

Ophthalmic Clinical Trials

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Overview of Clinical Trials

DIABETIC RETINOPATHY	3
Therini DME (Recruiting)	3
Sangiovese (Opening Soon)	3
CHOROIDAL NEOVASCULARIZATION	3
MALBEC (Recruiting)	3
BENOBIO (Recruiting)	4
GEOGRAPHIC ATROPHY	5
ADARx (Recruiting)	5
BioJiva (Opening Soon)	5
.....	5
MACULAR TELANGIECTASIA TYPE II	5
MacTel NHOR (Recruiting)	5
CENTRAL MACULA OEDEMA.....	5
(2° TO NI UVEITIS, RVO, DR OR CATARACT SURGERY)....	5
KLARITY KIORA (Recruiting)	6
AUTOSOMAL DOMINANT OPTIC ATROPHY	6
Myrtle (Recruiting)	6
LEBER CONGENITAL AMAUROSIS	6
HYPERION (Recruiting)	6
MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE	7
STAR-MOG (Recruiting)	7
THERINI	8
SANGIOVESE	10
MALBEC	14

BENOBIO	16
ADARx.....	19
BioJiva.....	22
MacTel NHOR.....	24
KLARITY KIORA	25
MYRTLE.....	27
HYPERION.....	30
Star-MOG	32

Diabetic retinopathy

Therini DME (Recruiting)

3x IVT injection of THN391

- Previously treated or DMO Tx naïve (dx within 9 months) for cohort 2-3
- BCVA 6/12-6/120
- DMO with CST $\geq 325\mu\text{m}$
- CI-DME with NPDR dx within 9 months if treatment naïve
- 20-week duration
- HbA1c $\leq 12\%$

Sangiovese (Opening Soon)

MK-8748 7mg or 10mg vs aflibercept 2mg

- Adults ≥ 18 years with diagnosis of DME
- BCVA 6/9.6 to 6/96
- DME with CST $\geq 325\mu\text{m}$
- DME dx within 9 months if treatment naïve
- 108 weeks duration
- HbA1c of $\leq 12\%$

Choroidal neovascularization

MALBEC (Recruiting)

2 dose levels (7 mg and 10 mg) of EYE201/MK-8748 in comparison to aflibercept 2 mg.

- Treatment-naïve CNV 2nd to AMD
- Adults ≥ 50 years of age
- BCVA 6/7.5 – 6/95
- 96-week duration

BENOBIO (Recruiting)

1x IVT injection of BBC1501, a BET inhibitor

- Non-responders to at least two doses of **Eylea, Lucentis, Vabysmo, Avastin** (Reduction of less than 50µm)
- BCVA 6/18 and 6/120
- Washout of 6 weeks required

Geographic Atrophy

ADARx (Recruiting)

Subcutaneous injection of ADX-038 subcutaneous injection vs placebo every 3 months for a total of 7 doses

- ≥60 to ≤89 years of age
- BCVA ≥6/96
- Geographic Atrophy secondary to AMD
- GA lesion ≥2.5 and ≤12.5 mm²
- 47 months duration

BioJiva (Opening Soon)

1000mg of BRX011 oral capsules vs placebo

- ≥55 years old
- Geographic Atrophy secondary to AMD
- GA lesion ≥ 1.25 mm² and ≤ 17.5mm²
- BCVA ≥ 6/60
- 22 months duration

Macular Telangiectasia Type II

MacTel NHOR (Recruiting)

Registry study

- Blood sample and data collection
- New or existing patients to the hospital
- Single visit

Central macula oedema (2° to NI UVEITIS, RVO, DR or Cataract Surgery)

KLARITY KIORA (Recruiting)

An intravitreal injection (IVT) of KIO-104, an active pharmaceutical ingredient (API)

- BCVA 6/9-6/240
- CST $\geq$ 350
- ME secondary to non-infectious uveitis, RVO, DR or cataract surgery
- 16 weeks

Autosomal Dominant Optic Atrophy

Myrtle (Recruiting)

Single and Repeat Dose Cohorts of IVT PYC-001

- Adult participants confirmed *OPA1* gene mutation-associated ADOA
- $\geq$ 18 years
- BCVA 6/12 to 6/60
- Rx Treatment naive participants with mild to moderate VF loss and RNFL loss in study eye as determined by GMPE RNFL and visual field structure function data

Leber Congenital Amaurosis

HYPERION (Recruiting)

Safety study of Sepofarsen IVT

- $\geq$ 18 years -OR- 6 to <18 years with a parent or legal guardian
- Subjects with LCA10 due to the c.2991+1655A>G mutation.
- BCVA equal to or worse than 20/50
- Detectable outer nuclear layer in the macular area
- 24 months

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

STAR-MOG (Recruiting)

Evaluate efficacy of optimised corticosteroid tapering regime vs placebo

- Each group are randomised 1:1 for treatment and placebo

Onset MOGAD group: 51 subjects for each arm

- All ages with first presentation of suspected clinical phenotype for MOGAD (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, cerebral monofocal or polyfocal deficits, brainstem/cerebellar demyelination or cerebral cortical encephalitis)

Relapsing MOGAD group: 66 subjects for each arm

- 12 months of B Cell depletion with rituximab following relapse of MOGAD vs placebo
- All ages with known diagnosis of MOGAD per 2023 MOGAD interational diagnostic criteria, stable at least one month prior to suspected relapse and have had relapse within prior 12 months
- 5 years

THERINI

A Phase 1b Open-Label, Multiple Ascending Dose Study of the Safety, Tolerability, and Biological Activity of Intravitreal THN391 in Diabetic Macular Oedema Secondary to Non-Proliferative Diabetic Retinopathy

Trial details:

The primary objective of this study is to assess the safety and tolerability of THN391 administered by intravitreal (IVT) injection every 4 weeks for a total of 3 doses in participants with centre-involving diabetic macular oedema (DMO) secondary to non-proliferative diabetic retinopathy (DR). Intravitreal (IVT) THN391 administration reduced vascular permeability and choroidal neovascularisation lesion area in animal models of DR and neovascular AMD, suggesting a role for anti-fibrin therapy in managing retinal vascular diseases.

THN391 was safely administered intravenously in healthy volunteers in an ongoing program intended for patients with Alzheimer's Disease. This first-in-human study of IVT THN391 will evaluate the safety and tolerability of multiple ascending doses (MAD) in participants with non-proliferative DR with centre-involving DMO.

Inclusion:

Participant Inclusion:

1. Able and willing to provide written informed consent after the nature of the study has been explained and prior to the commencement of any study procedures.
2. Male or female, 18 to 80 years of age (inclusive at the time of informed consent).
3. Females must not be pregnant or lactating. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and Day 1 and be willing to have additional pregnancy tests as required throughout the study. WOCBP must agree to use acceptable, highly effective contraception from Screening until 90 days after the last dose of IP. WOCBP with same-sex partners (abstinence from penile-vaginal intercourse) or who are abstinent from heterosexual intercourse are not required to use contraception when this is their preferred and usual lifestyle. Women not of childbearing potential must be postmenopausal for ≥ 12 months (postmenopausal status is to be confirmed through testing of follicle-stimulating hormone [FSH] levels ≥ 40 IU/L at Screening for amenorrhoeic female participants) or surgically sterile. Women who are not of childbearing potential are not required to use contraception.
4. Males must either be surgically sterile (> 30 days since vasectomy with no viable sperm) or, if engaged in sexual relations with a WOCBP, either his partner must be surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or an acceptable, highly effective contraceptive method must be used from Screening until 90 days after the last dose of IP. Males with same-sex partners (abstinence from penile-vaginal intercourse) or who are abstinent from heterosexual intercourse are not required to use contraception when this is their preferred and usual lifestyle. Males must not donate sperm from the first dose of IP until at least 90 days after the last dose of IP.
5. Able and willing to attend the necessary visits to the study site.
6. Diagnosis of diabetes mellitus (Type 1 or Type 2), according to the American Diabetes Association and/or World Health Organization criteria.

Study Eye Inclusion:

7. Centre-involving macular oedema associated with non-proliferative DR in the study eye, confirmed by the CRC.
8. Decreased visual acuity in the study eye attributable primarily to centre-involving DMO, in the opinion of the PI.
9. BCVA between 70 and 35 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) testing (approximately 20/40 to 20/200, inclusive, by Snellen chart) in the study eye.
10. Central subfield thickness of ≥ 325 μm confirmed by the CRC.
11. For DMO treatment-experienced participants (Cohorts 1 to 3): Prior DMO treatment with VEGF antagonists in the study eye.
12. For DMO treatment-naïve participants (Cohorts 2 and 3 only): DMO diagnosed within

9 months before Screening and no prior treatment for DMO in the study eye.

Participant Exclusion:

1. Major illness or major surgical procedure within 1 month prior to Day 1.
2. Uncontrolled diabetes, in the opinion of the PI or indicated by glycosylated haemoglobin (HbA1c) > 12% at Screening.
3. Uncontrolled blood pressure, in the opinion of the PI, or > 180 mmHg systolic and/or > 100 mmHg diastolic blood pressure.
4. History of uveitis, retinitis, other autoimmune eye illnesses, or any clinically significant ocular complaints, in the opinion of the PI.
5. Prior use of medications known to be toxic to the retina, lens, or optic nerve (eg, deferoxamine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, and ethambutol).
6. History of significant hypersensitivity, intolerance, or allergy to any drug compound or other substance, unless approved by the PI.
7. History of severe allergic or anaphylactic reactions, or sensitivity to the IP or its constituents, or to any components used in the protocol-defined study procedures (eg, fluorescein).
8. Receipt of any IP within the 30 days prior to Screening or 5 half-lives of the IP, whichever is longer.
9. Clinically significant abnormal laboratory parameters at Screening, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin > 1.5 × upper limit of normal (ULN); estimated glomerular filtration rate (eGFR) < lower limit of normal or creatinine > 1.5 × ULN. Repeat testing at Screening is acceptable for out-of-range values following approval by the PI or designee.
10. A recent (within 1 year of Screening) clinically significant history of drug or alcohol use, abuse or dependence that, in the opinion of the PI, could interfere with the participant's participation or compliance in the study.
11. Anything that the PI considers that would jeopardise the safety of the participant, prevent complete participation in the study, or compromise interpretation of study data.
12. Employee of the PI or study centre with direct involvement in the proposed study or other studies under the direction of that PI or study centre, as well as family members of the employees or the PI.

