Oxular Limited

Clinical Trial Protocol

Clinical Trial Protocol Title:

A Multi-Center, Randomized, Parallel-Group, Phase 2, Masked, Three-Arm Trial to Compare Safety, Tolerability, Efficacy, and Durability of Two Dose Levels of Suprachoroidal Sustained-Release OXU-001 (Dexamethasone Microspheres; DEXAspheres®) Using the Oxulumis® Illuminated Microcatheterization Device Compared with Intravitreal Dexamethasone Implant (OZURDEX®) in Subjects with Diabetic Macular Edema (OXEYE).

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Confidentiality Statement

Signatures

I hereby confirm that I approve of this clinical trial protocol and agree to comply with its terms as laid out in this document.

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List of Abbreviations

4WF	Four Wide-Field Fundus Photography
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-VEGF	Anti-Vascular Growth Factor
AMD	Age Related Macular Degeneration
AS-OCT	Anterior Segment – Optical Coherence Tomography
AUC	Area Under the Curve
BCVA	Best Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
BM	Biomicroscopy
CEP	Clinical Evaluation Plan
CFP	Color Fundus Photography
Cmax	Maximal Concentration
CMO	Contract Manufacturing Organization
ConjIncision	Conjunctiva Incision
CRC	Central Reading Center
CRF	Case Report Form
CRVO	Central Retinal Vein Occlusion
CST	Central Subfield Thickness
DMA	Dexamethasone Acetate
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DXM	Dexamethasone
EDI-OCT	Enhanced Depth Imaging Optical Coherence Tomography
EMA	European Medicines Agency
EoS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
GCP	Good Clinical Practice

HbA1c	Hemoglobin A1c
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IR	(Near) Infrared Imaging
IRB	Institutional/Independent Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
IVRS	Interactive Voice Response System
IVT	Intravitreal
IWRS	Interactive Web Response System
LAR	Legally Authorized Representative
LLOQ	Lower Limit of Quantitation
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
ME	Macular Edema
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
OU	Oculus Uterque – Both Eyes
PDR	Proliferative Diabetic Retinopathy
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PPS	Per Protocol Set
PRN	Pro Re Nata (as needed)
PRP	Panretinal Photocoagulation
QC	Quality Check
RSI	Reference Safety Information
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAS	Safety Analysis Set

SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SoA	Schedule of Assessments
SSC	Study Steering Committee
SS-OCT	Swept-Source Optical Coherence Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Triamcinolone Acetonide
TEAE	Treatment-Emergent Non-Serious Adverse Effect
TEDAE	Treatment Emergent Non-Serious Device Adverse Effect
Tmax	Time to maximal concentration
UPT	Urine Pregnancy Test
USADE	Unanticipated Serious Adverse Device Effect
US FDA	United States Food and Drug Administration
UWF	Ultra-Wide Field
VEGF	Vascular Endothelial Growth Factor
WFI	Water for Injection

1 Protocol Summary

1.1 Synopsis

Title	A Multi-Center, Randomized, Parallel-Group, Phase 2, Masked, Three-Arm Trial to Compare Safety, Tolerability, Efficacy, and Durability of Two Dose Levels of Suprachoroidal Sustained-Release OXU-001 (Dexamethasone Microspheres; DEXAspheres®) Using the Oxulumis® Illuminated Microcatheterization Device Compared with Intravitreal Dexamethasone Implant (OZURDEX®) in Subjects with Diabetic Macular Edema (OXEYE).
Sponsor Protocol #:	OXUCT-102
ClinicalTrials.gov Identifier:	NCT05697809
EU CT Identifier No.:	2023-503496-17-00
Phase:	Phase 2
Brief Title	Suprachoroidal Sustained-Release OXU-001 compared to Intravitreal Ozurdex® in the Treatment of Diabetic Macular Edema
Rationale	There is a great unmet need for Diabetic Macular Edema (DME) therapies, which have compared to standard-of-care anti-VEGF therapies a broader spectrum of pharmacological activities and thereby also address the strong inflammatory component of DME. In addition, therapies with a long duration of action of more than 6 months would reduce the treatment burden of patients. Ocular corticosteroids have the potential to address this unmet need, as they have not only shown strong anti-edema effects similar to anti-VEGF treatments, but also a broad anti-inflammatory effect. Progressive, continued retinal and choroidal inflammation is a key driver of the progression of diabetic eye disease.

	Provided an acceptable safety profile, ocular steroids can deliver visual benefits in DME patients that are treatment-naïve as well as in those who showed limited, short-lived, or no visual improvement with intravitreal (IVT) administered anti-VEGF drugs. The use of current steroid therapies for DME, including IVT Ozurdex®, is limited by the typical and frequent adverse reactions; specifically, cataract formation and increased intraocular pressure (IOP), which usually require administration of additional ophthalmic drugs, *e.g.,* IOP lowering eye drops, glaucoma surgery, or lens replacement surgery. Due to these safety concerns and the limited durability of only 3-6 months for the most frequently used IVT steroid implant, the current benefit-risk profile of IVT steroids in DME patients is suboptimal. Accordingly, there remains a high unmet medical need for efficacious ocular treatments for diabetic macular edema (DME) with a more favorable benefit-risk profile. OXU-001 is a combination sustained-release formulation of dexamethasone acetate (DMA) microspheres (DEXAspheres®) administered suprachoroidally with the Oxulumis® ophthalmic illuminated microcatheterization device (an ophthalmic administration device). The targeted durability of OXU-001 based on preclinical experiments is up to 12 months. OXU-001 has the potential for longer durability because of the combination of a sustained-release drug formulation plus a simple and routine delivery to the suprachoroidal space. OXU-001 is expected to have a sustained anti-edema effect and a reduced incidence of steroid-related ocular adverse events (AEs). The current trial has the objective of generating clinical data to assess the following aspects of suprachoroidal OXU-001 in DME:

	• The safety of suprachoroidal, sustained-release steroid treatment in DME with respect to reduction of the risk of steroid-induced complications by posterior deployment of OXU-001. • The therapeutic effects of OXU-001 to provide clinically meaningful visual and anatomical benefits for an extended time (>6 months) by reducing DME. • The extent of systemic exposure to dexamethasone (DXM) following sustained release suprachoroidal administration for the duration of the clinical trial. The objectives for evaluating the device safety and performance are separately outlined in the latest version of the Oxulumis® Clinical Evaluation Plan (CEP) Version OXUCT-102.

Objectives and Endpoints	Objectives	Main Endpoints
<u>Part A</u> (Open-Label): Two parallel, randomized treatment arms with mid-dose and high dose sustained-release OXU-001 in treatment-naïve or anti-VEGF previously treated DME subjects in the study eye		
Safety	1. To evaluate the safety, tolerability, and feasibility of suprachoroidal OXU-001 in subjects with DME	1. Frequency and severity of • ocular and systemic adverse events (serious, adverse events of special interest, and treatment-emergent adverse events) • device adverse effects (serious adverse device effects and treatment-emergent device adverse effects)
Exploratory Efficacy	1. To evaluate the durability of suprachoroidal OXU-001 in subjects with DME	1. Time from baseline, (Visit 2), to subjects requiring follow-on treatment (per pre-specified criteria).

	2. To explore the efficacy of suprachoroidal OXU-001 determined by change in visual acuity, edema control, and impact on vision-related quality of life in subjects with DME	2. Mean Change BCVA (ETDRS) at Week 24 compared to baseline. 3. Mean Change in central subfield thickness at Week 24 compared to baseline. 4. Mean Change BCVA (ETDRS) through Week 52 compared to baseline. 5. Mean Change in central subfield thickness through Week 52 compared to baseline. 6. Mean change in NEI VFQ-25 Total Score at Week 24, and Week 52 compared to baseline.
Pharmaco-kinetics (PK)	Assess systemic exposure of dexamethasone after administration of OXU-001.	1. Dexamethasone levels in plasma will be measured at scheduled timepoints (pre-dose, and post-dose at 60min, 1 day, 1 week, 4 weeks, 24 weeks, and 52 weeks after administration of OXU-001). The following PK parameters will be evaluated: 1. Time to maximal concentration (Tmax) 2. Maximal concentration (Cmax) 3. Area under the curve (AUC)

Part B: Randomized, controlled, masked trial with two dose levels of sustained-release OXU-001 compared to Ozurdex® in treatment-naïve or anti-VEGF previously treated DME subjects in the study eye (at least 50% treatment-naïve).		
Primary	1. To evaluate the safety and tolerability of suprachoroidal OXU-001 in subjects with DME	1. Frequency and severity of • ocular and systemic adverse events (serious, adverse events of special interest, and treatment-emergent non-serious adverse events) • device adverse effects (serious adverse device effects and treatment-emergent non-serious adverse device effects).
Exploratory	1. To evaluate the durability of suprachoroidal OXU-001 in subjects with DME. 2. To explore the efficacy of suprachoroidal OXU-001 determined by change in visual acuity, edema control, and impact on vision-related quality of life in subjects with DME.	1. Time from baseline, Visit 2, to subjects requiring follow-on treatment (per pre-specified criteria). 2. Mean Change BCVA (ETDRS) at Week 24 compared to baseline. 3. Mean Change in central subfield thickness (SD-OCT) at Week 24 compared to baseline. 4. Mean Change in BCVA (ETDRS) through Week 52 compared to baseline. 5. Mean Change in central subfield thickness through Week 52 compared to baseline. 6. Proportion of subjects requiring follow-on treatment at study

		visits from Week 12 through Week 52. 7. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) gain of BCVA from week 4 to week 52 compared to baseline. 8. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) loss of BCVA from week 4 to week 52 compared to baseline. 9. Proportion of subjects with BCVA >68 letters (ETDRS) at each study visit from week 4 to week 52. 10. Mean change in NEI VFQ-25 Total Score Week 24, and Week 52 compared to baseline.
Overall Design	This is a fifty-two-week (52-week) trial with two parts. The total time of trial participation can be up to 58 weeks, if the maximum time interval for performing activities of the Baseline Visit (V2) of 14 days is used. Part A is an open-label, randomized, single-dose two treatment arm comparison of two dose levels of sustained-release suprachoroidal OXU-001 (DEXAspheres® administered using the Oxulumis® illuminated microcatheterization device). Part B is a randomized, masked, active comparator, single-dose, comparison of two dose levels of suprachoroidal OXU-001 and IVT Ozurdex® (0.7mg dexamethasone) to evaluate the safety, tolerability, efficacy, and durability in subjects with DME. In Part A and Part B, a follow-up period of 52 weeks appears to be justified as preclinical experiments suggest a durability of 9-12 months before follow-on treatment may be needed.	

	The study population will consist of a total of approximately 128 adult female or male subjects with DME with approximately 18 subjects included in Part A and approximately 110 subjects included in Part B that: 1. Have been diagnosed with Type 1 or Type 2 diabetes mellitus. 2. Have DME involving the center of the fovea with central subfield thickness (CST) in the study eye at the screening visit, confirmed by the CRC, of at least 320 µm on SD OCT (measurement from the Retinal Pigment Epithelium, RPE, to the Inner Limiting Membrane, ILM, inclusively). 3. Have BCVA between 34 and 78 letters (using an ETDRS chart, approximate Snellen acuity of 20/200–20/32) in the study eye. 4. Are treatment-naïve or previously treated with IVT anti-VEGF in the study eye. Only one (1) eye will be determined as the study eye and only the study eye will receive a single administration of study treatment on Visit 2, Day 0. Study eyes need to meet all inclusion criteria and none of the exclusion criteria. If both eyes meet the relevant criteria, the eye with the worse BCVA will be selected as the study eye; if both eyes meet the relevant criteria and have the same BCVA, the investigator can select the study eye. If one eye is previously treated (for allowed prior treatments see Section 5.2 and Section 7.8.1), the other eye may still qualify as a treatment-naïve study eye if all inclusion criteria and none of the exclusion criteria are met. Subjects' fellow eye may continue to receive non-study treatment following guidelines and standards at the investigational site. Subjects in Part A should not receive steroid treatment in their fellow eye, as this may have an impact on the PK assessment of OXU-001. Treatment of the fellow eye is not considered part of the study treatment. The treatment arms in Part A and Part B are as follows:

Part A (Open Label) consists of two parallel, randomized treatment arms, treated with mid-dose, DMA 1.5mg (Arm A1) and high dose, DMA 3.0mg (Arm A2) with a total of approximately 18 subjects who are treatment-naïve or were previously treated with IVT anti-VEGF in the study eye in the study eye. No minimum number of treatment-naïve subjects is fixed. Subjects will be followed for 52 weeks (maximum time of participation for a subject can be up to 58 weeks if the maximum14-day interval for V2 activities is needed), with a safety analysis at Week 6, and further analyses at Week 24, and Week 52.

Treatment Arm	Intervention	Subjects
A1	One (1) treatment with suprachoroidal **mid dose (DMA 1.5mg)** OXU-001	N=9
A2	One (1) treatment with suprachoroidal **high dose (DMA 3.0mg)** OXU-001	N=9

Part B (Masked) consists of three (3) randomized masked arms with a total of approximately 110 subjects (B1, B2, and B3) who are either previously treated or treatment-naïve (in the study eye).

Treatment Arm	Intervention	Subjects
B1	One (1) treatment with suprachoroidal **Dose 1 (mid dose DMA 1.5mg)** OXU-001	n=44
B2	One (1) treatment with suprachoroidal **Dose 2 (tbc. DMA 3.0mg or 0.75mg),** based on the outcome of Part A 6 weeks) OXU-001	n=44
B3	One (1) treatment with intravitreal Ozurdex® (dexamethasone 0.7mg)	n =22

Enrollment for Part B will commence after a safety analysis when the last subject in Part A has completed the Week 6 visit. The focus of the analysis will be on patient-relevant safety events, including *e.g.,* the

	occurrence rate of moderate and severe ocular AEs, AESI, and ocular SAEs reviewed by DMC, and Sponsor. In Part B two different dose levels of OXU-001 will be administered, Dose 1 in treatment arm B1 and Dose 2 in treatment arm B2 compared to IVT Ozurdex 0.7mg (treatment arm B3). Dose 1 is planned to be OXU-001 1.5mg (mid-dose) and Dose 2 OXU-001 3.0mg (high dose). If potential safety concerns arise from the week 6 analysis in Part A with the high dose (treatment arm A2), the dose in Part B may be adjusted to administer the mid-dose in B1 (Dose 1, 1.5mg) and the low dose in B2 (Dose 2, 0.75mg) OXU-001. Subjects will be followed for 52 weeks (maximum time of participation for a subject can be up to 58 weeks if the maximum 14-day interval for V2 activities is needed). The OXUCT-102 trial will include both subjects that are treatment-naïve and subjects that have been previously treated with anti-VEGF therapy in the study eye. For treatment-naïve subjects the other (fellow) eye may receive treatment for DME according to standard-of-care. In Part A fellow eye treatment for DME with IVT steroids is forbidden, as it might interfere with PK assessments. In Part A, subjects will be randomly assigned to receive either a mid-dose (1.5mg) or high dose (3.0mg) OXU-001 in a 1:1 fashion. A randomized parallel-group design appears justified as there is ample experience with sustained-release formulations of dexamethasone in retinal disorders and the release kinetics and the dose range of the proposed human dosages (1.5 and 3.0mg sustained-release OXU-001) have been modeled to be comparable with the release kinetics of previously investigational intravitreal dexamethasone 0.35mg and the marketed 0.7mg implant. In Part B, both treatment-naïve and anti-VEGF previously treated subjects (in the study eye) will be enrolled (n=110). Enrollment of previously treated and treatment-naïve subjects will be competitive, with at least 55 subjects being treatment-naïve in the study eye. Enrollment of subjects that are anti-VEGF previously treated in the study eye will stop once 55 subjects with previous anti-VEGF treatment in the study eye are

	randomized to allow reaching the foreseen number of treatment-naïve subjects. Subjects will be stratified based on their anti-VEGF treatment history. In both Part A and Part B, subjects in whom the administration of study treatment could not be completed, will be replaced in order to reach the targeted numbers of treated subjects. The following masking procedures will apply in Part B: Subjects will be masked to their assignment to one of the treatment arms (B1-B3). Subjects will only receive one study treatment on Visit 2, Day 0, *i.e.,* either suprachoroidal administration of study treatment (OXU-001) or IVT Ozurdex. No sham treatment for the respective other treatment will be applied. In this trial, the administration of OXU-001 with the Oxulumis illuminated microcatheter will be performed with two different procedural variants depending on subject characteristics and procedural success: • Standard Variant: Administration with the Oxulumis® device without an incision of the conjunctiva/tenons. The standard variant can be performed in any setting, *i.e.*, in-clinic, in a procedure room or in an operating room. • ConjIncision Variant: Incision of the conjunctiva/tenons at the start of the OXU-001 administration to increase visibility and access for the scleral engagement phase of the OXU-001 administration. The incision opening of the conjunctiva/tenons needs to be closed by using standard surgical techniques and material (*e.g.,* fibrin glue, suturing material): This variant can be used at the discretion of the treating physician (unmasked investigator in Part B) either a) initially if subject characteristics and/or medical history suggest this variant, or b) if with the Standard Variant, study treatment cannot be administered. The ConjIncision Variant can only be performed in a sufficiently equipped environment for opening and closing the

	conjunctiva/tenons. An adequate procedural setting, techniques and material used follows the surgical standard in the respective geographic region (*i.e.,* an adequately equipped procedure room or an operating room). The treating physician will determine at the Screening Visit (V1), if initially the Standard Variant or the ConjIncision Variant will be used in a respective subject. The baseline visit activities will be planned accordingly with three different schedules for baseline visit activities: • OXU-001 Standard Variant without surgical incision is typically performed in an in-clinic or procedure room setting • OXU-001 ConjIncision Variant with conjunctiva/tenons incision is typically performed in a surgically equipped procedure or operating room • Move from OXU-001 Standard to ConjIncision Variant. In this scenario procedural attempts are typically started in-clinic. If the OXU-001 Standard Variant cannot be completed, the procedure is switched to the ConjIncision Variant and depending on the facility will then be either performed in the same facility (surgically equipped procedure room) or has to be rescheduled in a surgical facility, which may not be available the same day due to scheduling or proximity to the clinic/investigational site. The maximum time interval to complete all baseline visit activities is 14 days including potential rescheduling of treatments in case switch of the procedural variants is needed. In Part B, if an unmasked treating physician decides directly for the ConjIncision Variant, a facility that allows incision of the conjunctiva/tenons will be booked for masking purposes even if the subject will be finally randomized to receive Ozurdex®. For Ozurdex® the ConjIncision Procedural Variant, *i.e.,* surgical incision of the conjunctiva/tenon is not allowed.

