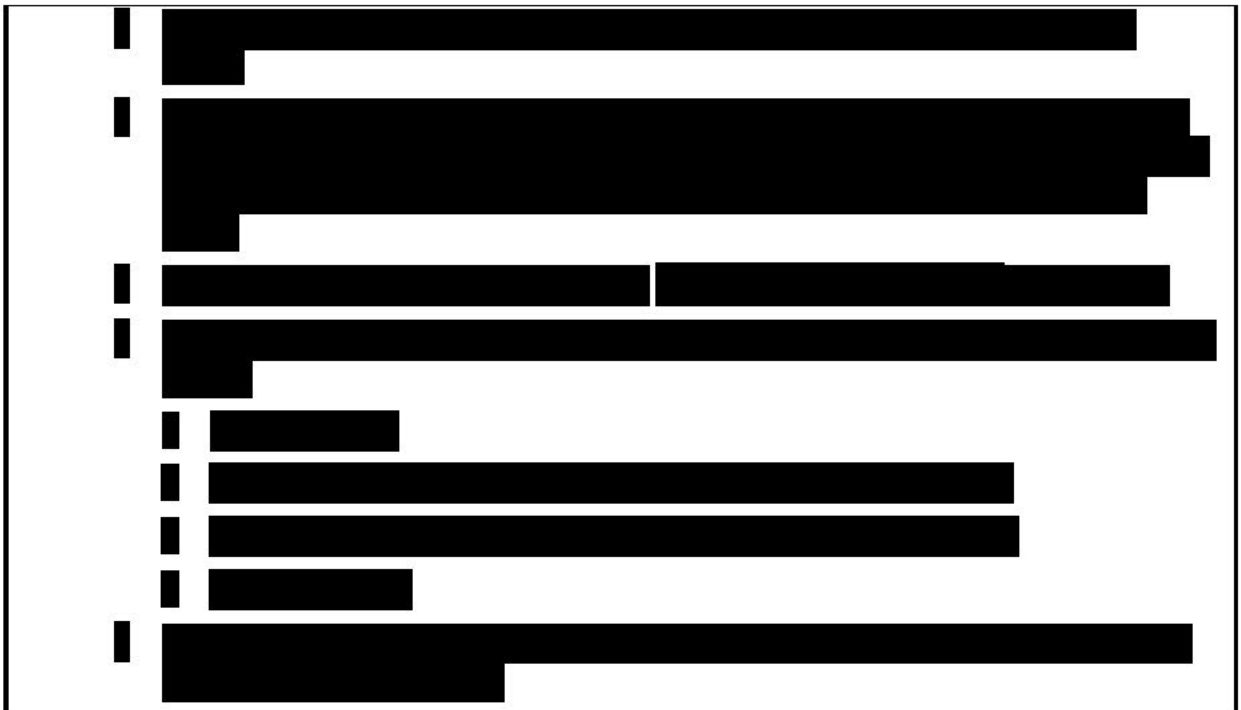
Safety

- Change from baseline in Center-Subfield Macula Edema (center-subfield measure)
- Change from baseline in macular fluid volume
- Change from baseline in best corrected visual acuity (BCVA) using the early treatment diabetic retinopathy study (ETDRS) visual acuity scale
- Change from baseline in fluorescein fundus angiography (FFA)
- Change from baseline in corneal thickness based on pachymetry assessed at a consistent time of day
- Change from baseline in corneal endothelial cell count (dose expansion cohort)

Pharmacokinetics

- Characterize the PK profile of EXN407 in plasma (dose escalation and dose expansion cohort[s])

[redacted]



Methodology:

General

This is a first in human (FIH), Phase Ib/II study of EXN407. It is a randomized, double-masked, vehicle-controlled, multiple dose, dose-escalating study to evaluate the safety and tolerability of EXN407 in subjects with center involved DME, with CMT between 280-420 µm and BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12). For brevity these criteria may also be written as "better than or equal to a 69 ETDRS score" in the study eye, which is considered secondary to diabetes mellitus.

The Screening period is from 28 to 3 days prior to randomization and the start of study treatment (i.e., from study days -28 to -3). Subjects that meet all eligibility criteria as assessed by the evaluating Investigator at Screening will enter a run-in period (from post-screening to Day -1) where the subject (or subject's partner as applicable) will administer Systane Ultra UD eye drops twice per day (BID) using Systane Ultra unit-dose (UD) droppers. The run-in period serves to familiarize and train subjects in topical administration via eye dropper. Please refer to Section 12.2 for more details on the run-in period.

Selection of Study Eye

EXN407 or vehicle-control solution will be administered unilaterally to the study eye only. The Investigator should identify the eye in which evident center involved DME is present with a CMT between 280-420 µm as determined by SD-OCT and all other inclusion/exclusion criteria are met. All SD-OCT assessments for a subject should be taken with the same make and model of equipment throughout the duration of the study.

If both eyes qualify on the basis of evident DME with CMT of between 280-420 µm, and other inclusion/exclusion criteria, then the Investigator should choose the eye with the worse (greater) CMT as the study eye. If CMT is the same, then the eye with worse visual function as assessed by BCVA will be selected as the study eye. If both eyes have the same BCVA then the right eye will be selected.

Dose Escalation (A) Cohorts

The study will assess the safety and tolerability of EXN407 at up to three escalating dose (concentration) levels and placebo (vehicle) consisting of an excipient formulation adjusted for osmolality. EXN407 or vehicle-control will be administered as a single 30 µL drop unilaterally to the study eye only, and the drops will be administered BID for 7 days. Subjects will be assessed for safety, tolerability and efficacy at follow-up visits.

Analysis and Adaptive Design

All visit-based data will be analyzed for the study eye at each visit as well as change from baseline. Comparisons with the non-dosed contralateral eye will also be evaluated in each subject. All protocol evaluations will also be completed on the non-dosed contralateral eye. No vehicle-control or other study treatments will be administered to the contralateral eye. The response to active treatment will be compared to vehicle on a group basis (pooling vehicle subjects).

The protocol is adaptive regarding the number and size of cohorts and dose level progression, which will be informed by emergent data and documented decision making by the dose escalation committee (DEC) following review of available safety and tolerability data from each cohort. The dose levels proposed in this protocol can potentially be reduced or altered based on DEC review.

Allocation to Study Treatment

Sequential dose cohorts of EXN407 (with vehicle-control) are planned.

With exception of the first cohort, each of the remaining ascending dose cohorts will consist of 4 subjects (3 subjects randomized to receive EXN407 and 1 subject randomized to receive vehicle). Of note, the first cohort will incorporate an additional subject to provide a sentinel dosing subgroup (2 subjects, 1 subject randomized to receive EXN407 and 1 subject randomized to receive vehicle) followed after an interval of at least one week by the remaining subjects (2 subjects randomized to receive EXN407 and 1 subject randomized to receive vehicle).

The interval between cohorts, and between the sentinel pair and the remainder of the first cohort, will be at least 1 week.

Each eligible subject in the dose escalation cohorts (numbered cohorts 1, 2, 3, etc.) will receive EXN407 or vehicle BID in 14 doses (1 drop of 30 µL at each dosing occasion, therefore 14 drops in total; with the contingency that if the first drop is not properly administered a second drop can be administered at the time) over a 7 day period.

Dose Expansion (E) Cohort

The highest well-tolerated dose of EXN407 (as recommended by the DEC) will be evaluated in a subject expansion cohort consisting of up to a maximum of 40 subjects (randomized to receive EXN407 at the selected dose or vehicle, in a 2:1 ratio). Each eligible subject in the expansion cohort will receive study drug for up to 84 days, resulting in a total of 168 doses (168 single drops 30 µL volume) of EXN407 or vehicle.

Stopping Criteria and Dose Holding

Subjects who do not meet individual subject stopping criteria at the clinical evaluation visits will continue dosing until final day of dosing. Subjects who meet the stopping criteria will be discontinued from dosing but continue to receive safety and efficacy evaluation and all

scheduled clinical assessments as well as follow-up at an EOS Visit 28 days post the subject's last dose where possible.

Detailed stopping criteria for individual subjects and guidance for study Investigators are provided in Section 8.5.1.1. However, these criteria include an increase from baseline in CMT of >75 µm and a loss of 15-letters of vision. In the case of these two specific stopping criteria being met, at the discretion of the Investigator, rescue medication comprising a marketed anti-VEGF therapeutic will be made available to the patient. The Sponsor would reimburse the cost to the site to a maximum of two doses, or until the drug became approved by the Pharmaceutical Benefit Scheme or other health insurance, whichever occurs first.

The study Investigator in conjunction with the study MM [redacted] and also Sponsor's MM may decide to discontinue study drug for an individual subject, based on pre-defined decision rules for reasons of safety. Subjects who discontinue study drug will continue to be followed for safety and efficacy outcomes for the remainder of the study.

Detailed stopping criteria for cohorts are provided in Section 8.5.2. Current cohort doses can be held, and dose escalations planned for the next cohort can be stopped based on cohort stopping criteria, until discussion by the Principal Investigator (PI), DEC, study MM [redacted] and also the Sponsor MM has resulted in a decision.

Proposed Doses

The proposed doses are:

- Placebo (vehicle, i.e., excipient only)
- Low-Dose 0.5 mg/mL (0.05%) EXN407, one drop administered twice per day
- Mid-Dose 1 mg/mL (0.1%) EXN407, one drop administered twice per day
- High-Dose 1.5 mg/mL (0.15%) EXN407, one drop administered twice per day

Initial Dosing and Dose Escalation

No intra-subject dose escalation/de-escalation will occur.

Safety review will be conducted by the DEC before each cohort initiating dosing, and on an ad hoc basis as needed. The Sponsor will also perform safety review on an ongoing basis.

Subjects in dose escalation cohorts (numbered Cohorts 1, 2, 3, etc.) will return to the study center to complete safety assessments at Days 3, 4, 8, and 36 (EOS).

Dose Expansion Cohort

The highest well-tolerated dose (as determined by the DEC) will be evaluated in a dose expansion cohort in which subjects will receive treatment with EXN407 or vehicle for up to 3 months.

Subjects in the dose expansion cohort will return for safety and efficacy evaluations at Day 8, Day 15, Day 29, Day 57, Day 85 (treatment completion visit) and Day 113 (EOS Visit) post first dose, and will have a telephone contact at Day 22.

DEC, Study MM, Sponsor MM and Investigator Communication Plan

At each specific point at which key decisions are required, such as assessment of sentinel subjects, initiation of dosing in the remainder of the cohort, or any decision to dose escalate / de-escalate to an additional cohort, a decision will be made and documented by the DEC and the study MM ([redacted]) and also Sponsor MM. Details of the DEC's composition, roles and responsibilities will be described in a DEC charter. The Sponsor will chair the DEC,

which will be comprised of a Sponsor-led group. An analysis of safety and tolerability will be undertaken, discussed and a decision will be taken and documented for dose escalation, or dose de-escalation or to expand an existing cohort.

Screening

During the Screening period, subjects will be assessed according to the eligibility criteria. Measures of retinal structure and visual function including SD-OCT and BCVA will be measured twice, for Screening and pre-dose on Day 1 (baseline), prior to each subject's first dose of the randomized study drug or vehicle. Other measures of retinal anatomy such as CFP will be measured at least once prior to the subject's first dose of study drug. Fluorescein fundus angiography will be assessed at the Screening Visit. Any pre-dose assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator, or if the assessment could not be completed. In the case of repeat assessments, the measure reflecting the highest level of visual function will be considered the baseline value unless regarded as an implausible reading in the opinion of the Investigator. Structural tests will be averaged and used as the baseline (pre-treatment value)

Subjects who meet all eligibility criteria will be enrolled into the study and will receive their first dose of the study drug on Day 1. EXN407 or vehicle will be instilled into the subject's study eye under supervision of the Investigator (or delegate). Subjects will be monitored for signs of irritation and inflammation for an initial period of 2 hours post-dose, for their first dose on Day 1 only. Subjects in dose escalation cohorts (numbered cohorts 1, 2, 3, etc.) will additionally return to the clinic at Day 3 and Day 4.

Pharmacokinetics

Plasma samples will be collected for PK analysis as shown in Table 5.

Individual concentrations of EXN407 and estimated PK parameters will be tabulated and summarized for subjects who receive EXN407. Summary statistics will be provided by treatment group.

Individual plasma EXN407 concentration data will be listed and summarized with descriptive statistics (sample size [N], arithmetic mean, standard deviation [SD], coefficient of variation (CV%), median, minimum, maximum and geometric mean). Individual and mean EXN407 concentration-time profiles will also be presented graphically.

The following EXN407 non-compartmental PK parameters will be estimated, as appropriate:

Time of the maximum plasma drug concentration (Tmax), maximum observed drug plasma concentration (C_{max}), area under the curve (AUC) from time zero to the time of the last measurable concentration (AUC_{0-t}), apparent terminal elimination rate constant (kel), AUC from time zero to infinity ($AUC_{0-\infty}$), apparent elimination half-life ($t_{½}$), apparent total body clearance (CL/F), apparent volume of distribution at the terminal phase (Vz/F).

For dose escalation cohorts, dose proportionality will be evaluated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Dose proportionality will be assessed, where possible, using the power model with log-transformed PK parameter values and log-transformed dose. The power model will be used to estimate the slope parameter and the 90% confidence intervals for the slope.

Dose Escalation Cohort:

For subjects in the dose escalation cohorts, blood draws for PK will be collected at Day 3 (± 1 day): pre-dose and 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1, 2, 3 and 4 hours (±10 minutes) post-dose.

Dose Expansion Cohort:

For subjects in the dose expansion cohort blood draws for PK will be collected at Day 8 (±1 day): pre-dose and 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1, 2, 3 and 4 hours (±10 minutes) post-dose.

Stopping Criteria and Rescue Medication

The Investigator, the study MM ([redacted]) and also the Sponsor MM and/or the DEC may decide to stop treatment for an individual subject due to an AE, systemic or ophthalmic. Stopping criteria are described in Section 8.5. Due to the naturally progressive nature of the disease, ophthalmic stopping criteria will specifically apply if any subject shows deterioration in their retinal health due to acceleration in the rate of disease, in the opinion of the Investigator. In such an occurrence, if a subject receives rescue medication, they will cease further dosing, be withdrawn from the [redacted] part of the study and the last clinical observation will be carried forward.

Number of Subjects (Planned):

Up to approximately 48 subjects are planned to be enrolled in the study:

- Three (3) subjects are expected to be randomized to low-dose, 2 subjects are expected to be randomized to placebo (cohort 1, N=5 total).
- Three (3) subjects to mid-dose, 1 subject to placebo (cohort 2, N=4 total).
- Three (3) subjects to high-dose, 1 subject to placebo (cohort 3, N=4 total).
- The remaining subjects (up to 40 additional subjects) will be assigned to maintain/down-dose cohorts and/or expand to additional cohorts at the same dose level, dependent on emergent data and the outcome of near real-time safety review by the DEC.

An algorithm regarding progression to cohort expansion will be defined in the DEC charter. The final number of subjects is dependent on whether any dose levels are repeated and which dose is expanded, following evaluation of emergent data by the DEC but is not expected to exceed approximately 48 enrolled subjects in total.

As the main aim of this study is to generate information on the safety and tolerability of EXN407, subjects who are withdrawn from the study for reasons other than safety issues may be replaced at the discretion of the Sponsor and the Investigator.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria at Screening and enrolment.

1. Subject is at least 18 years of age inclusive, at the time of signing the informed consent
2. BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12) in the study eye using the ETDRS visual acuity scale at Screening or BCVA less than 69 ETDRS score (an approximate Snellen equivalent of 20/50 or 6/15) but who, in the Investigator's opinion, is unsuitable for treatment with anti-VEGF by intravitreal injection or refuses it. Subjects should have no more than a 7-letter difference in BCVA at Screening and baseline Visit.
3. A female subject is eligible to participate if she agrees to use highly effective contraceptive measures (if heterosexually active and a woman of childbearing potential [WOCBP]) from Screening until study completion, including the follow-up period. Acceptable methods of contraception include the use of condoms AND the use of an effective contraceptive that includes:
   a. Oral contraceptives (The Pill),
   b. Long-acting implantable hormones,
   c. Injectable hormones,
   d. A vaginal ring or an intrauterine device (IUD).