Study Eye Exclusion:

13. Presence or history of an ocular condition that can adversely affect visual acuity or prevent improvement in visual acuity despite reduction macular oedema.
14. Macular oedema in the study eye considered to be due to a cause other than DMO.
15. Fovea macula in the study eye has substantial non-perfusion (ischemic) on Screening fluorescein angiography (FA), as determined by the CRC.
16. Substantial posterior capsule opacity in the study eye that, in the opinion of the PI, is likely to decrease visual acuity.
17. Presence of an epiretinal membrane or vitreo-retinal interface changes in the study eye which, in the opinion of the PI following input from the CRC, is the primary cause of macular oedema, or is severe enough to prevent improvement in visual acuity despite reduction in macular oedema.
18. Uncontrolled glaucoma with IOP > 21 mmHg.
19. Any history of vitrectomy in the study eye.
20. Aphakia, history of cataract surgery within 3 months before Screening, or any other previous intraocular surgery in the study eye.
21. Intraocular injections of VEGF antagonists in the study eye within 6 weeks prior to Day 1.
22. DMO treatment-naïve participants (no prior treatment for DMO in the study eye) are excluded from Cohort 1.
23. Intraocular steroids: Ozurdex® and triamcinolone acetonide (Kenalog) in the study eye within 24 weeks before Day 1. Any prior use of other forms of intraocular steroids in the study eye.
24. Any ocular condition (eg, foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, visually significant cataract, non-retinal condition, etc) such that, in the opinion of the PI following input from the CRC, visual acuity would not improve following resolution of DMO in the study eye.
25. A history of or active ocular condition in the study eye (other than DMO) that, in the opinion of the PI, might alter visual acuity during the study period (eg, uveitis or other inflammatory eye disease, neovascular glaucoma, etc.), or it is expected that the participant will require a procedure within the study period that may alter visual acuity in the study eye (eg, retinal photocoagulation treatment).

26. Active or history of retinal detachment in the study eye.
27. History of macular laser photocoagulation in the study eye within 6 months before screening.
28. Proliferative DR (excluding inactive / previous proliferative DR) or evidence of retinal neovascularisation in the study eye, as determined by the CRC, that is expected to require treatment within the next 6 months, as determined by the investigator.

SANGIOVESE

A Randomized, Double-Masked, Multicenter, 3-Arm, Pivotal Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal (IVT) MK-8748 Compared With Aflibercept (2 mg) in Participants With Diabetic Macular Edema (DME)

Primary Objective: assess efficacy of MK-8748 (7 mg or 10 mg) compared with aflibercept 2 mg with respect to mean change in BCVA (ETDRS letters) from baseline to Year 1, defined as the average of the Week 48 and Week 52 visits

Secondary Objective: evaluate efficacy and time to treatment effect of MK-8748 (7mg or 10mg) compared to aflibercept 2 mg on the anatomical endpoints listed.

INCLUSION:

Type of Participant and Disease Characteristics

1. Has Type 1 or Type 2 diabetes mellitus and a HbA1c of $\leq 12\%$.
2. Has a BCVA ETDRS letter score between 75 and 24 (20/32 to 20/320 Snellen equivalent) inclusive, in the study eye at Screening and on Day 1. In the event that both eyes are eligible, the worse-seeing eye should be enrolled in the trial.
3. Has a decrease in vision in the study eye determined by the Investigator to be primarily the result of DME.
4. For participants who are treatment-naïve for DME, the diagnosis must have been made within 9 months of screening. For all treatment-experienced participants, the first treatment should have been no longer than 3 years prior to the Screening visit. If the participant has received anti-VEGF therapy previously, the last treatment must have been ≥ 90 days prior to the Screening visit. For participants treated previously with 8 mg aflibercept (EYLEA HD®) or faricimab (VABYSMO®), treatment must have been ≥ 120 days prior to the Screening visit.
5. Has a CST of ≥ 325 μm in the study eye on SDOCT as determined by the IRC at screening.

Demographics

6. Is an individual of any sex/gender, ≥ 18 years of age inclusive, at the time of providing the informed consent. Follow local regulatory requirements if the legal age of consent for participation is >18 years of age.

Assigned Male Sex at Birth

7. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for study intervention is 100 days after the last dose of study intervention.

- Refrains from donating sperm.
- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant.
- Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Note: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required

Assigned Female Sex at Birth

8. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 100 days after the last dose of study intervention.

9. A WOCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Additional requirements for pregnancy testing

during and after study intervention are in Section 8.3.5.

10. A WOCBP is eligible to participate if they use a contraceptive method that is highly effective (with a failure rate of <1% per year), or if they adhere to penile-vaginal intercourse abstinence as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5, during the intervention period and for at least the time needed to eliminate study intervention after the last dose of study intervention. In addition, the participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for study intervention is 100 days

Note: The investigator or designee should evaluate the potential for contraceptive method failure (ie, noncompliance, recent initiation) in relationship to the first dose of study intervention. Contraceptive use by WOCBP should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the local contraception requirements for any of the study interventions are more stringent than the requirements above, the local requirements are to be followed. Medical history, menstrual history, and recent sexual activity should be reviewed by the investigator or designee to decrease the risk for inclusion of a WOCBP with an early undetected pregnancy

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent for the study.

12. Ability and willingness to undertake all scheduled visits and assessments

Inclusion Criteria Confirmed on Day 1

13. Has no significant clinical or anatomical ocular changes from Screening to Day 1.

14. Has a BCVA ETDRS letter score between 75 and 24 (20/32 to 20/320 Snellen equivalent) inclusive, in the study eye at Day 1.

15. Has BCVA ≥ 35 letters in the fellow eye at Day 1

EXCLUSION:**Medical Conditions**

1. Is pregnant or breastfeeding.

2. Has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

3. Has had renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis or has renal failure anticipated to require hemodialysis or peritoneal dialysis at any time during study.

4. Has history of stroke (cerebral vascular accident) or myocardial infarction within 180 days prior to Day 1.

5. Has any active malignancy.

6. Has any history of organ transplant.

7. Has newly diagnosed or previously untreated diabetes mellitus and initiated oral or injectable anti-diabetic medication within 3 months prior to Day 1. (This does not impact any changes to a participant's medication regimen that may be deemed necessary for optimal glycemic control over the course of the study).

8. Currently has evidence of, or a history of any clinically significant autoimmune, cardiovascular, hematologic, hepatic, metabolic, peripheral vascular, renal, or respiratory disease, which, in the opinion of the Investigator, would prevent the participant from completing the required assessments for this study.

9. Has a known hypersensitivity to any of the components of MK-8748 formulation, aflibercept, or prior hypersensitivity to mAbs.
10. Has an allergy to fluorescein dye.
11. Has history of cataract surgery and/or minimally invasive glaucoma surgery in the study eye within 90 days of screening.
12. Has any treatment for complications of cataract surgery with steroids or YAG laser capsulotomy in the study eye within 90 days of screening.
13. Has had pan-retinal photocoagulation or macular (focal, grid, or micropulse) thermal laser photocoagulation in the study eye within 90 days of screening.
14. Has tractional retinal detachment in the study eye.
15. Has advanced or uncontrolled glaucoma (defined as IOP ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye.
16. Has had glaucoma-filtering surgery (trabeculectomy or tube shunt) in the study eye.
17. Has any history of retinal detachment or treatment or surgery for retinal detachment in the study eye.
18. Has significant media opacities, including cataract, in the study eye that might interfere with VA, assessment of safety, OCT, or fundus photography in the opinion of the reading center.
19. Has a cataract in the study eye that, in the judgment of the Investigator is expected to require surgical extraction within 4 months of screening.
20. Has aphakia in the study eye.
21. Has had vitrectomy in the study eye.
22. Has known or former (if the participant has undergone refractive and/or cataract surgery) refractive error with a spherical equivalent of $\geq \pm 8$ diopters in the study eye.
23. Has active retinal disease other than the condition (DME/diabetic retinopathy) under investigation in the study eye.
24. Has any history or evidence of a concurrent ocular condition present in the study eye that could require either medical or surgical intervention or affect macular edema or alter VA during the study (eg, vitreomacular traction, epiretinal membrane, CNV due to NVAMD or other causes, such as pathological myopia, angioid streaks, presumed ocular histoplasmosis syndrome, and multifocal choroiditis).
25. Has macular edema in the study eye considered to be secondary to a cause other than DME (eg, retinal vein occlusion, Irvine-Gass syndrome).
26. Has active iris or angle neovascularization or neovascular glaucoma in the study eye.
27. Has active PDR in the study eye (eg, any vitreous or preretinal hemorrhage, active neovascularization at optic disc, or active neovascularization elsewhere) as determined by the IRC at screening.
28. Has structural damage to the center of the macula in the study eye that, in the opinion of the Investigator or Sponsor, is likely to preclude improvement in BCVA, including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, organized hard exudates in the foveal center, or other evidence of chronic disruption of the macular architecture

Prior/Concomitant Therapy

29. Is currently using drugs with known retinal toxicity (eg, hydroxychloroquine, pentosan polysulfate sodium).
30. If treatment-experienced for DME, has a history of any of the following treatments within the noted time windows:
 - a. Has had prior treatment with 8 mg aflibercept (EYLEA HD®) or faricimab (VABYSMO®) within 120 days prior to the Screening visit in the study eye
 - b. Has had an IVT injection with other anti-VEGF treatments (eg, ranibizumab, bevacizumab, aflibercept [2 mg], pegaptanib sodium) or approved anti-VEGF biosimilars in the study eye within 90 days of the Screening visit
 - c. Has had prior IVT brolucizumab in the study eye at any time
 - d. Had prior IVT investigational agents in either eye at any time
 - e. Had treatment with ocriplasmin (JETREA®) in the study eye at any time

f. Had previous use of ILUVIEN® at any time, of OZURDEX® IVT implants within 180 days of the Screening visit, or any other intraocular or periocular corticosteroids in the study eye within 90 days of the Screening visit

Prior/Concurrent Clinical Study Experience

31. Has previously participated in any study of MK-8748.

Diagnostic Assessments

32. Has uncontrolled blood pressure, defined as systolic ≥ 180 mmHg and/or diastolic ≥ 100 mmHg while a participant is at rest during the Screening Period. If a participant's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the Screening Period. If the participant's blood pressure is controlled by antihypertensive medication, the participant should be taking the same medication continuously for at least 30 days prior to Day 1.