	In Part B, the assessment teams at the investigational site performing the efficacy and selected questionnaire assessments (*i.e.*, BCVA, Subject's Experience Assessment, and NEI-VFQ25) are fully masked to the subject's treatment assignment, as well as the graders at the central reading center assessing the CST values (CRC). This may require specific readers for other imaging like Color Fundus Photography (CFP) 4 Wide-Field IR Plus images, or peripheral OCT, as those assessments may show findings (*e.g.*, suprachoroidal drug deposits) that give hints on the treatment assignment. Study treatments will be administered by unmasked retinal physicians trained on the Oxulumis procedure, who will need to know the treatment assignment of subjects (for details on the masking see Section 7.3). On Visit 2 (Day 0), for both Parts A and B, subjects will receive study treatment using either the OXU-001 Standard, or the OXU-001 ConjIncision Variant as outlined above with impact on scheduling of the baseline visit activities as summarized in Table 3 and Table 4 of the Schedule of Activities. In addition to the screening and baseline visits, (Visits 1 and 2, respectively), clinic visits will occur on Day 1, and Week 1, 4, 6, 8, and then every four (4) weeks thereafter for a total duration of fifty-two (52) weeks. In Part A, the Week 6 visit is scheduled to capture and assess any potential safety signals which may start around this time after steroid treatment (*e.g.,* IOP increase). A safety review will occur after all active study participants have completed Week 6 visit prior to initiating randomization in Part B. For Part B, the Week 6 safety visit is optional and may be scheduled at the discretion of the investigator based, *e.g.*, if subjects tend to present with relevant IOP increase through Week 4 post-treatment. Starting at the Week 12 visit, for both Parts A and B, subjects will be evaluated by the investigator (masked investigator in Part B) against prespecified criteria indicating the need for follow-on treatment (*i.e.,* indicating the end of the current treatment interval). Criteria are as follows:

	1. At least 75µm thickening in CST on SD-OCT compared to best CST value since the baseline visit, Visit 2, Day 0, or 2. A decrease in BCVA of ≥10 letters (ETDRS) from the best achieved BCVA since the baseline visit, Visit 2, Day 0, that, in the opinion of the investigator, is due to the worsening of DME. For subjects showing no reduction of edema or no improvement of BCVA after Visit 2, Day 0, the values assessed at the baseline visit will be considered the best CST or BCVA value. If according to the assessment of the above criteria, by the investigator (masked investigator in Part B), the need for administration of follow-on treatment is indicated, subjects will be managed according to local standard of care for the rest of the trial duration. Standard of care treatments may include IVT anti-VEGF, ocular IVT steroids, or other non-investigational treatments. In Part B, when follow-on treatment criteria are met based on masked assessment, the unmasked investigator will determine the kind of follow-on treatment to be administered (*e.g.,* IVT anti-VEGF treatment, IVT steroid, or other) considering the treatment history and the response to the study treatment received. After receiving the first follow-on treatment in the study eye, subjects will continue on the regular visit schedule through the End-of-Study (EoS) visit at Week 52. This trial includes a data monitoring committee (DMC). The DMC's main responsibility is to periodically review unmasked trial data and provide recommendations regarding the study to the Sponsor. Details will be described in the DMC charter. In Part A, whole blood samples will be collected for measurement of plasma concentrations of dexamethasone on Visits 1, 2, 3, 4, 5, 11, and 18 (screening, Day 0, at 60min post-dose, Day 1, Week 1, 4, 24, and 52, respectively) as specified in the SoAs in Section 1.3 to assess systemic exposure of dexamethasone after administration of OXU-001.

Brief Summary	This is a fifty-two-week (52-week) study with a randomized open-label Part A enrolling approximately 18 DME subjects, treatment-naïve or previously treated in the study eye, followed by a randomized masked Part B. Part B will include a total of approximately 110 DME subjects (55 treatment-naïve and 55 anti-VEGF previously treated in the study eye). The objective of the study is to assess the safety, tolerability, efficacy, and durability of two dose levels of sustained-release dexamethasone microspheres (DEXAspheres®, OXU-001) delivered to the suprachoroidal space with the Oxulumis® microcatheter compared to intravitreal dexamethasone implant (OZURDEX®). **Part A:** 18 DME subjects are randomized to receive a single treatment with OXU-001 (1:1) mid-dose (Arm A1, N=9) or OXU-001 high dose (Arm A2, N=9). Dose groups will be enrolled in parallel. **Part B:** Parallel enrollment in the three treatment arms of Part B will start once a safety evaluation of Part A (at least 6 weeks of data of all treated subjects) has been collected and reviewed by the DMC and Sponsor. Part B will include approximately 110 subjects to receive one of three randomly assigned single treatments (2:2:1), OXU-001 Dose 1 (B1, 1.5mg) (N=44), OXU-001 Dose 2 (B2, 3.0mg or 0.75mg depending on the Part A six-week safety review) (N=44), or Ozurdex (B3, N=22). After signing an informed consent form (ICF) and completing the screening procedures on Visit 1 (Day-30 to Day-2), during Visit 2 (Day 0), subjects in Part A will be randomly assigned to receive either mid-dose (1.5mg) or high dose (3.0mg) OXU-001 in a 1:1 fashion (at least n=9 for each arm). In Part B, subjects will be randomly assigned to one of three study arms: Arm B1; Arm B2, or Arm B3, receiving OXU-001 Dose 1 (1.5mg),

	OXU-001 Dose 2 (3.0mg or 0.75mg based on a Part A Week 6 safety review) or Ozurdex® 0.7mg at a ratio of 2:2:1, respectively. Clinic visits will occur on Days -30 to -2 (screening), Day 0 (baseline and treatment visit), Day 1, and Weeks 1, 4, 6, 8, and then every four (4) weeks thereafter for a total of fifty-two (52) weeks after treatment completion. In Part A, the visit scheduled for Week 6 is mandatory and will serve to assess any safety signals (*e.g.,* IOP increase) observed. A safety review will occur after all active study participants have completed Week 6 visit prior to initiating randomization in Part B. For Part B, the Week 6 safety visit is optional and may be scheduled at the discretion of the investigator based, *e.g.,* if subjects tend to present with relevant IOP increase through Week 4 post-treatment. Starting at the Week 12 visit, subjects will be assessed using pre-specified criteria for the need for follow-on treatment. If subjects show a need for follow-on treatment, they will be treated following the standard of care at the respective study site. The primary outcome measure of this study is how frequently (ocular) adverse events, AESIs, and SAEs occur in each arm. Other outcome measures include time to follow-on treatment, the change in BCVA, and CST.

Eligibility Criteria	Inclusion Criteria: Subjects are eligible to be included in the study only if ALL of the following criteria apply: 1. Able to understand and sign an informed consent form. 2. At least eighteen (18) years of age at the time of screening. 3. Have been diagnosed with Type 1 or Type 2 diabetes mellitus. 4. Have DME involving the center of the fovea with central subfield thickness (CST) in the study eye at the screening visit, confirmed by the CRC, of at least 320 µm on SD OCT (measurement from the Retinal Pigment Epithelium, RPE, to the Inner Limiting Membrane, ILM, inclusively). 5. Have BCVA in the study eye between 34 and 78 letters ETDRS (approximate Snellen acuity of 20/200-20/32) at the screening visit. For eligibility assessments, only the ETDRS BCVA letter score is considered relevant. 6. For women who are not postmenopausal (*i.e.,* at least 12 months of non-therapy-induced amenorrhea or surgically sterile (absence of ovaries and/or uterus)) agreement to remain abstinent or use combined contraceptive methods that result in a failure rate of less than 1% per year from the treatment visit (Visit 2, Day 0) until the end of trial participation, or, if subjects discontinue trial participation prior to Week 52 completion, for at least 52 weeks from the treatment visit (Visit 2, Day 0). Examples of contraceptive methods with an expected failure rate of less than 1% per year include male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (*e.g.,* two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of less than 1% per year. Barrier methods must always be supplemented with the use of a spermicide. 7. Males must agree to use a barrier method of contraception starting from the treatment visit (Visit 2, Day 0) until the end of trial

	participation, or, if subjects discontinue trial participation prior to Week 52 completion, for at least 52 weeks from the treatment visit (Visit 2, Day 0). 8. Subject must be willing not to participate in any other clinical trial including an investigational medicinal product (IMP) or an investigational device until the end of trial participation. Exclusion Criteria: Subjects are eligible to be included in the study only if NONE of the following criteria apply: 1. Presence of any significant ocular or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with the concurrence of the Oxular Medical Monitor, may 1. put the subject at risk because of participation in the trial, or 2. influence the results of the trial, or 3. influence the subject's ability to participate in the trial, or 4. may require medical or surgical intervention during study participation (*e.g.*, cataract, vitreous hemorrhage, retinal detachment, or macular hole). 2. Macular edema considered due to a cause other than diabetes mellitus in either eye. 3. Condition, in the study eye, in which visual acuity is not expected to improve from the resolution of macular edema (*e.g.,* foveal atrophy, clinically relevant loss of ellipsoid zone, pigment abnormalities, vitreomacular traction, or nonretinal causes) as determined by the investigator with concurrence of the Oxular Medical Monitor supported by a review by the CRC. 4. Conditions in the study eye that may render the administration of study treatment, intravitreal implant insertion, or suprachoroidal microcatheter insertion and deployment difficult or subject the

	patient to excessive risk of complications. Examples include but are not limited to ocular surface disease with significant conjunctival edema and/or inflammation, ocular hypotony, scleral staphylomas, necrotizing scleritis, scleral melting, excessive choroidal scarring *e.g.,* associated with pan-retinal photocoagulation, amongst others. 5. Macular laser photocoagulation or panretinal laser photocoagulation (PRP) in the study eye performed within sixteen (16) weeks prior to screening. 6. Active proliferative diabetic retinopathy (PDR) or sequelae of PDR (including iris neovascularization, vitreous hemorrhage, tractional retinal detachment, extensive scarring following PRP) at screening in the study eye. 7. History of recurrent or active intraocular inflammation in either eye (*e.g.,* uveitis) within twelve (12) weeks prior to screening. 8. Infectious eye disease like infectious blepharitis, keratitis, or conjunctivitis in either eye within four (4) weeks of screening. 9. IOP ≥ 22 mmHg, or glaucomatous disc changes (*i.e.,* a cup disc ratio greater than 0.8) in the study eye at screening. History of glaucoma surgery, and/or current anti-glaucoma therapy with more than two active substances (in separate or a combination preparation) are exclusionary. 10. History of closed-angle glaucoma. 11. IOP <6mmHg (hypotony) in the study eye at screening. 12. Spherical equivalent of the refractive error of −6 diopters of myopia or worse (prior to cataract or refractive surgery) at screening. 13. Cataract or other media opacity that limits the ability to obtain the planned imaging assessments. 14. History of retinal detachment.

	15. Prior treatment with IVT anti-VEGF **in the study eye** 1. Treatment-naïve group (Part A and B): Any IVT anti-VEGF treatments in the study eye are exclusionary regardless of the time interval since injection. 2. Previously treated group (Part A and B): Subjects in the previously treated group are excluded if they meet any of the below criteria for the study eye at screening: a) Subject has received less than three (3) anti-VEGF injections since treatment initiation (at least three injections must have been received for eligibility). b) Time interval between the first anti-VEGF injection and screening is more than sixty-four (>64) weeks. c) Last injection with ranibizumab or bevacizumab within four (4) weeks prior to screening. d) Last injection with aflibercept within eight (8) weeks prior to screening. e) Last injection with faricimab or brolucizumab within twelve (12) weeks prior to screening. f) Prior treatment with SUSVIMO (Port Delivery System) implant is exclusionary. 16. Prior ocular treatment with steroid injections (periocular, subtenon, intravitreal) or intravitreal implants **in the study eye** A history of topical ocular steroids is not exclusionary. 17. Part A only: Prior ocular treatment with steroid injections (periocular, subtenon, intravitreal) or intravitreal implants **in the fellow eye** (due to potential interference with PK measurements).

	1. Last injection (intra- or periocular/subtenon) with triamcinolone acetonide within 12 weeks before screening. 2. Last injection (suprachoroidal) steroids, *e.g.*, Xipere™, within twelve (12) weeks before screening. 3. Last injection (IVT) with dexamethasone implant (Ozurdex®) within 24 weeks before screening. 4. Prior treatment with longer duration implants (*e.g.,* fluocinolone acetonide IVT implant, Iluvien) is exclusionary. 18. Prior treatment with suprachoroidal steroids in the study eye is exclusionary. 19. Concurrent use of **systemic** glucocorticoid medications or systemic steroids within twelve (12) weeks before screening is exclusionary. Intranasal, inhaled, and extra-ocular topical corticosteroids are allowed. 20. Prior IVT or suprachoroidal treatment with investigational agents in either eye (*e.g.,* agents with anti-VEGF activity, or combined pharmacologic activity, gene therapies, cell therapies, or any other therapeutic modality) at any time. 21. Participation in a clinical trial in which an investigational drug (with other routes of administration than IVT or suprachoroidal) was administered within 90 days of screening or 5 half-lives of the investigational drug, whichever is longer. 22. Treatment with ocriplasmin (Jetrea®) at any time. 23. History of vitreoretinal surgery (including surgery for retinal detachment or scleral buckle) in the study eye. Vitrectomy is only exclusionary, if within 12 weeks prior to screening. 24. Any other previous ophthalmic surgeries, uncomplicated cataract surgery, or uncomplicated trauma in the study eye within twelve

	(12) weeks prior to screening. Complicated cataract surgery or trauma that may impact access and/or drug delivery to the suprachoroidal space are exclusionary. 25. Part B only: Any history of surgical complications in the study eye that may increase the risk of anterior chamber migration of intravitreal implants (*e.g.,* torn or ruptured posterior lens capsule, implantation of any iris-fixated or sclera-fixated intraocular lenses, iridectomy) regardless of the time interval between the procedure and the study enrollment. 26. Hypersensitivity to OXU-001, or any of the excipients in the OXU-001 formulation or Oxulumis® device components. 27. Part B only: Hypersensitivity to components of Ozurdex® for subjects. 28. Active malignancy or history of malignancy within the past five (5) years. 29. Uncontrolled diabetes with a hemoglobin A1c (HbA1c) > 12% or any other uncontrolled systemic disease at screening. 30. Uncontrolled hypertension, defined as blood pressure with a systolic value of ≥ 160mmHg or a diastolic value of ≥ 100 mmHg upon repeat assessment at screening. 31. History of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure, or any acute coronary event within 90 days before screening. 32. Subjects who are pregnant or breastfeeding at the screening visit, or who test positive for pregnancy at the screening visit or are unwilling to use adequate birth control methods to prevent pregnancy throughout the study. 33. Subjects who were previously randomized in this trial, but in whom administration of study treatment could not be completed.

<table>
<tr><td>Number of Subjects</td><td>A total of approximately one hundred and twenty-eight (128) subjects will be treated over the two parts (A, B) of the trial. This includes eighteen (18) subjects in Part A and one hundred and ten (110) subjects in Part B. Subjects in whom the administration of study treatment could not be completed, will be replaced in order to reach the targeted numbers of treated subjects.</td></tr>
<tr><td>Study Arms & Duration</td><td>The duration of the study f1or each subject will be a maximum of fifty-eight (58) weeks, which includes up to four (4) weeks of screening, an up to 14-day interval for performing activities of the baseline visit V2, and an up to fifty-two (52) weeks post-treatment observation period.

The study comprises two parts, Part A and Part B.

Part A (Open Label) consists of two parallel, randomized arms treated with mid-dose, 1.5mg (Arm A1) and high dose 3.0mg (Arm A2) with a total of approximately 18 subjects who are treatment-naïve or previously treated with IVT anti-VEGF in the study eye.
<table>
<tr><td>Treatment Arm</td><td>Intervention</td><td>Subjects</td></tr>
<tr><td>A1</td><td>One (1) treatment with suprachoroidal mid dose (DMA 1.5mg) OXU-001</td><td>N=9</td></tr>
<tr><td>A2</td><td>One (1) treatment with suprachoroidal high dose (DMA 3.0mg) OXU-001</td><td>N=9</td></tr>
</table>
Part B (Masked) consists of three (3) masked arms with a total of approximately 110 subjects randomized to three arms in a 2:2:1 fashion (B1, B2, and B3). Subjects in Part B are treatment-naïve or previously treated with anti-VEGF (in the study eye).
<table>
<tr><td>Treatment Arm</td><td>Intervention</td><td>Subjects</td></tr>
<tr><td>B1</td><td>One (1) treatment with suprachoroidal Dose 1 (mid dose DMA 1.5mg) OXU-001</td><td>n=44</td></tr>
</table>
</td></tr>
</table>

	B2	One (1) treatment with suprachoroidal **Dose 2 (tbc. DMA 3.0mg or 0.75mg**, based on Part A 6 weeks) OXU-001	n=44
	B3	One (1) treatment with intravitreal Ozurdex® (dexamethasone 0.7mg)	n =22
Data Monitoring Committee	A data monitoring committee (DMC) will be appointed for this study. The composition and responsibilities of the committee are included in the DMC Charter.		

1.2 Study Schematic

Figure 1 Study Overview Part A

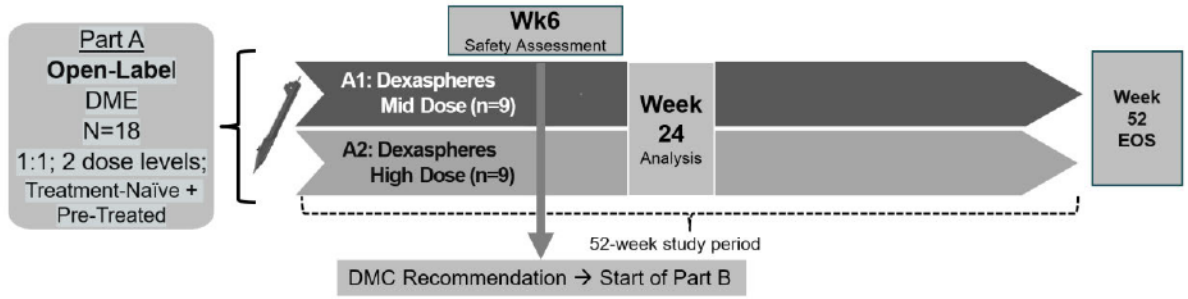
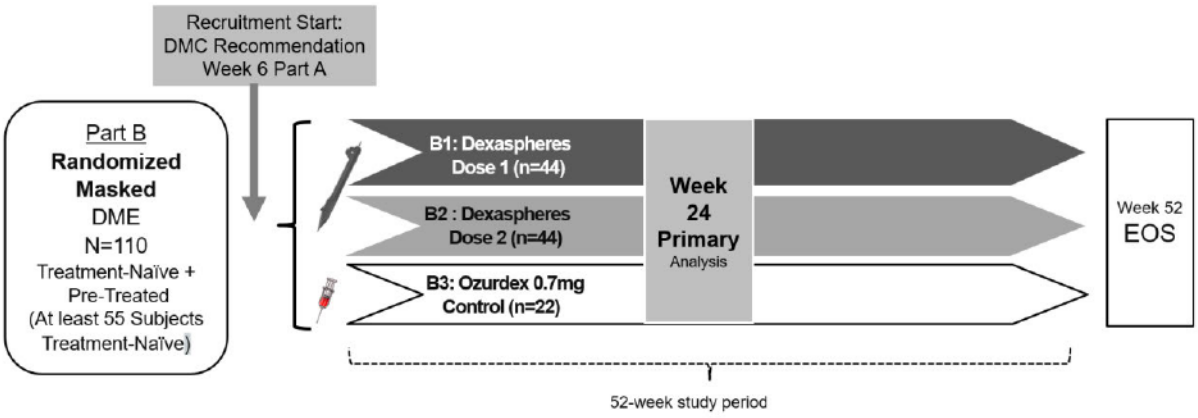


Figure 2 Study Overview Part B



Key of abbreviations: EOS: End of Study, Dexaspheres: OXU-001.