   Rhythm methods are not considered as highly effective methods of birth control.
4. A female subject must also not be breast feeding and must have a negative pregnancy test prior to start of dosing if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at Screening:
   a. Is postmenopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
   b. Can provide documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
   c. Is amenorrheic for 12 months and serum follicle-stimulating hormone levels in the postmenopausal range for the institution.
5. Sexually active male subjects where the sexual partner is a WOCBP must be willing to use barrier contraception i.e., condoms, and another acceptable form of contraception (see Inclusion Criteria 3 for acceptable forms) during the study and for 3 months after the last dose of study medication.
6. Diabetes mellitus (Type 1 or Type 2). Any of the following will be considered to be sufficient evidence that diabetes is present:
   a. Current regular use of insulin for the treatment of diabetes
   b. Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
   c. Documented diabetes according to the American Diabetes Association and/or World Health Organization (WHO) criteria

7. Confirmation by the evaluating Investigator and central reading center of center involved DME in the study eye observed by both FFA and SD-OCT at the Screening Visit, with a CMT between 280-420 μm, and BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12)

   or

   Confirmation by the evaluating Investigator and central reading center of center involved DME in the study eye observed by both FFA and SD-OCT at the Screening Visit, with a CMT between 280-420 μm, and BCVA less than a 69 ETDRS score (an approximate Snellen equivalent of 20/50 or 6/15) but who, in the Investigator's opinion, is unsuitable for treatment with anti-VEGF by intravitreal injection or refuses it.

8. Ocular media is consistent with SD-OCT imaging and cataracts are not expected in the subject for the duration of the study
9. The subject has no other retinal disease
10. Subject is capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form, and willing and able to return for all study visits, and comply with all protocol requirements and procedures
11. Subject or the subject's partner successfully demonstrates their ability to self-administer/administer eye drops at Screening, with multiple attempts allowed at the discretion of the Investigator

Exclusion Criteria

Deviations from Inclusion Criteria are not allowed due to the potential of the deviation to impact the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria at Screening must not be enrolled in the study:

1. Any other retinal disease in the study eye, other than center involved DME or diabetic retinopathy
2. Poor vision (Visual acuity [VA] 6/60 or worse) in the contralateral eye
3. Intraocular inflammation (including trace or greater) in the study eye. History of idiopathic or autoimmune uveitis in either eye
4. Ocular disorders/additional eye disease in the study eye, which in the opinion of the Investigator or central reading center may confound interpretation of study results, that compromise protocol assessments or that are likely to require intervention during the ~4.5 months of study, including, but not limited to atrophy of the retinal pigment epithelium, sub-retinal fibrosis, organized hard exudate plaque, retinal vascular occlusion, retinal detachment, macular hole, vitreomacular traction, macular epiretinal membrane within center of macula as evident with OCT evaluation, clinically significant cataract, vitreal opacities or hemorrhage, glaucoma with documented visual field loss, ischemic optic neuropathy, retinitis pigmentosa or choroidal neovascularization of any cause (e.g., Age-related macular degeneration (AMD), ocular histoplasmosis, or pathologic myopia)

5. Uncontrolled intraocular pressure >25 mmHg in the study eye despite treatment with 2 or more glaucoma medications
6. Use of intravitreal anti-VEGF drugs including ranibizumab, bevacizumab, aflibercept **in the study eye** within 6 months of the Screening Visit, or in the **fellow (non study) eye** within 3 months of the Screening Visit. Use of topical corticosteroids or topical non-steroidal anti-inflammatory agents **in the study eye** within 28 days of the Screening Visit. Use of intravitreal corticosteroids in either eye or systemic steroids within 12 months of the Screening Visit. Prior use of Iluvien (without time limitation).

   N.B. There are no restrictions to prior use **in the fellow (non study) eye** of topical non-steroidal anti-inflammatory agents and topical corticosteroids. Subjects who have been treated with anti-VEGF in either eye but failed to respond adequately to that treatment, i.e., it failed to prevent DME progression, will be excluded.
7. Within 180 days prior to the Screening Visit, use of medications known to be toxic to the retina, lens or optic nerve (e.g., desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, and ethambutol)
8. The following procedures will exclude a potential subject if conducted within 180 days of planned first Screening Visit:
   a. Intraocular surgery in the study eye
   b. Laser photocoagulation in the study eye
9. Prior or current use of any systemically administered anti-angiogenic agent (e.g., bevacizumab, sunitinib, cetuximab, sorafenib, pazopanib), approved or investigational
10. Uncontrolled diabetes as indicated by HbA1c >12% at Screening, or if HbA1c is ≤12%, diabetes mellitus is uncontrolled in the opinion of the Investigator
11. Poorly controlled hypertension at Screening despite lifestyle modifications and pharmacotherapy; systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110mmHg (mean of 3 measurements according to protocol specified conditions)
12. Current severe heart failure (New York Heart Association class III or IV)
13. QTcF >480 msec in any subject including those with Bundle Branch Block
14. History of (within 90 days of Screening date) cerebral vascular accident (stroke) or myocardial infarction (MI)
15. Current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones, with concurrence from the Sponsor study responsible physician) or evidence of abnormal liver function tests [total bilirubin or alkaline phosphatase >2x upper limit of normal (ULN); or Alanine aminotransferase (ALT) or Aspartate amino transferase (AST) >3 x ULN] or other hepatic abnormalities that in the opinion of the Investigator would preclude the subject from participation in the study
16. Significant renal impairment including subjects on chronic renal dialysis and subjects with a history of nephrectomy or kidney transplant (regardless of renal function)

17. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions, or severe allergic responses.
18. History of sensitivity to fluorescein, any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or the study MM ([redacted] or Sponsor MM, contraindicates subject participation
19. Use of another investigational product (IP) within 1 month or 5 half-lives or twice the duration of biological effect (whichever is the longest) preceding the first dose of study medication
20. Alcohol or drug abuse within the past 180 days, or current mental condition (psychiatric disorder, senility or dementia), which may affect study compliance or prevent understanding of the aims, investigational procedures or possible consequences of the study. Alcohol abuse is defined as >21 alcohol units per week (where 1 unit = 284 mL of beer, 25 mL of 40% spirit or a 125 mL glass of wine).
21. Positive pregnancy test (all female subjects of childbearing potential must have a urine β-human chorionic gonadotropin [hCG] pregnancy test performed at Screening and within 7 days prior to randomization) or is known to be pregnant or lactating.
22. Known to have, or history of a positive test result for, hepatitis B or C, human immunodeficiency virus (HIV), syphilis, tuberculosis; or known to have currently active COVID-19.
23. Evidence of clinical instability or abnormal clinical laboratory findings prior to randomization that, in the opinion of the Investigator, makes the subject unsuitable for the study.
24. A condition that, in the opinion of the Investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
25. Individuals in poor glycemic control who, within the last four months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next four months should not be enrolled.
26. Employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator.

Note: Investigators should assure that all study enrolment criteria have been met and determine that the subject has not had any interval change in clinical status since Screening. Before randomization, subjects whose status changes after Screening, such that they now no longer meet an inclusion criterion / meet an exclusion criterion, should be excluded from participation.

Investigational Product, Dosage and Mode of Administration:

EXN407 is a solution for topical ophthalmic administration by eye drop. EXN407 will be administered BID as a single drop from a single-use sterile blow-fill-seal (BFS) eye drop ampoule. Each drop will be 30 µL in volume.

EXN407 will be provided at three concentrations:

- 0.5 mg/mL (0.05%)
- 1.0 mg/mL (0.1%)
- 1.5 mg/mL (0.15%)

Duration of Treatment:

Screening and Run-in period: 3-28 days

Treatment period:

- 7 days for dose escalation cohorts (numbered cohorts 1, 2, 3, etc.)
- 3 months for dose expansion cohort (84 days ± up to 7 days for Visit windows)

Follow-up period:

- 28 days for dose escalation cohorts (± 2 days)
- 28 days for dose expansion cohort (± 7 days)

The overall study duration for an individual subject in the dose escalation cohorts will be approximately 64 days and up to 66 days with the follow-up Visit window.

The overall study duration for an individual subject in the dose expansion cohort will be approximately 5 months (141 days) and up to 5.5 months (156 days) with visit windows.

Reference Therapy, Dosage and Mode of Administration:

The placebo is a matched placebo for EXN407 ophthalmic solution, consisting of vehicle (no active drug, excipient only) for topical administration by eye drop. Placebo (vehicle) will be administered BID as a single drop from a single-use sterile BFS eye drop ampoule. Each drop will be 30 µL in volume. The placebo (vehicle) will be masked.

Statistical Methods:

A detailed methodology for the statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be signed off prior to the database lock.

All computations will be performed using SAS® version 9.2 (SAS Institute, Cary, NC). Since the primary objective of the study is to evaluate ocular safety and tolerability, no formal hypothesis testing will be performed for any continuous or categorical variables. All statistical analyses will be descriptive in nature and any statistical inference will be carried out according to the analysis plan and interpreted in view of the exploratory nature of the study.

Descriptive statistics (number of non-missing values (n), arithmetic mean, SD, 95% confidence interval for mean [where specified], median and range) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. All descriptive summaries will be presented by treatment group/cohort and nominal visit/time point (where applicable).. Data from the placebo subjects will be pooled (if appropriate).

Baseline demographics and disease characteristics, safety and efficacy endpoints will be summarized descriptively by treatment group and for all subjects combined. Plasma concentrations of EXN407 will be summarized by treatment group and protocol specified time point, and PK parameters calculated where relevant.

Unless stated otherwise, unscheduled data will not be included in the descriptive summaries.

All subject data will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by treatment group, subject number, date/time and visit.

Analysis Populations

Subject inclusion into each population will be determined prior to the final analysis.

Intent-to-treat population (ITT):

All randomized subjects, regardless of whether they receive study drug or not, will be included in the ITT population. It will be based on the treatment assigned to a subject, not what they actually received. All disposition and demographic data analysis will be based on the ITT population. The ITT population will be used for all data listings.

Safety population:

The Safety population will comprise all randomized subjects who received any amount of study drug.

Summaries, listings, and analyses will be based on the treatment actually received. Screen failures and randomized subjects who did not receive any medication will be excluded from the safety analysis set.

The Safety population will be used for the summaries of all safety assessments.

Pharmacokinetic population:

The PK population will comprise all subjects who received any dose of the study drug who had no important protocol deviations affecting the PK parameters and have a sufficiently evaluable concentration-time profile to allow determination of at least one PK parameter from among AUC, C_{max} or T_{max}.

Note: Planned analyses of PK data will be described in a separate PK analysis plan.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AMD	Age-related macular degeneration
Anti-VEGF	Anti–vascular endothelial growth factor
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
BFS	Blow-Fill-Seal
BID	Twice per day
BMI	Body mass index
BP	Blood pressure
BRB	Blood-retinal barrier
CDK	Cyclin-dependent kinase
CFP	Color fundus photography
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
CLK	CDC-like kinase
CMGC	Cyclin-dependent kinase, mitogen-activated protein kinase, glycogen synthase kinase and CDC-like kinase
CMT	Center-subfield macular thickness (center subfield is defined as the circular region centered on the anatomic fovea with a radius of 500 microns)
CSR	Clinical study report
CTN	Clinical Trials Notification
DEC	Dose escalation committee
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity score
ETDRS	Early treatment diabetic retinopathy study
eCRF	Electronic case report form

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
ELM	External limiting membrane
EOS	End of study
ERG	Electroretinogram
ET	Early termination
FFA	Fluorescein fundus angiography
FIH	First in human
FSH	Follicle-stimulating hormone
GAT	Goldman applanation tonometry
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin [hCG]
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IP	Investigational product
ITT	Intent-to-treat
IUD	Intrauterine device
LDPE	Low density polyethylene
MedDRA®	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Medical Monitor
NHMRC	National Health and Medical Research Council
NHP	Non-human primates
NOEL	No observed effect level
OCT	Optical coherence tomography
OTC	Over-the-counter (medications)
pIC50	50% of maximum inhibitory effect

Abbreviation or Specialist Term	Explanation
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred term
QID	Four times daily
RPE	Retinal pigment epithelium
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System organ class
SRPK1	Serine-Arginine Protein Kinase-1
SRSF	Serine/arginine rich splicing factors
TEAEs	Treatment emergent adverse events
TrkA	Tropomyosin receptor kinase A
UD	Unit-dose
ULN	Upper limit of normal
VA	Visual acuity
VEGF-A	Vascular endothelial growth factor A
WHO	World Health Organization
WOCBP	Woman of childbearing potential

5. FACILITIES AND PERSONNEL

Table 3: Facilities and Personnel

Sponsor	Exonate Ltd. WTL Moorfield Rd, Duxford, Cambridgeshire, CB22 4PS United Kingdom
Local [redacted] Sponsor	[redacted]
[redacted] Clinical Project Manager	[redacted]
[redacted] Clinical Project Manager	[redacted]
Clinical Study Leader	[redacted] Exonate Ltd. WTL Moorfield Rd, Duxford, Cambridgeshire, CB22 4PS United Kingdom
Exonate Medical Director	[redacted] Exonate Ltd. WTL Moorfield Rd, Duxford, Cambridgeshire, CB22 4PS United Kingdom
Exonate MM	[redacted] Exonate Ltd. WTL Moorfield Rd, Duxford, Cambridgeshire, CB22 4PS United Kingdom
[redacted] Local MM	[redacted]

Biostatistical Analysis	[redacted]
Data Management	[redacted]
Project Management	[redacted]
Monitoring	[redacted]

6. BACKGROUND AND INTRODUCTION

6.1. Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss and blindness in the working age population (20-74 years of age) in most developed countries (Klein, 2007[1]). While the pathophysiology is not fully understood, the severity of the condition is directly related to the degree and duration of hyperglycemia secondary to diabetes mellitus. The increasing number of individuals with diabetes worldwide suggests that DR is likely to be a growing contributor to vision loss and associated functional impairment in the future (Yau 2012[2]). DME is the leading cause of vision loss in DR patients and is a direct consequence of inner blood-retinal barrier (BRB) breakdown (Antonetti 2006[3]; Curtis 2008[4], Funatsu 2009[5]). DME affects approximately 7% of diabetics, and approximately 21 million individuals worldwide (Yau 2012[2]). Current DME treatments are surgical and include laser therapy or, particularly when disease affects central vision, frequently administered intravitreal anti-VEGFs or corticosteroids (Elman 2010[6]; Nguyen 2012[7]).

Corticosteroids demonstrate similar reduction of edema as anti-VEGF agents, however because of the risks of secondary cataract and elevation of intraocular pressure, steroid use in DME is limited to short term therapy. Anti-VEGF agents are effective therapeutics in resolving retinal edema and increasing vision in a significant proportion of DME patients. However, a substantial proportion of patients are either refractory or become refractory to the continued use of anti-VEGF therapy. Moreover, all currently marketed anti-VEGF therapeutics are administered as intravitreal injections at dosing intervals as frequently as monthly, requiring repeated clinic visits and representing a substantial burden to patients, especially to the working population.

Vascular endothelial growth factor A (VEGF-A) pre-mRNA can be processed in the eye to yield a number of isoforms of which two are VEGF165a and VEGF165b, which results from alternative exon splicing from a single VEGF pre-mRNA. VEGF165a induces vascular proliferation, and increased vascular permeability (Batson 2017[8]). Conversely, VEGF165b is proposed to have anti-proliferative properties, does not function as a vascular permeability factor, yet maintains other VEGF-dependent functions, and has been proposed to have cyto-protective properties (Harper 2008[9]). Marketed anti-VEGF therapeutics are targeted at the inhibition of all VEGF isoforms, whether pro- or anti-angiogenic. Data on neovascular AMD, another condition in which VEGF contributes to its pathogenesis, suggests that long-term outcomes are relatively poor, which may be due, in part, to anti-VEGF-induced retinal atrophy after prolonged duration of treatment (Rofagha 2013[10]).

The alternative splicing of VEGF is in a constant equilibrium, which is controlled by Serine-Arginine Protein Kinase-1 (SRPK1), where activating SRPK1 favors VEGF165a production, while inhibiting it promotes the expression of VEGF165b (Batson 2017[8]).

EXN407 is a potent and selective SRPK1 inhibitor, which is designed to have profound ocular permeability and reach the retina/choroid following topical ophthalmic dosing. Two studies were performed to determine inhibitory dose response effect of EXN407 on SRPK1 kinase activity (Study 140472 *Dundee* and Study 143793 *Eurofins*). EXN407 inhibited human recombinant SRPK1 activity giving 50% of maximum inhibitory effect (pIC50) of -8.23 ± 0.21. This is equivalent to an IC50 value of 5.87 nM (3 ng/mL).

The selectivity of EXN407 has been assessed across a panel of 480 kinases (Study 143936 *Dundee* and Study 143750 *Eurofins*), as summarized in Study 143800.