Ocular Exclusion Criteria for Fellow Eye:

33. Has BCVA < 35 letters in the fellow eye.

Ocular Exclusion Criteria for Both Eyes:

34. Had prior IVT complement inhibitors in either eye at any time.

35. Has any history of uveitis in either eye.

36. Has active or suspected ocular or periocular infection or inflammation in either eye at Day 1.

37. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study

Choroidal neovascularization

MALBEC

A randomized, double-masked, active-controlled, 96-week, pivotal Phase 2/3 study to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of 2 dose levels (7 mg and 10 mg) of EYE201/MK-8748 in comparison with the active control, aflibercept 2 mg, in participants with treatment-naïve NVAMD.

Primary objective: To demonstrate that EYE201/MK-8748 (7 mg or 10 mg) is non-inferior to aflibercept 2 mg with respect to mean change in BCVA (ETDRS letters) from baseline to Year 1, defined as the average of the Week 48 and Week 52 visits.

Trial details:

Eligible participants with treatment-naïve

NVAMD will be assigned in a 1:1:1 ratio to 1 of the following 3 treatment groups:

- 7 mg of EYE201/MK-8748 via IVT injection
- 10 mg of EYE201/MK-8748 via IVT injection
- 2 mg of aflibercept via IVT injection

Treatment Period of 92 weeks, and a Safety Follow-up visit (Week 96)

Inclusion:

1. Be willing and able to understand the study procedures and risks involved and provide written informed consent before the first study-related activity
2. Be male or female ≥50 years of age
3. If female, have a negative serum pregnancy test at Screening and further negative urine tests immediately before each dose of study medication if the participant is a female of childbearing potential (defined as any female who has begun menstruation and who is not permanently sterile, and is not postmenopausal [defined as a female who has not had a menstrual period for at least 12 months without an alternative medical cause]); such participants must agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception as described in Appendix C from Screening up to and including 100 days after the last dose of study medication. If the participant is initiating hormonal contraception at the time of Screening or within 1 cycle of Day 1, participant agrees to use a double-barrier method of contraception until completing 1 full cycle of hormonal contraception. An acceptable double-barrier combination method is a condom with either diaphragm or sponge with spermicide
4. If male, be surgically sterile for at least 6 weeks, or agree to use an acceptable method of contraception, such as a condom, and a second highly effective method of contraception as described in Appendix C from Screening up to and including 100 days after the last dose of study medication
5. Have treatment-naïve CNV secondary to AMD including subfoveal, juxtafoveal and extrafoveal lesions (evidenced by fluid, subretinal hyperreflective material, or leakage) or retinal angiomatous proliferations (RAP) and polypoidal choroidal vascularization (PCV) lesions, with a total lesion size (including blood, scar/atrophy & neovascularization) of ≤9 disc areas (DA) (22.53 mm²), of which at least 50% must be active CNV in the study eye
6. The diagnosis must have been made within 21 days prior to Day 1 of the study treatment (the maximum Screening Period for these participants is, therefore, 21 days)
7. Have a decrease in vision in the study eye that has been determined by the Investigator to be primarily the result of NVAMD
8. Have an ETDRS BCVA letter score between 78 and 24 (20/32 to 20/320 Snellen equivalent), inclusive, in the study eye. In the event both eyes are eligible, the worse-seeing eye should be enrolled in the trial
9. Have a presence of IRF and/or SRF affecting the central subfield of the study eye on SD-OCT as determined by the IRC at Screening

Exclusion:**General Exclusion Criteria:**

1. Have uncontrolled blood pressure at Screening, defined as systolic ≥ 180 mmHg and/or diastolic ≥ 100 mmHg while a participant is at rest
If a participant's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the Screening period. If the participant's blood pressure is controlled by antihypertensive medication, the participant should be taking the same medication continuously for at least 30 days prior to Day 1
2. Have history of stroke (cerebral vascular accident) or myocardial infarction within 180 days prior to Day 1
3. Have any active malignancy
4. Currently have evidence of, or a history of, any clinically significant autoimmune, cardiovascular, hematologic, hepatic, metabolic, peripheral vascular, renal, or respiratory disease that would preclude trial participation in the opinion of the Investigator

Ocular Exclusion Criteria:

5. Have a history of cataract surgery and/or minimally invasive glaucoma surgery in the study eye within 90 days of Screening
6. Have had Yttrium-Aluminium Garnet laser capsulotomy in the study eye within 90 days of Screening
7. Have had any prior macular laser photocoagulation in the study eye
8. Have uncontrolled glaucoma (defined as IOP ≥ 30 mmHg despite treatment with antiglaucoma medication) in the study eye
9. Have had glaucoma-filtering surgery (trabeculectomy or tube shunt) in the study eye
10. Have any history of retinal detachment or treatment or surgery for retinal detachment in the study eye
11. Have any history of uveitis in either eye
12. Have significant media opacities, including cataract, in the study eye that might interfere with VA, assessment of safety, optical coherence tomography (OCT), or fundus photography as determined by the IRC
13. Have a cataract in the study eye that in the judgment of the Investigator is expected to require surgical extraction within 12 months of Screening
14. Have aphakia in the study eye
15. Have allergy to fluorescein dye
16. Have had vitrectomy in the study eye
17. Have known or former (if participant has undergone refractive and/or cataract surgery) refractive error with a spherical equivalent of ≥ -8 diopters in the study eye
18. Have active retinal disease other than the condition under investigation in the study eye
19. Have any history or evidence of a concurrent ocular condition present in the study eye that, in the opinion of the Investigator, could require either medical or surgical intervention or affect macular edema or alter VA during the study (e.g., vitreomacular traction; epiretinal membrane; other causes of CNV, such as pathological myopia, angioid streaks, presumed ocular histoplasmosis syndrome, and multifocal choroiditis)
20. Have structural damage to the center of the macula in the study eye that, in the opinion of the Investigator or Sponsor, is likely to preclude improvement in BCVA, including atrophy of the RPE, subretinal fibrosis or scar, significant macular ischemia, organized hard exudates in the foveal center, or other evidence of chronic disruption of the macular architecture
21. Have active or suspected ocular or periocular infection or inflammation in either eye at Day 1
22. Have a known hypersensitivity to any of the components of EYE201/MK-8748 or aflibercept formulation or prior hypersensitivity to monoclonal antibodies
23. Have history of prior treatment with ocriplasmin (JETREA®), ILUVIEN®, OZURDEX® IVT implants, or other intraocular or periocular corticosteroids in the study eye at any time
24. Have previously received anti-VEGF therapy or other IVT therapy in the study eye
25. Be currently using drugs with known retinal toxicity (eg, hydroxychloroquine, pentosan

sulfate)

26. Presence of amblyopia, amaurosis, or ocular disorders with BCVA < 38 letters (ETDRS testing charts) in the fellow eye at Screening

27. Have any subfoveal atrophy or scarring, complete RPE and outer retinal atrophy involving the fovea, blood over the fovea, or subfoveal fibrosis in the study eye. Additionally, no more than 25% of the total lesion size may be made up of scarring or atrophy, as determined by the reading center

28. Have had previous photodynamic therapy with verteporfin in the study eye

29. Have the presence of significant and large serous PEDs such as those with a vertical height of $\geq 400 \mu\text{m}$

30. Have the presence of a tear of the RPE

31. Have any subretinal hemorrhage that comprises more than 50% of total lesion size in the study eye

32. Have previously received anti-complement IVT therapy (pegcetacoplan or avacincaptad pegol) in the study eye

33. Previous therapeutic radiation in the region of the study eye

34. History of macular pathology unrelated to AMD affecting vision or contributing to the presence of fluid including central serous chorioretinopathy

BENOBIO

A Phase 1, Open Label, Dose Escalation Study to Evaluate the Safety of BBC1501 Intravitreal Injection for Neovascular Age-Related Macular Degeneration

Primary objective: To evaluate the safety and tolerability of BBC1501 monotherapy when administered via intravitreal (IVT) injection in patients with nAMD

Trial details: Treatment is administered as a single intravitreal injection of BBC1501, which is a BET inhibitor.

Study duration will be up to 12 weeks. Patients who have neovascular AMD will initially be treated with the lowest dose and observed for Dose Limiting Toxicities (DLTs). After 3 patients are observed with no DLTs, the next patients to be enrolled will receive a higher dose.

The three doses are:

- 1.25 μg
- 2.5 μg
- 5 μg

Inclusion:

1. Able to provide voluntary written informed consent on the approved ICF, understand the study requirements, and are willing to follow and complete all the study required procedures.

2. Male or female aged ≥ 50 years.

3. Participants who as per Investigator's judgment are non-responders (Section 5.4) to at least 2 prior anti-VEGF treatments (one of which was either aflibercept, ranibizumab or brolicizumab, Faricimab and bevacizumab) for nAMD in the study eye as confirmed by OCT. Response to available treatment is defined as a reduction of $\geq 30\%$ of excess macular thickness or a reduction of $\geq 50 \mu\text{m}$, relative to the last CST measurement prior to the IVT anti-VEGF.

4. Active CNV lesions, secondary to nAMD as confirmed with SD-OCT (or SS-OCT), FFA and fundus photography (FP) in the study eye.

5. BCVA between 73 and 21 letters, inclusive, in the study eye using ETDRS testing or BCVA between 20/60 and 20/400 letters, inclusive, in the study eye by Snellen chart.

6. Participant has CST of at least 300 μm if measured by Cirrus OCT or 325 μm if measured by Spectralis OCT, with presence of intraretinal and/or subretinal fluid.

7. Participants who have had a washout period of at least six weeks prior to first administration of the investigational medicinal product (IMP) for any IVT anti-VEGF medication and who, in the opinion of the PI, have disease sufficiently stable to enable this interval.