Notes:

1. In Part B, Dose 1 in Arm B1 will be OXU-001 1.5mg. Depending on the outcome of the Week 6 Safety Review in Part A, Dose 2 in Arm B2 will be 3.0mg or 0.75mg OXU-001.
2. The need for follow-on treatment will be assessed from Week 12 on, using pre-defined criteria (in Part A and Part B).

1.3 Schedule of Activities

Table 1 Part A Schedule of Activities

	Screen	BL	Post-Baseline Follow-Up															
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Days/Week	**Day -30 to -2**	**D0**	**D1**	**W1**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52 EoS/ ET[j]**
Windows (days)[a]		**0-14**	**+1**	**±3**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
ICF	X																	
Eligibility	X	X* [b]																
Randomization		X*																
NEI-VFQ-25	X										X							X
Demographics	X																	
Medical History	X	X*																
Concomitant Medication	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs and ADEs	X	X***	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, Height, Weight[c]	X										X							X
Lab. Assessment	X										X							X
Pregnancy Test[d]	X	X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA[e]	OU	OU*	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Slit-lamp BM	OU	OU*	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
IOP	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Axial length[f]	OU																	
Dil. Ophthalmoscopy	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Anterior Segment OCT[f]	OU	SE**	SE	SE	SE													
SD-OCT[g]	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Peripheral-OCT [f]	OU	SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU

	Screen	BL	Post-Baseline Follow-Up															
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Days/Week	**Day -30 to -2**	**D0**	**D1**	**W1**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52 EoS/ ET[j]**
Windows (days)[a]		**0-14**	**+ 1**	**± 3**	**± 5**	**± 5**	**± 5**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Color fundus photog.	OU	SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Fluorescein ang.	OU										OU							OU
Overall Assessment of Expected Procedural Complexity	X																	
Study Intervention[h]		SE																
Follow-on Tx [i]								SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE
Pharmacokinetic blood sampling	X	X**	X	X	X						X							X
Procedure Documentation and Assessment		X**																
Patient Experience Assessment		X**	X	X	X													

For a recommendation on the sequence of assessment in respect to dilation see Section 9: Study Assessments and Procedures
AEs = adverse events; BCVA = best corrected visual acuity; BL= baseline; BM = biomicroscopy; CFP = color fundus photography; EoS = end of study; ET = early termination;; ICF = informed consent form; NEI VFQ-25= National eye institute 25-item visual function questionnaire; OCT = ocular coherence tomography; OU = both eyes; PK = pharmacokinetics; SD-OCT = spectral-domain ocular coherence tomography; SE = study eye; Tx = treatment.
(*) Pre-treatment, (**) Post-treatment, (***) Pre and post-treatment (see also Section 9.2)

a) Visit dates and visit windows are calculated from the actual date of the study treatment administration (Study Visit 2, Day 0). Only for the visit window of the Screening Visit, an extension of the visit window to 37 days can be approved by the Oxular Medical Monitor based on an individual request of the investigator stating important medical and/or organizational reasons. For a detailed overview of variants of baseline visit activities for Part A including the variant to skip some post-baseline assessments in case the treatment administration would be directly performed in an operating/surgically equipped procedure room see Table 3.

b) Partial review only: A list of eligibility criteria must be confirmed (see Section 5). BCVA and central subfield thickness eligibility will be based on the assessment at the screening visit (Visit 1).
c) Vital signs include measuring body temperature, blood pressure and heart rate. Height will only be measured at screening.
d) Females of childbearing potential only. A pregnancy test (serum at screening and urine at all other visits) must be negative for the subject to receive study treatment. Additional pregnancy tests may be performed at any time during the study as required.
e) Duplicate measurements of BCVA in the study eye are mandatory. For the fellow eye, duplicate measurements at screening and single measurements at all subsequent visits.
f) At equipped sites only.
g) Imaging with SD-OCT devices will include 4-Wide-Field Near infrared (IR) Plus imaging at sites equipped with a Heidelberg Spectralis device.
h) On Day 0, monitoring of subjects for 60 minutes post-treatment with at least 2 measurements of IOP. Discharge only if IOP is normal or IOP lowering measures have been taken, total monitoring time until normalization may be longer than 60 minutes.
i) Follow-on treatment determination based on prespecified criteria (Section 7.5.2). Follow-on treatment will be administered if the prespecified criteria are met.
j) For subjects who decide to stop participation in this trial, an early termination visit with the activities outlined in this column should be performed.

Table 2 Part B Schedule of Activities

	Screen	BL	Post-Baseline Follow-Up															
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Days/Week	**Day -30 to -2**	**D0**	**D1**	**W1**	**W4**	**W6 optional[a]**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52 EoS/ ET[k]**
Windows[b]		**0-14**	**+1**	**±3**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
ICF	X																	
Eligibility[c]	X	X* [c]																
Randomization		X*																
NEI-VFQ-25	X										X							X
Demographics	X																	
Medical History	X	X*																
Concomitant Medication	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs and ADEs	X	X***	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, Height, Weight [d]	X										X							X
Lab. Assessment	X										X							X
Pregnancy Test [e]	X	X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Slit-lamp BM	OU	OU*	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Dil. Ophthalmoscopy	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
BCVA [f]	OU	OU*	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Axial length[g]	OU																	
SD-OCT[h]	OU	OU*/SE**	SE	SE	SE	SE	SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Peripheral-OCT[g]	OU	SE**	SE	SE	SE		SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Color fundus photog.	OU	SE**	SE	SE	SE		SE	OU	SE	SE	OU	SE	SE	SE	SE	SE	SE	OU
Fluorescein ang.	OU										OU							OU

	Screen	BL	Post-Baseline Follow-Up															
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Days/Week	**Day -30 to -2**	**D0**	**D1**	**W1**	**W4**	**W6 optional[a]**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52 EoS/ ET[k]**
Windows[b]		**0-14**	**+1**	**±3**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Overall Assessment of Expected Procedural Complexity	X																	
Study Intervention[i]		SE																
Follow-on Tx [j]								SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE
Procedure Documentation and Assessment		X**																
Patient Experience Assessment		X**	X	X	X													

For a recommendation on the sequence of assessment in respect to dilation see Section 9: Study Assessments and Procedures
AEs = adverse events; BCVA = best corrected visual acuity; BL= baseline; BM = biomicroscopy; CFP = color fundus photography; EoS = end of study; ET = early termination; ICF = informed consent form; NEI VFQ-25= National eye institute 25-item visual function questionnaire; OCT = ocular coherence tomography; OU = both eyes; PK = pharmacokinetics; SD-OCT = spectral-domain ocular coherence tomography; SE = study eye; Tx = treatment.
(*) Pre-treatment, (**) Post-treatment, (***) Pre and post-treatment (see also Section 9.2)

a) Week 6 optional safety visit at the discretion of the investigator, if safety-relevant changes, *e.g.*, trends for IOP increase have been detected up to week 4.
b) Visit dates and visit windows are calculated from the actual date of the study treatment administration (Study Visit 2, Day 0). Only for the visit window of the Screening Visit, an extension of the visit window to 37 days can be approved by the Oxular Medical Monitor based on an individual request of the investigator stating important medical and/or organizational reasons. For a detailed overview of variants of baseline visit activities for Part B see Table 4
c) Partial review only: A list of eligibility criteria must be confirmed (see Section 5). BCVA and central subfield thickness eligibility will be based on the assessment at the screening visit (Visit 1).
d) Vital signs include measuring body temperature, blood pressure and heart rate. Height will only be measured at screening.
e) Females of childbearing potential only. A pregnancy test (serum at screening and urine at all other visits) must be negative for the subject to receive study treatment. Additional pregnancy tests may be performed at any time during the study as required.

f) Duplicate measurements of BCVA in the study eye are mandatory. For the fellow eye, duplicate measurements at screening and single measurements at all subsequent visits.
g) At equipped sites only.
h) Imaging with SD-OCT devices will include 4-Wide-Field Near infrared (IR) Plus imaging at sites equipped with a Heidelberg Spectralis device.
i) On Day 0, monitoring of subjects for 60 minutes post-treatment with at least 2 measurements of IOP. Discharge only if IOP is normal or IOP lowering measures have been taken, total monitoring time until normalization may be longer than 60 minutes.
j) Follow-on treatment determination based on prespecified criteria as assessed by the masked investigator (see Section 7.5.2). Follow-on treatment will be administered if the prespecified criteria are met. The decision on the kind of follow-on treatment to be administered will be made by an unmasked investigator, based on the treatment history and study treatment received.
k) For subjects who decide to stop participation in this trial, an early termination visit with the activities outlined in this column should be performed.

Table 3 Part A - Baseline Visit V2 - Alternatives Scheduling Options

The need for different settings for the OXU-001 Standard in-clinic procedure and/or the OXU-001 ConjIncision Variant mandates three (3) potential operational scenarios for V2 activities in Part A.

Days/Week	Baseline Visit V2, start on Day0; all Visit 2 activities need to be completed within 14 days[a)]				
Alternative No.	1	2		3	
Procedural Variant	OXU-001Standard Variant	n.a.	Direct to OXU-001 ConjIncision Variant	First OXU-001Standard Variant	Move to OXU-001 ConjIncision Variant
Administration of Study Treatment	Completed	n.a.	Completed	Not-Completed	Completed
Setting[b]	In-Clinic or Procedure Room	Assessments at Investigational Site	Surgically Equipped Procedure Room or OR	In-Clinic or Procedure Room	Surgically Equipped Procedure Room or OR
Eligibility[c]	X*	X*		X*	
Randomization	X*	X*		X*	
Medical History	X*	X*		X*	
Concomitant Medication	X*	X*	X*	X*	X*
AEs and ADEs	X*/**	X*	X**	X*/***	X**
Pregnancy Test[d]	X*	X*	X*	X*	X*
IOP[e]	OU*/SE**		OU*/SE**	OU*	OU*/SE**
Slit-lamp BM	OU*	OU*		OU*	
Dil. Ophthalmoscopy	OU*/SE**	OU*	OU*/SE**	OU*/SE ***	OU*/ SE**
BCVA[f]	OU*	OU*		OU*	
SD-OCT[g]	OU*/SE**	OU*		OU*/SE***	
Anterior Segment OCT[h]	SE**				
Peripheral-OCT[h]	SE**				
Color fundus photog.	SE**			SE***	
Study Intervention[i]	SE	n.a.	SE	SE	SE
Pharmacokinetic blood sampling[j]	X**		X**		X**
Procedure Documentation and Assessment	X**		X**	X***	X**
Patient Experience Assessment	X**		X**		X**

For a recommendation on the sequence of assessment in respect to dilation see Section 9: Study Assessments and Procedures
AEs = adverse events; BCVA = best corrected visual acuity; BL= baseline; BM = biomicroscopy; CFP = color fundus photography; ICF = informed consent form; NEI VFQ-25=

National eye institute 25-item visual function questionnaire; OCT = ocular coherence tomography; OR = Operating Room,; OU = both eyes; SD-OCT = spectral-domain ocular coherence tomography; SE = study eye; n.a.
(*) Pre-treatment, (**) Post-(completed)treatment, (***) post non-completed treatment session (see also Section 9.2)

a) Visit dates and visit windows are calculated from the actual date of completing the study treatment administration. The study treatment administration has to occur within 14 days after the start of Visit 2 activities. If necessary, the 2nd treatment session also has to occur within this 14-day window (Study Visit 2, Day 0). Only for the visit window of the Screening Visit, an extension of the visit window to 37 days can be approved by the Oxular Medical Monitor based on an individual request of the investigator stating important medical and/or organizational reasons.
b) Details of the setting for administration of study treatments may vary between study countries. The OXU-001 Standard variant of the procedure can be administered in the clinic or in a procedure room. For this variant, the procedure room does not need surgical equipment. For the OXU-001 ConjIncision Variant, which means an incision of the conjunctiva/tenons to facilitate the scleral engagement of the device, a surgical setting is needed as the conjunctiva/tenons have to be opened and closed, *e.g.,* with fibrin glue or suturing.
c) Partial review only: A list of eligibility criteria must be confirmed (see Section 5). BCVA and central subfield thickness eligibility will be based on the assessment at the screening visit (Visit 1).
d) Females of childbearing potential only. A pregnancy test (serum at screening and urine at all other visits) must be negative for the subject to receive study treatment. A pregnancy test must be repeated in case assessments and study treatment occur on different days, or in Alternative No.3, when the OXU-001 ConjIncision Variant is scheduled on another day. Additional pregnancy tests may be performed at any time during the study as required.
e) On Day 0, monitoring of subjects for 60 minutes post-treatment, (but not post treatment sessions with no dose administered,) with at least 2 measurements of IOP. Discharge only if IOP is normal or IOP lowering measures have been taken, total monitoring time until normalization may be longer than 60 minutes.
f) Duplicate measurements of BCVA in the study eye are mandatory. For the fellow eye, duplicate measurements at screening and single measurements at all subsequent visits.
g) Imaging with SD-OCT devices will include 4-Wide-Field Near infrared (IR) Plus imaging at sites equipped with a Heidelberg Spectralis device.
h) At equipped sites only.
i) In Alternative No.3, the Standard Variant in-clinic procedure cannot be completed and therefore a repeat treatment session is needed using the OXU-001 ConjIncision Variant. In Alternative No.2, treating physicians may start with the OXU-001 Standard Variant at their own discretion and move to the ConjIncision Variant if needed.
j) Pharmacokinetic sampling will only be mandatory, post dose, when the administration procedure has been completed successfully.

Table 4 Part B - Baseline Visit V2 - Alternatives Scheduling Options

The operational scheduling in Part B needs to consider that the randomized procedure may be suprachoroidal OXU-001. As in Part A, there are three different alternatives for operational scenarios using the OXU-001 Standard in-clinic procedure and/or the OXU-001 ConjIncision Variant.

Days/Week	Baseline Visit V2, start on Day0; all Visit 2 activities need to be completed within 14 days[a)]				
Alternative No.	1	2		3	
Procedural Variant	OXU-001Standard Variant	n.a.	Direct to OXU-001 ConjIncision Variant	First OXU-001Standard Variant	Move to OXU-001 ConjIncision Variant
Administration of Study Treatment	Completed	n.a.	Completed	Not-Completed	Completed
Setting[b]	In-Clinic or Procedure Room	Assessments at Investigational Site	Surgically Equipped Procedure Room or OR	In-Clinic or Procedure Room	Surgically Equipped Procedure Room or OR
Eligibility[c]	X*	X*		X*	
Randomization	X*	X*		X*	
Medical History	X*	X*		X*	
Concomitant Medication	X*	X*	X**	X*	X*
AEs and ADEs	X*/**	X*	X***	X*/***	X**
Pregnancy Test[d]	X*	X*	X*	X*	X*
IOP[e]	OU*/SE**		OU*/SE**	OU*	OU*/SE**
Slit-lamp BM	OU*	OU*		OU*	
Dil. Ophthalmoscopy	OU*/SE**	OU*	OU*/SE**	OU*/SE***	OU*/SE**
BCVA[f]	OU*	OU*		OU*	
SD-OCT[g]	OU***	OU*		OU*/SE***	
Peripheral-OCT[h]	SE**				
Color fundus photog.	SE**			SE*/***	
Study Intervention[i]	SE	n.a.	SE	SE	SE
Procedure Documentation and Assessment	X**		X**	X***	X**
Patient Experience Assessment	X**		X**		X**

For a recommendation on the sequence of assessment in respect to dilation see Section 9: Study Assessments and Procedures
AEs = adverse events; BCVA = best corrected visual acuity; BL= baseline; BM = biomicroscopy; CFP = color fundus photography; ICF = informed consent form; NEI VFQ-25= National eye institute 25-item visual function questionnaire; OCT = ocular coherence tomography; OR = Operating Room,; OU = both eyes; SD-OCT = spectral-domain ocular

coherence tomography; SE = study eye; n.a.
(*) Pre-treatment, (**) Post-(completed) treatment, (***) Post-(non-completed) treatment session (see also Section 9.2)

a) Visit dates and visit windows are calculated from the actual date of completing the study treatment administration. The study treatment administration has to occur within 14 days after the start of Visit 2 activities, If necessary, the 2nd treatment session, also has to occur within this 14-day window (Study Visit 2, Day 0). Only for the visit window of the Screening Visit, an extension of the visit window to 37 days can be approved by the Oxular Medical Monitor based on an individual request of the investigator stating important medical and/or organizational reasons.
b) Details of the setting for administration of study treatments may vary between study countries. The OXU-001 Standard variant of the procedure can be administered in the clinic or in a procedure room. For this variant, the procedure room does not need surgical equipment. For the OXU-001 variant ConjIncision Variant, which means an incision of the conjunctiva/tenons to facilitate the scleral engagement of the device, a surgical setting is needed as the conjunctiva/tenons have to be opened and closed, *e.g.,* with fibrin glue or suturing.
c) Partial review only: A list of eligibility criteria must be confirmed (see Section 5). BCVA and central subfield thickness eligibility will be based on the assessment at the screening visit (Visit 1).
d) Females of childbearing potential only. A pregnancy test (serum at screening and urine at all other visits) must be negative for the subject to receive study treatment. A pregnancy test must be repeated in case assessments and study treatment occur on different days, or in Alternative No.3, when the OXU-001 ConjIncision Variant is scheduled on another day. Additional pregnancy tests may be performed at any time during the study as required.
e) On Day 0, monitoring of subjects for 60 minutes post-treatment, (but not post treatment sessions with no dose administered) with at least 2 measurements of IOP. Discharge only if IOP is normal or IOP lowering measures have been taken, total monitoring time until normalization may be longer than 60 minutes.
f) Duplicate measurements of BCVA in the study eye are mandatory. For the fellow eye, duplicate measurements at screening and single measurements at all subsequent visits.
g) Imaging with SD-OCT devices will include 4-Wide-Field Near infrared (IR) Plus imaging at sites equipped with a Heidelberg Spectralis device.
h) At equipped sites only.
i) In Alternative No.3, the Standard Variant in-clinic procedure cannot be completed and therefore a repeat treatment session is needed using the OXU-001 ConjIncision Variant. In Alternative No.2, unmasked treating physicians may start with the OXU-001 Standard Variant at their own discretion and move to the ConjIncision Variant if needed.