In the first screen of 50 kinases, SRPK1 was inhibited by EXN407 at 1 μM with 1% kinase activity remaining. All other kinases in this study had >60% activity remaining except Tropomyosin receptor kinase A (TrkA) (47% activity remaining) (Study 140936 *Dundee*).

In a subsequent larger screen of 430 kinases, in addition to SRPK1, 4 kinases had less than 50% kinase activity remaining after treatment with EXN407 (1 μM) (Study 143750 *Eurofins*). These four kinases are all closely related to SRPK1 in the CMGC kinase family. These kinases were followed up in IC50 determinations (Study 143799). TrkA was not inhibited by EXN407, with 74% kinase activity remaining.

These results demonstrate that EXN407 selectivity inhibits SRPK1 with some inhibition of only four other closely related kinases out of a kinome panel of a total of 480 kinases.

In radioactive filter binding assays, EXN407 showed inhibition of six kinases closely related to SRPK1 in the CMGC kinase family; SRPK2, SRPK3, CLK1, CLK2, CDK12 and CDK13 but with reduced potency compared to SRPK1 inhibition (Study 143799).

When tested at a concentration of 1 μM against a panel of 430 kinases, no additional kinases were inhibited >50% by EXN407 (Study 143799).

Overall, EXN407 selectivity inhibits SRPK1 with 5-fold selectivity over CDK12 and greater selectivity (7.5 to 165-fold) over closely related kinases including SRPK2, SRPK3, CLK1, CLK2, CDK13.

It is proposed that inhibition of SRPK-1 will increase the VEGF165b/ VEGF165a ratio, limiting the vascular permeability inducing effects of VEGF165a. The protective effects of limiting VEGF165a production are augmented through increased expression of VEGF165b, to achieve better control of center involved DME in patients with diabetes mellitus.

In a mouse model of laser-induced choroidal neovascularization, EXN407 66 ng/mL (10 μL, BID) eye drops significantly reduced vessel growth quantified by area and intensity of new vasculature after 7 days compared to vehicle-control (Study 143833).

To validate the *in vivo* functional effect of EXN407 on neovascularization observed in the mouse model, pharmacodynamic readouts were analyzed in larger animals with eyes that provide a closer analog for the anatomy of the human eye. Non-human primates (NHP) were treated with 35 μL eye drops twice daily at 0.5 mg/mL, 1.0 mg/mL or 1.5 mg/mL of EXN407 for 3 weeks and eyes were enucleated 1 hour after the final dose. Eyes were dissected and the retina processed for immunoblotting for the immediate downstream target of SRPK1, pSRSF1 and the pro-angiogenic disease mediator VEGF-A_{xxx}a. The results show angiogenic VEGF-A is significantly reduced in NHP retinas after 0.5 mg/mL eye drops at a measured retinal concentration of 1.66 ng/mL (3 nM) and retinal pigment epithelium (RPE)/choroid concentration of 72.92 ng/mL (141 nM). Moreover, EXN407 significantly reduced retinal pSRSF1 at all three doses compared to untreated control retinas and this corresponded to a significant reduction in total VEGF-A_{xxx}a but no reduction in anti-angiogenic VEGF-A_{xxx}b isoforms. These data show that inhibition of SRPK1 in large animal eyes after eye drop administration reverses the balance of VEGF-A by reducing pro-angiogenic VEGF-A_{xxx}a isoforms compared to anti-angiogenic VEGF-A.

Moreover, data based on longer-term follow-up of large, randomized trials of anti-VEGF therapy for DME suggest that earlier anti-VEGF treatment of center involved DME with visual acuity loss may decrease long-term treatment burden (Wykoff 2016[11]).

Worldwide, there are many patients who do not receive treatment for DME, particularly those with good visual acuity. The decision as to when to initiate intravitreal therapy for DME varies globally, and is determined by investigator judgment. Currently in the United States, many patients who have vision greater than or equal to 20/40 decline intravitreal injections to treat their DME given their relatively good visual acuity and the invasiveness and risks of the intravitreal procedure.

Presently in Australia, patients with a visual acuity better than an approximate Snellen equivalent of 20/32 (6/9, 78 letters) or worse than 20/160 (6/48, 39 letters) are not offered intravitreal anti-VEGF injections, due to the lack of reimbursement from the public healthcare system. However, patients do experience clear center involved DME and could benefit from treatment that manages the VEGF165b/ VEGF165a ratio in the eye, making this patient population ideal to test the safety, tolerability and efficacy of topically dosed EXN407 in a monotherapy setting. Due to the limited progression of the disease at this stage, it is often the case that patients with BCVA approaching 20/40 declined an intravitreal injection in both Australia and the United States and, as such these patients are also considered relevant to this clinical study.

6.2. Summary of Nonclinical and Clinical Studies

6.2.1. Nonclinical Studies

EXN407 has undergone an extensive nonclinical safety evaluation. All nonclinical studies conducted for EXN407 are described in detail in the EXN407 IB.

In vitro pharmacology studies were performed to determine inhibitory dose response effect of EXN407 on SRPK1, to assess the selectivity of EXN407, and to assess the inhibitory dose response effect of EXN407 on kinases closely related to SRPK1. Functional studies were also conducted.

In vivo, EXN407 was extensively evaluated in mouse, rat and NHP models for toxicity, ocular tolerance, and pharmacokinetics. Plasma binding was assessed in plasma from the mouse, rat, rabbit, dog, cynomolgus monkey and human.

The results demonstrate EXN407 concentrations in ocular tissues follow a dose dependent relationship and are above levels required for efficacy in RPE cells, consistent with pharmacodynamic readouts at these concentrations on SRPK1 inhibition and pro-angiogenic VEGF-A_{xxx}a reduction. EXN407 has sufficient posterior ocular permeability to distribute to the RPE/choroid for efficacy, combined with much lower systemic exposure, which would limit potential for any effects outside the eye.

6.2.2. Clinical Studies

This is a FIH Phase Ib/II study of EXN407.

6.3. Summary of Potential Risks and Benefits

EXN407 is an investigational drug and the safety profile in humans has not yet been established because it has not been administered to any human subjects. It is therefore recommended that subjects are carefully monitored during administration of EXN407 until sufficient human experience is obtained to determine its safety.

Hypersensitivity reactions may occur in susceptible individuals.

No adverse reactions have been noted after *in vivo* good laboratory practice (GLP) repeat dose ocular toxicity studies in the rat and monkeys administered repeat doses of up to 0.015 mg/eye/dose (1.5 mg/mL, total dose of 0.06 mg/eye/day) and up to 0.0525 mg/eye/dose (1.5 mg/mL, total dose of 0.21 mg/eye/day), respectively (total four doses per eye per day) for 13 weeks. Total human dose in this study will be up to 0.09 mg/day (1.5 mg/mL).

As systemic absorption is anticipated to be very low based upon nonclinical data, the possibilities of direct drug related systemic adverse effects are also anticipated to be very low.

One potential benefit to subjects with a visual acuity better than an approximate Snellen equivalent of 20/32 (6/9, 78 letters) or worse than 20/160 (6/48, 39 letters) who are not offered intravitreal anti-VEGF injections, due to the lack of reimbursement from the public healthcare system for example in Australia, or who decline injection, but who do experience clear center involved DME is that they could potentially benefit from treatment that manages the VEGF165b/ VEGF165a ratio in the eye.

EXN407 has the potential to be a non-invasive alternative to intravitreal anti-VEGF injections. Subjects with DME who may be unsuitable for or put off by the need for an intravitreal injection may benefit from EXN407 eye drops. It is important to note that subjects who participated in the landmark studies with anti-VEGFs had had DME on average for 1.6 - 2.4 years (Nguyen 2012[7]). Despite this, approximately 30% of those randomized to receive sham treatment did not need any rescue treatment during the first 6 months of follow-up. Since participants in this study will be identified early, the slight delay caused by the study is not expected to be a significant risk for disease progression. To ensure subject safety, all subjects will be closely monitored and, if any subject shows a clinically significant deterioration in CMT and/or BCVA, they will be withdrawn in a timely manner and offered the standard of care.

6.4. Dosage and Treatment Periods

Up to three dose levels of EXN407 (with vehicle-control) are planned across three or more sequential cohorts. No intra-subject dose escalation or decrease will occur.

The dose levels to be explored are described in Table 4. Decisions to escalate or expand the dose will be dependent upon review of emerging safety data by a DEC. The Sponsor will chair the DEC, which will be comprised of a Sponsor-led group. The DEC will conduct a review of safety data from each preceding cohort prior to commencing dosing in each proceeding cohort. Details will be provided in a DEC charter document.

Table 4: EXN407 Dose Levels

EXN407	Dose Expansion
Low-Dose 0.5 mg/mL (0.05%) EXN407 OR placebo (vehicle, i.e., excipient only)	The highest well-tolerated EXN407 dose (as determined by the DEC, study MM [redacted] and Sponsor MM), treatment with EXN407 or vehicle for up to 3 months
Mid-Dose 1.0 mg/mL (0.1%) EXN407 OR placebo (vehicle, i.e., excipient only)	
High-Dose 1.5 mg/mL (0.15%) EXN407 OR placebo (vehicle, i.e., excipient only)	

Both EXN407 and placebo (vehicle) are to be administered as one drop BID

6.4.1. Initial Dosing Initiation and Continuation

Cohort 1 Sentinel Subjects (low-dose)

The first two subjects in cohort 1 will be sentinel subjects (1 subject each randomized to EXN407 and vehicle) and will be dosed at least 1 week prior to the other three subjects of the cohort.

Immediately after dosing, and 48 hours and 72 hours post dosing (days 3 and 4) subjects in cohort 1 will be examined clinically for signs of intolerability of the study drug. If in the opinion of the Investigator the study drug has acceptable tolerability the subject will continue to be dosed through Day 7. Following the completion of all assessments on Day 8 (Visit 5A) for the low-dose cohort (cohort 1) sentinel subject pair, the DEC will review the experience of these subjects. If the safety and tolerability of study drug in both sentinel subjects is acceptable in the opinion of the DEC, and none of the stopping criteria are met, a recommendation to progress to the expansion cohort at a given dose level will be made to the Sponsor by the DEC, and all remaining subjects in cohort 1 may commence dosing.

6.4.2. Dose Escalation Cohorts

Cohort 1

Once data at the Day 8 time point for the sentinel subjects are reviewed and judged satisfactory by the DEC, all remaining (3) subjects in this cohort can initiate dosing as described previously.

Following completion of all assessments on Day 8 (Visit 5A) for the entirety of cohort 1, the DEC will review safety and tolerability data. Once all applicable data through the Day 8 time point are reviewed and judged satisfactory by the DEC, a recommendation will be made to the Sponsor and documented regarding dose progression/escalation.

Cohorts 2 Onward

Following DEC evaluation and approval of the safety of the previous dose level, the next higher dose level may initiate dosing for four subjects, who will be clinically evaluated at 48 hours, 72 hours and 7 days post-dose initiation (Day 8). Following completion of the 1-week clinical assessment comprising 7 days of continuous dosing, the DEC will review the safety and tolerability data. Once all applicable data at the 1-week point are reviewed and judged

satisfactory by the DEC, a recommendation to the Sponsor will be made and documented regarding dose progression.

Alternatively, safety data from the previous cohort may result in a DEC recommendation to repeat the previous dose level in the next sequential numbered cohort for an additional four subjects. These additional subjects will be clinically evaluated at 48 hours, 72 hours and 7 days post-dose initiation (Day 8). If the DEC judge the additional safety and tolerability data at that dose level to be satisfactory, a recommendation will be made and documented regarding dose progression and the next higher dose level can initiate dosing in the next sequential numbered cohort.

As there are three dose levels (low-, mid- and high-dose) with this adaptive design there can be as many as six dose escalation cohorts following the sentinel pair (should there be two cohorts at each dose level due to safety and tolerability findings at each DEC meeting).

6.4.3. Dose Expansion Cohort

The highest well-tolerated dose of EXN407 (as determined by the DEC – see Section 8.4) will be evaluated in a subject expansion cohort consisting of up to a maximum of 40 subjects (randomized to receive EXN407 at the selected dose or vehicle, in a 2:1 ratio). Subjects will receive treatment for 84 days, with 28 days of post-treatment follow-up and an EOS Visit. The DEC will meet to discuss safety and tolerability at intervals to be defined in the DEC charter.

6.4.4. Rationale for Starting Dose

Dosing EXN407 BID at 1.5 mg/mL (30 µl per dose) via topical instillation is predicted to be safe for human eyes, and the selected concentration is supported by *in vivo* animal studies as being effective and safe. EXN407 GLP NHP toxicology study (13-week dosing, followed by 4-week recovery period), as well as a pharmacological activity mouse and NHP study, were performed to identify appropriate doses for human treatment. In the mouse model of laser-induced choroidal neovascularization, EXN407 66 ng/mL (10 µL, BID) eye drops significantly reduced vessel growth quantified by area and intensity of new vasculature after 7 days compared to vehicle-control (Study 143833). In the monkey pharmacodynamics (PD) studies, intraocular treatment with 1.5 mg/mL of EXN407 (35 µl, BID) significantly reduced retinal pSRSF1 and total VEGF-A_{xxx}a compared to control. Further, no adverse effects were observed at 1.5 mg/mL (35 µl) of clinical formulation of EXN407 administered to healthy NHP eyes four times daily, for 13 weeks. Similar, 10-day tolerability study in rabbits showed that, after multiple daily instillations of 50 µL of EXN407 up to 1.5 mg/mL over 10 days, no body weight changes and no particular ocular clinical observations (Draize, McDonald Shadduck, electroretinogram [ERG], Intraocular pressure [IOP] or Corneal sensitivity) or macroscopic and microscopic findings were observed compared to control.

Overall, based on the GLP 13-week repeat dose ocular topical toxicity study in monkeys, the NOEL was considered to be the highest dose of 0.0525 mg/eye/dose or 0.21 mg/eye/day (QID). The proposed FIH dose is 0.015 mg/eye/dose (BID) or 0.030 mg/eye/day and the highest proposed human dose is 0.045 mg/eye/dose (BID) or 0.090 mg/eye/day. Thus, the FIH dose for a single eye drop and BID dosing is 14-fold and 7-fold lower than the no observed effect level (NOEL) in the monkey 13-week study. The top proposed human dose for a single eye drop and BID dosing is 4.7-fold and 2.3-fold lower than the NOEL dose in the monkey study.

In terms of systemic exposure, at the top human dose of 0.045 mg/eye/dose (BID) or 0.090 mg/eye/day, the C_{max} would not exceed 2.3 nM as supported by the C_{max} obtained in the 10-day repeat dose rabbit study and 13-week GLP repeat dose monkey study at the highest 1.5 mg/mL dose.

6.5. Subject Population

The study will be conducted in male and female subjects with diabetes mellitus (Type 1 or Type 2) and center involved DME in the study eye, aged ≥18 years (inclusive) at the time of informed consent.

Women of childbearing potential (WOCBP) will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow-up period, and for at least 90 days after the last dose of study drug. WOCBP must demonstrate negative pregnancy testing at Screening and before administration of study drug. This is in line with regulatory Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (FDA 2010).

6.6. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and with the NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The conduct of the study will be in accordance with the ICH Integrated Addendum to E6(R1): Guideline for GCP ICH E6(R2), annotated with any applicable country specific amendments.

This study will be conducted under a protocol reviewed and approved by an IEC and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

7. TRIAL OBJECTIVES AND PURPOSE

7.1. Objectives

7.1.1. Primary Objectives

The primary objective of the study is to evaluate the ocular safety and tolerability of EXN407 ophthalmic solution in subjects with diabetic macular edema (DME) secondary to diabetes mellitus.

7.1.2. Secondary Objectives

The secondary objectives of the study are:

- *Safety*: To evaluate the systemic safety and tolerability of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus
- *Safety*: To evaluate changes in ocular functional and structural measures with the use of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus
- *Pharmacokinetics:* To evaluate the systemic pharmacokinetics of EXN407 ophthalmic solution in subjects with DME secondary to diabetes mellitus

7.1.3. [redacted]

7.2. Endpoints

7.2.1. Safety and Tolerability

The safety and tolerability endpoints of the study are:

- Primary:
  - Frequency and severity of ocular AEs in the study and contralateral eyes
- Secondary:
  - Frequency and severity of non-ocular AEs
  - Changes from baseline in safety parameters, including vital sign measurements, physical examination findings, ECG, and laboratory parameters
  - Changes from baseline in ophthalmic examination findings, including ophthalmoscopy.