Exclusion:

Ocular:

1. Use of any of the following treatments or anticipated result of the following assessment to the study eye:
 - a. IVT or periocular corticosteroid, within 90 days prior to Visit 1 (Day 1) and throughout the study.
 - b. Glaucoma, evidenced by an IOP of > 21 mmHg or chronic hypotony (< 6 mmHg) in the study eye.
 - c. Evidence of any other ocular disease other than nAMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, pseudo-vitelliform macular degeneration, or moderate/severe myopia).
 - d. Participants with advanced nAMD and no prognosis of BCVA as per Investigator's judgment (e.g. due to macular OCT signs of atrophy or photoreceptors disruption, or macular/foveal subretinal hemorrhage).
 - e. History of vitrectomy in the study eye.
2. Need for ocular surgery in the study eye during the course of the study.
3. YAG laser capsulotomy within 30 days prior to Visit 1 (Day 1) in the study eye.
4. Intraocular surgery, including lens removal or laser, within 90 days prior to Visit 1 (Day 1) in the study eye.
5. Ocular or periocular infection in either eye.
6. Pupillary dilation inadequate for quality stereoscopic FP in the study eye.
7. Media opacity that would limit clinical visualization, intravenous FFA, or spectral domain optical coherence tomography (SD-OCT) evaluation in the study eye.
8. History of herpetic infection in the study eye or adnexa.
9. Presence of known active toxoplasmosis, inactive toxoplasmosis, or toxoplasmosis scar in either eye.
10. Presence of any form of ocular malignancy including choroidal melanoma in either eye.

Non-ocular:

11. Prior treatment with any agent targeting the endoglin pathway (including a fusion protein that binds bone morphogenic protein).
12. Prior treatment with BBC1501 injectable solution.
13. Use of any of the following treatments or anticipated use of any of the following treatments during the study:
 - a. Systemic treatment with anti-VEGF agents (e.g., bevacizumab, Ranibizumab, Aflibercept, Brolucizumab, sorafenib, dasatinib and nilotinib)
 - b. Agents targeting the endoglin pathway (e.g., Atezolizumab).
14. Allergy or hypersensitivity to IMP, fluorescein dye, or other study-related procedures/medications.
15. Any of the following laboratory abnormalities at screening:
 - a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 2.5 \times$ upper limit of normal (ULN);
 - b. Total bilirubin ≥ 1.5 mg/dL;
 - c. Peripheral white blood cell (WBC) count < 3000/ μ L;
 - d. Platelet count < 75000/ μ L;
 - e. Serum creatinine $\geq 1.5 \times$ ULN or creatinine clearance ≤ 50 mL/min (calculated per institutional standard or using the Cockcroft-Gault formula if a local guideline is not available).
16. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia).
17. History of hemorrhage, epistaxis, hemoptysis ($> \frac{1}{2}$ teaspoon bright red blood), or treatment with anticoagulants within 90 days prior to Visit 1 (Day 1).
18. Myocardial infarction, stroke, or history of transient ischemic attacks within 180 days prior to Visit 1 (Day 1).
19. Major surgery within 90 days prior to Visit 1 (Day 1). Participants who have undergone major surgery > 90 days prior to Visit 1 (Day 1) may be excluded if the Investigator considers their recovery is insufficient to be suitable for the study. Major surgery is defined as any surgery involving a risk to the life

of the participant, including any operation upon an organ within the cranium, chest, abdomen, or pelvic cavity.

20. Therapeutic radiation to the head or neck within 90 days prior to Visit 1 (Day 1).

21. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 (Day 1) or planning to participate in other investigational drug or device clinical trials for the duration of the study. This includes both ocular and non-ocular clinical trials.

22. Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 while participant is sitting). If a participant's initial reading exceeds these values, a second reading may be taken approximately 30 minutes later. If a participant's blood pressure needs to be controlled by antihypertensive medication, the participant can be eligible if medication is taken continuously for at least 30 days prior to Visit 1 (Day 1).

23. Poorly uncontrolled type 2 diabetes (HbA1C > 8.5%).

24. Atrial fibrillation not controlled by the participant's primary care physician or cardiologist within 30 days prior to Visit 1 (Day 1) (e.g., heart rate < 100 bpm without significant symptoms).

25. Clinically significant concurrent illness or laboratory abnormality.

26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the participant at high risk for treatment complications.

27. Any systemic infection within 30 days prior to Visit 1 (Day 1).

28. Females who are pregnant or lactating, and are not willing and able to use acceptable, highly effective double contraception from screening until 90 days after study completion, including the Follow-up period. Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening and Day 1 and be willing to have additional pregnancy tests as required throughout the study. Women not of childbearing potential must be postmenopausal for > 12 months (postmenopausal status is to be confirmed through testing of follicle stimulating hormone (FSH) levels $\geq$ 40 IU/L at screening for amenorrhoeic female participants, see Section 10.2 for details).

29. Males who are not surgically sterile (> 10 weeks since vasectomy with no viable sperm), or are not willing to use an acceptable, highly effective contraceptive method (Section 10.2) from screening until study completion, including the Follow-up period if engaged in sexual relations with a WOCBP who is not surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy). Males must not donate sperm from the first dose of IMP until at least 4 weeks after IMP administration.

30. Use of marijuana, alcohol abuse or illegal medication within 30 days prior to Visit 1 (Day 1) and throughout the study.

31. Unable to comply with study procedures or follow-up visits.

Geographic Atrophy

ADARx

A Phase 2, Randomized, Masked, Placebo-Controlled Study of Subcutaneously Administered ADX-038 in Participants With Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

The primary objectives:

1. To evaluate the effect of ADX-038 on the preservation of photoreceptors in adult participants with GA secondary to AMD
2. To evaluate the effect of ADX-038 on GA lesion growth
3. To evaluate the effect of ADX-038 on vision loss

Inclusion

To be eligible to participate in this study, participants must meet all the inclusion criteria below. A participant must have one eye, known as “the study eye”, that meets all the ocular inclusion criteria. If both eyes meet the ocular inclusion criteria, the eye with the greater lesion growth rate estimated by FAF during the Screening period will be designated as the study eye. The other eye will be designated “the fellow eye”. If both eyes have the same FAF-estimated lesion growth rate, then the eye with the larger GA lesion size will be the study eye.

1. Age ≥ 60 years and ≤ 89 years at the time of signing informed consent.
2. Has provided written informed consent and any authorizations required by local law and is willing to comply with all study requirements for the duration of the study.

Study Eye-Specific Criteria

3. Has a clinical diagnosis of GA of macula secondary to AMD as determined by the Investigator.
4. Has a GA lesion that meets all following criteria during the Screening Period, as determined by the CRC’s assessment of FAF imaging.
 - a. GA lesions ≥ 2.5 and ≤ 12.5 mm².
 - b. If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm² (0.5 disc area), with the overall aggregate area of GA as specified in inclusion #4a.
 - c. At least 1 GA lesion must be at least in part within a 1.5 mm radius ring centered on the fovea
 - d. The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any area of peripapillary atrophy.
 - e. Presence of any pattern of hyper autofluorescence (AF) in the junctional zone of GA (lack of hyper AF is exclusionary).
 - f. Lesions involving the foveal center as determined by the CRC are permitted but the maximum number of participants enrolled with lesions involving the foveal center will be limited to approximately 72.
5. Has a GA lesion that meets all following criteria as determined by the CRC’s assessment of OCT imaging during the Screening period.
 - a. EZ/RPE ratio ≥ 1.19
 - b. Minimal distance of GA lesion(s) to foveal center ≤ 1500 μ m
6. Has a BCVA of ≥ 24 letters using the ETDRS chart at both Screening and Day 1. If a participant has a lesion involving the center point of the fovea as determined by the CRC, participant must have a BCVA of ≥ 50 letters using the ETDRS chart at both Screening and Day 1.
7. Has adequate clarity of ocular media and adequate pupillary dilation, and fixation to permit the collection of good quality images, as determined by the Investigator.

General Criteria

8. The following vaccine requirements need to be completed at least 2 weeks prior to Day 1:
 - a. Completed vaccination schedule for *Streptococcus pneumoniae* and *Neisseria*

meningitidis serotypes (MenACWY) with appropriate boosters per local guidance.

b. Completed at least 2 doses of a 3-dose vaccine series for *Neisseria meningitidis* serotype B (MenB). The third dose may be administered during the study but may occur after Day 1.

9. Participants agree to receive vaccine boosters for MenACWY, MenB, and *Streptococcus pneumoniae* as appropriate per local guidance during the study.

10. Women of childbearing potential (WOCBP) are defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception. WOCBP must have a negative serum pregnancy test during Screening and a negative urine pregnancy test on Day 1 before study drug administration and must agree to use highly effective contraceptive methods (refer to Section 13.2) if engaged in sexual activity of childbearing potential from the time of signing the informed consent form (ICF) until the EOS Visit or 28 days after the last dose of study drug, whichever is longer.

Women are considered not of childbearing potential if they are permanently sterile or if they have had no menses for 12 months without an alternative medical cause (refer to Section 13.2).

11. Women must not be breastfeeding.

12. Fertile men must agree to use acceptable contraceptive methods if engaged in sexual activity with a partner of childbearing potential (refer to Section 13.2) from the time of signing the ICF until the EOS Visit or 28 days after the last dose of study drug, whichever is longer.

13. Fertile men must agree not to donate sperm after study drug administration on Day 1 until the EOS Visit or 28 days after the last dose of study drug, whichever is longer.

Exclusion

Participants who meet any of the following criteria will be excluded from the study. Ocular specific exclusion criteria only apply to the study eye, unless otherwise specified.

1. Has GA secondary to causes other than AMD, such as Stargardt disease, cone rod dystrophy, or toxic maculopathies like drug-induced plaquenil maculopathy in either eye.
2. Has a history of or active CNV associated with AMD or any other cause, including any evidence of retinal pigment epithelium tears or neovascularization anywhere based on OCT imaging and/or fluorescein angiography as assessed by the Investigator and the CRC before study drug administration. CNV in the fellow eye is allowed.
3. Has an active ocular disease that, in the opinion of the Investigator, compromises or confounds visual function, including but not limited to uveitis, other macular diseases (e.g., clinically significant epiretinal membrane, full thickness macular hole, diabetic retinopathy or macular edema) or uncontrolled glaucoma/ocular hypertension. Benign conditions, in the opinion of the Investigator, such as peripheral retina dystrophy, are not exclusionary.
4. Has a history of thermal laser therapy in the macular region.
5. Had intraocular surgery (including lens replacement surgery) within 3 months prior to Day 1.
6. Has history of surgical repair for retinal detachment. History of laser surgery for retinal tears is allowed.
7. Has aphakia or the absence of the posterior capsule. (Note: YAG laser posterior capsulotomy for posterior capsule opacification performed ≥ 60 days prior to Screening is permitted.)
8. Has any ocular condition other than GA secondary to AMD that may require surgery or medical intervention during the study or, in the opinion of the Investigator, could compromise visual function during the study.
9. Has pathologic myopia as defined as spherical equivalent of the historical refractive error demonstrating >8 diopters of myopia or evidence of myopic maculopathy as determined by the CRC.
10. Received prior treatment with any genome-altering therapy for GA, including gene

therapy and gene editing.