2 Introduction

2.1 Study Rationale

There is a great unmet need for DME therapies, which have a broader spectrum of pharmacological activities and thereby also address the strong inflammatory component of DME. In addition, therapies with a long duration of action of more than 6 months would reduce the treatment burden of patients. Ocular corticosteroids have the potential to address this unmet need, as they have not only shown strong anti-edema effects similar to anti-VEGF treatments, but also a broad anti-inflammatory effect. Progressive retinal and choroidal inflammation is a key driver of the progression of diabetic eye disease.

Provided an acceptable safety profile, ocular steroids can deliver visual benefits in DME subjects that are treatment-naïve as well as in those who have shown limited, short-lived, no visual improvement with IVT administered anti-VEGF drugs.

The use of current steroid therapies for DME, including IVT Ozurdex®, is limited by the typical and frequent adverse reactions; specifically, cataract formation and increased intraocular pressure (IOP), which usually require administration of additional ophthalmic drugs, *e.g.,* IOP lowering eye drops; glaucoma surgery or lens replacement surgery. Due to these safety concerns and the limited durability of only 3-6 months for the most frequently used IVT steroid implant, there remains a high unmet medical need for efficacious ocular treatments for diabetic macular edema (DME) with a more favorable benefit-risk profile.

OXU-001 is a combination therapy of sustained-release dexamethasone acetate microspheres (DEXAspheres®) administered suprachoroidally with the Oxulumis® ophthalmic illuminated microcatheterization device (an ophthalmic administration device). Based on preclinical experiments, a follow-up period of 52 weeks appears to be justified as a therapeutic effect for 9-12 months is expected before follow-on treatment may be needed. OXU-001 is expected to have a sustained anti-edema effect and a reduced incidence of steroid-related ocular adverse events (AEs) compared to current standard intraocular steroid treatments.

The current trial has the objective of generating clinical data to assess the following aspects of suprachoroidal treatment with OXU-001 in DME:

1. The safety of suprachoroidal, sustained-release steroid treatment in DME with respect to reduction of the risk of steroid-induced complications by posterior deployment of the OXU-001.
2. The therapeutic effects of OXU-001 to provide clinically meaningful visual and anatomical benefits for an extended time (>6 months) by reducing DME.
3. The systemic exposure to dexamethasone following sustained release suprachoroidal administration for the duration of the clinical trial.

2.2 Background

The efficacy and safety of ocular steroids in the management of DME are well documented. In their recent Cochrane review, Rittiphairoj *et al.* reported findings from 10 clinical trials involving 4,505 eyes of 4,348 subjects treated with IVT steroids compared to other treatments (Rittiphairoj *et al*., 2020). Despite potential efficacy with regards to visual acuity and reduction of macular edema, the authors concluded that benefits from IVT steroids should be weighed against IOP elevation, the use of IOP-lowering medication, and, in phakic patients, the progression of cataracts. Similar conclusions have been recently published in a review of IVT pharmacotherapies for DME by an author group from the American Academy of Ophthalmology (Ehlers *et al.*, 2022).

According to the Ozurdex® US Prescribing Information (Allergan Inc. 2014 (Version 2020)), 61% of phakic patients in the Ozurdex® arm in DME trials of 3-year duration, required cataract surgery by the final visit in the study. Mean IOP in the study eye at baseline was the same in both treatment groups (15.3 mmHg). The mean increase from baseline IOP did not exceed 3.2 mmHg across all visits in the Ozurdex® group with the mean IOP peaking at the 1.5-month visit post injection and returning to approximately baseline levels by month 6 following each injection. The rate and magnitude of IOP elevation following Ozurdex® treatment did not increase upon repeated injection of Ozurdex®. 28% of patients treated with Ozurdex® had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the 3-year studies, with the majority of these patients requiring more than one medication.

To overcome these potential side effects of ocular steroids, *i.e.,* IOP elevation, and cataract progression, several groups have tried to deliver triamcinolone acetonide (TA), a commonly used steroid for intravitreal delivery to manage posterior segment inflammation, via the

suprachoroidal space for DME and other retinal pathologies. By changing the site of delivery from the vitreous cavity to the suprachoroidal space, the target tissues associated with these complications (*i.e.,* lens and anterior segment of the eye) are expected to be exposed to lower concentrations of steroids, and hence may be less prone to developing these side effects.

Recently, clinical trials (Wykoff *et al.*, 2018; Barakat *et al.*, 2021) using microinjection techniques in the pars plana, confirmed the clinical feasibility of suprachoroidal delivery with an acceptable safety profile and good efficacy. In the HULK trial (Wykoff *et al.*, 2018), an open-label, 20 subject study evaluating the use of TA applied to the suprachoroidal space with a microinjector in the management of DME, treatment-naïve patients (n=10) had 8.5 ETDRS letters improvement at month 6, while those previously treated (n=10) improved only 1.1 letters with 10% of the patients (n=2 of 20) experiencing ≥ 10 mmHg increase in IOP during the study. There were three cases of cataract progression. Notably, there was injection site pain in 1 of 20 patients and inadvertent intravitreal drug deposit in 1 of 20 patients.

In the TYBEE Phase 2 trial (Barakat *et al.*, 2021), 71 patients with DME were randomized to receive either 4 monthly doses of aflibercept (Day 0, Weeks 4, 8, and 12) followed for two more months with the option to receive pro-re-nata (PRN) aflibercept on Weeks 16 and 20 (aflibercept arm), or 2 TA injections (4 mg) administered to the suprachoroidal space (Day 0 and week 12) with the option for PRN aflibercept on weeks 4, 8, 16 and 20 (combination arm). The primary endpoint was the mean change in BCVA from baseline at Week 24. Despite anatomical improvement in terms of CST (-226.5 µm mean change at week 24) for the combination arm compared to the aflibercept arm (-176.1 µm), the change in BCVA at week 24 for the combination arm (12.3 ETDRS letters) was not statistically different from the aflibercept arm (13.5 ETDRS letters, test with two-sided significance level of 0.10). IOP increase of more than 30mmHg occurred in 3 patients in the active group and 0 patients in the control group. IOP increases of more than 10mmHg occurred in 5 and 0 patients in the active and control groups, respectively (Barakat *et al.*, 2021).

The use of microcatheter delivery to the suprachoroidal space was reported in 11 patients (eyes) with advanced neovascular AMD that failed conventional therapy (Chang 2009). Treatment consisted of a single dose of bevacizumab (Avastin) and/or triamcinolone administered by suprachoroidal catheterization. Most patients received a combination of bevacizumab (Avastin) and triamcinolone. The average preoperative BCVA was 1.78 ± 0.41 logMAR units, which increased to 1.40 ± 0.60 at three months and was 1.63 ± 0.71 at 12 months. Overall, BCVA showed a trend towards improvement but did not reach

statistical significance. After three months, the BCVA appeared to regress towards preoperative levels. The average central subfield foveal thickness appeared to decrease after surgery at all time points. Total macular volume significantly decreased from baseline levels at six months. Only two of 11 eyes had an elevation of IOP above 21 mmHg at any postoperative visit beyond one week, both eyes reaching an IOP of 24 mmHg and resolving without treatment. Of the six eyes that were phakic at baseline, one eye with a pre-existing grade 2+ nuclear sclerotic cataract developed a 1+ posterior subcapsular cataract during the follow-up period.

Tetz and co-workers (Tetz, Rizzo, and Augustin 2012) investigated the suprachoroidal administration of a combination of bevacizumab and triamcinolone to the submacular suprachoroidal space, via a microcatheter, in eyes with advanced neovascular AMD that failed to respond to conventional therapy. A slight improvement in the average BCVA at one month and six months was observed, but statistical significance was not reached at any time point compared with baseline. Initial central subfield foveal thickness was 407.2 µm (SD=229.8), decreasing at one month to 333.3 µm (SD=179.4), remaining stable at three months and trending towards initial levels at six months (384.8 µm, SD=265.7).

No serious complications were encountered during the administration of therapy. Only one of 21 eyes included in the study experienced a transient elevation in IOP at three months, which was medically controlled. In two eyes, an increase in nuclear sclerotic cataracts was noted.

Rizzo and co-workers (Rizzo *et al*., 2012) evaluated 6 eyes with retinal vein occlusion or diffuse DME accompanied by massive subfoveal hard exudates that were unresponsive to multiple IVT injections. The eyes underwent a single treatment in which a combination of bevacizumab and triamcinolone were administered to the submacular suprachoroidal space via a microcatheter. BCVA improved by 2+ lines on a reading chart in 4 eyes and remained stable in 2 eyes. At 1 to 2 months, the hard exudates had almost completely resolved in all eyes. No complications were observed.

In compassionate use patients in Switzerland, Oxulumis® was used to deliver 2.4mg to 4mg Triesence® in a total of 5 patients with 9 treatments (including 3 repeat treatments and 1 bilateral treatment) with refractory macular edema, mostly post-surgical cystoid macular edema. These patients showed, in contrast to their pretreatment, after suprachoroidal administration of TA, good anatomical response with a quick onset, as well as visual

improvements. No device-related AEs and no challenges with IOP rises after TA administration were described (for details see Investigator's Brochure).

2.3 Nonclinical experiences with DMA microspheres in the suprachoroidal space

While there is no animal model covering preclinically all relevant aspects of clinical suprachoroidal DME treatment, some aspects of DME such as retinal inflammation or VEGF-driven vascular permeability can be studied in acute animal models.

The extent of pharmacodynamic (PD) effects of preliminary microsphere formulations have been estimated during primary PD studies using a human-VEGF induced retinal vascular hyperpermeability model in rabbits. The effect of the drug has been assessed using fluorophotometry or fluorescein angiography. Dexamethasone acetate microspheres (in various sphere sizes, polymer composition, and doses) administered suprachoroidally were compared to intravitreal Ozurdex® at 14, 42, and up to 60 days. The use of early formulations and a surgical component to the suprachoroidal administration, different from the final Oxulumis® design and procedure, in rabbits during early development led to high variability between these studies. Nevertheless, a trend for increased durability of effect versus Ozurdex® was observed, and results support that microsphere formulations are well tolerated when administered suprachoroidally and result in delivery of steroids comparable to existing steroid medications currently used clinically for the treatment of eye diseases with a need for anti-edema and anti-inflammatory activity.

Dexamethasone (DXM) and DMA concentrations in choroid, retina, vitreous humor, aqueous humor, and lens tissues have been evaluated using a validated bioanalytical method in pharmacokinetic (PK) studies in rabbits for 120 days and 220 days. Two of the studies compared a single administration of DMA microspheres utilizing different release rates and doses administered in the suprachoroidal space versus a single Ozurdex® intravitreal administration (allometric 0.35mg dose). The studies demonstrated comparable drug levels in the choroid and retina and lower levels in anterior tissues versus Ozurdex®. One of the Oxular formulations (170 µg DMA) in the first PK study and two (1655 µg DMA and 960 µg DMA) in the second PK study maintained detectable choroid and retinal drug levels, respectively, through the 120 days, whereas DXM levels following Ozurdex® administration were not maintained after day 60 in keeping with published data. In a third PK study, which was a formal GLP pharmacokinetic study bracketing release rates and doses of 4 different formulations of microspheres (a single dose of 600 µg to 1550 µg DMA) intended to be used

in GLP toxicology studies and for the selection of the Phase 2 clinical study's formulation, distribution to compartments of the eye was similar for all treatments. The highest concentration was observed in the choroid and the lowest concentration was observed in the lens and in the vitreous, whatever the treatment and for both DXM and DMA. In all eye structures, the concentrations of DXM were lower than the concentration of DMA. In plasma, DXM and DMA were quantifiable (>LLOQ) only in few samples, demonstrating a very low systemic absorption of the DXM and DMA.

For further details of the nonclinical studies, refer to the Investigator's Brochure.

Based on these nonclinical pharmacodynamics and pharmacokinetics data on OXU-001 as well as prior clinical data for suprachoroidal delivery of steroids, we expect the preclinical PK and toxicology findings of OXU-001 to translate to a better safety profile with respect to exposure of anterior segments of the eye and IOP and increase and a meaningfully longer durability profile compared to Ozurdex®.

2.4 Benefit/Risk Assessment

This study is the first clinical trial to assess suprachoroidal OXU-001, limiting the ability to delineate the clinical benefit/risk profile. Clinical experience originates from the use of the Oxulumis® to administer Triesence® (triamcinolone acetonide) in compassionate use in patients with macular edema of different etiologies indicates visual and anatomical improvement and from a clinical trial in DME (OXUCT-103, CAPE, NCT05512962). No severe, serious adverse events or adverse device effects have been reported so far. In the CAPE trial, to-date, the use of the Oxulumis® to administer Triesence to the suprachoroidal space with volumes of up to 100µl in trial subjects with DME has been well tolerated. Treatment-emergent ocular adverse events (AEs) were generally of mild to moderate intensity and of limited duration. No treatment-related non-ocular AEs were observed. No serious adverse events (SAEs) or serious unexpected adverse reactions (SUSARs) have been observed. One (1) adverse event of special interest (AESI; severe ocular pain of limited duration) has been observed in a subject receiving 100µl study treatment.

Preclinical data from rabbits also indicate low exposure of the lens and anterior chamber components to dexamethasone when treated with suprachoroidal OXU-001, and strong anti-edema and anti-inflammatory effects. The principal expectations of therapeutic effects with OXU-001, therefore, build on the ample and decade-long experience with intraocular steroids,

including Ozurdex® (Boyer *et al.*, 2014), and recently suprachoroidal triamcinolone acetonide (Yeh *et al.*, 2020).

The suprachoroidal administration procedure of OXU-001, in contrast to IVT injection reaches more posterior parts of the retina, towards the macula, through the suprachoroidal space. The suprachoroidal route of administration is, therefore, expected to result in favorable safety and tolerability, particularly regarding complications, such as increased IOP and cataract formation in addition to potential improvement in efficacy due to the expected higher exposure of dexamethasone in the retina and choroid.

OXU-001 used in the current study is expected to satisfy an unmet medical need to:

1. Reduce the risk of steroid-induced complications and adverse events
2. Prolong and sustain the efficacy of steroid treatment in DME
3. Enhance the efficacy of steroid treatment in DME

Theoretical risks associated with the suprachoroidal delivery procedures include endophthalmitis, choroidal hemorrhage, choroidal effusion, retinal penetration, and retinal detachment, amongst others. In addition, the eligibility criteria of this trial exclude subjects with structural lesions of the eyewall (*e.g.,* subjects with scleral ectasia or scleral defect, which may have a risk of scleral perforation) which further reduces any potential procedural risks. This risk has so far not been observed as AEs in 9 subjects in compassionate use and in 20 treated subjects in the ongoing CAPE trial (OXUCT-103, CAPE, NCT05512962). Ocular AEs observed with the Oxulumis® device include expected events for the type of treatment and drug administered including subconjunctival hemorrhage, inadvertent intravitreal drug deposit, incomplete dose administration, non-completion of the study procedure, and ocular pain and/or discomfort.

To immediately become aware of the occurrence of novel potential risks, in the OXU-001 program reporting of Adverse Events of Special Interest has been defined in Section 9.5.6.

The following features of the Oxulumis® may mitigate and limit the potential risk of adverse events with suprachoroidal ophthalmic administration:

1. The atraumatic, flexible design of the microcatheter
2. The rounded ball-like catheter tip
3. The control over the speed of delivery by adjustment of the Oxulumis® device

4. The 15-20° tangential insertion of Oxulumis® is relative to the surface of the eye. Steeper angles of approach may only be necessary with initial engagement of the insertion needle. Using an angle of approach of 45° and more to the sclera throughout the procedure may be associated with an increased risk of penetration of the vitreous cavity).

Still, as the Oxulumis® procedure is relatively novel, non-completion of microcatheter placement may happen in an in-clinic setting, requiring the use of a procedural variant that uses an incision of the conjunctiva and/or tenon to increase visibility of the scleral engagement in the insertion phase of the Oxulumis® procedure. To facilitate the decision on the initial setting for the study procedure, the treating physician (unmasked investigator in Part B) will assess the expected procedural complexity as low, medium, or high. To assist this assessment, a guidance document is included as part of this protocol, which mentions aspects to consider for the overall expert judgment on complexity (see Section 12.4) Information about the known and expected benefits and risks and potential adverse events (AEs) of OXU-001 can be found in the Investigator's Brochure (IB) Reference Safety Information. As there have been so far no SAEs observed for the Oxulumis®, at the start of OXUCT-102 no serious adverse reactions (SAR) can be defined and the list of AESI defined for the OXU-001 program is based on theoretical considerations.

Benefits associated with Ozurdex® administration include the potential DME resolution (*i.e.*, improved BCVA and normalization of retinal thickness) as summarized in a recent clinical review (Rittiphairoj *et al.*, 2020). Risks associated with IVT Ozurdex® administration include cataract development or deterioration (68%), IOP elevation (28% at least 10mmHg, 15% at least 30mmgHg), and endophthalmitis (<2%). More details about the adverse reactions associated with IVT Ozurdex® can be found in regulatory documents as applicable for the respective trial countries (US, EU, Israel). It is important to note that cataract progression is specifically observed with repeat and long-term Ozurdex® treatment (Boyer *et al.*, 2014). In the MEAD 3-year study of Ozurdex®, cataract progression was mostly seen after month 12 and over 75% of the cataract surgeries with Ozurdex® were performed between month 18 and 30. So the risk with a potential single administration of Ozurdex® in Part B treatment arm B3 in the current trial appears justified to have a randomized, masked head-to-head comparison of OXU-001 and Ozurdex®. In addition, lens opacity will be tightly monitored at all study visits with the slit lamp exam.