7.2.2. Safety

Secondary endpoints that relate to safety are:

- Changes from baseline in Center-Subfield Macula Edema (center-subfield measure)
- Changes from baseline in macular fluid volume
- Change from baseline in BCVA using the ETDRS visual acuity scale
- Change from baseline in FFA
- Change from baseline in corneal thickness based on pachymetry assessed at a consistent time of day
- Change from baseline in corneal endothelial cell count (dose expansion cohort)

7.2.3. Pharmacokinetics

The PK endpoints of the study are:

Characterize the PK profile of EXN407 in plasma (dose escalation and dose expansion cohort[s]).

7.2.4. [redacted]

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This FIH, Phase Ib/II study of EXN407 is a randomized, double-masked, vehicle-controlled multiple dose, dose-escalating study to evaluate the safety and tolerability of EXN407 in subjects with center involved DME, with CMT between 280-420 µm and BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12) in the study eye, which is considered secondary to diabetes mellitus. For brevity, the BCVA criteria will be noted as ”better than or equal to 69 ETDRS score”.

A schematic of the study design is provided in Figure 1.

Study visits and assessments will occur as delineated in the Schedule of Assessments presented in Table 5.

The Screening period is from 28 to 3 days prior to randomization and the start of study treatment (i.e., from study days -28 to -3). Subjects that meet all eligibility criteria at Screening will enter a run-in period (from post-screening to Day -1) where the subject (or subject’s partner as applicable) will administer eye drops BID using Systane Ultra UD droppers. The run-in period serves to familiarize and train subjects in topical administration via eye dropper. Please refer to Section 12.2 for more details on the run-in period. The task of instructing subjects in self-administration of study treatment will be performed by appropriately qualified, trained and delegated site staff.

Re-screening could take place for back up subjects (who qualified for the study, but were not randomized immediately due to places in the current cohort filling up) or for subjects who did not meet all Inclusion Criteria or who meet an exclusion criterion initially, but due to a change in clinical condition may have become eligible. Please refer to Section 8.3.1.1 for more details on re-screening procedure and criteria.

Selection of Study Eye

EXN407 or vehicle-control solution will be administered unilaterally to the study eye only. The Investigator should identify the eye in which evident center involved DME is present with a CMT between 280-420 µm as determined by SD-OCT and meeting all other inclusion/exclusion criteria. All SD-OCT assessments for a subject should be taken with the same make and model of equipment throughout the duration of the study.

If both eyes qualify on the basis of evident DME with CMT of between 280-420 µm, and other inclusion/exclusion criteria, then the Investigator should choose the eye with the worse (greater) CMT as the study eye. If CMT is the same, then the eye with worse visual function as assessed by BCVA will be selected as the study eye. If both eyes have the same BCVA then the right eye will be selected.

Dose Escalation (A) Cohorts

The study will assess the safety and tolerability of EXN407 at up to three escalating dose (concentration) levels and placebo (vehicle) consisting of an excipient formulation adjusted for osmolality. EXN407 or vehicle-control will be administered as a single 30 µL drop by unilateral eye drop administration to the study eye only, and the drops will be dosed BID for 7 days.

Subjects will be assessed throughout the treatment period for safety, tolerability and efficacy at follow-up visits.

Analysis and Adaptive Design

All visit-based data will be analyzed for the study eye at each visit and assessed for any change from baseline. Comparisons with the non-dosed contralateral eye will also be evaluated in each subject. All protocol evaluations will also be completed on the non-dosed contralateral eye. No vehicle-control or other study treatments will be administered to the contralateral eye. The response to active treatment will be compared to vehicle on a group basis (pooling vehicle subjects).

The protocol is adaptive regarding the number and size of cohorts and dose level progression, which will be informed by emergent data and recommendation by the DEC following review of available safety and tolerability data from each cohort. The number of dose levels proposed in this protocol can potentially be reduced or altered based on DEC review and Sponsor decision.

Allocation to Study Treatment

With exception of the first subject cohort, each of the remaining ascending dose subject cohorts will consist of four subjects (3 subjects randomized to receive EXN407 and 1 subject randomized to receive placebo). Of note, the first cohort will incorporate an additional subject to provide a sentinel dosing subgroup (2 subjects, 1 subject randomized to receive EXN407 and 1 subject randomized to receive placebo) followed after an interval of at least one week by the remaining subjects (2 subjects randomized to receive EXN407 and 1 subject randomized to receive placebo).

There is no sentinel dosing subgroup in any of the remaining ascending dose subject cohorts. The rationale for not implementing a sentinel dosing subgroup for subsequent cohorts is multifactorial, considering the lack of toxicity findings in preclinical studies, the route of administration (topical rather than systemic), the target not being novel or immunomodulatory, and the increment in escalating doses being small.

The interval between cohorts, and between the sentinel pair and the remainder of the first cohort, will be at least 7 days.

Each eligible subject in the dose escalation cohorts (numbered cohorts 1, 2, 3, etc.) will receive EXN407 or vehicle BID over an 7 day period (1 drop of 30 µL at each dosing occasion, therefore 14 drops in total; with the contingency that if the first drop is not properly administered a second drop can be administered at the time).

Dose Expansion (E) Cohort

The highest well-tolerated dose of EXN407 (as recommended by the DEC) will be evaluated in a subject expansion cohort consisting of up to a maximum of 40 subjects (randomized to receive EXN407 at the selected dose or vehicle). Each eligible subject in the expansion cohort will receive study drug for up to 84 days, resulting in a total of 168 doses (168 single drops of 30 µL volume) of EXN407 or vehicle.

Subjects who do not meet individual subject stopping criteria at the clinical evaluation visits will continue dosing until the final day of dosing. Subjects who meet the stopping criteria will be discontinued from dosing but continue to receive safety and efficacy evaluation and all

scheduled clinical assessments as well as follow-up at an EOS Visit 28 days post the subject's last dose.

Detailed stopping criteria and guidance for Investigators are provided in Section 8.5.

8.2. Number of Subjects

Up to approximately 48 subjects will be enrolled into this study.

- Three (3) subjects are expected to be randomized to low-dose, 2 subjects are expected to be randomized to placebo (cohort 1, N=5 total)
- Three (3) subjects to mid-dose, 1 subject to placebo (expected to be cohort 2, N=4 total)
- Three (3) subjects to high-dose, 1 subject to placebo (expected to be cohort 3, N=4 total).

The remaining subjects (up to 40 additional subjects) will potentially be assigned to additional cohorts of four subjects at a given dose level (three EXN407 subjects, one placebo subject), and the remainder will be assigned to the dose expansion cohort once the highest well-tolerated dose is identified. Decisions to escalate to the next higher dose level, to recruit an additional cohort at the same dose level, or to move to the dose expansion cohort, are dependent on emergent data and the outcome of near real-time safety review by the DEC. An algorithm regarding progression to cohort expansion will be defined in the DEC charter.

The sample size for this study is deemed to be sufficient to evaluate the safety and tolerability of EXN407 in this population and to gather efficacy data that will aid in powering future clinical trials.

The final number of subjects is dependent on whether any dose levels are expanded following evaluation of emergent data by the DEC but is not expected to exceed approximately 48 enrolled subjects in total.

As the main aim of this study is to generate information on the safety and tolerability of EXN407, subjects who are withdrawn from the study for reasons other than safety issues may be replaced at the discretion of the Sponsor and the Investigator.

8.3. Treatment Assignment

8.3.1. Randomization

[redacted] Limited will prepare a system for randomization of subjects and will manage the randomization of eligible study subjects per this system. A randomization list will be prepared using a statistical software package by a [redacted] Biostatistician.

Each subject will be provided with a unique screening number post-documentation of informed consent. Once deemed eligible for enrolment in the study, the subject will be assigned a sequential randomization number prior to first dosing. Subjects who withdraw from the study, for any reason, without completing all necessary Screening assessments will be considered screen failures. Re-screening of screen failures (subjects screen failed for any reason) can be

performed only with the agreement of the study MM ([redacted]) / Sponsor MM. Please refer to Section 8.3.1.1 for more details on the re-screening process.

8.3.1.1. Re-Screening

Re-screening will be allowed in this study. The two most likely scenarios in which re-screening will take place are listed below. Other scenarios will be considered on a case-by-case basis and at the Investigator's discretion and following MM approval. Out of range laboratory assessments from first screening are to be repeated at re-screening. If the subject is proficient in dropper use after their initial run-in, then a further run-in is not required.

1) Back up subjects during dose escalation, who qualified for the study but were not randomized due to the current cohort filling up, can be put forward for inclusion in the subsequent cohort. Dose escalation or dose expansion subjects who qualified for the study but were not randomized due to scheduling or other constraints may also be re-screened. If the screening window has elapsed, and subjects are able to complete Visit 1A or 1E within 8 weeks of initial Screening, the following assessments do not need to be repeated during re-screening:

    - Demographics: Screening assessments missed from first Screening should be performed, if possible
    - Medical, Surgical and Ocular History: only changes to previous recordings should be noted
    - Twelve-Lead ECG
    - Hematology
    - Serum Chemistry
    - Coagulation
    - Urinalysis
    - Follicle-stimulating hormone
    - Corneal Endothelial Cell Count (if conducted not more than 6 months before Visit 1A or 1E)
    - Fluorescein fundus angiography

The remaining Screening assessments that would still be done:

- Informed Consent
- Height and Weight
- Review of Eligibility Criteria
- SD-OCT
- Concomitant Medications

- Ophthalmic Exam
- BCVA
- Physical Exam
- Vital Sign Measurements
- Urine Pregnancy Test
- CFP
- IOP
- Corneal Pachymetry
- Out of range laboratory values

2) Subjects who did not meet all Inclusion Criteria or who meet an exclusion criterion initially, but due to a change in clinical condition may have become eligible, can be re-screened at the discretion of the Investigator (e.g., HbA1c >12% originally, but patient has reduced this through better disease management). In this scenario, with the concurrence of the Sponsor's MM, it will not be necessary to completely re-screen the subject, and the following assessments can be skipped (if previous readings were taken within the allocated timeframe):

   - Corneal Endothelial Cell Count (if conducted not more than 6 months before Visit 1A or 1E)
   - Fluorescein fundus angiography (if conducted not more than 8 weeks before Visit 1A or 1E)

8.4. Dose Adjustment Criteria and Dose Escalation Committee (DEC)

The DEC will be established prior to Screening, the details of which will be set out in a DEC charter.

The DEC will provide recommendations about stopping, modifying or continuing the trial. The DEC will meet for cohort safety review to provide dose escalation recommendations.

Recommendations to escalate/maintain the dose will be made by the DEC in discussion with the PI, and based on a review of available clinical safety and safety laboratory data after completion of 7 days of treatment for each dose escalation cohort. An algorithm regarding progression to cohort expansion will be defined in a DEC charter. Details of the DEC's composition, roles and responsibilities will be described in the DEC charter. The Sponsor will chair the DEC. The DEC charter will include a definition of what safety observations would require a decision about dosing to be made.

8.5. Stopping Criteria and Rescue Medication

The Investigator, the study MM ([redacted]), the Sponsor MM or the DEC may decide to stop treatment for an individual subject for meeting the stopping criteria for individual subjects described in Section 8.5.1. Subjects who do not meet individual subject stopping criteria at the clinical evaluation visits will continue dosing until the final day of dosing. Subjects who discontinue study drug will continue to receive safety and efficacy evaluation and all scheduled clinical assessments as well as follow-up.

Due to the naturally progressive nature of the disease, ophthalmic stopping criteria will specifically apply if any subject shows deterioration in their retinal health due to acceleration in the rate of disease, in the opinion of the Investigator. In such an occurrence, if a subject receives rescue medication, they will cease further dosing with study drug, and the last clinical observation will be carried forward for exploratory efficacy analyses. Assessments required for safety endpoints as well as exploratory efficacy will still be performed for any subjects receiving rescue medication, whereas the following assessments that are only required for efficacy endpoints will not:

- DRSS
- Automated Perimetry

The Sponsor MM and/or the DEC may recommend stopping dosing for a cohort or suspend progression to the next higher dose level due to meeting the stopping criteria for a cohort described in Section 8.5.2.

8.5.1. Safety Criteria for Stopping Doses for Individual Subjects

Subjects may withdraw at any time as detailed in Section 15.1. Additionally, if at any time during the study the Investigator determines that a subject's safety is or has been compromised, the subject may be withdrawn from the study. Subjects may be discontinued from study drug prior to their completion of the study due to any of the following safety criteria being met.

8.5.1.1. Individual Subject Stopping Criteria

Any of the following criteria will be considered as stopping criteria for the study eye in individual subjects:

- An increase from baseline in CMT ≥75 µm when seen across two consecutive visits
- A loss of ≥15-letters of vision as determined by ETDRS, from the best previous in-study BCVA, due to DME, with current BCVA not better than baseline
- A loss of ≥10-letters of vision from best previous in-study BCVA (determined by ETDRS), due to DME, seen across two consecutive visits, with current BCVA score not better than baseline
- Persistent intolerable ocular irritation or redness
- Development of persistent corneal opacities or severe keratitis

- An ≥10% increase in corneal thickness in the study eye based on pachymetry assessed at a consistent time of day
- Intraocular pressure (IOP) increase of 12 mmHg or more (from baseline measurements) confirmed upon repeat testing
- Occurrence of any severe graded AE that is assessed by the Investigator to be related to study drug
- Occurrence of any serious adverse event assessed by the Investigator to be related to study drug
- If a subject's CMT is 420 µm or less, the subject is withdrawn from the study if there is BOTH a loss of BCVA of ≥10 letters AND an increase in CMT of ≥50 µm
- If a subject's CMT is >420 µm, the subject is withdrawn if there was also EITHER a loss of BCVA of ≥10 letters OR an increase in CMT of ≥50 µm
- The Investigator believes it is in the best interest of the subject to discontinue study drug dosing and/or initiate an anti-VEGF or other rescue therapy.

8.5.2. Safety Criteria for Suspending or Stopping a Cohort

8.5.2.1. Dose Escalation Cohorts (First in Human)

Any of the following criteria will be considered as stopping criteria for either stopping a cohort or stopping progression to the next higher dose level:

- The mean $AUC_{0\text{-last}}$ from PK plasma results is greater than the max AUC reported in the 13-week topical ocular toxicity study in NHP (Study 57012928) [i.e., 8.04 (hr*ng)/ml]
- ≥50 % of subjects within a cohort meet stopping criteria or are withdrawn by the PI (for other than personal or administrative reasons)
- ≥1 Serious adverse event (SAE) which was considered treatment related and occurred while on study drug within 7 days of treatment
- ≥2 AEs which were severe and considered treatment related and which occurred while on study drug within 7 days of treatment

8.5.2.2. Dose Expansion (Using Highest Well-Tolerated Dose from Dose Escalation)

Any of the following criteria will be considered as stopping criteria for stopping a dose expansion cohort:

- ≥50 % of subjects within a cohort meet stopping criteria or are withdrawn by the PI (for other than personal or administrative reasons)
- ≥1 SAEs considered treatment related which were either severe, life-threatening or fatal
- ≥2 AEs which were severe and considered treatment related and occurred while on study drug within 7 days of treatment

- ≥2 SAEs considered treatment related which were either mild or moderate severity, not life-threatening and not fatal

8.5.3. Use of Rescue Medication

In the case of any of the first two individual subject stopping criteria being met in the study eye, at the discretion of the Investigator, rescue medication comprising a marketed anti-VEGF therapeutic will be made available to the subject for the study eye. The two specific individual subject stopping criteria for rescue medication eligibility are:

- An increase from baseline in CMT ≥75 μm when seen across two consecutive visits
- A loss of ≥15-letters of vision as determined by ETDRS, from the best previous in-study BCVA, due to DME, with current BCVA not better than baseline

The Sponsor will reimburse the cost to the site to a maximum of two doses, or until the drug is funded by the Pharmaceutical Benefits Scheme or the cost is covered by health insurance, whichever occurs first. In such an occurrence, if a subject receives rescue medication, the subject will cease further dosing.

In the non-study eye, treatment (including anti-VEGF administered intravitreally) may be used as per standard of care. Subjects receiving treatment in the non-study eye may remain in the study at the discretion of the study Investigator.

8.5.4. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable to this study.