11. Has a history or current use of non-genome-altering IVT therapy of any kind for any indication, including IVT complement inhibitors (approved or investigational), within 6 months to randomization in study eye. Prior or concurrent use of IVT in the fellow eye is allowed.

12. Has known or suspected hereditary or acquired complement deficiency.

13. Has a history of recurrent invasive infections caused by encapsulated bacteria (e.g., meningococcus or pneumococcus).

14. Has a major concurrent comorbidity, including but not limited to severe kidney disease (e.g., estimated glomerular filtration rate <30 mL/min/1.73 m², dialysis), advanced cardiac disease (e.g., New York Heart Association class IV), or severe pulmonary disease (e.g., severe pulmonary hypertension [World Health Organization class IV]). Any major cardiovascular event in the past year prior to Day 1, including a myocardial infarction or a cerebrovascular event requiring hospitalization, is also exclusionary.

15. Has an active malignancy and/or history of malignancy in the past 5 years prior to Day 1, with the exception of completely excised non-melanoma skin cancer or low-grade cervical intraepithelial neoplasia and with no evidence of recurrence for ≥ 3 years prior to Day 1.

16. Has a history of splenectomy.

17. Has a history of active tuberculosis (TB [treated or untreated]), untreated latent TB infection, or evidence of active TB during Screening (preferred testing is by QuantiFERON-TB Gold Plus test when available and per local regulations).

Note: Participants with history of treated latent TB are permitted to enroll if they have evidence of completion of treatment and they meet all other eligibility criteria.

18. Active systemic viral (including COVID-19), bacterial, or fungal infection must have a full recovery for at least 14 days prior to Day 1 in order to participate.

19. Has known HIV infection (per participant history and/or medical records) or positive HIV test during Screening.

20. Has a positive serology test for hepatitis B surface antigen (HBsAg) or positive serology test for hepatitis C virus (HCV) with a detectable RNA concentration during Screening.

21. Has liver injury as indicated by any of the following abnormal liver function tests during Screening; tests should be repeated if there is a significant clinical change during Screening:

a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>1.5 \times$ upper limit of normal (ULN).

b. Total bilirubin $>1.5 \times$ ULN (unless due to Gilbert's syndrome, in which case participants are excluded if direct bilirubin $> \text{ULN}$ and indirect bilirubin $> 3 \times \text{ULN}$).

22. Has any of the following laboratory parameters during Screening, tests should be repeated if there is a significant clinical change during Screening:

a. White blood cell count $>1.2 \times \text{ULN}$ or $<0.8 \times$ lower limit of normal.

b. Hemoglobin <9 g/dL.

c. Platelet count $<80,000/\mu\text{L}$

23. Received prior or concurrent treatment with any systemic complement inhibitors within 6 months to randomization.

24. Participated in an interventional drug study within the last 90 days or 5 half-lives, whichever is longer, prior to Screening.

25. Is receiving concomitant treatment with any ocular or systemic medication that is known to be toxic to the retina at the time of Screening (e.g., hydroxychloroquine, intraocular moxifloxacin, tamoxifen). Note: Participants taking oral supplements specifically for GA/AMD (e.g., vitamin C, vitamin E, β -carotene, lutein/zeaxanthin) must be on a stable dose for at least 3 months prior to Day 1.

26. Is receiving systemic or IVT /topical (i.e., applied to eye) corticosteroids or immunosuppressive agents at the time of Screening. Agents include, but are not limited to, cyclosporine, tacrolimus, mycophenolate or mycophenolic acid, cyclophosphamide, methotrexate, cyclophosphamide, or intravenous immunoglobulins. Inhaled, intranasal, and topical (applied to skin) corticosteroids are permitted.

27. Donated any blood products (>200 mL) within 30 days prior to Screening.
28. Received a blood transfusion within 90 days prior to Screening.
29. Received administration of a live or live-attenuated vaccine 28 days or fewer prior to Randomization.
30. Has known hypersensitivity to ADX-038 or any of its excipients.
31. Has any other significant medical conditions that, in the opinion of the Investigator, would make the participant unsuitable for inclusion in the study, or could interfere with study assessments or put the participant at risk for experiencing significant adverse effects during the study.

BioJiva

A Phase 1/2 Study of the Safety and Efficacy of BRX011 Oral Administration Once Daily in Subjects with Geographic Atrophy Secondary to Age-related Macular Degeneration

The primary objectives:

1. To evaluate the safety and tolerability of BRX011 at a dose of 1000 mg daily relative to placebo in subjects with GA
2. To evaluate the efficacy of BRX011 at a dose of 1000 mg daily relative to placebo in subjects with GA, determined by the annual rate of change in the square root of GA area from baseline as measured by fundus autofluorescence (FAF)

Inclusion

To participate in the study, subjects must meet the following requirements:

1. Age ≥ 55 years
2. Visual acuity in the study eye at Screening/Baseline
 - a. BCVA ≥ 35 letters using ETDRS charts ($\geq 20/200$ Snellen equivalent)
 - b. LLD > 5 letters
3. Clinical diagnosis of GA secondary to AMD without subfoveal involvement in at least one eye as determined by the central reading center (CRC) using FAF and/or SD-OCT, i.e., well demarcated area(s) of GA with no evidence of prior or active CNV in the study eye. CNV in the fellow eye is permitted.
4. The GA lesion area must meet the following criteria, as determined by the CRC based on FAF and/or SD-OCT at Screening/Baseline:
 - a. If GA is monofocal, the lesion area must be $\geq 1.25 \text{ mm}^2$ and $\leq 17.5 \text{ mm}^2$
 - b. If GA is multifocal, at least one of the lesions must be 1.25 mm^2 and the sum of all lesions must be $\leq 17.5 \text{ mm}^2$
 - c. The entire GA lesion must be imaged in its entirety and not contiguous with any areas of peripapillary atrophy
 - d. GA in part must be within 1500 microns from the foveal center
 - e. The photoreceptor (PR) to retinal pigment epithelium (RPE) ratio (PR/RPE) of GA lesion must be ≥ 1.19 , as determined by OCT-based measurement
5. Clarity of ocular media, adequate pupillary dilation, and fixation to permit the evaluation of the eye, as determined by the investigator
6. Female subjects must be of non-child-bearing potential (WONCBP), defined as:
 - a. A woman who had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
 - b. A woman ≥ 60 years of age
 - c. A woman ≥ 55 and < 60 years of age who fulfills at least one of the following:
 - (1) A cessation of menses for at least 12 months and a follicle stimulating hormone (FSH) test confirming non-childbearing potential (refer to laboratory reference ranges for confirmatory levels)
 - (2) A cessation of menses for at least 24 months without FSH levels confirmed.
7. Willing and able to give informed consent and to comply with the study procedures and assessments

Exclusion

Subjects meeting one or more of the following may not enter the study:

1. GA secondary to a condition other than AMD such as Stargardt disease, cone rod dystrophy or toxic maculopathies like plaquenil maculopathy in either eye; presence of GA that is already touching the optic disc in the study eye
2. Any history documented (by anatomic evidence such as FA or SD-OCT) or active CNV, including any evidence of retinal pigment epithelium tears or evidence of neovascularization anywhere, as assessed by the CRC in the study eye
3. Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention during the study period or, in the opinion of investigator, could confound efficacy or safety evaluation during the study period (e.g. retinal detachment, significant cataract, uncontrolled glaucoma defined as IOP $\geq$ 30 mmHg despite maximum treatment with IOP-lowering medications, proliferative diabetic retinopathy in either eye)
4. Presence of an active ocular disease that, in the opinion of the investigator, may confound visual function, including but not limited to, other macular diseases (e.g., clinically significant epiretinal membrane [ERM], full thickness macular hole) in the study eye. Benign conditions, in the opinion of the investigator, such as peripheral retina dystrophy are not exclusionary
5. History of vitrectomy surgery, submacular surgery, other surgical intervention for AMD, corneal transplant, glaucoma filtration surgery, or cataract surgery within 3 months prior to Screening/Baseline in study eye
6. History of intravitreal injection of anti-vascular endothelial growth factor (VEGF) therapies in the study eye at any time, history of intravitreal injection of any agent (e.g., triamcinolone) in the study eye within the last 3 months prior to study enrollment. A single intraoperative administration of a corticosteroid during cataract surgery at least 3 months prior to Screening is permitted
7. History of laser therapy in the macular region in the study eye, prior treatment with photobiomodulation, external-beam radiation therapy or transpupillary thermotherapy in study eye
8. Previous cell-based intraocular treatment in the study eye or previous expression vector-mediated intraocular treatments in either eye (i.e., gene therapy), any previous treatment with any deuterated molecules for eye diseases (e.g., deuterated vitamin A)
9. History of idiopathic or autoimmune-associated uveitis, ocular or intraocular conditions, and infectious or inflammatory ocular disease. Active uveitis and infectious conjunctivitis, keratitis, scleritis or endophthalmitis
10. Any screening laboratory value (hematology, serum chemistry or urinalysis) that, in the opinion of the investigator, is clinically significant relative to study participation
11. Active malignancy within the previous 12 months except for appropriately treated carcinoma in situ of cervix, resolved non-melanoma skin carcinoma, and prostate cancer with a Gleason score of less than or equal to ($\leq$) 6, and a stable prostate-specific antigen for greater than or equal to ($\geq$) 12 months
12. Uncontrolled medical (e.g., uncontrolled blood pressure, atrial fibrillation) or psychiatric condition that, in the opinion of the investigator, is clinically significant and not suitable for study participation or consistent follow-up
13. Intake of omega-3 supplements (e.g., fish oil, cod liver oil, krill oil, edible algae oil, flax oil) or prescription omega-3 drugs (e.g., Lovaza®, Vascepa®, Epanova®) in the past 4 weeks prior to Screening and throughout the duration of the study; intake of supplements containing Lutein, zeaxanthin and/or meso-zeaxanthin (e.g., Ocuvite®, PreserVision®, SYSTANE ICAPS® or other AREDS supplements) in the past 4 weeks prior to Screening and throughout the duration of the study
14. Participation in an interventional clinical study within the past 30 days of Screening, or interventional GA studies within the past 5 months prior to Screening
15. Treatment with SYFOVRE® or IZERVAY® within 3 months prior to Screening

Macular Telangiectasia Type II

MacTel NHOR

Natural history observation and registry Study Of macular telangiectasia type 2 - The mactel study

The primary objectives:

1. Characterize and document the clinical features and the structural and functional changes of MacTel Type 2 from the earliest to the vision-threatening stages;
2. Collect genetic samples of affected individuals and their family members to establish whether there is a genetic basis for the condition; and
3. Develop a scientific basis to initiate the conduct of clinical studies for MacTel therapies that are emerging for the treatment of other retinal vascular diseases. The results of these clinical studies, to be conducted under separate protocols, will be used to design randomized, controlled clinical trials with adequate power to evaluate potential treatments.