As part of the risk mitigation strategy, the study will include two parts, Part A and Part B. Part A will include eighteen (18) DME subjects, treatment-naïve or previously treated with IVT anti-VEGF therapies. Subjects will be randomized to one of two dose levels of OXU-001, a 1.5mg mid-dose and a 3.0mg high dose, in a 1:1 fashion with approximately 9 subjects in each dose group. After the last subject treated in Part A has reached the Week 6 visit, a safety review will occur with focus on early and procedural risks, and the change in IOP throughout the period of observation. The study DMC, based on a review of the Week 6 safety, will give a recommendation for the start of Part B, including a recommendation if the 1.5mg and 3.0mg OXU-001 should be tested in Part B.

The foreseen Doses in Part B are Dose 1 in arm B1 (DMA 1.5mg, mid-dose) and Dose 2 in arm B2. Dose 2 is intended to be OXU 001 DMA 3.0mg. In case of potential safety concerns with *e.g.*, early significant IOP increase in the A2 arm with 3.0mg through Week 6, arm B2 will use 0.75mg OXU-001 as Dose 2.

The randomization scheme is 2:2:1 with Arm B3, the Ozurdex® arm including only half the number of subjects compared to the OXU-001 Arms B1 and B2, to optimize the number of subjects on Ozurdex®.

To detect adverse events and other unforeseen risks and to potentially initiate countermeasures in a timely fashion, subjects will be monitored closely for 60 minutes after administration of OXU-001 to the suprachoroidal space. This monitoring includes ophthalmoscopy and at least two IOP measurements. Monitoring times longer the 60 minutes may be required to observe normalization of the IOP post treatment. A post-administration ophthalmic exam and IOP measurements will also be performed after the administration of Ozurdex®. Additionally, visits following treatment, on day 1, week 1, week 4, week 6 (mandatory in Part A, optional in Part B), week 8, and every 4 weeks thereafter, will include multiple safety evaluations to ensure the detection and management of any emerging adverse events. Questionnaires to investigator and subject interviews will assess details of performing the Oxulumis procedure and pain and discomfort.

Taking into account the measures used to minimize risk to subjects in this study, the potential risks identified in association with OXU-001 are justified by the anticipated benefits that may be afforded to subjects with DME.

3 Objectives, Endpoints, and Estimands

3.1 Objectives and Endpoints

Table 5 Objectives and Endpoints

Objectives and Endpoints	Objectives	Main Endpoints
<u>Part A</u> (Open-Label): Two parallel, randomized treatment arms with mid-dose and high dose sustained-release OXU-001 in treatment-naïve or anti-VEGF previously treated DME subjects in the study eye		
Safety	1. To evaluate the safety, tolerability, and feasibility of suprachoroidal OXU-001 in subjects with DME	1. Frequency and severity of • ocular and systemic adverse events (serious, adverse events of special interest, and treatment-emergent adverse events) • device adverse effects (serious adverse device effects and treatment-emergent device adverse effects)
Exploratory Efficacy	1. To evaluate the durability of suprachoroidal OXU-001 in subjects with DME 2. To explore the efficacy of suprachoroidal OXU-001 determined by change in visual acuity, edema control, and impact on vision-related quality of life in subjects with DME	1. Time from baseline Visit 2, to subjects requiring follow-on treatment (per pre-specified criteria). 2. Mean Change BCVA (ETDRS) at Week 24 compared to baseline. 3. Mean Change in central subfield thickness at Week 24 compared to baseline.

		4. Mean Change BCVA (ETDRS) through Week 52 compared to baseline. 5. Mean Change in central subfield thickness through Week 52 compared to baseline. 6. Mean change in NEI VFQ-25 Total Score at Week 24, and Week 52 compared to baseline.
Pharmaco-kinetics (PK):	1. Assess systemic exposure of dexamethasone after administration of OXU-001.	1. Dexamethasone levels in plasma will be measured at scheduled timepoints (pre-dose, and post-dose at 60min, 1 day, 1 week, 4 weeks, 24 weeks, and 52 weeks after administration of OXU-001). The following PK parameters will be evaluated: 1. Time to maximal concentration (Tmax) 2. Maximal concentration (Cmax) 3. Area under the curve (AUC)
Part B: Randomized, controlled, masked trial with two dose levels of sustained-release OXU-001 compared to Ozurdex® in treatment-naïve or anti-VEGF previously treated DME subjects in the study eye (at least 50% treatment-naïve).		
Primary	1. To evaluate the safety and tolerability of suprachoroidal OXU-001 in subjects with DME	1. Frequency and severity of • ocular and systemic adverse events (serious, adverse events of special interest, and treatment-emergent non-serious adverse events)

		• device adverse effects (serious adverse device effects and treatment-emergent non-serious adverse device effects)
Exploratory	1. To evaluate the durability of suprachoroidal OXU-001 in subjects with DME. 2. To explore the efficacy of suprachoroidal OXU-001 determined by change in visual acuity, edema control, and impact on vision-related quality of life in subjects with DME.	1. Time to subjects requiring follow-on treatment. 2. Mean Change BCVA (ETDRS) at Week 24 compared to baseline. 3. Mean Change in central subfield thickness (SD-OCT) at Week 24 compared to baseline. 4. Mean Change in BCVA (ETDRS) through Week 52 compared to baseline. 5. Mean Change in central subfield thickness through Week 52 compared to baseline. 6. Proportion of subjects requiring follow-on treatment at study visits from Week 12 through Week 52. 7. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) gain of BCVA from week 4 to week 52 compared to baseline. 8. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) loss of BCVA from week 4 to week 52 compared to baseline. 9. Proportion of subjects with BCVA >68 letters (ETDRS) at

		each study visit from week 4 to week 52. 10. Mean change in NEI VFQ-25 Total Score at Week 24, and Week 52 compared to baseline.

For all efficacy endpoints, the pre-treatment assessments on the baseline visit V2, Day 0, will be considered the baseline values for the comparison of post-treatment values. The most recent baseline assessments of V2 prior to treatment will be considered the baseline value in case any repeat assessments happen during V2 activities.

The objectives for evaluating the device safety and performance are separately outlined in the latest version of the Oxulumis® Clinical Evaluation Plan (CEP) Version OXUCT-102.

3.2 Estimands

For the objective of this clinical trial currently, no estimand is defined. Data generated in this clinical trial in treatment-naïve or previously treated DME subjects for patient-relevant outcomes like BCVA and disease-related outcomes like measurements of macular edema will inform estimands for subsequent clinical trials. Also, clinical experience with the Oxulumis® ophthalmic procedure will contribute to building estimands for future trials of OXU-001.

4 Study Design

4.1 Overall Design

The study population will consist of approximately 128 adult female or male subjects with DME with approximately 18 subjects treated in Part A and approximately 110 subjects treated in Part B that:

1. Have been diagnosed with Type 1 or Type 2 diabetes mellitus.
2. Have DME involving the center of the fovea with central subfield thickness (CST) in the study eye at the screening visit, confirmed by the CRC, of at least 320 µm on SD OCT (measurement from RPE to ILM, inclusively).
3. Have BCVA between 34 and 78 letters (using an ETDRS chart, approximate Snellen acuity of 20/200–20/32) in the study eye.
4. Are treatment-naïve or previously treated with IVT anti-VEGF in the study eye.

Only one (1) eye will be determined as the study eye and only the study eye will receive a single administration of study treatment on Visit 2, Day 0. Study eyes need to meet all inclusion criteria and none of the exclusion criteria. If both eyes meet the relevant criteria, the eye with the worse BCVA will be selected as the study eye; if both eyes meet the relevant criteria and have the same BCVA, the investigator can select the study eye.

If one eye is previously treated (for allowed prior treatment see Section 5.2 and Section 7.8.1), the other eye may still qualify as a treatment-naïve study eye if all inclusion criteria and none of the exclusion criteria are met.

The subjects' fellow eye may continue to receive treatment following guidelines and standards at the investigational site. Subjects in Part A should not receive steroid treatment in their fellow eye, as this may have an impact on the PK assessment of the study treatment. Treatment of the fellow eye is not considered part of the study treatment.

The study has two parts (Part A and Part B). It will include both subjects that are treatment-naïve and subjects that have been previously treated with anti-VEGF therapies.

Part A is the open-label part of the study composed of two (2) parallel, treatment arms randomized in a 1:1 scheme and will include approximately 18 subjects. No minimum number of treatment-naïve subjects is fixed in Part A.

Table 6 Part A Treatment Arms, Interventions, and Number of Subjects

Treatment Arm	Intervention	Subjects
A1	One (1) treatment with suprachoroidal **mid dose (DMA 1.5mg)** OXU-001	N=9
A2	One (1) treatment with suprachoroidal **high dose (DMA 3.0mg)** OXU-001	N=9

Part B is the masked, randomized, controlled part of the study. This part is composed of three (3) parallel arms randomized in a 2:2:1 scheme as follows:

Table 7 Part B Treatment Arms, Interventions, and Number of Subjects

Treatment Arm	Intervention	Subjects
B1	One (1) treatment with suprachoroidal **Dose 1 (mid dose DMA 1.5mg)** OXU-001	n=44

B2	One (1) treatment with suprachoroidal **Dose 2 (tbc. DMA 3.0mg or 0.75mg;** dose based on the outcome of Part A 6 weeks) OXU-001	n=44
B3	One (1) treatment with intravitreal Ozurdex® (dexamethasone 0.7mg)	n =22

In Part B, a total of 110 subjects, who are treatment-naïve or previously anti-VEGF treated (in the study eye) will be treated. Enrollment of previously treated and treatment-naïve subjects will be competitive, with at least 55 subjects being treatment-naïve in the study eye. Enrollment of subjects that are anti-VEGF previously treated in the study eye will stop once 55 subjects with previous anti-VEGF treatment in the study eye are randomized to allow reaching the foreseen number of treatment-naïve subjects. Subjects will be stratified based on their anti-VEGF treatment history.

In this trial the administration of OXU-001 with the Oxulumis illuminated microcatheter will be performed with two different procedural variants depending on subject characteristics and procedural success:

- Standard Variant: Administration with the Oxulumis® device without an incision of the conjunctiva/tenons. The standard variant can be performed in any setting, *i.e.,* in-clinic, in a procedure room or in an operating room.

- ConjIncision Variant: Incision of the conjunctiva/tenons at the start of the OXU-001 administration to increase visibility and access for the scleral engagement phase of the OXU-001 administration. The incision opening of the conjunctiva/tenons needs to be closed by using standard surgical techniques and material (*e.g.*, fibrin glue, suturing material): This variant can be used at the discretion of the treating physician either a) initially if subject characteristics and/or medical history suggest this variant, or b) if with the Standard OXU-001 administration variant, study treatment cannot be administered.

  The ConjIncision OXU-001 Variant can only be performed in a sufficiently equipped environment for opening and closing the conjunctiva/tenons. An adequate procedural setting, techniques and material uses follows the surgical standard in the respective geographic region (*i.e.,* an adequately equipped procedure room or an operating room).

The treating physician will determine at the screening visit (V1), if initially the Standard Variant or the ConjIncision Variant will be used in a respective subject. The baseline visit activities will be planned accordingly with three different schedules for baseline visit activities:

- OXU-001 Standard Variant without surgical incision is typically performed in an in-clinic or procedure room setting
- OXU-001 ConjIncision Variant with conjunctiva/tenons incision is typically performed in a surgically equipped procedure or an operating room
- Switch from OXU-001 Standard to ConjIncision Variant. In this scenario procedural attempts are typically started in-clinic. If the OXU-001 Standard Variant cannot be completed, the procedure is switched to the ConjIncision Variant and depending on the facility will then be either performed in the same facility (surgically equipped procedure room) or has to be rescheduled in a surgical facility, which may be distant to the core investigational site

The maximum time interval to complete all baseline visit activities is 14 days including potential rescheduling of treatments in case switch of the procedural variants is needed.

In Part B, if a treating physician decides directly for the ConjIncision Variant, a facility that allows incision of the conjunctiva/tenons will be booked for masking purposes even if the subject will be finally randomized to receive Ozurdex®. For Ozurdex® the ConjIncision Procedural Variant, *i.e.*, surgical incision of conjunctiva/tenon the is not allowed.

Part A: Open-label, parallel, randomized, two treatment arm part of the study with approximately 18 anti-VEGF treatment-naïve or previously treated subjects receiving a single treatment of mid-dose (Arm A1) or high-dose (Arm A2) OXU-001. Subjects will be followed for 52 weeks after treatment completion, with a safety analysis when the last enrolled subject has completed Week 6 visit and further analysis at Week 24 and Week 52.

Part B: Randomized, masked part including approximately 110 previously treated or treatment-naïve subjects. Treatment-naïve subjects will comprise at least 55 subjects. The focus of the analysis will be on patient-relevant safety events, including *e.g.,* the occurrence rate of moderate and severe ocular AEs, AESI, and ocular SAEs reviewed by DMC, and Sponsor.

In Part B two different dose levels of OXU-001 will be administered. Dose 1 in treatment arm B1 and Dose 2 in treatment arm B2 will be compared to IVT Ozurdex 0.7mg (treatment arm B3). Dose 1 is planned to be OXU-001 1.5mg (mid-dose) and Dose 2 OXU-001 3.0mg (high dose). If potential safety concerns arise from the week 6 analysis in Part A with the high dose (treatment arm A2), the dose in Part B may be adjusted to administer the mid-dose of OXU-001 in B1 (Dose 1, 1.5mg) and the low dose in B2 (Dose 2 0.75mg). Subjects will be followed for 52 weeks after treatment completion. In Part B, subjects and the teams at the investigational site assessing efficacy and selected questionnaire assessments (*i.e.*, BCVA, Subject's Experience Assessment, and NEI-VFQ25) and at the CRC readers assessing the CST, are masked to the subject's treatment assignment. The masked site team will not have any other study roles, which could lead to involuntary unmasking.

The following masking procedures will apply in Part B (see Section 7.3):
Subjects will be masked to their assignment to one of the treatment arms (B1-B3). Subjects will only receive one study treatment on Day 0 (Visit 2), *i.e.,* either suprachoroidal administration of study treatment (OXU-001) or IVT Ozurdex. No sham treatment for the respective other treatment will be applied. In a limited number of subjects in the OXU-001 treatment arms, the study treatment will need to be repeated in a surgically equipped procedure or operating room using the OXU-001 ConjIncision Procedural Variant. In this subgroup, an increased risk of getting hints to the assignment of an OXU-001 treatment arm exists. Still, even in this setting no information about OXU-001 dose group can be obtained.

In addition, the assessment teams at the investigational site performing the efficacy and selected questionnaire assessments (*i.e.*, BCVA, Subject's Experience Assessment, and NEI-VFQ25) are masked to the subject's treatment assignment, as well as the graders at the central reading center (CRC) assessing the CST values. No information about the need for rescheduling Part B subject for the OXU-001 ConjIncision Procedural Variant will be shared. This may require specific readers or similar operational measures for the CST assessment, as other imaging like CFP, 4 Wide-Field IR Plus images, or peripheral OCT may show findings (*e.g.*, suprachoroidal drug deposits) giving hints on the treatment assignment. Study treatments will be administered by unmasked retinal physicians trained on the Oxulumis procedure, who will need to know the treatment assignment of subjects.

On Visit 2 (Day 0), in either Part A or B, subjects will receive study treatment according to their randomized assignment. The selection of the treatment setting and of the respective variant of the OXU-001 administration procedure will follow the pre-treatment expert

assessment on the expected procedural complexity. Alternatives No.1-3 are summarized in Table 3 and Table 4 for Part A and Part B. Treatments can be scheduled in-clinic (No.1), directly in a surgically equipped procedure room or operating room (No.2) or can in case of non-completion in an in-clinic setting move to a surgically equipped procedure room or operating room (No.3). The OXU-001 ConjIncision Procedural Variant should only be performed in a surgically equipped procedure room or an operating room. Depending on the alternative scenarios and caused by expectedly different equipment of the treatment settings, the schedule of activity varies as shown in Table 3 and Table 4 for Part A and Part B.

In addition to the screening and baseline visits, (Visits 1 and 2, respectively), clinic visits will occur on Day 1, and Week 1, 4, 6, 8, and then every four (4) weeks thereafter for a total duration of fifty-two (52) weeks after treatment completion.

In Part A, the Week 6 visit is scheduled to capture and assess any potential safety signals which may start around this time after steroid treatment (*e.g.*, IOP increase). A safety review will occur after all active study participants have completed Week 6 visit prior to initiating randomization in Part B.

For Part B, the Week 6 safety visit is optional and may be scheduled at the discretion of the investigator based, *e.g.*, if subjects tend to present with relevant IOP increase through Week 4 post-treatment.

Starting at the Week 12 visit, for both Parts A and B, subjects will be evaluated by the investigator (masked investigator in Part B) against prespecified criteria indicating the need for follow-on treatment (*i.e.,* indicating the end of the current treatment interval). Criteria are as follows:

1. At least 75µm thickening in CST on SD-OCT compared to best CST value since the baseline visit, Visit 2, Day 0

   or

2. A decrease in BCVA of ≥10 letters (ETDRS) from the best achieved BCVA since the baseline visit, Visit 2, Day 0, that, in the opinion of the investigator, is due to the worsening of DME.

For subjects showing no reduction of edema or no improvement of BCVA after Visit 2, Day 0, the baseline visit will be considered the best CST or BCVA value.

If according to the assessment of the above criteria, by the investigator (masked investigator in Part B), the need for administration of follow-on treatment is indicated, subjects will be managed according to local standard of care for the rest of the trial duration. Standard of care treatments may include IVT anti-VEGF, ocular IVT steroids, or other non-investigational treatments.

In Part B, when follow-on treatment criteria are met based on masked assessment, the unmasked investigator will determine the kind of follow-on treatment to be administered (*e.g.,* IVT anti-VEGF treatment, IVT steroid, or other) considering the treatment history and the response to the study treatment received. After receiving the first follow-on treatment in the study eye, subjects will continue on the regular visit schedule through the End-of-Study visit at Week 52.

Subjects who require therapy for complications of diabetic eye disease, *e.g.,* newly developed PDR and/or other complications will continue to be followed in this trial and will receive treatment for DME once follow-on treatment criteria are met (see Section 7.5.2 for details).

Subjects who decide to discontinue study participation for any reason will undergo all end of study visit assessments and procedures and the visit will be considered an end of study visit. If for any reason the study treatment cannot be administered, an extra end of study visit is not necessary and only activities for Visit 2 need to be completed as applicable. If any AEs/ADEs would be ongoing in a subject in whom treatment could eventually not be administered , unscheduled visits should be performed to follow-up such events.

If the fellow eye requires management for DME, this should be carried out according to the local standard of care but is not considered a study treatment.

In Part A, treatment of the fellow with ocular steroids should be avoided in order not to confound PK assessments until the study eye has received follow-on therapy. After receiving follow-on treatment in the study eye, subjects will continue on the regular visit schedule through the End-of-Study visit at Week 52.