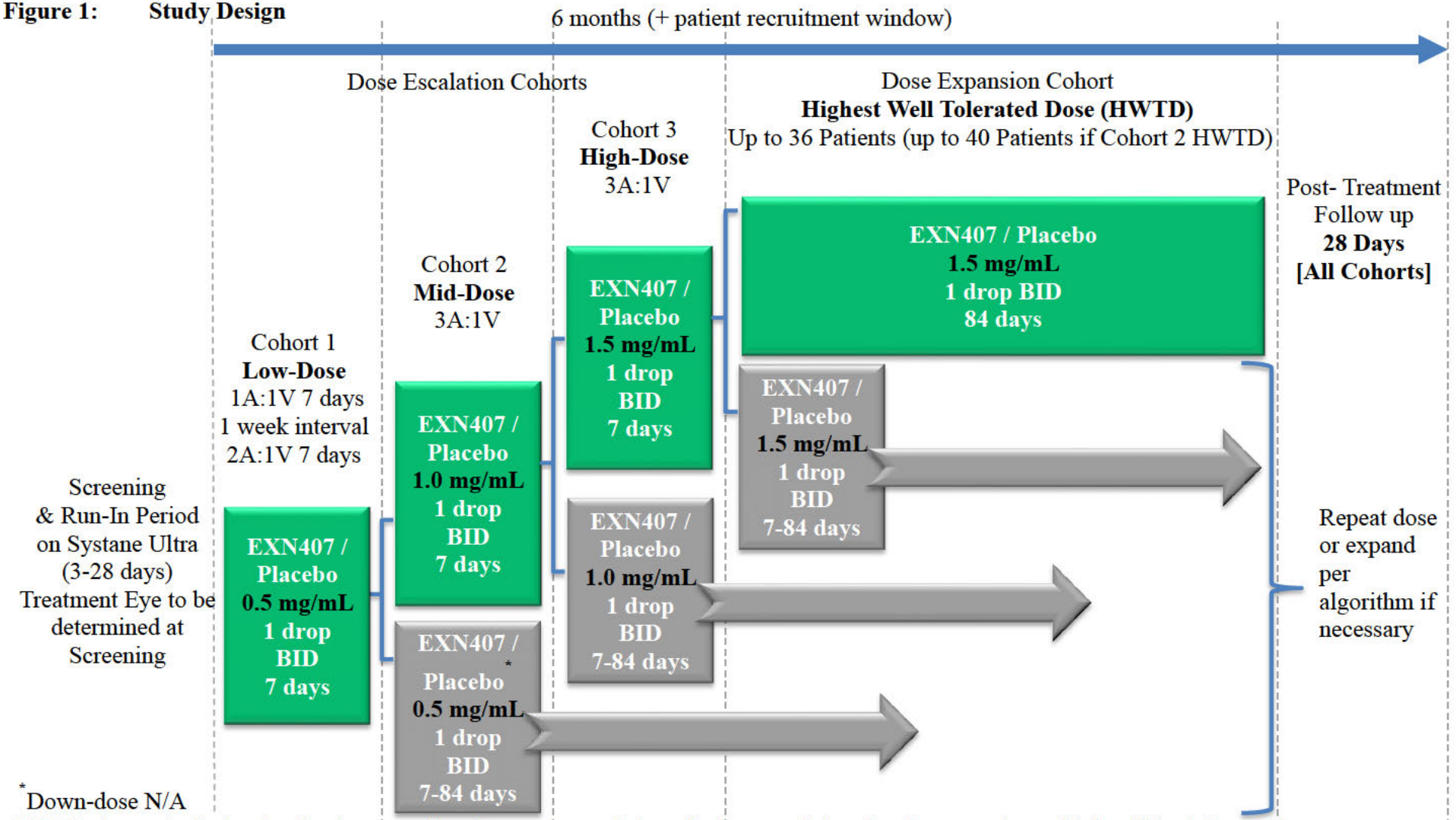
8.6. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study. This may be determined by the Sponsor, the Investigator, the DEC, the IEC or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IEC, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early study termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during termination or study suspension.

Figure 1: Study Design



NOTE: the study design is adaptive regarding the number and size of cohorts and dose level progression, which will be informed by emergent data and documented decision making by the DEC.

At least 1 week interval between each cohort for data evaluation & dose down / cohort expansion decision

Table 5: Schedule of Assessments			**DOSE ESCALATION COHORTS 1, 2 & 3**							**DOSE EXPANSION COHORT**					
Visit Numbers	**Screen V 1A/1E**	**Run-in[1]**	**2A**	**3A**	**4A**	**5A**	**6A**	**2E**	**3E**	**4E**	**4Ea**	**5E**	**6E**	**7E**	**8E**
Assessment	**Day -28 to -3**	**Post-screen to Day -1**	**Day 1 (BL-A)**	**Day 3**	**Day 4**	**Day 8**	**EOS / Follow-up or ET[2] - Day 36**	**Day 1 (BL-E)**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 85**	**EOS / Follow-up or ET[2] - Day 113**
Visit Window				**±1 day**	**±1 day**		**±2 days**		**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Informed Consent	X														
Demographics	X														
Height and Weight[3]	X		X			X	X	X		X		X	X	X	X
Review of Eligibility Criteria	X		X					X							
Medical, Surgical and Ocular History	X														
SD-OCT	X		X			X	X	X	X			X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X (phone contact)	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X		X	X	X	X
12 Lead ECG[4]	X		X	X		X	X		X					X	X

[1] The run-in period is from post-screening to Day -1 pre-randomization, with no associated visit.

[2] Subjects who withdraw early from the study will be encouraged to return to the clinic for an ET visit 28 days after their last dose of study drug (±2 days for A cohorts, ±7 days for E cohorts), with all of the same procedures as the regular EOS visits

[3] Height is to be measured once at Screening only, weight will be collected at all other visits noted

[4] 12-lead ECG: A single ECG recording will be made during pre-screening and on Day 1, Day 8 and Day 36 (EOS) for the escalation cohort and Day 85 and Day 113 (EOS) for the expansion cohort. On Day 3 and Day 8 (PK days for dose escalation and expansion, respectively) ECGs will also be collected and should be recorded near the 1 hour time point. Provision has been made for the ECG to be undertaken either in the clinic or the patients home.

Table 5: Schedule of Assessments			**DOSE ESCALATION COHORTS 1, 2 & 3**							**DOSE EXPANSION COHORT**					
Visit Numbers	**Screen V 1A/1E**	**Run-in[1]**	**2A**	**3A**	**4A**	**5A**	**6A**	**2E**	**3E**	**4E**	**4Ea**	**5E**	**6E**	**7E**	**8E**
Assessment	**Day -28 to -3**	**Post-screen to Day -1**	**Day 1 (BL-A)**	**Day 3**	**Day 4**	**Day 8**	**EOS / Follow-up or ET[2] - Day 36**	**Day 1 (BL-E)**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 85**	**EOS / Follow-up or ET[2] - Day 113**
Visit Window				**±1 day**	**±1 day**		**±2 days**		**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Ophthalmic Exam/ Ophthalmoscopy[5]	X		X	X	X	X	X	X	X			X	X	X	X
BCVA[6]	X		X			X	X	X	X	X		X	X	X	X
Physical Exam[7]	X		X				X	X				X	X	X	X
Urinalysis	X		X			X	X	X	X			X	X	X	X
Hematology	X		X			X	X	X	X			X	X	X	X
Serum Chemistry	X		X			X	X	X	X			X	X	X	X
Coagulation	X		X			X	X	X	X			X	X	X	X
Vital Sign Measurements[8]	X		X			X	X	X	X	X		X	X	X	X
Urine Pregnancy test[9]	X		X					X							
FSH test[10],	X														
Randomization			X					X							
Study Drug Dispensing			X					X				X	X		

[5] Ophthalmic Exam/ Ophthalmoscopy: Day 1 in dose escalation and dose expansion, exam will be conducted both pre-dose and post-dose.On PK days (Visit 3A/3E),exam conducted post-dose.
[6] BCVA will be performed by ETDRS visual acuity scale, to be done prior to all procedures requiring pupil dilation: FFA, etc.
[7] Complete physical examination will be performed at Screening and on Day 1 predose for escalation and expansion cohorts. All other examinations may be symptom directed.
[8] Vital signs: for dose escalation and dose expansioncohorts - on Day 1, vital signs done pre-dose and 2 hours post-dose (±15 minutes). For dose expansion cohort on Day 8, vital signs done pre-dose.
[9] Urine pregnancy test will only be performed for WOCBP
[10] FSH test is only required for postmenopausal subjects

Table 5: Schedule of Assessments			**DOSE ESCALATION COHORTS 1, 2 & 3**							**DOSE EXPANSION COHORT**					
Visit Numbers	**Screen V 1A/1E**	**Run-in[1]**	**2A**	**3A**	**4A**	**5A**	**6A**	**2E**	**3E**	**4E**	**4Ea**	**5E**	**6E**	**7E**	**8E**
Assessment	**Day -28 to -3**	**Post-screen to Day -1**	**Day 1 (BL-A)**	**Day 3**	**Day 4**	**Day 8**	**EOS / Follow-up or ET[2] - Day 36**	**Day 1 (BL-E)**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 85**	**EOS / Follow-up or ET[2] - Day 113**
Visit Window				**±1 day**	**±1 day**		**±2 days**		**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Study Drug Admin[11]			X	X				X	X						
FFA	X					X			X					X	
Blood draw for PK[12]				X					X						
CFP	X		X[13]			X	X	X	X			X	X	X	X
Treatment Tolerability Assessment			X					X							
IOP[14]	X		X	X	X	X	X	X	X			X	X	X	X
Corneal endothelial cell count	X[15]														X[15]
Corneal pachymetry	X		X			X	X	X				X	X	X	X
Automated Perimetry								X				X	X	X	X

[11] Dosing will be performed in clinic on Day 1 and on PK days: Day 3 (dose escalation) or Day 8 (dose expansion)

[12] Blood draws for PK will be collected for the escalation cohort at Day 3(+/-1 day) and expansion cohort - at Day 8 (+/- 1 day): pre-dose and 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1, 2, 3,and 4 hours (±10 minutes) post-dose;

[13] If not performed already during Screening, CFP will be obtained (required to be completed at least once prior to the subject's first dose of study drug)

[14] IOP tonometry will be conducted both pre-dose and post-dose on Day 1 (2A and 2E) only. The IOP assessment will be conducted only post-dose on visit 3A and 3E.

[15] Corneal endothelial cell count assessment is required for dose expansion cohort subjects only. Documented assessment within 6 months prior to V2E is acceptable, however the post treatment assessment must be performed using the same site and equipment; Post treatment assessment is to be performed within the one month follow up period

Table 5: Schedule of Assessments			**DOSE ESCALATION COHORTS 1, 2 & 3**							**DOSE EXPANSION COHORT**					
Visit Numbers	**Screen V 1A/1E**	**Run-in[1]**	**2A**	**3A**	**4A**	**5A**	**6A**	**2E**	**3E**	**4E**	**4Ea**	**5E**	**6E**	**7E**	**8E**
Assessment	**Day -28 to -3**	**Post-screen to Day -1**	**Day 1 (BL-A)**	**Day 3**	**Day 4**	**Day 8**	**EOS / Follow-up or ET[2] - Day 36**	**Day 1 (BL-E)**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 85**	**EOS / Follow-up or ET[2] - Day 113**
Visit Window				**±1 day**	**±1 day**		**±2 days**		**±1 day**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Practice dropper administration[16]		X													

Abbreviations: BL = baseline, BCVA = Best corrected Visual Acuity, CFP = Color Fundus Photography, ECG = Electrocardiogram, EOS = End of Study, FFA = fluorescein fundus angiography, FSH = Follicle-Stimulating Hormone, IOP = intraocular pressure, M = Month, OCT = Optical Coherence Tomography, PK = Pharmacokinetic, SD-OCT = Spectral Domain Optical Coherence Tomography, UD = Unit-dose, WOCBP=Women of Childbearing Potential

[16] Subjects that meet all eligibility criteria at Screening as assessed by the evaluating Investigator, will enter a run-in period (from post-screening to Day 1) where the subject (or subject's partner as applicable) will administer eye drops BID using Systane Ultra UD droppers

9. SELECTION AND WITHDRAWAL OF SUBJECTS

Deviations from eligibility criteria are not allowed due to the potential of the deviation to impact the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

9.1. Subject Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria at Screening and enrolment.

1. Subject is at least 18 years of age inclusive, at the time of signing the informed consent
2. BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12) in the study eye using the ETDRS visual acuity scale at Screening or BCVA less than a 69 ETDRS score (an approximate Snellen equivalent of 20/50 or 6/15) but who, in the Investigator's opinion, is unsuitable for treatment with anti-VEGF by intravitreal injection or refuses it. Subjects should have no more than a 7-letter difference in BCVA at Screening and baseline visit.
3. A female subject is eligible to participate if she agrees to use highly effective contraceptive measures (if heterosexually active and a WOCBP) from Screening until study completion, including the follow-up period. Acceptable methods of contraception include the use of condoms AND the use of an effective contraceptive that includes:
   a. Oral contraceptives (The Pill),
   b. Long-acting implantable hormones,
   c. Injectable hormones,
   d. A vaginal ring or an IUD.

   Rhythm methods are not considered as highly effective methods of birth control.
4. A female subject must also not be breast feeding and must have a negative pregnancy test prior to start of dosing if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at Screening:
   e. Is postmenopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
   f. Can provide documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
   g. Is amenorrheic for 12 months and serum follicle-stimulating hormone levels in the postmenopausal range for the institution.
5. Sexually active male subjects where the sexual partner is a WOCBP must be willing to use barrier contraception i.e., condoms, and another acceptable form of contraception (see Inclusion Criteria 3 for acceptable forms) during the study and for 3 months after the last dose of study medication.

6. Diabetes mellitus (Type 1 or Type 2). Any of the following will be considered to be sufficient evidence that diabetes is present:
   a. Current regular use of insulin for the treatment of diabetes
   b. Current regular use of oral anti-hyperglycemic agents for the treatment of diabetes
   c. Documented diabetes according to the American Diabetes Association and/or WHO criteria
7. Confirmation by the evaluating Investigator and central reading center of center involved DME in the study eye observed by both FFA and SD-OCT at the Screening Visit, with a CMT between 280-420 μm, and BCVA better than or equal to a 69 ETDRS (an approximate Snellen equivalent of 20/40 or 6/12).

   or

   Confirmation by the evaluating Investigator and central reading center of center involved DME in the study eye observed by both FFA and SD-OCT at the Screening Visit, with a CMT between 280-420 μm, and BCVA less than a 69 ETDRS score (an approximate Snellen equivalent of 20/50 or 6/15) but who, in the Investigator's opinion, is unsuitable for treatment with anti-VEGF by intravitreal injection or refuses it.
8. Ocular media is consistent with SD-OCT imaging and cataracts are not expected in the subject for the duration of the study
9. The subject has no other retinal disease
10. Subject is capable and willing to give written informed consent, which includes compliance with the requirements and restrictions listed in the consent form, and willing and able to return for all study visits, and comply with all protocol requirements and procedures
11. Subject or the subject's partner successfully demonstrates their ability to self-administer/administer eye drops at Screening, with multiple attempts allowed at the discretion of the Investigator

9.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria at Screening must not be enrolled in the study:

1. Any other retinal disease in the study eye, other than center involved DME or DR
2. Poor vision (VA 6/60 or worse) in the contralateral eye
3. Intraocular inflammation (including trace or greater) in the study eye. History of idiopathic or autoimmune uveitis in either eye
4. Ocular disorders/additional eye disease in the study eye, which in the opinion of the Investigator or central reading center may confound interpretation of study results, that compromise protocol assessments or that are likely to require intervention during the ~4.5 months of study, including, but not limited to atrophy of the RPE, sub-retinal fibrosis, organized hard exudate plaque, retinal vascular occlusion, retinal detachment,

macular hole, vitreomacular traction, macular epiretinal membrane within center of macula as evident with OCT evaluation, clinically significant cataract, vitreal opacities or hemorrhage, glaucoma with documented visual field loss, ischemic optic neuropathy, retinitis pigmentosa or choroidal neovascularization of any cause (e.g., AMD, ocular histoplasmosis, or pathologic myopia)

5. Uncontrolled intraocular pressure >25 mmHg in the study eye despite treatment with 2 or more glaucoma medications
6. Use of intravitreal anti-VEGF drugs including ranibizumab, bevacizumab, aflibercept **in the study eye** within 6 months of the Screening Visit, or in the **fellow (non study) eye** within 3 months of the Screening Visit. Use of topical corticosteroids or topical non-steroidal anti-inflammatory agents **in the study eye** within 28 days of the Screening Visit. Use of intravitreal corticosteroids in either eye or systemic steroids within 12 months of the Screening Visit. Prior use of Iluvien (without time limitation).