Inclusion

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to review and understand the informed consent document and agree to the form's contents. (In cases with significant visual impairment, the informed consent may be read to the participant);
2. Stated willingness to comply with all study procedures;
3. Male or female, aged >18; and
4. Diagnosed with or suspected to be affected by MacTel Type 2; OR an immediate family member of a NHOR participant with MacTel; OR a healthy volunteer (control) or a volunteer (control) affected with a disorder thought to be related to MacTel Type 2.

Exclusion

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Inability to provide informed consent or undergo required procedures; and
2. Confounding (excluding diabetic retinopathy) ocular disorder that impacts the ability of the Reading Center to analyze images.

Central macula oedema

KLARITY KIORA

A phase 2, open-label, multiple dose study of the safety, tolerability and efficacy of intravitreal KIO-104 in patients with macular edema (KLARITY-1)

Trial details: This is a multi-centre, open label study to assess the safety, tolerability, and efficacy of KIO-104 administered by IVT injection to the study eye1 of eligible participants with ME secondary to non-infectious uveitis, retinal vein occlusion, diabetic retinopathy or cataract surgery.

Inclusion

Participants must meet all the following criteria:

1. Be aged 18 to 85 years inclusive at the time of consent.
2. Provide informed consent prior to any study procedures, as stipulated by local laws, Ethics Committee (EC) and Regulatory Authority (RA) guidelines.
3. Be willing and able to follow all study instructions, attend all study visits, and complete all study assessments.
4. Have a clinical diagnosis of ME in the study eye7 secondary to noninfectious uveitis, retinal vein occlusion, diabetic retinopathy or cataract surgery.
5. If currently receiving systemic corticosteroid therapy or immunosuppressive therapy (or any combination thereof), be on a stable dose of therapy for at least 3 months prior to Screening and during the study.
6. Have a Central Subfield Thickness (CST) of $\geq 350 \mu\text{m}$.
7. Have a Best Corrected Visual Acuity (BCVA) in the study eye of:
 - a. $\leq 20/32$ (Feet); $\log\text{MAR} \geq 0.2$
 - b. $\geq 20/800$ (Feet); $\log \text{MAR} \leq 1.6$
8. Have media clarity and pupillary dilation sufficient for adequate visualization and assessment of the study eye.
9. Be willing to avoid disallowed medications and treatments for the duration of the study.
10. Agree to follow appropriate contraception requirements from screening until 3 months after the last dose of the study drug.
 - a. Participants assigned female at birth who are of child-bearing potential (OCBP) must agree to a pregnancy test at Screening and prior to each dose of investigational medicinal product (IMP) and use an acceptable method of birth control including oral, transdermal, injectable, or implantable hormonal contraception, intrauterine device, abstinence from intercourse with partner assigned male at birth, or surgical sterilisation of partner assigned male at birth.
 - b. Participants assigned female at birth are not OCBP if they have had a hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or are post-menopausal by at least 12 months. Post-menopausal status of amenorrheic female participants should be confirmed at Screening through testing of folliclestimulating hormone (FSH) as per analysing laboratory threshold.
 - c. Participants assigned male at birth with a partner OCBP must be surgically sterile for at least 3 months prior to starting study drug, or ensure their partner uses contraception as outlined above, and must use a male condom. Participants assigned male at birth must not donate sperm from Screening until 3 months after the last dose of IMP.
 - d. Participants who have practiced true abstinence for at least 1 year due to usual and preferred lifestyle choice are exempt from contraceptive requirements. If a participant who is abstinent becomes sexually active, they must agree to use appropriate contraception as described above.

Exclusion

Participants must not meet any of the following criteria:

1. Have media opacities (cornea, anterior or posterior synechia, cataract, vitreous haze and others) of either eye that preclude investigation and documentation of the posterior pole and intravenous fluorescein angiography, or optical coherence tomography evaluation in the study eye.
2. Receive local or systemic biologicals (i.e. tumour necrosis factor [TNF]-blockers, B-cell blockers, cytokines, cytokine-blockers, receptor antagonists) 90 days prior to Day 1 or planned during the study.
3. Receive treatment with cyclophosphamide or chlorambucil during the study.
4. Receive intravitreal injections (including but not limited to anti-vascular endothelial growth factors) 90 days prior to Day 1 or planned during the study.
5. Receive a posterior subtenon's or orbital floor injection of steroids 90 days prior to Day 1 or planned during the study.
6. Have any implantable corticosteroid-eluting device (Ozurdex, Iluvien, Retisert, triamcinolone intravitreal implant, fluocinolone intravitreal implant) in the study eye, with the following exceptions:
 - a. If the device had been removed more than 90 days prior to Day 1 of the study.
 - b. If Ozurdex® had been implanted at least 6 months before Day 1 of the study.
 - c. If Iluvien® or Retisert® had been implanted at least 3 years before Day 1 of the study.
 - d. Use of topical steroids are permissible provided the participant is receiving a stable dose for at least 3 months prior to Screening and during the study.
7. Have ocular surgery (including cataract extraction, vitreoretinal or scleral buckling surgery) in the study eye, within 90 days prior to Day 1, or planned during the study.
8. Have a capsulotomy in the study eye, within 30 days prior to Day 1, and during the study.
9. Have Intraocular pressure (IOP) ≥ 25 mmHg in the study eye (glaucoma patients maintained on no more than one topical medication with IOP < 25 mmHg are allowed to participate).
10. Have ocular hypotony (IOP < 6 mmHg).
11. Have aphakia or anterior chamber lens in the study eye
12. Have visible scleral thinning, scleral ectasia or keratoconus in the study eye.
13. Have presence of any ocular malignancy in either eye.
14. Have evidence of any other clinically significant ocular disease that might interfere with the study assessments.
15. Have ocular or periocular (either eye) or systemic infection and/or a temperature greater than 38.0°C, or the use of systemic or topical ocular antibiotics within 14 days of Day 1.
16. Have a psychiatric condition that, in the investigator's opinion, precludes compliance with the protocol; past or present psychoses; past or present bipolar disorder; disorder requiring lithium; or within five years prior to screening, a history of suicide plan.
17. Have any clinically significant abnormality at screening determined by medical and ophthalmic history, vital signs, clinical biochemistry, hematology, urinalysis, or a 12-lead electrocardiogram (ECG), as assessed by the investigator, which might interfere with the study assessments or the ability of the participant to complete the study.
18. Have any other medical condition or significant co-morbidities, or any finding during screening, which in the view of the investigator is likely to interfere with the study or put the participant at risk, confound study data, or interfere significantly with study participation.
19. Have participated in any other investigational drug or device clinical trial within 90 days prior to Day 1 or planning to participate in other investigational drug or device clinical trials during the study and within 90 days following Day 1. This includes both ocular and non-ocular clinical trials.
20. Receive any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran, aspirin and others) within 14 days prior to Day 1 or planned during the study.
21. Have a known allergy or hypersensitivity to the study medication, any component of the delivery vehicle, any corticosteroids, any diagnostic agents used during the study (e.g., fluorescein, dilation drops), or any other standard of care medications likely to be used during the study (e.g., antibiotic drops, povidone, rescue medications).
22. Be pregnant or breast-feeding, or plan to become pregnant during the study.

Autosomal Dominant Optic Atrophy

MYRTLE

A Phase 1b Open-Label, Randomized, Single Dose and Repeat Dose Study to Evaluate the Single and Repeat Dose Safety and Tolerability of Intravitreally Administered PYC-001 in Participants with Confirmed OPA1 Mutation-Associated Autosomal Dominant Optic Atrophy

Trial details:

The primary objective of both single dose and repeat dose cohorts is to evaluate the safety and tolerability of a single and multiple doses of intravitreally administered PYC-001 in participants with confirmed OPA1 mutation associated with ADOA

Further, to determine optimal dose and dosing regimen for PYC-001.