This clinical trial will include a data monitoring committee (DMC). The DMC's main responsibility is to periodically review the unmasked trial data and provide recommendations regarding the trial to the Sponsor based on unmasked benefit/risk assessment. Details on these reviews including timing and review intervals will be laid out in a DMC Charter.

4.1.1 Scientific Rationale for the Study Design

Dividing the study into two parts:

The study is divided into two parts to check for potential safety events occurring in the first 6 weeks after administration of two dose levels of suprachoroidal sustained-release OXU-001 in a total of 18 subjects. The open-label design of Part A will facilitate the safety review. Subjects will be randomized to one of two dose levels to avoid bias with the assignment of doses by the investigator. A review of the safety data for subjects in Part A after the last enrolled subject reached 6 weeks. At this timepoint, potential early safety concerns (with the administration procedure or with OXU-001), which might impact the conduct of the randomized, masked Part B are expected to have manifested.

Control Arm selection:

Ozurdex® was selected as a comparator as it is the current standard of care for marketed intravitreal steroids for DME in the US and Europe. Also, the active drug is Dexamethasone, similar to the Dexamethasone acetate in OXU-001 avoiding a potential impact on the study results by differences in steroid potency. A randomization of dose levels in Part A and a randomization to one of two dose levels or a comparator arm in Part B will allow for better interpretability of the trial results. It will also facilitate interpretation of Ozurdex® results within this trial and cross trial. Of note, the treatment practice in DME has relevantly changed since the first Ozurdex® trials, so that patients are referred earlier to treatment and with a trend to less extensive visual acuity loss, which is reflected in the eligibility criteria of this trial.

Randomization ratio:

The randomization ratio is 2:2:1 with Arm B3, the Ozurdex® arm having only 22 subjects (vs. 44 subjects in OXU-001 Arms B1 and B2) to balance the generation of highly useful comparative data whilst minimizing any exposure to side effects of the comparator (Ozurdex®). Of note, the impact of Ozurdex® on lens opacities typically manifests in the 2nd year of continued treatment (*i.e.*, implants administered at intervals of 6 months or shorter) with the peak in cataract surgeries in the MEAD trial between 18 and 30 months. A single Ozurdex® administration in the current trial is expected to have a comparably limited impact on lens opacities. If subjects would have been randomized and could not be treated, these subjects will be replaced until the targeted number of subjects per trial part are reached.

Stratification for prior anti-VEGF treatment:

Subjects are stratified into those previously treated with anti-VEGF therapy and those who are anti-VEGF naïve as the treatment history with anti-VEGF is known to impact response to steroids both anatomically and functionally. In Part A, no minimum number of treatment-naïve subjects is defined. Therefore, no stratification will be applied in Part A.

Variants of the Oxulumis® procedure

In this trial, the administration of OXU-001 with the Oxulumis illuminated microcatheter will be performed with two different procedural variants depending on subject characteristics and procedural success:

1. Standard Variant: Administration with the Oxulumis® device without an incision of the conjunctiva/tenons. The standard variant can be performed in any setting, *i.e.,* in-clinic, in a procedure room or in an operating room.

2. ConjIncision Variant: Incision of the conjunctiva/tenons at the start of the OXU-001 administration to increase visibility and access for the scleral engagement phase of the OXU-001 administration. The incision opening of the conjunctiva/tenons needs to be closed by using standard surgical techniques and material (*e.g.*, fibrin glue, suturing material): This variant can be used at the discretion of the treating physician either a) initially if subject characteristics and/or medical history suggest this variant, or b) if with the Standard OXU-001 administration variant, study treatment cannot be administered.

Allowing these variants will allow for a very high completion rate of the procedure.

Primary endpoint selection:

As this is the first study assessing OXU-001 in human subjects, safety is the primary endpoint.

Follow-on treatment criteria:

CST thickening and BCVA loss are the two main triggers for treatment in patients with DME in a clinical setting. Accordingly, criteria for worsening of edema and vision loss were

selected as pre-specified criteria for the need for follow-on treatment in this study based on natural disease fluctuation and experience from other studies assessing similar populations.

Duration of the study:

The duration of the study (52 weeks from treatment completion) is based on the expected duration of the efficacy of OXU-001. We expect that the majority of subjects will have met the follow-on treatment criteria by week 52 in the OXU-001 treatment arms of this clinical trial.

4.2 Justification of Dose

To determine the doses for the first-in-human clinical trial, outcomes from primary pharmacokinetic studies of the effects of DMA microsphere formulations administered via the suprachoroidal space in rabbit models of hVEGF-induced retinal vascular leakage have been evaluated (volume of a rabbit eye is approximately 40% of the human eye volume). In rabbits, up to 5mg in 40 µL of DMA microsphere formulation has been well-tolerated in these models when administered as a single suprachoroidal injection to both eyes with post-treatment follow-up for 105 days. In another study, suprachoroidally administered microsphere formulations containing approximately 0.9 to 1.3 mg of DMA were compared to a sham suprachoroidal procedure or the positive control Ozurdex implant (allometric dose of 0.35 mg dexamethasone) injected into the vitreous. DMA microsphere formulations demonstrated a dose-dependent suppression of induced fluorescein leak but less peak suppression than Ozurdex® up to the first 30 days after administration. Thereafter, the Ozurdex effect rapidly dissipated because of drug depletion while edema suppressive effects of the microsphere formulations were maintained up to the end of the study at day 60. The selection of the dose levels for the clinical trial, therefore, has been based on achieving meaningful effect while also considering cumulative effects of longer exposure duration as compared to Ozurdex®. As the microsphere suspensions are expected to continue slow-release of DMA over a period in excess of 6 months, longer-term pharmacokinetic studies in rabbits with DMA microsphere formulations containing up to approximately 1.5 mg DMA show the microspheres to be well tolerated up to study end at 220 days post-administration. Accordingly, a 3.0 mg DMA microsphere dose (extrapolated from the allometric 1.5 mg DMA dose in rabbits) is considered the target therapeutic dose for human use. Doses of 1.5mg and 3.0mg will be evaluated in parallel in Part A as cumulative effects of slow-release DMA may be equally effective as 3.0 mg while reducing the dose exposure. The Week 6 safety assessment in Part A

of the OXUCT-102 trial is considered an appropriate timepoint to look for indications of dose-dependent adverse effects, *e.g.,* IOP increases. Based on this systemic data review with the participation of an independent DMC, doses for the randomized Part B of the trial will be confirmed. If there is an early indication for dose-dependent safety concerns with the 3.0mg dose, but not with the 1.5mg dose, the second dose in Part B will be chosen to contain 0.75 mg DMA microspheres.

4.3 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last visit.

5 Study Population

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if ALL the following criteria apply:

1. Able to understand and sign an informed consent form.
2. At least eighteen (18) years of age at the time of screening.
3. Have been diagnosed with Type 1 or Type 2 diabetes mellitus.
4. Have DME involving the center of the fovea with central subfield thickness (CST) in the study eye at the screening visit, confirmed by the CRC, of at least 320 µm on SD OCT (measurement from the RPE to ILM, inclusively).
5. Have BCVA in the study eye between 34 and 78 letters ETDRS (approximate Snellen acuity of 20/200–20/32) at the screening visit. For eligibility assessments, only the ETDRS BCVA letter score is considered relevant.
6. For women who are not postmenopausal (*i.e.,* at least 12 months of non-therapy-induced amenorrhea or surgically sterile (absence of ovaries and/or uterus) agreement to remain abstinent or use combined contraceptive methods that result in a failure rate of less than 1% per year from the treatment visit (Visit 2, Day0) until the end of trial participation, or, if subjects discontinue trial participation before Week 52, for at least 52 weeks from the treatment visit (Visit 2, Day 0).l. Examples of contraceptive methods with an expected failure rate of less than 1% per year include male sterilization, hormonal implants, proper use of combined oral or injected hormonal contraceptives, and certain

intrauterine devices. Alternatively, two methods (*e.g.,* two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of less than 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

7. Males must agree to use a barrier method of contraception starting from the treatment visit (Visit 2, Day0) until the end of trial participation, or, if subjects discontinue trial participation before Week 52, for at least 52 weeks from the treatment visit (Visit 2, Day 0).
8. Subject must be willing not to participate in any other clinical trial including an investigational medicinal product (IMP) or an investigational device until the end of trial participation.

Note on inclusion criterion No.4: Practically, the initial eligibility determination at the site will use the 320 µm threshold for CST for all participants and for all SD-OCT devices allowed in this trial (see Section 9.3.6). The CRC will then also assess the CST and confirm eligibility.

5.2 Exclusion Criteria

Subjects are eligible to be included in the study only if NONE of the following criteria apply:

1. Presence of any significant ocular or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with the concurrence of the Oxular Medical Monitor, may
    1. put the subject at risk because of participation in the trial, or
    2. influence the results of the trial, or
    3. influence the subject's ability to participate in the trial, or
    4. may require medical or surgical intervention during study participation (*e.g.*, cataract, vitreous hemorrhage, retinal detachment, or macular hole).
2. Macular edema considered due to a cause other than diabetes mellitus in either eye.
3. Condition, in the study eye, in which visual acuity is not expected to improve from the resolution of macular edema (*e.g.,* foveal atrophy, clinically relevant loss of the ellipsoid zone, pigment abnormalities, vitreomacular traction, or nonretinal causes) as determined by the investigator with the concurrence of the Oxular Medical Monitor supported by a review by the CRC.
4. Conditions, in the study eye, that may render the administration of study treatment intravitreal implant insertion or suprachoroidal microcatheter insertion and

deployment difficult or subject the patient to excessive risk of complications. Examples include but are not limited to ocular surface disease with significant conjunctival edema and/or inflammation, ocular hypotony, scleral staphylomas, necrotizing scleritis, scleral melting, excessive choroidal scarring *e.g.,* associated with pan-retinal photocoagulation, amongst others.

5. Macular laser photocoagulation or panretinal laser photocoagulation (PRP) in the study eye performed within sixteen (16) weeks prior to screening.
6. Active proliferative diabetic retinopathy (PDR) or sequelae of PDR (including iris neovascularization, vitreous hemorrhage, tractional retinal detachment, extensive scarring following PRP) at screening in the study eye.
7. History of recurrent or active intraocular inflammation in either eye (*e.g.,* uveitis) within 12 weeks prior to screening.
8. Infectious eye disease like infectious blepharitis, keratitis, or conjunctivitis in either eye within four (4) weeks of screening.
9. IOP ≥ 22 mmHg, or glaucomatous disc changes (*i.e.,* a cup disc ratio greater than 0.8) in the study eye at screening. History of glaucoma surgery, and/or current anti-glaucoma therapy with more than two active substances (in separate or a combination preparation) are exclusionary.
10. History of closed-angle glaucoma.
11. IOP <6mmHg (hypotony) in the study eye at screening.
12. Spherical equivalent of the refractive error of −6 diopters of myopia or worse (prior to cataract or refractive surgery) at screening.
13. Cataract or other media opacity that limits the ability to obtain the planned imaging assessments.
14. History of retinal detachment.
15. Prior treatment with IVT anti-VEGF **in the study eye**

    1. Treatment-naïve group (Part A and B):

       Any IVT anti-VEGF treatments in the study eye are exclusionary regardless of the time interval since injection.

    2. Previously treated group (Part A and B):

    Subjects in the previously treated group are excluded if they meet any of the below criteria for the study eye at screening:

a) Subject has received less than three (3) anti-VEGF injections since treatment initiation. (at least three injections must have been received for eligibility)

b) Time interval between the first anti-VEGF injection and screening is more than sixty-four (>64) weeks.

c) Last injection with ranibizumab or bevacizumab within four (4) weeks prior to screening.

d) Last injection with aflibercept within eight (8) weeks prior to screening.

e) Last injection with faricimab or brolucizumab within twelve (12) weeks prior to screening.

f) Prior treatment with SUSVIMO (Port Delivery System) implant is exclusionary.

16. Prior ocular treatment with steroid injections (periocular, subtenon, intravitreal) or intravitreal implants **in the study eye**. A history of topical ocular steroids is not exclusionary.

17. Part A only: Prior ocular treatment with steroid injections (periocular, subtenon, intravitreal) or intravitreal implants **in the fellow eye** (due to potential interference with PK measurements).

    1. Last injection (intra- or periocular/subtenon) with triamcinolone acetonide within twelve (12) weeks before screening.

    2. Last injection (suprachoroidal) steroids, *e.g.*, Xipere™, within twelve (12) weeks before screening.

    3. Last injection (IVT) with dexamethasone implant (Ozurdex®) within twenty-four (24) weeks before screening.

    4. Prior treatment with longer duration implants (*e.g.,* fluocinolone acetonide IVT implant, Iluvien) is exclusionary.

18. Prior treatment with suprachoroidal steroids in the study eye is exclusionary.

19. Concurrent use of **systemic** glucocorticoid medications or systemic steroids within twelve (12) weeks before screening is exclusionary. Intranasal, inhaled, and extra-ocular topical corticosteroids are allowed.

20. Prior IVT or suprachoroidal treatment with investigational agents in either eye (*e.g.,* agents with anti-VEGF activity, or combined pharmacologic activity, gene therapies, cell therapies, or any other therapeutic modality) at any time.
21. Participation in a clinical trial in which an investigational drug (with other routes of administration than IVT or suprachoroidal) was administered within 90 days of screening or 5 half-lives of the investigational drug, whichever is longer.
22. Treatment with ocriplasmin (Jetrea®) at any time.
23. History of vitreoretinal surgery (including surgery for retinal detachment or scleral buckle) in the study eye. Vitrectomy is only exclusionary, if within twelve (12) weeks prior to screening.
24. Any other previous ophthalmic surgeries, uncomplicated cataract surgery, or uncomplicated trauma in the study eye within twelve (12) weeks prior to screening. Complicated cataract surgery or trauma that may impact access and/or drug delivery to the suprachoroidal space are exclusionary.
25. Part B only: Any history of surgical complications in the study eye that may increase the risk of anterior chamber migration of intravitreal implants (*e.g.,* torn or ruptured posterior lens capsule, implantation of any iris-fixated or sclera-fixated intraocular lenses, iridectomy) regardless of the time interval between the procedure and the study enrollment.
26. Hypersensitivity to OXU-001, or any of the excipients in the OXU-001 formulation or Oxulumis® device components.
27. Part B only: Hypersensitivity to components of Ozurdex® for.
28. Active malignancy or history of malignancy within the past five (5) years.
29. Uncontrolled diabetes with a hemoglobin A1c (HbA1c) > 12% or any other uncontrolled systemic disease at screening.
30. Uncontrolled hypertension, defined as blood pressure with a systolic value of ≥ 160mmHg or a diastolic value of ≥ 100 mmHg upon repeat assessment at screening.
31. History of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure, or any acute coronary event within 90 days before screening.
32. Subjects who are pregnant or breastfeeding at the screening visit, or who test positive for pregnancy at the screening visit or are unwilling to use adequate birth control methods to prevent pregnancy throughout the study.

33. Subjects who were previously randomized in this trial, but in whom administration of study treatment could not be completed.

6 Study Interventions Administered

The following study interventions (Table 8) may be administered during the conduct of this trial. A description of the treatment arms for Part A (Table 9), and Part B (Table 10) are also provided in this section.

Table 8 Study Intervention(s) Administered in Part A and Part B

Intervention Label	OXU-001 High Dose	OXU-001 Mid Dose	OXU-001 Low Dose	Ozurdex®
Intervention Name	OXU-001 High Dose (DEXAspheres®) using Oxulumis®	OXU-001 Mid Dose (DEXAspheres®) using Oxulumis®	OXU-001 Low Dose (DEXAspheres®) using Oxulumis®	Ozurdex® (dexamethasone implant)
Intervention Description	Single suprachoroidal administration of sustained-release OXU-001 (DEXAspheres®) using the Oxulumis® as standard procedure or procedural variant with a conjunctiva/tenon incision			Single intravitreal administration Ozurdex® (dexamethasone implant using applicator)
Dose Formulation	Sustained-release Microspheres			Sustained-release implant
Dose Strength(s)	3.0mg/60µL	1.5mg/60µL	0.75mg/30µL	0.7mg/implant
Dosage Level(s)	1 injection			1 implant
Route of Administration	Suprachoroidal microcatheterization (Oxulumis® Ophthalmic Administration Device)			Intravitreal (IVT) injection

Intervention Label	OXU-001 High Dose	OXU-001 Mid Dose	OXU-001 Low Dose	Ozurdex®
Use **Trial Part**	Investigational Part A and in Part B, pending confirmation by Week 6 Safety Review in Part A	Investigational Part A and Part B	Investigational in Part B only if the safety review suggests the use of a lower dose	Active comparator Part B
IMP and NIMP/AxMP.	IMP			
Sourcing	Provided centrally by the sponsor			
Packaging and Labeling	OXU-001 (DEXAspheres®) and Oxulumis® will be provided separately in sealed packages cross-labeled for their intended use together. Each package will be labeled per country requirement.			Ozurdex® and applicator will be provided packaged together in the manufacturer's sealed package bearing the approved label for each country.
Current Name(s) or Alias(es)	OXU-001, DEXAspheres®/ Dexamethasone microspheres administered using Oxulumis®			Ozurdex®, dexamethasone implant

Table 9 Treatment Arms in Part A

Arm Title	Arm A1	Arm A2
Associated Intervention Labels	OXU-001 Mid Dose	OXU-001 High Dose
Arm Type	Experimental	Experimental
Description	Subjects will receive a single administration of suprachoroidal sustained-release **OXU-001 Mid Dose (1.5 mg)** using the Oxulumis® during the baseline visit. Subjects will be observed for the need for follow-on therapy based on prespecified criteria for up to 52 weeks after treatment completion.	Subjects will receive a single administration of suprachoroidal sustained-release **OXU-001 High Dose (3.0 mg)** using the Oxulumis® during the baseline visit. Subjects will be observed for the need for follow-on therapy based on prespecified criteria for up to 52 weeks after treatment completion.

Table 10 Treatment Arms in Part B

Arm Title	Arm B1	Arm B2	Arm B3
Associated Intervention Labels	OXU-001 Mid Dose	OXU-001 High Dose or OXU-001 Low Dose, if suggested by Part A Safety Review	Ozurdex®
Arm Type	Experimental		Active comparator
Description	Subjects will receive a single administration of suprachoroidal sustained-release OXU-001 Mid Dose (1.5 mg) using Oxulumis® during the baseline visit. Subjects will be observed for the need for follow-on therapy based on prespecified criteria for up to 52 weeks after treatment completion.	Subjects will receive a single administration of suprachoroidal sustained-release OXU-001 High Dose (3.0 mg), or Low Dose (0.75 mg), if indicated from Part A, using Oxulumis® during the baseline visit. Subjects will be observed for the need for follow-on therapy based on prespecified criteria for up to 52 weeks after treatment completion.	Subjects will receive a single administration of Ozurdex® Dexamethasone implant (0.7 mg) during the baseline visit. Subjects will be observed for the need for follow-on therapy based on prespecified criteria for up to 52 weeks after treatment completion.