   N.B. There are no restrictions to prior use **in the fellow (non study) eye** of topical non-steroidal anti-inflammatory agents and topical corticosteroids. Subjects who have been treated with anti-VEGF in either eye but failed to respond adequately to that treatment, i.e., it failed to prevent DME progression, will be excluded.
7. Within 180 days prior to the Screening Visit, use of medications known to be toxic to the retina, lens or optic nerve (e.g., desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, and ethambutol)
8. The following procedures will exclude a potential subject if conducted within 180 days of planned first Screening Visit:
   a. Intraocular surgery in the study eye
   b. Laser photocoagulation in the study eye
9. Prior or current use of any systemically administered anti-angiogenic agent (e.g., bevacizumab, sunitinib, cetuximab, sorafenib, pazopanib), approved or investigational
10. Uncontrolled diabetes as indicated by HbA1c >12% at Screening or if HbA1c is ≤12% and diabetes mellitus is uncontrolled in the opinion of the Investigator
11. Poorly controlled hypertension at Screening despite lifestyle modifications and pharmacotherapy; systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg (mean of 3 measurements according to protocol specified conditions)
12. Current severe heart failure (New York Heart Association class III or IV)
13. QTcF >480 msec in any subject including those with Bundle Branch Block
14. History of (within 90 days of Screening date) cerebral vascular accident (stroke) or MI
15. Current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones, with concurrence from the Sponsor study responsible physician) or evidence of abnormal liver function tests [total bilirubin or alkaline phosphatase >2 × ULN; or ALT or AST >3 × ULN] or other hepatic abnormalities that in the opinion of the Investigator would preclude the subject from participation in the study

16. Significant renal impairment including subjects on chronic renal dialysis and subjects with a history of nephrectomy or kidney transplant (regardless of renal function)
17. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions, or severe allergic responses
18. History of sensitivity to fluorescein, any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or the study MM ([redacted] or Sponsor MM, contraindicates subject participation
19. Use of another IP within 1 month or 5 half-lives or twice the duration of biological effect (whichever is the longest) preceding the first dose of study medication
20. Alcohol or drug abuse within the past 180 days, or current mental condition (psychiatric disorder, senility or dementia), which may affect study compliance or prevent understanding of the aims, investigational procedures or possible consequences of the study. Alcohol abuse is defined as >21 alcohol units per week (where 1 unit = 284 mL of beer, 25 mL of 40% spirit or a 125 mL glass of wine)
21. Positive pregnancy test (all female subjects of childbearing potential must have a urine β-hCG pregnancy test performed at Screening and within 7 days prior to randomization) or is known to be pregnant or lactating
22. Known to have, or history of a positive test result for, hepatitis B or C, HIV, syphilis or tuberculosis; or known to have currently active COVID-19
23. Evidence of clinical instability or abnormal clinical laboratory findings prior to randomization that, in the opinion of the Investigator, makes the subject unsuitable for the study
24. A condition that, in the opinion of the Investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control)
25. Individuals in poor glycemic control who, within the last four months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next four months should not be enrolled
26. Employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator

Note: Investigators should assure that all study enrolment criteria have been met and determine that the subject has not had any interval change in clinical status since Screening. Before randomization, subjects whose status changes after Screening, such that they now meet an exclusion criterion, should be excluded from participation.

9.3. Subject Withdrawal Criteria

Subjects may withdraw their consent to participate in the study at any time. If a subject withdraws consent, the date and reason for consent withdrawal should be documented.

Subject data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early withdrawal of individual subjects can include but are not limited to:

- Protocol deviations or subject non-compliance (must be specified on the appropriate eCRF)
- Serious or severe AEs
- Administrative decision by the Investigator or the Sponsor
- Death
- Other (must be specified)

Wherever possible, the tests and evaluations, including those listed for the EOS/follow-up Visit, should be performed for all subjects who discontinue prior to the completion of the study.

Subjects will be encouraged to complete all necessary assessments and continue follow-up as recommended, noting that the safety follow-up period for continuing subjects is 28 days post their last dose of study drug.

9.4. Medication, Contraception and Other Restrictions

9.4.1. Medication

Prior use as detailed below or current use of the following medications are prohibited:

- Use of intravitreal anti-VEGF drugs including ranibizumab, bevacizumab, aflibercept **in the study eye** within 6 months of the Screening Visit, or use in the **fellow (non study) eye** within 3 months of the Screening Visit .
- Use of topical corticosteroids or topical non-steroidal anti-inflammatory agents **in the study eye** within 28 days of the Screening Visit.
- Use of intravitreal corticosteroids in either eye or systemic steroids within 12 months of the Screening Visit.
- Prior use of Iluvien (without time limitation). Any systemically administered anti-angiogenic agent (e.g., bevacizumab, sunitinib, cetuximab, sorafenib, pazopanib), approved or investigational.

N.B. There are no restrictions to prior use **in the fellow (non study) eye** of topical non-steroidal anti-inflammatory agents and topical corticosteroids.

9.4.2. Rescue Medication

Rescue medication is outlined in Section 8.5.

9.4.3. Contraception

A female subject is eligible to participate if she agrees to use highly effective contraceptive measures (if sexually active and a WOCBP) from Screening until study completion, including the follow-up period. Acceptable methods of contraception include the use of condoms AND the use of an effective contraceptive that includes:

- Oral contraceptives (The Pill)
- Long-acting implantable hormones
- Injectable hormones
- A vaginal ring or an IUD

Rhythm methods are not considered as highly effective methods of birth control.

A female subject must also not be breast feeding and must have a negative pregnancy test prior to start of dosing if of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at Screening:

- Is postmenopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
- Can provide documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
- Is amenorrheic for 12 months and serum follicle-stimulating hormone levels in the postmenopausal range for the institution

Sexually active male subjects where the sexual partner is a WOCBP must be willing to use barrier contraception i.e., condoms, and another acceptable form of contraception during the study and for 3 months after the last dose of study medication.

9.4.4. Fasting

There is no requirement for fasting in this study.

10. TREATMENT OF SUBJECTS

10.1. Description of Study Drug

Table 6: Investigational Product

	Investigational Product
Product Name:	EXN407
Dosage Form:	EXN407 ophthalmic solution is supplied in single-use low density polyethylene (LDPE) BFS ampoules, which allow for product administration directly to the eye
Unit-Dose	EXN407 will be provided at three concentrations: 0.5 mg/mL (0.05%) 1.0 mg/mL (0.1%) 1.5 mg/mL (0.15%)
Route of Administration	For topical ophthalmic administration by eye drop
Physical Description	EXN407 ophthalmic solution is presented as a preservative-free, sterile, clear, colorless solution
Manufacturer	[redacted]

10.2. Concomitant Medications

All medications, including over-the-counter (OTC) medications, vitamins, and herbal supplements, taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the Investigator to determine whether the subject is suitable for inclusion in the study.

The use of any IP or investigational medical device within 30 days prior to Screening is prohibited. Additional restrictions relating to concomitant medication use are outlined in Section 9.4.

All medications, including OTC medications, vitamins, and herbal supplements, taken by subjects during the course of the study will be recorded in the eCRF and coded using the most current WHO drug dictionary available at [redacted]. Prior and concomitant medications will be listed by subject and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (PT).

10.3. Treatment Compliance

Study drug will be administered at the clinic under supervision and instruction of assigned clinical staff at the day of first dosing, and on days where a pre-dose PK sample is required

(escalation cohorts Day 3, expansion cohort Day 8). Subjects will self-administer their IP without supervision thereafter.

10.4. Treatment Tolerability Assessment

Subjects will be asked by the Investigator or delegated study staff to provide a verbal assessment of the tolerability of the treatment administration via dropper. They will be asked to describe the level of comfort / discomfort on a scale of 0-10, with 0 being no discomfort and 10 being very uncomfortable. The subject will be asked immediately following dosing, then again at 1 and 2 minutes following dosing.

10.5. Masking (Blinding)

Masking procedures for the study will be described in detail in the Randomization Plan.

The Sponsor study team, Investigator, MM, study personnel, and subjects are not to make any effort to determine which study drug therapy is being received.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific subject, the Investigator may unblind a subject's treatment assignment via Medidata Randomization and Trial Supply Management (RTSM). However, prior to any unblinding, the Investigator is strongly advised to discuss options with the MM, Sponsor or appropriate study personnel. The Investigator will record in source documentation, the date and reason for revealing the blinded treatment assignment for that subject and the names and roles of personnel unblinded.

As soon as possible, and without revealing the subject's study treatment assignment (unless important to the safety of subjects remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

If the Investigator considers an AE to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, the Investigator may break the study code for that subject.

Randomization codebreak procedures are provided in Section 14.10.

All unblinding events must be reported to the MM and [redacted] promptly.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

The Sponsor will supply the study drug (both EXN407 and vehicle) to the investigational site. The study drug provided for this study was manufactured under current Good Manufacturing Practices (cGMP) and is suitable for human use.

11.2. Study Drug Packaging and Labelling

The Sponsor is responsible for the preparation and labelling and providing details of batch numbers, safety and stability data.

The study drug will be labelled in accordance with local regulatory requirements and will be shipped at a temperature of 2-8°C.

11.3. Study Drug Storage

Upon receipt, the study drug must be stored at 2-8ºC.

The Investigator or designee will be fully responsible for the security, accessibility and storage of the study drug while it is at the investigational facility.

11.4. Study Drug Preparation

EXN407 topical ophthalmic solution and placebo to match are presented for the proposed clinical study in single-use LDPE BFS ampoules, which allow for product administration directly to the eye. Each ampoule contains a nominal volume of 0.45 mL. A day pack of five ampoules is provided in a foil overwrap. Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

11.5. Administration

The Investigator or designee is responsible for the education of study staff and subjects as to the correct administration of the study drug, and subjects (or a subject's partner where applicable) will self-administer/administer the study drug following instruction from the Investigator or their delegate.

11.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record given to the study monitor.

11.7. Study Drug Handling and Disposal

On completion of the study, any surplus study drug supplies will be destroyed following site standard operating procedure for drug destruction, upon receipt of written approval from the Sponsor. Evidence of the destruction of any surplus study drug will be supplied to the study monitor. If no supplies remain, this will be documented in the dispensing record.

12. STUDY SCHEDULE

A Schedule of Assessments is provided in Table 5.

Where possible, assessments should be conducted in order of least invasive to most invasive.

12.1. Visit 1A/1E - Screening (Day -28 to Day -7)

Prior to enrolling into the study, and before the performance of any study procedures, potential subjects will attend a Screening Visit at which time they will be provided with full information concerning details of the study assessments and procedures. They will also be provided with an Informed Consent Form (ICF). Prior to being asked to sign the consent form, subjects will be given time to review study information and ask any questions.

After the consent form is signed, Screening assessments will be carried out as follows:

- Documentation of Demographics
- Documentation of medical, surgical and ocular history
- Documentation of Prior and Concomitant Medications
- Height and weight measurements, which will be used to automatically calculate body mass index (BMI) upon entry to the eCRF
- Vital Sign Measurements - systolic and diastolic blood pressure (BP), heart rate, respiratory rate, body temperature
- Physical Exam - Complete physical examination including: general appearance, head, ears, eyes, nose, throat, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes
- Single 12-lead ECG
- Collection of urine for urinalysis
- Urine Pregnancy test (WOCBP only)
- FSH testing (for postmenopausal subjects only)
- Collection of blood for hematology, serum chemistry and coagulation assessments
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA – to be done prior to all procedures requiring pupil dilation: FFA, etc.
- Corneal endothelial cell count (dose expansion cohort only [Visit 1E]; documented assessment within the 6 months prior to baseline is acceptable; however, post-treatment assessment must be conducted using the same equipment)
- CFP
- Tonometry to measure IOP
- Corneal pachymetry

- FFA
- Investigator review of all eligibility criteria

12.1.1. Identification of Study Eye and Contralateral Eye

Following completion of the ophthalmologic assessments, including SD-OCT and BCVA, the Investigator should identify the eye in which evident center involved DME is present with a CMT between 280-420 μm as determined by SD-OCT. All SD-OCT assessments for a subject should be taken with the same make and model of equipment throughout the duration of the study.

If both eyes qualify on the basis of evident DME with a CMT between 280-420 μm, and BCVA better than or equal to a 69 ETDRS score (an approximate Snellen equivalent of 20/40 or 6/12) then the Investigator should choose the eye with the worse (greater) CMT as the study eye. If CMT is the same in both eyes then the eye with the worse visual function as assessed by BCVA will be selected as the study eye. If both eyes have the same BCVA then the right eye will be selected.

All protocol evaluations will also be completed on the non-dosed contralateral eye. No vehicle-control or other study treatments will be administered to the contralateral eye.

12.2. Run-in Period (Post-Screening to Day -1 Pre-randomization)

Subjects that meet all eligibility criteria at Screening as assessed by the evaluating Investigator will enter a run-in period (from post-Screening to Day -1) where the subject (or subject's partner as applicable) will administer eye drops BID using Systane Ultra UD droppers. The run-in period serves to familiarize and train subjects in topical administration via eye dropper. There is no associated visit for this run-in period.

This is to mean that upon completion of the Screening procedures, if the Investigator considers the subject eligible based upon all results in hand, the run-in period may commence immediately. The Investigator does not need to await return of external reports. The Investigator will have their assessment of CMT on hand for initial determination of eligibility and study eye, before the subject enters run-in. There is no concern regarding use of the Systane Ultra UD eye drops in patients and full eligibility cannot be determined until subjects attend the baseline visit and confirm proficiency in administration of eye drops.

Upon initiating the subject's run-in period, sites should inform [redacted] that the Investigator has initially assessed the patient as eligible (pending remaining reports and run-in proficiency).

A central reading facility (EyeKor) is being used to determine eligibility based upon center involved DME (in particular CMT reading). The turnaround time for this is 3 business days. The run-in period can be shortened to a minimum duration that allows for the results to be available for eligibility confirmation and randomization purposes at Visit 2A/2E.

For rescreening patients, if the patient is proficient in dropper use after their initial run-in, then a further run-in is not required.

12.3. Dose Escalation (A) Cohorts 1, 2, 3, etc.

12.3.1. Visit 2A - Day of First Dosing (Day 1)

12.3.1.1. Before Dosing

Prior to dosing on Day 1, subjects will be randomized to one of the following treatments:

- EXN407
- Placebo (vehicle)

The following assessments should be performed prior to the administration of study drug unless otherwise noted:

- A verbal check by the Investigator that the subject experienced no issues with self-administration of Systane® Ultra UD eye drops during the run-in period
- Concomitant Medications
- Documentation of AEs since the Screening Visit (from time of consent)
- Weight measurement
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Physical Exam - Complete physical examination including: general appearance, head, ears, eyes, nose, throat, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes
- Single 12 lead ECG
- Urine sample collected for urinalysis
- Urine Pregnancy test (WOCBP only)
- Blood draw for hematology, serum chemistry and coagulation
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA
- Tonometry to measure IOP
- Corneal pachymetry
- Investigator review of all eligibility criteria

If not performed already during Screening, the following measures of retinal anatomy will be measured (required to be completed at least once prior to the subject's first dose of study drug):

- CFP

Any pre-dose assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator, or if the assessment could not be completed. In the case

of repeat assessments, the measure reflecting the highest level of visual function will be considered the baseline value unless regarded as an implausible reading in the opinion of the Investigator. Structural tests will be averaged and used as the baseline (pre-treatment value).

Following final review of all eligibility criteria and randomization the study drug will be dispensed ready for administration.

12.3.1.2. Dosing

Subjects will be dosed according to their assigned treatment. EXN407 or vehicle will be instilled into the subject's study eye under supervision and instruction of the Investigator (or delegate) at this visit, and subjects will self-administer their IP without supervision thereafter.

Subjects will administer further doses BID for 7 days.

12.3.1.3. Post Dosing

Subjects will remain in the clinic through the completion of all scheduled postdose procedures. Subjects will be monitored for signs of ocular irritation and inflammation for an initial period of 2 hours post-dose, for their first dose on Day 1 only.

The following procedures will be conducted post-dose:

- Treatment tolerability assessment (immediately post-dose, and at 1 and 2 minutes post-dose. See Section 10.4)
- Ophthalmic Exam/ Ophthalmoscopy
- Tonometry to measure IOP
- Vital Sign Measurements at 2 hours post-dose (±15 minutes)
- AEs (continuous)

12.3.2. Visit 3A - Day 3

Subjects will return to the clinic to be assessed for safety and tolerability of the study drug on Day 3 with a window of ±1 day, while still receiving BID dosing. Day 3 and Day 4 should not fall on the same day.

For sites conducting PK at the clinic: Subjects will be required to wait to take their morning dose, and to administer this in the clinic following the completion of all pre-dose assessments.

For sites conducting PK via home nurse visit: Subjects will be required to wait to take their morning dose until after the pre-dose PK sample of the home nurse appointment, which can be scheduled ±1 day of Day 3. This home nurse visit can take the place of the in-clinic visit, and the ophthalmic exam and tonometry can be omitted. The ECG cannot be omitted.