Adult participants will be distributed:

Single Dose Cohort:

- Single 60 µg dose

Repeat Dose Cohorts:

- Repeat dose:
- Cohort 1: 10 µg (low dose)
- Cohort 2: 30 µg (medium dose)
- Cohort 3: 60 µg (high dose)

And Two dosing regimens:

Group A: Once every 8 weeks

Group B: Once every 12 weeks

Inclusion Criteria:

1. Must give written informed consent before any study-related activity is carried out and must be able to understand the full nature and purpose of the study, including possible risks and adverse effects;
2. Adult males and females, aged 18 years and above at screening;
3. Body mass index ≥ 18.0 and ≤ 32.0 kg/m², with a body weight ≤ 100 kg at screening;
4. Have a recent (within five years) genetic diagnosis of OPA1 mutation-associated (haploinsufficiency) ADOA and/or confirmed diagnosis during screening, as determined by the PI. In case of complex mutation profile, eligibility will be determined in consultation with the Sponsor. Rollover participants are exempt from this criterion as their genetic diagnosis was confirmed in PYC-001-101;
5. Treatment naïve participants with best-corrected visual acuity (BCVA) of between $\leq 20/40$ (≤ 70 Early Treatment of Diabetic Retinopathy Study [ETDRS] letters) and $\geq 20/200$ (≥ 35 ETDRS letters). If both eyes meet this eligibility criteria, the eye with better fixation as determined by the PI in consultation with the Sponsor will be selected as the study eye and the other eye will be designated as the fellow eye. In the event that both eyes are eligible and have adequate fixation to reliably perform all study assessments, the worse eye as determined by the physician will be taken as the study eye. PYC-001-101 participants are exempt from this criterion and will have the same study eye and fellow eye as determined in PYC-001-101;
6. Treatment Naïve participants (participants from PYC-001-101 are exempt from this criterion) with mild to moderate visual field loss and retinal nerve fiber layer (RNFL) loss in the study eye only as determined by the Spectralis Glaucoma Module Premium Edition (GMPE) RNFL & visual field structure function data (map), defined as:
 - a. Mild disease = RNFL abnormalities (outside normal range) in no more than one of six sectors;
 - b. Moderate disease = RNFL abnormalities (outside normal range) in no more than three of six sectors;
 - c. Severe disease = RNFL abnormalities (outside normal range) in four of six sectors;
 - d. Advanced disease = RNFL abnormalities (outside normal range) in six of six sectors;
7. Medically healthy (in the opinion of the PI), as determined by pre-study medical history, and without clinically significant abnormalities including (assessments may be repeated at the discretion of the PI if an out-of-range value is determined to be erroneous):

- a. Physical examination without any clinically relevant findings;
 - b. Systolic blood pressure (BP) in the range of 90 to 160 mmHg and diastolic BP in the range of 50 to 95 mmHg after five minutes in sitting or supine or semi-supine position;
 - c. Heart rate (HR) in the range of 45 to 110 bpm after five minutes rest in sitting or supine or semi-supine position;
 - d. Body temperature (tympanic), between 35.5 35.5°C and 37.7°C;
 - e. No clinically significant findings in clinical chemistry, hematology, coagulation and urinalysis tests at screening (see Section 5.4 for specific ranges).
8. Female participants must be of non-childbearing potential, ie, surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least six weeks before the screening visit) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause and a follicle stimulating hormone [FSH] level consistent with postmenopausal status, per local laboratory guidelines). Females receiving hormone replacement therapy (HRT) may be considered for inclusion if the need for HRT is for no other medical reason than to treat symptoms associated with menopause. If female participants are of childbearing potential, they must:
- a. Have a negative pregnancy test at the screening visit and on study Day -1;
 - b. Agree not to attempt to become pregnant or donate ova from signing of the consent form until at least 130 days after final IVT dose administration of PYC-001;
 - c. Agree to use adequate contraception (defined as use of a condom by the male partner combined with use of a highly effective method of contraception (defined in Appendix 13.1) from one month prior to screening until at least 130 days after final IVT dose administration of PYC-001 , if not exclusively in a same-sex relationship or abstinent as a committed lifestyle.
9. Male participants must:
- a. Agree not to donate sperm from signing the consent form until at least 190 days after final IVT dose administration of PYC-001;
 - b. If engaging in sexual intercourse with a female partner who could become pregnant, agree to use adequate contraception (defined as use of a condom combined with use of a highly effective method of contraception (defined in Appendix 13.1) from signing the consent form until at least 190 days after final IVT dose administration of PYC-001;
 - c. If engaging in sexual intercourse with a female partner who is not of childbearing potential or a same-sex partner, agree to use a condom from signing the consent form until at least 190 days after final IVT dose administration of PYC-001 and;
10. Willing and able to comply with all study assessments and adhere to the protocol schedule and restrictions.

Exclusion Criteria:

Participants will be excluded from the study if there is evidence of any of the following (to be assessed at the Screening visit and on study Day -1, unless otherwise specified):

- 1. Participant has a known allergy to PYC-001 or any of its excipients;
- 2. Demonstrated clinically significant co-morbidities, which, in the opinion of the PI, would interfere with the participant's ability to participate in the study and/or confound study outcomes;
- 3. Females who are breastfeeding or planning to breastfeed;
- 4. Based on recent (within five years of screening [for rollover PYC-001-101 participants, within five years of entry into PYC-001-101]) genetic testing, the participant has mutations in genes that cause ADOA, other than OPA1 (for example in case of dominant negative ADOA and ADOA Plus) or has other pathological variants that result in an ADOA-like optic atrophic phenotype or other pathologic genetic findings indicating presence of additional confounding ocular diseases based on comprehensive genetic screening. Eligibility will be determined by the PI in consultation with the Sponsor as needed;
- 5. Have received any prior cell or gene therapy for a retinal condition, excluding participation in study PYC-001-101;
- 6. Within three months prior to study Day -1, have undergone any vitreoretinal surgery (scleral buckle, pars plana vitrectomy, retrieval of a dropped nucleus or intraocular lens, radial optic neurotomy, sheathotomy, cyclodestructive procedures or multiple filtration surgeries [two or more]) or any other ocular surgery in the study eye. This criterion does not apply for rollover participants from PYC-001-101;

7. Within three months prior to study Day -1, have placement of an Ozurdex® implant. This criterion does not apply for rollover participants from PYC-001-101;
8. Within three years prior to study Day -1, have placement of Retisert® or Iluvien® implants. This criterion does not apply for rollover participants from PYC-001-101;
9. Have ocular media opacity or poor pupillary dilation prohibiting quality ophthalmic evaluation or photography, as assessed by the PI in the study eye ;
10. Macular edema (intraretinal, sub-retinal or other fluid) in the study eye requiring treatment.
11. History of recurrent uveitis (idiopathic or immune-related) or active ocular inflammation;
12. Have used within 30 days of the Screening visit or is using any investigational drug or over-the-counter drug such as Idebenone or Vitamin B6 or a device which in the opinion of the PI or Sponsor could affect the optic nerve and/or influence functional vision or visual function during the study period. A decision will be made on a case-by-case basis by the PI in consultation with the Sponsor. Participation in observational studies is allowable based on PI discretion and consultation with the Sponsor's Medical Representative. Participation in PYC-001-101 is allowed;
13. Over-the-counter drugs like CoQ10 and other Nutraceutical usage will require a washout by five half-lives prior to baseline visit. Participants may need to stop taking the drug for the duration of the study based on Physician discretion and in consultation with the Medical Monitor;
14. Have a recent history (<6 months) of or current excessive recreational drug or alcohol use, in the opinion of the PI. Excessive alcohol use is defined as regular consumption of >10 standard drinks per week or >4 standard drinks per day, where one standard drink is defined as 10 grams of pure alcohol;
15. Positive alcohol breath test as assessed at screening, and on study Day -1 and study Day 1;
16. Positive urine drugs of abuse as assessed at screening and on study Day -1 and study Day 1;
17. Any retinal pathology other than ADOA or any other condition or prior therapy that in the opinion of the PI would make the volunteer unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements;
18. Presence of illness or pathology that, per investigator, include symptoms and/or the associated treatments that can alter visual function. For example, cancers or pathology of the central nervous system, including multiple sclerosis;
19. Positive test for human immunodeficiency virus, hepatitis B or C virus;
20. Clinically significant findings in clinical chemistry, hematology, coagulation and urinalysis tests at screening, defined as:
 - o Alanine transaminase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN) or bilirubin >1.5 × ULN (unless patient has Gilbert's syndrome);
 - o Estimated glomerular filtration rate <60 mL/min/1.73 m²;
 - o HbA1c level ≥7.0%;
 - o International normalized ratio ≥1.2;
 - o hemoglobin <10 g/dL, platelets <100,000/μL, and white blood cells within the normal range;
 - o Clinically significant abnormalities in the urine analysis.

Leber Congenital Amaurosis

HYPERION

A Double-Masked, Randomized, Placebo-Controlled, Paired-Eye Study to Evaluate the Efficacy, Safety and Tolerability of Sepofarsen in Subjects with Leber Congenital Amaurosis (LCA) due to the c.2991+1655A>G (p.Cys998X) Mutation in the CEP290 Gene

Trial details:

Hyperion is a 24-month, multi-center, double-masked, randomized, placebocontrolled, paired-eye study to evaluate the efficacy, safety, and tolerability of sepofarsen in subjects with LCA10 due to the c.2991+1655A>G mutation.

This is a placebo-controlled, paired-eye study in which one eye of each subject will serve as a control. Once eligibility is confirmed, the two eyes of each subject will be randomized such that one eye receives sepofarsen and the other eye receives placebo for the first year.

In the second year, for all subjects, the eye that was randomized to receive sepofarsen will continue to receive sepofarsen. For the eye that was randomized to placebo in the first year, treatment in the second year will be allocated, as follows: 50% of the eyes will continue to receive placebo, and 50% of the eyes will receive sepofarsen.

At each dosing visit, both eyes of each subject will be treated on the same day, if possible; the right eye should always be treated first. If treatment of the left eye cannot be done on the same day as the right eye, timing of the left eye dosing should occur within 5 days.

Sepofarsen and placebo will be administered via intravitreal (IVT) injection in accordance with the procedures outlined by the American Academy of Ophthalmology (Avery 2014) and as outlined in the Study Reference Manual.

Inclusion Criteria:

1. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures

-OR-

a minor (6 to < 18 years) with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any study related procedures and pediatric subjects able to provide age-appropriate assent for study participation.

2. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments, in the opinion of the Investigator.

OR

a minor (6 to < 18 years) able to complete all study assessments and comply with the protocol and has a parent or caregiver willing and able to follow study instructions and attend study visits with the subject as required, in the opinion of the Investigator.

3. Male or female with a confirmed clinical diagnosis of LCA10 and a molecular diagnosis of homozygosity or compound heterozygosity for the c.2991+1655A>G mutation, based on genotyping analysis at Screening. A historic genotyping report is acceptable with Sponsor approval.

4. BCVA (FrACT) equal to or worse than logMAR +0.4 (approximate Snellen equivalent 20/50) to +2.9 logMAR (this includes counting-finger and hand-motion subjects) based on quantifiable, reliable FrACT. LP subjects can be enrolled only with documented evidence of prior better vision.