6.1 OXU-001 – DEXAspheres Administered with the Oxulumis®

OXU-001 is an ophthalmic sustained-release dexamethasone acetate microsphere formulation (DEXAspheres®), which is intended for suprachoroidal administration using the Oxulumis® Ophthalmic Administration Device.

OXU-001 is classified as a medicinal product regulated in the US under 21 CFR 4 as a combination product as defined in 21 CFR 3.2 (e). In the EU, OXU-001 is regulated under Directive 2001/83/EC as a combination product, which includes the drug and the administration device.

To fulfill the GSPR requirements of the EU MDR Annex I for the medical device component, the objectives for evaluating the device safety and performance are separately outlined in the latest version of the Oxulumis® Clinical Evaluation Plan (CEP) Version OXUCT-102.

6.1.1 Dexamethasone Acetate Microspheres (DEXAspheres®)

The OXU-001 drug product is a suspension of polymer/drug microspheres containing dexamethasone acetate (DMA) in an excipient formulation, which is supplied as a sterile, lyophilized product requiring reconstitution just prior to administration. [redacted]

Subjects enrolled in the clinical trial will receive a standard volumetric dose of OXU-001 of 60 µl for the 3.0mg, and the 1.5mg dose, or 30µl for the 0.75mg dose. The drug content for the respective dose levels will be varied through the microsphere concentration from the lyophilized formulation to achieve the 3.0mg, 1.5mg, or 0.75mg OXU-001 study treatment (for a detailed description of reconstitution and drug handling see further information in the OXUCT-102 pharmacy manual). The sustained-release OXU-001 drug product is currently not approved in any country and therefore, is an investigational drug/medicinal product.

6.1.2 Oxulumis® Suprachoroidal Ophthalmic Administration Device

The Oxulumis® Ophthalmic Administration Device will be used to administer OXU-001 to the suprachoroidal space via illuminated microcatheterization.

In total for the ophthalmic administration procedure to the suprachoroidal space, the following three medical devices will be used in this clinical trial.

1. Oxulumis® investigational ophthalmic administration device (non-CE marked)

2. Merit Medical Luer syringe, 250µl (CE-marked)
3. Nova Eye Medical iLumin™ Fiber optic Illuminator (CE-marked)

6.1.2.1 Device Manufacturing Process

[redacted]

The CMO and all subcontractors are ISO 13485 certified. There are no special processes used in the manufacture of the Oxulumis® device. All processes have a history of use in the manufacture of medical devices.

The device components are received, quarantined, and inspected to meet their respective specifications. Released components are assigned quality control identifications and placed into inventory for production. Refer to the Oxulumis® Instructions for Use (Version: OXUCT-102) for device assembly and OXU-001 administration procedures.

6.1.2.2 Intended Performance and Contraindications

The Oxulumis® device is intended for the administration of therapeutic modalities, *e.g.,* drugs to the suprachoroidal space of an eye for the treatment of diseases and conditions of the posterior segment and uveal tract of the eye.

The device is intended for use only by certified medical practitioners trained in retinal disease management. These specialized physicians should be adept in intraocular drug administration and in the use of manual ophthalmic instruments. The use setting is similar to the setting for IVT injections, which may vary between geographies and includes procedure, operating rooms, or retinal physician's clinics. Only in subjects where the procedural ConjIncision Variant is performed, a treatment setting in a surgically equipped procedure /operating room is needed. The opening and closure of the conjunctiva/tenons to support the Oxulumis procedure is a small, routine procedure and will be performed in line with local surgical practice.

Contraindications for the administration of treatments with the Oxulumis® device are reflected in the exclusion criteria of this trial (see Section 5.2, *e.g.,* exclusion criteria 4 -12) and include but are not limited to ocular surface diseases with significant conjunctival edema and/or inflammation, active ocular or periocular infections, scleral ectasia, ocular hypotony, or structural abnormalities like choroidal coloboma, and chorioretinal anastomosis.

The materials used in the Oxulumis® were selected for appropriate mechanical properties, optical properties, and biocompatibility of the tissue and fluid contact components. The tissue and drug fluid pathway contacting portions of the Oxulumis® have been tested to ISO 10993 for biocompatibility assurance, however, subject-specific sensitivity may occur to the following tissue and drug fluid pathway contacting components of the device: [redacted]

6.1.2.3 Device Description

The Oxulumis® (Figure 3) is a sterile, manually operated, minimally invasive, single-use device designed to deploy a therapeutic drug delivery-guiding illuminated ophthalmic microcatheter into the suprachoroidal space to administer therapeutic modalities, including drugs. The illumination confirms that the microcatheter is deployed correctly, prior to administration of the therapeutic medicinal product. The device consists of a 27-gauge needle containing a microcatheter. The needle is inserted into the sclera in the region of the pars plana, at an acute angle to the sclera, while aiming posteriorly. The trigger is activated after the needle tip has fully entered the sclera; the needle is then advanced further until the microcatheter automatically deploys into the suprachoroidal space. After the microcatheter deploys, the therapeutic drug is manually administered through the microcatheter to the suprachoroidal space, using a syringe attached to the drug line of the Oxulumis® device. The therapeutic drug should only be administered after visual confirmation that the microcatheter was successfully deployed in the suprachoroidal space. This visual confirmation is enabled by the illumination of the microcatheter.

The Oxulumis® is comprised of the following components (Figure 4):

- The Oxulumis® device body consists of two subassemblies, the Microcatheter Hub subassembly and the Main Shaft subassembly; a protective cap, trigger, speed adjustment knob, and speed control activation pin are part of the device body.
- A flexible, illuminated microcatheter with a distal soft tip configured for suprachoroidal deployment.
- A fiber optic cable with a connector that attaches to a remote light source (Nova Eye Medical iLumin™ Fiber optic Illuminator) for illumination of the microcatheter.

- A microcatheter fluid line that terminates in a low dead space Luer connector for attachment to the drug product syringe.
- An optional sterile, single-use, disposable syringe stop, is provided in a separate peel pouch in the Oxulumis® package. The disposable syringe stop will not be utilized as a part of this clinical trial.

The following non-investigational medical devices are required for the drug administration with the Oxulumis®:

1. Merit Medical Luer syringe, 250µl (510k in US; CE-marked in EU)
2. Nova Eye Medical iLumin™ Fiber optic Illuminator (510k in US; CE-marked in EU)

The Oxulumis® device is packaged in a pouch. The pouch is sealed to create a sterile barrier. The Oxulumis® device is sterilized via e-beam irradiation by a third-party vendor. The pouched product is labeled and placed into a labeled single product box. With the product box, an IFU (Version: OXUCT-102) is provided. The language requirement of each country

will be met before distribution in that country. This product will be provided to medical professionals only.

Labels for the Oxulumis® device include outer box labels, a pouch label, and the IFU (Version: OXUCT-102).

6.1.2.4 Instructions for Installation and Use

Instructions for use of Oxulumis® are provided in the IFU (Version: OXUCT-102).

6.1.2.5 Summary of Necessary Training and Experience

The Oxulumis® device is intended for use only by certified medical practitioners trained in retinal disease management. These specialized physicians should be adept in intraocular drug administration and in the use of manual ophthalmic instruments. The sponsor or designees will perform a training on the device procedures before study investigators use the Oxulumis® device in this clinical trial.

6.1.2.6 Oxulumis® Accountability

The investigational devices will not be distributed to the investigation site until all agreements between the investigator and the sponsor are finalized and IRB/IEC approval has been obtained.

All investigational devices shall be kept in a secure place under appropriate storage conditions.

Use of investigational devices will be logged in a separate accountability form stored in the Investigator Site File and be reviewed at each monitoring visit.

The investigational devices may only be used in this clinical trial and according to the protocol. The unmasked investigator or an unmasked authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational devices.

Unused products are accounted for and returned to the Sponsor or their designee for destruction or are destroyed locally upon agreement with and approval from the sponsor or their designee.

6.2 Ozurdex®

Ozurdex® is an intravitreal implant containing 0.7mg dexamethasone in the Novadur® solid polymer sustained-release biodegradable drug delivery system. Ozurdex® is preloaded into a single-use, DDS® applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The Novadur® system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The PLGA matrix slowly degrades to lactic acid and glycolic acid. Ozurdex via IVT delivery with its applicator is US FDA-approved for the treatment of *i*) macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), *ii*) non-infectious uveitis affecting the posterior segment of the eye, and *iii*) DME in patients. In the EU, Ozurdex is approved for *i*) visual impairment due to DME who are pseudophakic or that are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, *ii*) macular edema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO), and *iii*) inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

For this clinical trial, Ozurdex® will be administered intravitreally according to its approved route and methods of administration. No other form of administration or procedural variant is allowed.

6.3 Lifestyle Considerations

No special lifestyle considerations or restrictions are required for participation in this clinical trial.

6.4 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical trial is not subsequently enrolled in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Subjects, who do not meet eligibility criteria at the initial screening visit but based on the investigator's judgement are likely to meet all eligibility criteria within the screening window of up to 30 days (*e.g.,* if arterial hypertension is above protocol-defined thresholds at the

initial screening visit), can be re-assessed within the screening window and enrolled if eligibility criteria are subsequently met.

Individuals who do not meet the criteria for participation in this clinical trial (screen failure) may be rescreened once after failing the initial screening. The rescreening can occur at any time after the reason for screen failure is addressed. Rescreened subjects should be assigned a new subject number, sign a new ICF for the rescreening event, and will need to receive a complete a new screening visit.

7 Study Intervention(s) and Concomitant Therapies

7.1 Drug Preparation, Handling Storage, and Accountability

Only subjects enrolled in this clinical trial may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or delegate (*e.g.*, the pharmacy) are responsible for study intervention accountability, reconciliation, and record maintenance (*i.e.,* receipt, reconciliation, and final disposition records).

Unused products are accounted for and returned to the Sponsor or their designee for destruction or destroyed locally upon agreement with and approval from the sponsor or their designee.

7.1.1 OXU-001

OXU-001 is described in Section 6.1. Refer to the OXUCT-102 Pharmacy Manual for detailed instructions on storage, preparation, handling, administration, accountability, and destruction.

7.1.1.1 Packaging and Labeling

OXU-001 is provided [redacted] in a single-dose, 2 mL vial for reconstitution with sterile Water for Injection (WFI). The OXU-001 drug product will be reconstituted to provide two dose levels as either a DMA

25mg/ml (1.5mg/60µl or 0.75mg/30µl, mid-dose and low dose DMA respectively) requiring reconstitution with 1 mL of WFI or a DMA 50mg/ml concentration (3mg/60µl) requiring reconstitution with 0.5 mL of WFI. The OXU-001 labeling complies with local regulations for the labeling of an investigational drug/medicinal product (for a detailed description of reconstitution and drug handling see further information in the OXUCT-102 pharmacy manual).

7.1.1.2 Storage

After manufacturing, OXU-001 is stored by a Good Manufacturing Practice (GMP) storage facility and shipped on dry ice for receipt by the respective clinical site prior to a subject's scheduled administration date. Upon receipt at the clinical site, OXU-001 shall be stored frozen at -20°C (-4° F) with a temperature of the storage location controlled to ±10° entered into inventory and managed according to pharmacy standard operating procedures or comparable until reconstituted and dispensed for subject administration.

7.1.1.3 Preparation

Reconstitution of OXU-001 shall be performed by qualified clinical personnel in accordance with the OXUCT-102 Pharmacy Manual based on the prescribed dosing concentration for the subject. Reconstitution of the lyophilized OXU-001 drug product shall be performed using standard aseptic and sterile techniques. If a vial is observed to be damaged and/or leaking, notify the investigator and sponsor, and do not dispense the OXU-001 drug product for administration to the subject.

7.1.1.4 Administration

The suprachoroidal injection procedure shall be carried out under controlled aseptic conditions as established for forms of intraocular drug therapies, *e.g.*, intravitreal drug administration and in case of the OXU-001 ConjIncision Variant with an incision of the conjunctiva/tenons only to administer OXU-001. Adequate anesthesia (topical or injection) and a broad-spectrum microbicide (*e.g.*, polyvidone-iodine, or chlorhexidine) are required to be applied to the periocular skin, eyelid, and ocular surface prior to the administration procedure.

OXU-001 shall be administered suprachoroidally using the Oxulumis® in accordance with the Oxulumis® IFU (Version OXUCT-102). OXU-001 shall be administered only by clinical trial

personnel who have received formal training from the sponsor (or designee) on the preparation and use of the Oxulumis device.

Following the suprachoroidal injection of OXU-001, monitor the subject for elevation in IOP for 60 min and for endophthalmitis in the visits following drug administration, *i.e.,* Day 1 and Day 7. Additionally, check for evidence of drug delivery to the wrong ocular compartment (*e.g.*, the therapeutic agent in the vitreous humor or subconjunctival) after the administration. Subjects should be instructed to report any symptoms suggestive of endophthalmitis without delay.

OXU-001 administered with the Oxulumis® is intended for one-time use and administration to a single eye only. Dispose of the drug vial and device as medical waste immediately after use.

7.1.2 Ozurdex®

Refer to and administer Ozurdex® according to the full prescribing product insert accompanying the drug.

7.2 Assignment to Study Intervention

7.2.1 Part A

Part A will include treatment-naïve or DME subjects previously treated in the study eye with IVT anti-VEGF (n=18). No minimum number of treatment-naïve subjects is fixed in Part A,. Subjects will be randomized using a 1:1 ratio, to receive either the mid-dose OXU-001 (treatment arm A1, n=9) or the high dose OXU-001 (treatment arm A2, n=9) according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). If subjects have been randomized but the study treatment cannot be administered, these subjects will be replaced to reach approximately 18 treated subjects in Part A. Enrollment of previously treated and treatment-naïve subjects will be competitive until the targeted subject number is reached.

7.2.2 Part B

Approximately 110 subjects will be randomized in a 2:2:1 ratio to receive either OXU-001 Dose 1 (mid-dose, 1.5mg, Arm B1), OXU-001 Dose 2 (dose level of OXU-001 either 3.0mg, or 0.75mg, depending on Week 6 safety review, Arm B2), or IVT Ozurdex® (0.7mg)

(Arm B3) according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Subjects will be randomized after the treating physician has made a decision on the location of the 1st treatment session (clinic, procedure, or operating room) following an expert judgement on the expected procedural complexity (for guidance on the complexity assessment see Section 12.4). No sham procedure will be performed for the conjunctival/tenon incision in case of randomization to the Ozurdex® treatment arm.

In Part B, both treatment-naïve and anti-VEGF previously treated subjects (in the study eye) will be enrolled. Enrollment of previously treated and treatment-naïve subjects will be competitive, with at least 55 subjects being treatment-naïve in the study eye. Enrollment of subjects that are anti-VEGF previously treated in the study eye will stop once 55 subjects with previous anti-VEGF treatment in the study eye are randomized to allow reaching the foreseen number of treatment-naïve subjects. Subjects will be stratified based on their anti-VEGF treatment history (see Section 4.1.1). If subjects have been randomized but the study treatment cannot be administered, these subjects will be replaced to reach approximately 110 treated subjects in Part B.

7.3 Masking

Part A: This part of the trial has an open-label, single-dose design with 1:1 randomization to one of two treatment arms. All subjects will receive investigational treatment.

Part B: This Part of the trial has a masked, active comparator, single-dose design with a 2:2:1 randomization to one of three treatment arms. In this part of the trial, the following roles are applied to support the scientific validity of the trial.

A. Roles **fully masked** to treatment assignment.

1. Subjects:

   Subjects will be fully masked to the study intervention. Assignment to treatment arms will only be disclosed after the end of the trial (after all subjects have completed the Week 52 visit). To limit the treatment burden for subjects, no sham treatment for the non-assigned treatment modality (IVT implant or suprachoroidal administration) will be performed. This is considered acceptable as regardless of the randomized treatment, subjects had never received any of the potential treatments before in the study eye per eligibility criteria. The unmasked treatment team is

expected to cover the study treatment and ancillary materials until the subject is positioned in the treatment chair and then again after completion of the procedure when the subject leaves the treatment room.

For masking purposes, the choice of the procedural setting (*i.e.*, the selection of the treatment alternative shown see Table 4) will be made before randomization, and it will not be changed even in case a subject in Part B is randomized to receive Ozurdex®.

The procedure alternative No.2 of directly moving to an OXU-0001 ConjIncision Procedural Variant in an surgically equipped procedure or operating room (see Table 4) will not carry an increased risk for a subjects getting hints to their randomization to the Ozurdex® or one of the OXU-001 treatment arms, as there will be only one study treatment in this trial.

In case of non-completion of the OXU-001 Standard Procedural variant (*i.e.,* Alternative No. 3), rescheduling of study treatment as in a surgically equipped procedure room or an operating room allowing the OXU-0001 ConjIncision Procedural Variant may provide hints for the subject in respect to the assignment, but still the randomized OXU-001 dose would remain completely masked. Subgroup analyses for the three different scheduling options (No.1-No3) will be performed.

2. Fully Masked site staff assessing main endpoints:
The site staff who assesses the NEI-VFQ 25, the Subject Experience Assessment and best corrected visual acuity (ETDRS) will be fully masked. These individuals will have no access to other study assessments or trial data nor to the eCRF and must not be informed rescheduling of the study treatment . Outcomes of these assessments will be entered into the eCRF by other site staff.

3. Fully Masked CRC Readers:
The fully masked readers at the CRC will only have access to SD-OCTs for assessing the CST. Other trial imaging, *e.g.*, CFP, 4 Wide-Field IR Plus images or peripheral OCT may provide hints to treatment assignment and will be analyzed separately with measures in place to secure masking, as detailed in Section B below).

B. Roles **masked to treatment assignment** but with risk of inadvertently getting hints to treatment assignment.

As the IVT Ozurdex implant or the suprachoroidal drug bleb of OXU-001 may be visualized during some of the study assessments, *e.g.*, indirect ophthalmoscopy, or peripheral OCT imaging, it cannot be excluded, that the following roles may get hints to the individually assigned study intervention. However, as these roles have no access to the treatment assignment of an individual subject, they will remain fully masked to the dose level assignment in the OXU-001 arms.

1. Masked Site Staff performing study assessments, including ophthalmic assessments:
   Site staff involved in performing ophthalmic assessments and imaging reviews for safety purposes, may see hints to the study intervention by detecting the IVT Ozurdex implant or the suprachoroidal drug bleb on ocular imaging.