If the ECG and PK samples are collected on different days, the subject will be required to wait to take their morning dose until at the clinic, to allow correct timing of the ECG assessment.

The following procedures will be conducted prior to the administration of the morning dose of study drug unless otherwise noted:

- Concomitant medications

- AEs since the last visit
- PK blood draw (pre-dose)

The following procedures will be conducted post-dose:

- PK blood draws (15 minutes, 30 minutes, and 1, 2, 3, and 4 hours post-dose)
- Ophthalmic Exam/ Ophthalmoscopy
- Tonometry to measure IOP
- Single 12-lead ECG (ECG recording will be made at approximately 1 hour post-dose)

12.3.3. Visit 4A - Day 4

Subjects will return to the clinic to be assessed for safety and tolerability of the study drug on Day 4 with a window of ±1 day, while still receiving BID dosing. Day 3 and Day 4 should not fall on the same day.

The following procedures will be conducted at the follow-up visit:

- Concomitant medications
- AEs since the last visit
- Ophthalmic Exam/ Ophthalmoscopy
- Tonometry to measure IOP

12.3.4. Visit 5A - Day 8

Subjects will return to the clinic for a follow-up visit on Day 8:

- Concomitant Medications
- AEs since the last visit
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Weight measurement
- BCVA – to be done prior to all procedures requiring pupil dilation
- Blood draw for hematology, serum chemistry and coagulation
- Single 12-lead ECG
- Collection of urine for urinalysis
- All remaining Ophthalmic Exams/ Ophthalmoscopy
- SD-OCT
- CFP
- Tonometry to measure IOP
- Corneal pachymetry

- FFA

12.3.5. Visit 6A – EOS / Day 36 (±2 Days)

Subjects will return to the clinic for their EOS visit on Day 36 with a window of ±2 days.

The following procedures will be conducted:

- Concomitant Medications
- AEs since the last visit
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Physical Exam (targeted physical exam only, see Section 14.1.4)
- Weight measurement
- BCVA – to be done prior to all procedures requiring pupil dilation
- Blood draw for hematology, serum chemistry and coagulation
- Single 12-lead ECG
- Collection of urine for urinalysis
- All remaining Ophthalmic Exams/ Ophthalmoscopy
- SD-OCT
- CFP
- Tonometry to measure IOP
- Corneal pachymetry

This visit marks the end of participation in this study.

12.4. Dose Expansion (E) Cohort

12.4.1. Visit 2E - Day of First Dosing (Day 1)

12.4.1.1. Before Dosing

Prior to dosing on Day 1, subjects will be randomized to treatment.

The following assessments will be carried out prior to the administration of study drug unless otherwise noted:

- Concomitant Medications
- AEs since the Screening Visit (from time of consent)
- Weight measurement
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature

- Physical Exam - Complete physical examinations including: general appearance, head, ears, eyes, nose, throat, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes
- Collection of urine for urinalysis
- Urine Pregnancy test (WOCBP only)
- Blood draw for hematology, serum chemistry and coagulation
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA
- CFP
- Tonometry to measure IOP
- Corneal pachymetry
- Automated Perimetry – to be performed by Humphrey Visual Field Analyzer
- Investigator review of all eligibility criteria

Following final review of all eligibility criteria and randomization the study drug will be dispensed ready for administration. Investigators should assure that all study enrolment criteria have been met and determine that the subject has not had any interval change in clinical status since Screening. Before randomization, subjects whose status changes after Screening, such that they now meet an exclusion criterion, should be excluded from participation.

12.4.1.2. Dosing

Subjects will be dosed according to their assigned treatment. Study drug will be administered under supervision and instruction of assigned clinical staff.

Subjects will administer doses BID for 84 days for a total of 168 doses. Subsequent doses do not have to be administered during study visits and at site (with the exception of Visit 3E – Day 8, where subjects may be required to wait to take their morning dose and administer this in the clinic or may be able to administer at home and have PK sampling conducted via a home visit, dependent upon Investigator preference and individual site arrangements), but should be administered approximately 12 hours apart by the subject.

12.4.1.3. After Dosing

Subjects will remain in the clinic through to the completion of all scheduled post-dose procedures.

The following procedures will be conducted post-dose:

- Treatment tolerability assessment (immediately post-treatment, and at 1 and 2 minutes post-treatment. See Section 10.4)
- Ophthalmic Exam/ Ophthalmoscopy

- Vital Sign Measurements at 2 hours post-dose (±15 minutes)
- Tonometry to measure IOP
- AEs (continuous)

12.4.2. Visit 3E - Day 8 (±1 Day)

Subjects will return to the clinic to be assessed for safety and tolerability of the study drug on Day 8 ±1 day, while still receiving BID dosing.

For sites conducting PK at the clinic: Subjects will be required to wait to take their morning dose, and to administer this in the clinic following the completion of all pre-dose assessments.

For sites conducting PK via home nurse visit: Subjects will be required to wait to take their morning dose until after the pre-dose PK sample of the home nurse appointment, which can be scheduled ±1 day of Day 8.

The following procedures will be conducted prior to the administration of study drug unless otherwise noted:

- Concomitant medications
- AEs since the last visit
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- BCVA – to be done prior to all procedures requiring pupil dilation
- Blood draw for hematology, serum chemistry and coagulation
-
- PK blood draw - pre-dose

The following procedures will be conducted post-dose:

- PK blood draws (15 minutes, 30 minutes, and 1, 2, 3, and 4 hours post-dose)
- Single 12-lead ECG at approximately 1 hour post-dose
- Collection of urine for urinalysis
- All remaining Ophthalmic Exams/ Ophthalmoscopy
- SD-OCT
- CFP
- Tonometry to measure IOP
- FFA

12.4.3. Visit 4E – Day 15 (±2 Days)

Subjects will return to the clinic to be assessed for safety and tolerability of the study drug on Day 15±2 days, while still receiving BID dosing.

The following procedures will be conducted:

- Concomitant medications
- AEs since the last visit
- Weight measurement
- BCVA
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature

12.4.4. Visit 4Ea – Day 22 (±2 Days)

Subjects will be contacted by telephone on Day 22 ±2 days, while still receiving BID dosing to be assessed for any AEs since the last visit.

12.4.5. Visit 5E - Day 29 (±2 Days)

Subjects will return to the clinic to be assessed for safety and tolerability of the study drug on Day 29 ±2 days, while still receiving BID dosing.

The following procedures will be conducted:

- Concomitant medications
- AEs since the last visit
- Weight measurement
- BCVA – to be done prior to all procedures requiring pupil dilation
- Physical Exam (targeted physical exam only, see Section 14.1.4).
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Blood draw for hematology, serum chemistry and coagulation
- Collection of urine for urinalysis
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- CFP
- Automated Perimetry – to be performed by Humphrey Visual Field Analyzer
- Tonometry to measure IOP
- Corneal pachymetry

12.4.6. Visit 6E - Day 57 (±2 Days)

Subjects will return to the clinic for a follow-up visit on Day 57 ±2 days and have following procedures conducted, while still receiving BID dosing:

- Concomitant medications
- AEs since the last visit
- Weight measurement
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Physical Exam (targeted physical exam only, see Section 14.1.4).
- Collection of urine for urinalysis
- Blood draw for hematology, serum chemistry and coagulation
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA – to be done prior to all procedures requiring pupil dilation
- CFP
- Automated Perimetry – to be performed by Humphrey Visual Field Analyzer
- Tonometry to measure IOP
- Corneal pachymetry

12.4.7. Visit 7E - Day 85 (±2 Days)

Subjects will return to the clinic for a follow-up Visit on Day 85 with a window of ±2 days.

The following procedures will be conducted:

- Concomitant medications
- AEs since the last Visit
- Weight measurement
- Vital Sign Measurements - systolic and diastolic BP, heart rate, respiratory rate, body temperature
- Physical Exam (targeted physical exam only, see Section 14.1.4)
- Single 12-lead ECG
- Collection of urine for urinalysis
- Blood draw for hematology, serum chemistry and coagulation
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA – to be done prior to all procedures requiring pupil dilation
- CFP
- Automated Perimetry – to be performed by Humphrey Visual Field Analyzer

- Tonometry to measure IOP
- Corneal pachymetry
- FFA

12.4.8. Visit 8E – EOS/Follow-up - Day 113 (±7 Days)

Subjects will return to the clinic for their EOS Visit on Day 113 with a window of ±7 days.

The following procedures will be conducted:

- Concomitant medications
- AEs since the last visit
- Weight measurement
- Vital Sign Measurements
- Physical Exam (targeted physical exam only, see Section 14.1.4).
- Single 12-lead ECG
- Collection of urine for urinalysis
- Blood draw for hematology, serum chemistry and coagulation
- Ophthalmic Exam/ Ophthalmoscopy
- SD-OCT
- BCVA – to be done prior to all procedures requiring pupil dilation
- Corneal endothelial cell count (assessment can be conducted within the one month post-treatment follow-up window)
- CFP
- Automated Perimetry – to be performed by Humphrey Visual Field Analyzer
- Tonometry to measure IOP
- Corneal pachymetry

12.5. Early Termination Visit (if applicable)

Subjects who withdraw early from the study will be encouraged to return to the clinic for an ET Visit 28 days after their last dose of study drug (±2 days for A cohorts, ±7 days for E cohorts), with all of the same procedures as the regular EOS visits (Section 12.3.5 for A cohorts or Section 12.4.8 for E cohorts).

This visit marks the end of participation for subjects that withdraw early from the study.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Blood Sample Collection

Blood samples for PK analysis will be obtained, at either the subject's residence or the clinic, according to the Investigator's decision and discussion with the subject. The determination of the sampling location will be based on site feasibility. Sampling will occur within 15 minutes prior to dosing and at the time points delineated in the Schedule of Assessments (Table 5).

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube and in the eCRF. The allowed time deviation window for blood sample collection before a deviation is recorded is documented in the Schedule of Assessments (Table 5).

13.2. Urine Sample Collection

There are no urine PK assessments planned for this study.

13.3. Sample Analysis

Plasma PK sample analysis will be performed using validated procedures and methods as outlined in the Laboratory Manual.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

14. ASSESSMENT OF SAFETY

14.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 5). However, if a subject is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

14.1.1. Demographic/Medical History

Medical history (including alcohol and smoking status), date of birth, age (calculated), sex, ethnicity, and race will be recorded at Screening.

14.1.2. Vital Signs

Vital signs will be measured at the time points specified in the Schedule of Assessments (Table 5) with subjects resting for at least 5 minutes in a supine position. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible, ensuring the blood draw is within the window specified in the protocol. The parameters to be measured are systolic and diastolic BP, heart rate, respiratory rate, body temperature.

Additional vital signs may be performed at other times if deemed necessary.

14.1.3. Weight and Height

Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the Schedule of Assessments (Table 5) and will be automatically used to calculate BMI in the eCRF. BMI will be calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (kg/m^2). Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

14.1.4. Physical Examination

Complete and targeted physical examinations will be performed by a licensed physician at the time points specified in the Schedule of Assessments (Table 5).

Complete physical examinations include: general appearance, head, ears, eyes, nose, throat, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.

Targeted physical examinations include: head, ears, eyes, nose, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.5. Electrocardiogram

A single 12-lead ECG will be taken at the time points delineated in the Schedule of Assessments (Table 5). Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with subjects in a supine position. Subjects must be in this position for at least 5 minutes before the reading is taken.

All ECG tracings will be reviewed by the PI or designee.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

14.1.6. Laboratory Assessments

Safety laboratory tests (hematology, biochemistry, coagulation, and urinalysis) will be performed at the time points specified in the Schedule of Assessments (Table 5). Additional clinical laboratory tests may be performed at other times if deemed necessary based on the subject's clinical condition.

Medically indicated laboratory tests (emergency / unscheduled tests) can be conducted at the local laboratory, however blood samples from all unscheduled draws should also be sent to the central laboratory.

A blood sample will be taken from each subject for hematology, coagulation and biochemistry analyses at the time points delineated in the study schedules.

14.1.6.1. Hematology

Hematology parameters to be tested are:

- Hemoglobin (HGB)
- Hematocrit (HCT)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes with differential including Eosinophils (ESN), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM), and Monocytes (MONO)

14.1.6.2. Biochemistry

Biochemistry parameters to be tested are:

- C-reactive protein (CRP)
- Urea (U)
- Creatinine (CREAT)
- Total Bilirubin (BILI) and Direct Bilirubin (BILIDIR)
- Urate (URATE)

- Albumin (ALB)
- Globulin (GLOBUL)
- Alkaline Phosphatase (ALP)
- Creatine Kinase (CK)
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Gamma-GT (GGT)
- Glucose (GLU)
- Sodium (NA)
- Potassium (K)
- Calcium (CA)
- Chloride (CL)
- Phosphate (PHOS)
- Bicarbonate (BICARB)
- HbA1c

14.1.6.3. Coagulation

Coagulation parameters to be tested are:

- International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (APTT)

14.1.6.4. Urinalysis

A urinalysis test (dipstick) will be performed for each subject. Urinary analysis will be performed at Screening and other times according to the study schedule. If abnormality is noted for protein, blood, nitrite or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of RBC, WBC, bacteria and casts will be performed.

Macroscopic urinalysis parameters to be tested are:

- pH (PH)
- Specific Gravity (SPGRAV)
- Creatinine (CREATININE)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)

- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

14.1.6.5. Pregnancy Testing

A urine β-hCG pregnancy test shall be performed at Screening and within 7 days prior to randomization for WOCBP only.

14.1.6.6. Follicle-stimulating Hormone Testing

Women not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least 12 months). Postmenopausal status will be confirmed through testing of FSH levels ≥40 IU/mL at Screening.

14.1.7. Ophthalmology Assessments

All ophthalmology assessments will be performed by the Investigator or suitably qualified delegate trained in the techniques and equipment.

14.1.7.1. OCT

The SD-OCT will be performed at times according to the Schedule of Assessments (Table 5), for confirmation and repeat observations of center involved DME in the study eye. A 5-layer OCT (Internal Limiting Membrane [ILM], RPE, Ellipsoid Zone [EZ], Inner Plexiform Layer [IPL], Outer Plesiform Layer [OPL]) will be performed on all assessments except for the Screening measurement.

14.1.7.2. Ophthalmic Exam / Ophthalmoscopy

Ophthalmic Exam will be performed via binocular indirect ophthalmoscopy at Screening and at other times according to the Schedule of Assessments (Table 5), to follow for ophthalmic AEs and changes throughout the study. Slit lamp biomicroscopy will be performed for anterior eye assessment.

14.1.7.3. BCVA

BCVA will be performed using the ETDRS visual acuity measure at Screening and at other times according to the Schedule of Assessments (Table 5), to assess visual acuity. BCVA will be performed prior to procedures requiring pupil dilation.

14.1.7.4. FFA

FFA will be performed at times according to the Schedule of Assessments (Table 5), for confirmation and repeat observations of center involved DME in the study eye. The injection of fluorescein will be performed per standard practice at the clinic. To minimize allergic reaction to fluorescein angiography, any subject who has had mild reactions to previous FFA (e.g., itching) will be given medication prior to undergoing FFA.

14.1.7.5. Color fundus photography (CFP)

Color fundus photography (CFP) will be performed at times according to the Schedule of Assessments (Table 5).

14.1.7.6. IOP / Tonometry

IOP will be measured at the timepoints delineated in the Schedule of Assessments (Table 5). In addition to typical methods of measuring IOP (i.e., Goldman applanation tonometry [GAT]), the iCare Tonometer or Tono-Pen methods of measurement will be accepted for use in this study.

14.1.7.7. Automated Perimetry

Automated Perimetry will be measured by Humphrey Visual Field Analyzer at the timepoints delineated in the Schedule of Assessments (Table 5).

14.1.7.8. Corneal endothelial cell count

Corneal endothelial cell count will be performed at the timepoints delineated in the Schedule of Assessments (Table 5).

14.1.7.9. Corneal pachymetry

Corneal pachymetry will be performed at the timepoints delineated in the Schedule of Assessments (Table 5).

14.2. Adverse and Serious Adverse Events

In this study, AEs will be reported for all subjects from the time of consent until the completion of the follow-up/EOS Visit. SAEs will be reported for all subjects (enrolled and not enrolled) from the time of consent. Adverse events reported from the time of consent to Day -1 will be recorded as pre-treatment AEs. TEAEs will be evaluated from the first administration of study drug until the follow-up/EOS Visit or up to a 30-day follow-up period for AEs deemed related to treatment. Adverse events that are ongoing at the EOS Visit will be marked as Not Recovered/Not resolved on the AE eCRF page (see Section 14.3.4).

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the subject's medical records and the eCRF.