5. Symmetrical disease between the two eyes as defined by a BCVA (FrACT) within 0.2 logMAR at baseline. If the BCVA (FrACT) asymmetry is greater than 0.2 logMAR, eligibility will be assessed in consultation with the Medical Monitor.

6. Detectable ONL in the macular area as determined by the CRC at Screening.

7. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator.

8. Non-pregnant and non-breastfeeding subjects. WOCBP and fertile males must comply with using highly effective methods of contraception (see Section 14.2 for definitions of WOCBP and fertile males

and details on highly effective contraception methods). Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the entry criteria for the study.

Exclusion Criteria:

1. Presence of pathogenic or likely pathogenic variants in genes (other than the CEP290 gene) which are known to be associated with other inherited retinal degenerative diseases or syndromes.
2. Any contraindication to IVT injection according to the Investigator's clinical judgement and the American Academy of Ophthalmology (Avery 2014). This includes any active or suspected intraocular inflammation or active or suspected ocular or periocular infection in either eye.
3. Presence of any significant ocular or non-ocular disease/disorder (including medication and laboratory test abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the study, may impact the subject's ability to participate in the study, or may interfere with assessment of efficacy and safety in the study.
4. Presence of unstable concurrent CME, or subject started on (or changed dose of) topical or systemic carbonic anhydrase inhibitor treatment in the 3 months prior to enrollment. CME is allowed if stable for 3 months (with or without treatment).
5. Presence of any ocular pathology in either eye that may make comparison of the eyes not feasible.
6. History or presence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus).
7. Presence of any of the following lens opacities/cataracts based on the AREDS lens grading scale: cortical opacity $\geq +2$, posterior subcapsular opacity $\geq +2$, or a nuclear sclerosis $\geq +2$, and which are: 1) clinically significant in the opinion of the Investigator, 2) would adequately prevent clinical and imaging evaluation of the retina.
8. Receipt within 1 month prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection, or planned intraocular surgery or procedure during the study. Subjects who received an intraocular or periocular surgery between 1 to 3 months prior to Screening, may only be considered for inclusion if there are no clinically significant complications of surgery present, and following approval by the Medical Monitor.
9. History of strabismus causing amblyopia that could cause comparison of visual function between the two eyes unfeasible, as assessed by the Investigator.
10. A history of glaucoma or an IOP greater than 24 mmHg that is not controlled with medication or surgery at the time of informed consent.
11. Use any investigational drug within 5 half-lives, use any investigational device within 90 days of Day 1, or plan to participate in another study of a drug and/or device during the study period.
12. Any prior receipt of genetic or stem-cell therapy for ocular or non-ocular disease.
13. Known hypersensitivity to antisense oligonucleotides or any constituents of the injection.
14. Current chronic treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to steroid implants, chronic systemic steroids, cytostatics, interferons, TNF-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects who have been treated on a short course of systemic steroids within the past 12 months or who require intermittent use of topical steroids may be considered for inclusion following approval by the Medical Monitor.
15. Current use of medications known to be toxic to the lens, retina, or optic nerve (eg, deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides).
16. History of malignancy within 5 years prior to screening, except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

Myelin oligodendrocyte glycoprotein antibody-associated disease

Star-MOG

*A phase III randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of treatment with cortico**ST**eroids at onset, And **R**ituximab during a relapse, of **Myelin Oligodendrocyte Glycoprotein** antibody-associated disease*

Trial details:

- 1) To evaluate the **efficacy** of an optimised corticosteroid tapering regime at the onset of MOGAD in delaying time to first centrally adjudicated relapse compared to a shorter course of corticosteroids followed by placebo (Onset MOGAD Group).
- 2) To evaluate the **efficacy** of 12 months of B cell depletion with rituximab following a relapse of MOGAD in delaying time to first centrally adjudicated relapse compared to placebo (Relapsing MOGAD Group)
- 3) To assess the **safety and tolerability** of:

an optimised corticosteroid tapering regime at the onset of MOGAD (Onset MOGAD Group)

12 months of B cell depletion with rituximab following a relapse of MOGAD (Relapsing MOGAD Group)

- 4) To evaluate the **influence of the proposed treatment regimens compared to placebo** on:

Disease activity | Neurological function | Visual function | Patient reported outcome measures | Impact on patients and carers on time missed from school/work

- 5) To evaluate the role of potential biomarkers in the management and prognostication of MOGAD
- 6) To evaluate the role of potential radiological biomarkers in the management and prognostication of MOGAD
- 7) To evaluate the role of potential visual biomarkers in the management and prognostication of MOGAD in patients with optic neuritis
- 8) To evaluate disease activity, neurological function, visual function. patient reported outcome measures and impact of treatment in MOGAD, including follow up beyond 12 months up until the end of data collection and data locking, in the subgroup of patients in whom this time point is reached
- 9) To use this evidence base to inform guidelines regarding the optimal management of MOGAD at onset and relapse

INCLUSION CRITERIA:

Onset MOGAD Group:

1. All children and adults who meet 2023 International Diagnostic Criteria for MOGAD¹, with suspected clinical phenotypes for MOGAD (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, brainstem/cerebellar demyelination, cortical encephalitis, cerebral monofocal or polyfocal deficits with demyelination) and serum MOG antibody clear positive by cell-based assay and exclusion of alternate diagnosis. If low positive or tested without titre provided or CSF restricted MOG antibody positive, then this patient is required to fulfill additionally required clinical and/or radiological supportive criteria as per International Diagnostic Criteria¹).
2. Willingness to provide informed consent and participate and comply with study requirements
3. Available to attend clinic visits within one month of each time point on the schedule of assessments.

Relapsing MOGAD Group:

1. All children and adults who meet 2023 International Diagnostic Criteria for MOGAD¹, with suspected clinical phenotypes for MOGAD (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, brainstem/cerebellar demyelination, cortical encephalitis, cerebral monofocal or polyfocal deficits with demyelination), and MOG antibody seropositive by cell-based assay at some point in the last 12 months before their relapse, and exclusion of alternate diagnosis.
2. A relapse within 12 months of recruitment into this trial. A relapse is defined by the occurrence of new or worsening, acute neurological symptom(s) with objective changes (clinical findings or signs) on clinical (neurological and ophthalmological) examination that persists for more than 24 hours as confirmed by the investigator, separated by a period of neurological recovery/stability from any prior disease activity by at least one month. The symptoms must be attributable to MOGAD, with other potential causes (such as infection, injury, changes in mood, adverse reactions to medications, or other diagnoses) ruled out.
3. For women of childbearing potential: participants who agree to use adequate contraception during the treatment period and for at least six months after the final dose of IMP or placebo.
4. Willingness to provide informed consent and participate and comply with study requirements
5. Available to attend clinic visits within one month of each time point on the schedule of assessments.

EXCLUSION CRITERIA:

Onset MOGAD Group:

1. Presentation clinically and radiologically consistent with multiple sclerosis
2. A clinical presentation considered atypical for MOGAD
3. AQP4-IgG seropositive
4. Significant, active and/or untreated infection (inclusive but not limited to active hepatitis B, hepatitis C, HIV, tuberculosis, syphilis, strongyloides, etc). Patients with active infection will require treatment before they can fulfill inclusion criteria.
5. Patients who will be given additional immunotherapy apart from the Investigational Medicinal Product (IMP) or placebo after four weeks post initiation of high dose corticosteroids (ie, any concurrent immunotherapy apart from the permitted IVIg/PLEX allowed in the treatment schedule).
6. Women of child-bearing potential who are planning pregnancy in the next twelve months or are currently pregnant
7. Any concomitant autoimmune disease other than MOGAD that requires ongoing immunotherapy throughout the trial period
8. A significant comorbidity that in the opinion of the site's principal investigator, would negatively affect MOGAD outcomes or preclude administration of corticosteroids
9. Circumstances/conditions which may interfere with the participant's ability to give informed consent
10. Any routine screening test results which the site investigator feels places the patient at risk if they proceed with the trial
11. Known hypersensitivity or allergic reaction to IMP

Relapsing MOGAD Group:

1. Presentation clinically and radiologically consistent with multiple sclerosis
2. A clinical presentation considered atypical for MOGAD
3. AQP4-IgG seropositive
4. Current B cell depletion as determined by B cell subsets at screening visit
5. Significant, active and/or untreated infection (inclusive but not limited to active hepatitis B, hepatitis C, HIV, tuberculosis, syphilis, strongyloides, etc). Patients with active infection will require treatment before they can fulfill inclusion criteria.
6. Women of child-bearing potential who are planning pregnancy in the next twelve months or are currently pregnant

7. Receipt of a live or live attenuated vaccine within six weeks prior to screening visit, or planned live or live attenuated vaccine during the study period
8. Any concomitant autoimmune disease other than MOGAD that requires ongoing immunotherapy throughout the trial period
9. A significant comorbidity that in the opinion of the site's principal investigator, would negatively affect MOGAD outcomes or preclude administration of rituximab
10. Any routine screening test results which the site investigator feels places the patient at risk if they proceed with the trial
11. Circumstances/conditions which may interfere with the participant's ability to give informed consent
12. Known hypersensitivity or allergic reaction to the IMP
13. Exclusion criteria related to previous or concomitant immunotherapy for MOGAD
 - B cell depletion in the six months prior to screening
 - Cyclophosphamide in the twelve months prior to screening
 - IL-6R antagonists such as satralizumab or tocilizumab in the six weeks prior to screening (including participation in the Roche Meteoroid study – satralizumab vs placebo)
 - Tacrolimus or cyclosporine in the six weeks prior to screening
 - FcRn mAbs in the six weeks prior to screening (including participation in the UCB CosMOG study – rozanolixizumab vs placebo)
 - Alemtuzumab in the 12 months prior to screening
 - Planned ongoing treatment with MS disease modifying therapy (glatiramer acetate, interferon, fumarates, teriflunomide, natalizumab, fingolimod, siponimod, ozanimod, cladribine, alemtuzumab after the documented MOGAD relapse prompting consideration for this trial)
 - Concurrent immunotherapy apart from IMP/placebo after randomisation while in the double blind phase of the trial, until time of first relapse (or to the end of 12 months in patients without a relapse) apart from permitted corticosteroids up to 4 weeks post randomisation