14.3. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant 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 definition of an AE include:

- 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 drug administration that occur during the reporting periods, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or concomitant medications (overdose per se will not be reported as an AE/ SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE
- Situations where an untoward medical occurrence did not occur (e.g., 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

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Seriousness
- Causality/relation to study treatment
- Action taken regarding study drug
- Action taken regarding AE
- Outcome

14.3.1. Severity of an Adverse Event

Severity of AEs will be graded by the Investigator as one of:

- **Mild (Grade 1):** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2):** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- **Severe (Grade 3):** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4):** A type of AE that places the subject at immediate risk of death.
- **Death (Grade 5):** Events that result in death.

14.3.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the subject's environment or clinical state, therapeutic interventions or concomitant drugs administered to the subject. This is especially so when an event occurs prior to the commencement of treatment with the study drug.

- **Unlikely:** The temporal association, subject history, and/or circumstances are such that the study drug is not likely to have had an association with the observed event. Other conditions, including concurrent illness, progression, or expression of the disease state, or reaction to a concomitant drug administered appear to explain the event.
- **Possible:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- **Probable:** The event follows a reasonable temporal sequence from the time of study drug administration and follows a known response to the study drug and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- **Definite:** The event follows a reasonable temporal sequence from the time of study drug administration or control abates upon discontinuation or cannot be explained by known characteristics of the subject’s clinical state.

14.3.3. Action Taken with Investigational Products

Should the Investigator need to alter the administration of the study drug from the procedure described in the protocol due to the well-being and safety of the subject then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

14.3.4. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered / Resolved
- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving
- Fatal
- Unknown

14.4. Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the study drug (active or placebo), that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the subject, or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization
- Development of drug dependency or drug abuse

An AE is considered "life-threatening" if, in the opinion of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure does not require reporting as a SAE to the clinical research organization's Safety Department.

14.4.1. Notification of a Serious Adverse Event

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and IEC, all SAEs, **must be reported to [redacted] within 24 hours** from the time the site investigational team first become aware of the event.

Initially reporting is achieved by completing an SAE report form and email to [redacted] via the assigned project email address, which will be provided upon study setup.

[redacted]

If completion of an SAE form and emailing is not possible, reporting by telephone to [redacted] is required and a completed [redacted] SAE form must be emailed at the first opportunity.

Initial notification of an SAE by telephone to [redacted] must be confirmed in writing 24 hours from the time the site investigational team first becomes aware of the event using the SAE report form as described above.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, scanned and emailed to the address at the bottom of the report form.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the subject's medical records and in the eCRF.

14.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., biochemistry, hematology, coagulation and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** by the PI and/or delegate or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. To be considered clinically significant, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

14.6. Recording Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and SAEs will be collected from the time of consent until the end of the study. The AE term should be reported in

standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study. AEs that occur during the study must be documented in the subject's medical record, on the AE eCRF and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 14.4. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on a [redacted] pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

14.7. Reporting Serious Adverse Events

Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to the Sponsor.

Additional follow-up information, if required or available, should all be emailed or faxed to the Sponsor within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IEC of all SAEs in accordance with the IEC's SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug related events that occur during the clinical trial. The investigational site is responsible for notifying its IEC of these additional SAEs.

14.8. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related or probably related to the study drug must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject dies or is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

14.9. Dose Limiting Toxicity

No dose limiting toxicities are anticipated.

14.10. Randomization Codebreak

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific subject, should the Investigator unblind a subject's treatment assignment. The unbinding procedures for this study will be according to the [redacted] RTSM which includes an unblinding module. However, prior to any unblinding, the Investigator is strongly advised to discuss options with the MM, Sponsor, or appropriate study personnel. The Investigator will record in source documentation, the date and reason for revealing the blinded treatment assignment for that subject and the names and roles of the personnel unblinded. The Local MM should be promptly informed.

15. STUDY COMPLETION AND DISCONTINUATION

15.1. Subject Withdrawal

In accordance with applicable regulations, a subject has the right to withdraw from the study, at any time and for any reason, without prejudice to his future medical care.

If a subject is withdrawn because of an AE, the Investigator must arrange for the subject to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up/EOS Visit or until the PI and MM determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of subjects from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or subject noncompliance.

If a subject asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

15.2. Subject Replacement

Subjects who are enrolled but who do not receive any dose of study drug will be replaced and the replacement subject will receive the same treatment as the subject they are replacing. Subjects who discontinue the study prior to completion of dosing may be replaced at the discretion of the Sponsor.

As the main aim of this study is to generate information on the safety and tolerability of EXN407, subjects who receive dosing with study drug and are subsequently withdrawn from the study for reasons other than safety issues may be replaced at the discretion of the Sponsor and the Investigator.

16. TERMINATION OR SUSPENSION OF THE STUDY

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study drug and/or treatment indicates a change in the known risk/benefit profile for the drug, such that the risk/benefit is no longer acceptable for subjects participating in the study. This may be determined by the Sponsor, the Investigator, the IEC or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

However, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs.

If the Sponsor, the IEC, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor, which will be followed by the investigational site during the termination or suspension of the study.

In the event that the study is terminated early, every effort should be made by the Investigator and investigational site staff to follow AEs and SAEs for all subjects up to a 30-day follow-up period after study termination.

The Investigator should notify the relevant IEC in writing of the study's completion or early discontinuation.

17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

17.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented between the Sponsor and the Investigator.

The Sponsor has appointed [redacted] to manage and monitor the study to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitor and regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that subject confidentiality is respected

During the study, the monitor will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs
- Confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IEC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

17.2. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

17.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

18. STATISTICS

A detailed methodology for the statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be signed off prior to the database lock. All computations will be performed using SAS® version 9.2 (SAS Institute, Cary, NC). Since the primary objective of the study is to evaluate ocular safety and tolerability, no formal hypothesis testing will be performed for any continuous or categorical variables. All statistical analyses will be descriptive in nature and any statistical inference will be carried out according to the analysis plan and interpreted in view of the exploratory nature of the study.

Descriptive statistics (number non-missing values [n], arithmetic mean, SD, 95% confidence interval for mean [where specified], median and range) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. The summaries will be presented by treatment group/cohort and nominal visit/time point (where applicable). Data from the placebo subjects will be pooled (if appropriate).

Baseline demographics and disease characteristics, safety, and [redacted] will be summarized descriptively by treatment group and for all subjects combined. Plasma concentrations of EXN407 will be summarized by treatment group and protocol specified time point, and PK parameters calculated where relevant.

Unless stated otherwise, unscheduled data will not be included in the descriptive summaries.

All subject data will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by treatment group, subject number, date/time and visit.

18.1. Analysis Populations

Subject inclusion into each population will be determined prior to the final analysis.

Intent-to-treat population:

All randomized subjects, regardless of whether they receive study drug or not, will be included in the ITT population. It will be based on the treatment assigned to a subject, not what they actually received. All disposition and demographic data analysis will be based on the ITT population. The ITT population will be used for all data listings.

Safety population:

The Safety population will comprise all randomized subjects who received any amount of study drug. Summaries, listings, and analyses will be based on the treatment actually received. Screen failures and randomized subjects who did not receive any medication will be excluded from the safety analysis set.The Safety population will be used for the summaries of all safety assessments.

Pharmacokinetic population:

The PK population will comprise all subjects who received any dose of the study drug who had no important protocol deviations affecting the PK parameters and have a sufficiently evaluable concentration-time profile to allow determination of at least one PK parameter from among AUC, C_{max} or T_{max}.

The number of subjects included in each of the defined analysis populations will be summarized. The number and percentage of subjects who completed the study as planned, subjects withdrawn from the study, as well as the primary reason for early termination will be presented.

18.2. Demographic Data and Baseline Comparability

Demographic data will be summarized by treatment group. Demographic data summary will include, but will not be limited to, age, sex and race. Baseline efficacy assessments will be summarized by treatment group and eye (study or contralateral eye). Demographic summaries will be based on the safety population. If the safety population differs significantly from the ITT population, the demographic and disposition summaries will be repeated for the ITT population.

18.3. Safety and Tolerability

All safety assessments, including concomitant medications, AEs, laboratory evaluations, vital signs, ECGs, and other safety assessments, will be analyzed using the Safety population.

18.3.1. Prior and Concomitant Medication

Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.

Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of the study medication. Medications that were stopped on the same date as the first study drug administration will be analyzed as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

Prior and concomitant medications will be coded using the most current version of the WHO drug dictionary available at the start of the study. Prior and concomitant medications will be listed by subject and concomitant medications summarized by Anatomical Main Group [1st level of the ATC classification], and preferred name and by treatment group using the Safety population.

18.3.2. Adverse Event

AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the start of the study. Treatment emergent adverse events (TEAEs) will be defined as AEs that occurred or worsened following the first administration of study medication. TEAEs will be summarized separately for ocular and non-ocular TEAEs by study and contralateral eye. The number of subjects experiencing TEAEs and the number of individual TEAEs will be summarized by treatment group, study and contralateral eye, system, organ, class (SOC) and PT, including summaries by severity and relationship to study drug.

18.3.3. Laboratory Evaluations

Descriptive statistics of observed values and changes from baseline will be presented for clinical laboratory (hematology, biochemistry and coagulation) by treatment group and visit (descriptive continuous data analysis).

Urinalysis results (normal and abnormal) will be tabulated by treatment group and visit in frequency tables (descriptive categorical data analysis).

18.3.4. Vital Signs

Vital signs (BP [systolic and diastolic], heart rate, respiratory rate, and temperature) will be summarized by treatment group and protocol specified collection time point. Observed values and changes from baseline will be presented (descriptive continuous data analysis).

18.3.5. Electrocardiograms

ECG values will be summarized by treatment group and protocol specified collection time point. Observed values and changes from baseline will be presented (descriptive continuous data analysis). ECG interpretation (Normal, abnormal not clinically significant and abnormal clinically significant) will be tabulated by visit and treatment group in frequency tables (descriptive categorical data analysis).

18.3.6. Ophthalmologic Assessments

Observations from ophthalmologic assessments will be summarized by protocol specified time point. Observed values and changes from baseline, summarized by treatment group, visit, and study and contralateral eye, will be presented (descriptive continuous data analysis).

The ophthalmologic assessments that will be summarized are listed below:

- Center-Subfield Macula Edema (center-subfield measure)
- Macular fluid volume
- BCVA using the ETDRS visual acuity scale
- FFA
- Corneal thickness based on pachymetry
- Corneal endothelial cell count
- CMT, macular volume, sub-retinal fluid, in the study and contralateral eye as assessed by SD-OCT
- Retinal anatomy as assessed by fluorescein angiography (leakage area) in the study eye and contralateral eye
- DRSS
- Proportion of subjects with a change from baseline value of ≥5, 10 and 15 ETDRS letter score (gain or loss) in the study eye versus contralateral eye
- Proportion of subjects who require anti-VEGF therapy in the study and contralateral eye during the study and need for anti-VEGF in the study eye at Day 85 (Visit 7E) and follow-up, as data permit
- Observations via CFP
- Observations via SD-OCT. To evaluate the following ETDRS grid sectors :

  - Central subfield
  - Inner inferior, inner nasal, inner superior, and inner temporal sectors
  - Outer inferior, outer nasal, outer superior, and outer temporal sectors
  - Retinal thickness
- Automated Perimetry

18.3.7. Other Safety Assessments

The following assessments will be listed by subject:

- Medical History
- Pregnancy Test/FSH Test
- Physical Examination

18.4. [redacted]

18.5. Pharmacokinetics

18.5.1. Blood Sample Collections

Plasma concentrations and actual blood sampling times will be listed by treatment and protocol specified time point and summarized using descriptive statistics — number of measurements, arithmetic mean, SD, and coefficient of variance (%CV), geometric mean, minimum, median, and maximum – at each scheduled time point. Individual and mean plasma concentration-time profiles will also be presented graphically for each treatment.

Pharmacokinetic parameters will be computed from the individual plasma concentrations using a non-compartmental approach. Planned analyses of PK data will be described in a separate PK analysis plan which will be appended to the CSR.

19. ETHICS

19.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IEC as appropriate. The Investigator must submit written approval to the Sponsor before enrolling any subject into the study.

The PI is responsible for informing the IEC of any amendment to the protocol in accordance with local requirements. In addition, the IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug (active). The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IEC according to local regulations and guidelines.

19.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and are consistent with ICH GCP applicable regulatory requirements.

19.3. Written Informed Consent

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time without prejudice. The subject should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures. The subjects will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the subject’s medical records, as required, and the ICF will be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject or legal representative. The date that informed consent was signed will be recorded on the eCRF.

19.4. Data Protection

Subjects will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, subjects will be identified in such reports only by study identification number, gender and age. All subject data will be held in strict confidence.

20. REGULATORY REQUIREMENTS

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

21. DATA HANDLING AND RECORDKEEPING

21.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

21.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 15 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, study drug accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include but are not limited to: IEC correspondence, study drug accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution as required by the local health authority and IEC.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, the PI must notify the Sponsor in writing of the new responsible person and/or the new location.

21.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug but only to the extent that the claim is not caused by the fault or negligence of the subjects or Investigator(s).

22. PUBLICATION POLICY

22.1. Publication of Results

The publication, presentation or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor. Authorship should be consistent with Good Publication Practices, and International Committee of Medical Journal Editors and relevant local guidelines.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Subject confidentiality will be maintained by referring to individual subjects by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor, the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The results summary will be posted to registries as required per local laws or regulations.

22.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from site staff and the local IEC. Study documents provided by the Sponsor (protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

The Investigator must ensure that the subject's anonymity is also maintained. Subjects should only be identified by their initials and a subject study number on the eCRFs and other source

documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

23. QUALITY CONTROL AND QUALITY ASSURANCE

23.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 17.3 for more details regarding the audit process.

The study will be carried out in accordance with the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for GCP ICH E6 (R2), annotated with any applicable country specific amendments.

23.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained as required by the local health authority and IEC. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements

24. CLINICAL STUDY REPORT

A clinical study report (CSR) will be prepared with reference to the Tripartite Harmonised ICH Guideline: Structure and Content of Clinical Study Reports E3 (November 1995) to include:

- Details of where the study was carried out
- Dates of the start and completion of each period of the study
- Details of the study drug and a statement of production will be provided by the Sponsor
- A statement confirming that the applicable IEC gave written approval for the study in accordance with local regulations
- A demographic listing for all subjects
- A list of all AEs according to study drug
- Details of any occurrences which may be of significance to the study outcome
- Details of all operations, calculations and transformations performed on the reported data

- The SAP and report will be produced by the Sponsor, or their agents, and will be incorporated into the final report
- A scientific interpretation of the results
- A description of the study methods used

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

25. SPONSOR AND INVESTIGATOR OBLIGATIONS

25.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant IEC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

25.2. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented and reported to the relevant IEC (if required) and will be included in the CSR.

26. LIST OF REFERENCES

1. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007 Jul-Aug;14(4):179-83. Review.
2. Yau, JWY for the META-EYE Disease Study Group. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care 2012, 35:556-564.
3. Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS, Kester M, Kimball SR, Krady JK, LaNoue KF, Norbury CC, Quinn PG, Sandirasegarane L, Simpson IA for the JDRF Diabetic Retinopathy Center Group. Diabetic Retinopathy: Seeing Beyond Glucose-Induced Microvascular Disease. Diabetes 2006; 55: 2401-2411.
4. Curtis TM, Gardiner TA, Stitt AW. Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis? Eye 2009; 23: 1496-1508.
5. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S, Association of Vitreous Inflammatory Factors with Diabetic Macular Edema. Ophthalmology 2009;116:73-79.
6. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris III FL, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK, Randomised Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. Ophthalmology 2010;117:1064-1077.
7. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS on behalf of the RISE and RIDE Research Group. Ranibizumab for Diabetic Macular Edema. Ophthalmology 2012;119:789-801.
8. Batson J, Toop HD, Redondo C et al., Development of Potent, Selective SRPK1 Inhibitors as Potential Topical Therapeutics for Neovascular Eye Disease. ACS Chem Biol. 2017 Mar 17;12(3):825-832
9. Harper SJ, Bates DO, VEGF-A Splicing: The Key To Anti-Angiogenic Therapeutics? Nat Rev Cancer. 2008 Nov;8(11):880-7.
10. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in anchor, marina, and horizon: a multicenter cohort study (seven-up). Ophthalmology. 2013 Nov;120(11):2292-9. doi: 10.1016/j.ophtha.2013.03.046. Epub 2013 May 3.]
11. Wykoff CC, Elman M, Regillo C, et al. Ophthalmology 2016;123:1716-1721.