   If members of these evaluation teams would inadvertently get information on the treatment assignment, this information must not be exchanged with other colleagues. This also includes the information about a need for a 2nd treatment session, in case the first treatment session in an in-clinic setting cannot be completed.

   Potentially unmasking information, which is pivotal for managing safety events, is recommended to be shared with the unmasked study team. The unmasked study team would then continue the management of potential safety events or complications.

2. Staff at CRC involved in assessment of imaging other than SD-OCT:
   This part of the CRC staff will be masked to the treatment assignment but may inadvertently get hints on treatment assignment (Ozurdex or OXU-001) from the acquired imaging.

C. Roles masked to OXU-001 dose level but not to treatment assignment.

1. Imaging technician at the investigational sites:
   Specifically for anterior segment imaging, and for peripheral imaging of the OXU-001 bleb injection, the imaging technicians will have to receive information on the region of OXU-001/Oxulumis insertion by the unmasked treating team. As such, the imaging technicians will be unmasked to the treatment (Ozurdex or OXU-001) but not to the OXU-001 dose level. This role must not talk to other members of the masked evaluation team or to fully masked roles about the treatment assignment.

D. Roles unmasked Site to treatment assignment including OXU-001 dose level.

1. IP handling and preparation personnel:
   The team involved in preparing the treatment (*e.g.*, drug reconstitution) and preparation for injection.

2. Treating physician and supporting roles:
   The treating retinal physician and supporting team assisting in the treatment administration and post-treatment follow-up. Activities include drug administration, post-intervention safety monitoring for 60 minutes, the completion of the Physician's assessment of the administration procedure and deciding on and applying follow-on treatment (by the retinal physician).

3. Sponsor team or delegates tasked with on-site or remote device training and procedure support:
   Sponsor employees or delegate personnel will be on-site for all study interventions. This group needs to know all information about the planned treatment to fully support the treating physician (including the OXU-001 dose level).

Sponsor, CRO, and other roles with respect to masking will be detailed in the Data Integrity/Masking Plan. Site staff, CRO, other vendors, and Sponsor staff will be trained on their roles prior to the start of randomization of subjects.

The IVRS/IWRS will be programmed with mask-breaking instructions. In case of an emergency, the investigator or external physicians, who may request unmasking in emergency situations have the sole responsibility for determining if unmasking of a subjects' intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unmasking is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unmasking a subject's intervention assignment unless this could delay emergency treatment for the subject. If a subject's intervention assignment is unmasked, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unmasking must be recorded in the source documentation and case report form (CRF), as applicable.

7.4 Study Intervention Compliance

The investigator (unmasked investigator in Part B) will administer the study intervention. The date and time of each treatment session and finally of the dose administered will be recorded

in the source documents. The study intervention and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

7.5 Dose Modification, Follow-on Treatment, and Treatment of Diabetic Retinopathy Complications

7.5.1 Dose Level Confirmation in Part B Treatment Arm B2

The randomized open-label Part A of this trial will treat 18 subjects with suprachoroidal sustained-release OXU-001. Subjects will be randomized to receive either mid-dose (Arm A1 1.5mg/60µl) or high dose (Arm A2 3.0mg/60µl) OXU-001. Short-term outcomes with a focus on safety in Part A will be evaluated once all 18 treated subjects have completed the Week 6 visit.

The focus of the evaluation will be on the occurrence of ocular AEs, AESIs, and SAEs. As the onset of clinically meaningful increases in IOP is usually seen within up to Week 6 after ocular administration of steroids, a specific focus will be on IOP increase per dose group. Categories of evaluation will include but are not limited to:

1. Subjects with at least 10mmHg increase after treatment administration.
2. Subjects with IOP of at least 30mmHg.

The evaluation will be discussed with the DMC. Based on the DMC recommendation, the sponsor will then, for the dose level in treatment arm B2, either:

1. Confirm dose level to be 3.0mg DMA administered in 60µl, or
2. Assign the lower dose level of 0.75mg DMA administered in 30µl

All other design elements of Part B will not be impacted.

7.5.2 Follow-on Treatment

Subjects will be followed with regular visits to assess the safety and the course of visual and anatomic outcomes. Starting at the Week 12 visit, subjects will be evaluated against prespecified criteria indicating the need for follow-up treatment (*i.e.,* indicating the end of the current treatment interval). Criteria are as follows:

1. At least 75µm thickening in CST on SD-OCT compared to best CST value since the baseline visit, Visit 2, Day 0; or

2. A decrease in BCVA of > 10 letters (ETDRS) from the best achieved BCVA since the baseline visit, Visit 2, Day 0, that, in the opinion of the investigator, is due to the worsening of DME.

For subjects showing no reduction of edema or no improvement of BCVA after Visit 2, Day 0, the baseline visit will be considered the best CST or BCVA value.

The CST values to inform the evaluation of the follow-on treatment will be derived from the SD-OCT outputs generated at the site. In Part B, the masked (evaluation) team will review CST and BCVA and will inform the unmasked treating investigator. The unmasked treating investigator will then select the appropriate follow-on treatment.

If according to the assessment of the above criteria (by a masked investigator in Part B), the need for administration of follow-on treatment is indicated, subjects will be managed according to local standard of care for the rest of the study duration. Standard of care treatments may include IVT anti-VEGF, ocular IVT steroids, or other non-investigational treatments. Treatment with a port delivery system during participation in this trial is forbidden due to the complexity of the surgical administration procedure and post administration follow-up and care.

In Part B, when follow-on treatment criteria are met based on masked assessment, the unmasked investigator will determine the kind of follow-on treatment to be administered (*e.g.,* IVT anti-VEGF treatment, IVT steroid, or other) considering the treatment history and the response to the study treatment received. For this purpose, the outcome of the BCVA and CST assessments are shared with the unmasked investigator tasked with the treatment of subjects.

After receiving the first follow-on treatment in the study eye, subjects will continue on the regular visit schedule through the End-of-Study visit at Week 52. Patients will not be masked to the assigned follow-on treatment.

7.5.3 Treatment of Diabetic Retinopathy Progression and Complications

A subject may receive treatment at any time if they experience diabetic retinopathy progression that requires urgent management (*i.e.,* progression to high-risk PDR or worse) or

management of diabetic retinopathy complications (vitreous hemorrhage, neovascular glaucoma, iris neovascularization, etc.).

As per exclusion criteria No.1, No.5, and No. 6 subjects with active PDR, or a foreseeable need for treatment of DR complications other than DME are not eligible for participation in this trial. Such DR complications should be managed before any consideration of inclusion in the OXUCT-102 trial. A subject's potential eligibility could be checked later after the time intervals laid out for treatments in the exclusion criteria (see Section 5.2).

Treatment options for DR complications for enrolled subjects generally include panretinal photocoagulation (PRP) for PDR, IVT anti-VEGF, and/or pars plana vitrectomy. Treatment options are best evaluated and decided by an unmasked retinal physician taking into consideration the study intervention administered. After receiving the treatment for complications in the study eye, subjects will continue on the regular visit schedule through the End-of-Study visit at Week 52, and may also receive follow-on treatment, if they met the respective criteria (see Section 7.5.2).

7.6 Continued Access to Study Intervention after the End of the Study

Continued access to treatment with OXU-001 will not be available after the completion of the study. Ozurdex® is an approved and marketed product and can be accessed by the subject/PI independently.

7.7 Treatment of Overdose

The study includes a single treatment with study intervention by the PI or delegate. The risk of overdose, defined for OXU-001 as a dose higher than the highest dose defined in the respective part of this trial, from receiving study intervention is very low. In the unlikely case of a higher dose of DEXAspheres® being administered, subjects will be monitored closely for the emergence of side effects such as increased IOP and cataract formation. Any emerging side effects will be managed based on the clinical discretion of the investigator and consultation with the sponsor (Oxular Medical Monitor).

7.8 Prior and Concomitant Therapy

For how to review concomitant medication, please see Section 9.2.6.

Intranasal, inhaled, and topical (extra-ocular) glucocorticoid medications or stable systemic steroids are allowed. For further guidance see also Section 7.8.1.

The use of ocular topical steroids during study participation should be limited to avoid an impact on study outcomes. In case of the intended use of topical ocular steroids, the Medical Monitor should be consulted prior to the start of the medication, if possible.

Generally, the medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8.1 Prohibited Medications and/or Treatments

Subjects should not receive any medications (approved or investigational) for their DME in the study eye other than the study drug as specified in Table 11 for the duration of participation in the study. This includes DME medications administered locally (*e.g.*, IVT, suprachoroidal, topical, juxtascleral, or periorbital routes).
Table 11 lists treatments:

- that are considered exclusionary and/or prohibited dependent on the subgroup (treatment-naïve or previously treated subjects)
- that qualify as follow-on treatment per subgroup as described in Section 7.5.2, as well as allowed treatment for the study eye or fellow eye.

Follow-on treatment of the study eye or newly started treatment in the fellow eye with a port delivery system is prohibited during participation in this trial due to the overall added complexity in the surgical administration procedure and post administration follow-up and care.

Table 11 Prohibited Medications and/or Treatments

	Study Eye **Previously treated**		**Study Eye Treatment -Naive**		Fellow Eye	
Therapy	**Exclusionary** interval before screening	Qualifies as **Follow-on** Treatment	**Forbidden** interval before screening	Qualifies as **Follow-on** Treatment	Part A **Forbidden** interval before screening	Part B **Forbidden** interval before screening
Ranibizumab or bevacizumab (IVT)	≤ 4 weeks	Yes	At any time	Yes	no restriction, allowed	no restriction, allowed
Aflibercept	≤ 8 weeks	Yes	At any time	Yes	no restriction, allowed	no restriction, allowed
Faricimab or brolucizumab	≤ 12 weeks	Yes	At any time	Yes	no restriction, allowed	no restriction, allowed
IVT Port Delivery System	At any time	Not allowed	At any time	Not allowed	Not allowed	Not allowed
Intra- or periocular/subtenon injection of triamcinolone acetonide	At any time	Yes	At any time	Yes	≤ 12 weeks	no restriction, allowed
IVT dexamethasone implant (Ozurdex®)	At any time	Yes	At any time	Yes	≤ 24 weeks	no restriction, allowed
IVT fluocinolone implant	At any time	Yes	At any time	Yes	At any time	no restriction, allowed

	Study Eye **Previously treated**		**Study Eye Treatment -Naive**		Fellow Eye	
Therapy	**Exclusionary** interval before screening	Qualifies as **Follow-on** Treatment	**Forbidden** interval before screening	Qualifies as **Follow-on** Treatment	Part A **Forbidden** interval before screening	Part B **Forbidden** interval before screening
Suprachoroidal Steroids, *e.g.*, Xipere™	At any time	not allowed	At any time	not allowed	≤ 12 weeks	At any time
Vitrectomy	≤ 12 weeks	Yes	≤ 12 weeks	Yes	no restriction, allowed	no restriction, allowed
Focal (Macular) Laser Photocoagulation	≤ 16 weeks	Yes	≤ 16 weeks	Yes	no restriction, allowed	no restriction, allowed
Panretinal Laser Photocoagulation (PRP)	≤ 16 weeks	Yes	≤ 16 weeks	Yes	no restriction, allowed	no restriction, allowed

	Study Eye **Previously treated**		**Study Eye Treatment -Naive**		Fellow Eye	
Therapy	**Exclusionary** interval before screening	Qualifies as **Follow-on** Treatment	**Forbidden** interval before screening	Qualifies as **Follow-on** Treatment	Part A **Forbidden** interval before screening	Part B **Forbidden** interval before screening
Investigational Therapies for ME (agents with anti-VEGF activity, or combined pharmacologic activity, gene therapies, cell therapies, or any other therapeutic medicinal product)	At any time	Not allowed	At any time	Not allowed	At any time	At any time
Anti-Glaucoma Drugs (max of 2 active components), if stable		Yes			no restriction, allowed	no restriction, allowed
Ocriplasmin (Jetrea)	At any time	n.a.	At any time	n.a.	no restriction, allowed	no restriction, allowed
Prior systemic therapy with anti-VEGFs	At any time	n.a.	At any time	n.a.	At any time	At any time

7.8.2 Concomitant Medications

For previous and concomitant medications, the original terms will be recorded on the Study Subjects' eCRF by the investigator. Previous and concomitant medications will be coded according to WHO-DD and verbatim original terms recorded on the eCRF will be presented as data listings.

7.9 Criteria for Temporarily Delaying Part(s) of the Study

After the review of the six weeks safety data of 18 subjects from Part A, and in case of unclear assessment of the benefit/risk balance of the treatment with OXU-001, the Sponsor may decide to delay the initiation of Part B until longer-term data is available for review and assessment. The decision to delay, terminate and re-initiate the trial will be made by the sponsor after consultation with the DMC.

The trial as a whole or parts of the study may be delayed in case of the development of events or situations that may affect the safety of the subjects, investigators, or staff members and/or integrity of the study (*e.g.*, extreme lockdown measures associated with COVID-19, natural disasters, and other force majeure events).

7.9.1 COVID-19 Related Precautions

Appropriate precautions to limit the spread of COVID-19, in accordance with the investigational site's standard procedures, should be taken.

The FDA guidance on the management of clinical trials during the COVID-19 pandemic (FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, August 2021) will be implemented in this study as applicable. A more limited impact on treatment is expected as this clinical trial will only administer a single treatment with study medication and standard-of-care therapy thereafter. The following measures will be taken:

1. Assessment of the feasibility of starting the clinical trial at the chosen sites in close collaboration with the sites and factoring in potential risk with repeat travel to the sites for study visits.

2. As this clinical trial was designed during the ongoing pandemic, no design changes related to the COVID-19 pandemic are expected, but a periodic risk assessment may result in adaptations necessitating an amendment.
3. If restrictions would not allow the travel of treated subjects to the investigation site, safety follow-ups could be performed by a local ophthalmologist.

8 Discontinuation of Study Intervention and Subject Disposition Discontinuation/ Withdrawal

8.1 Discontinuation of Study Intervention

Subjects will receive a single intervention at the baseline visit of this trial. Discontinuation of study intervention is therefore not applicable. See Section 8.2 below for discontinuation in case of inability to administer the study medication.

8.2 Subject Discontinuation/ Withdrawal from the Study

Subjects should remain in the study until the final visit (Week 52); however, a subject's participation in the study may be discontinued at any time. Should this occur, the reason for discontinuation must be documented in the withdrawal form. Reasons for discontinuation include the inability to administer trial medication with the Oxulumis® device despite usage of all alternative options described for V2 activities.

Subjects who decide to discontinue study participation for any reason will undergo all end of study visit assessments and procedures and the visit will be considered an end of study visit. If for any reason the study treatment cannot be administered, an extra end of study visit is not necessary and only activities for Visit 2 need to be completed as applicable.

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize the subject's future medical care or relationship with the investigator.

Subjects will be asked to specify the reason for the termination but have the right not to answer. In this case, only potentially ongoing adverse events or adverse device effects will be followed-up, if the subject agrees.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale.

The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until the completion of the study.

Reasons for a subject's withdrawal include, but are not limited to:

1. Subject refuses to continue participating in the study
2. Subject's non-compliance
3. Subject's participation is terminated by the PI or investigator, although the subject consented since participation is no longer medically appropriate
4. Subject is 'lost to follow up': if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site (see Section 8.3).

Note: If a subject misses one or more of the scheduled follow-up visits (inclusive of the assigned visit windows), this will be considered a missed visit. The subject may therefore still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal on a Withdrawal CRF. When the subject's withdrawal from the study is due to an adverse event the subject will be followed until the resolution of that adverse event or determination that the subject's condition is stable for a maximum duration of six (6) months. The status of the subject's condition should be documented at the time of withdrawal.

8.3 Lost to Follow-Up

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

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

1. The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

2. Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 2 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
3. Should the subject continue to be unreachable, the subject will be considered lost to follow-up.

9 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoAs in Section 1.3. Protocol waivers or exemptions are not allowed.

If not specifically indicated, descriptions apply for Parts A and B of this clinical trial.

Adherence to the study design requirements, including those specified in the SoAs, is essential and required for the trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Screening assessments can be performed on different days within a screening period of up to 30 days, if operationally required. Only for the visit window of the Screening Visit, an extension of the visit window to 37 days can be approved by the Oxular Medical Monitor based on an individual request of the investigator stating important medical and/or organizational reasons. Also, selected assessments like blood pressure measurements may be repeated on a different visit day after the initial screening, to meet eligibility criteria. Such repeat assessments need to be medically plausible, *e.g.*, if a subject has forgotten to take antihypertensive medication on the day of the initial screening visit, or if the BCVA assessment shows values just outside the eligibility corridor and a slight further decrease in BCVA during the screening period would be expected. If duplicate assessments are required, *e.g.*, for BCVA, these duplicates have to be performed on the same screening visit day, or in case they would need to be repeated, also the repeat measurement would have to be performed in duplicate. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (*e.g.,* SD-OCT imaging, IOP measurement, etc.) and obtained before signing of the ICF may be utilized for

screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoAs.

The following general recommendations apply for the sequence of study assessments:

- The NEI VFQ-25 instrument is recommended to be assessed first on a visit day to avoid bias by outcomes of study assessments (see also Section 9.2.10).
- As some of the assessments, specifically imaging assessments are performed after dilation of the pupil(s), assessment can be grouped in pre-dilation and post-dilation assessments.
    - The following assessments are recommended to be performed before dilation:
        - Vital signs, pregnancy test, BCVA, IOP, slit-lamp biomicroscopy, and anterior segment OCT.
    - The following assessments are recommended to be performed after dilation:
        - Axial length, SD-OCT including 4 Wide-Field IR Plus imaging, peripheral OCT, color fundus photo, safety, and PK lab (PK only in Part A), fluorescein angiography, and dilated ophthalmoscopy.
        - Venipuncture for lab assessments and pre-dosing PK (Part A, Visit 2, Day 0) may be performed after dilation so that the blood sample collection can be combined with the venipuncture needed for the fluorescein angiography.

In the event of a significant study-continuity issue (*e.g.,* caused by a pandemic), alternate strategies for subject visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Access to safety, imaging, or other data that could potentially unmask the study will be limited to unmasked individuals as specified in Section 7.3.

9.1 Evaluations Performed During Investigational Visits

Evaluations will be performed at specific visits as shown in the SoAs in Section 1.3.

9.1.1 Baseline Visit V2 Activities

Activities of the baseline visit need to be adapted based on the setting for the administration of study treatment (in-clinic/procedure room or surgically equipped procedure room/operating room, Alternative Schedule No.1 and No. 2), and the need to switch the setting in case of non-

completion of administration of study treatment in-clinic/procedure room (Alternative Schedule No.3). The three alternatives foreseen in this trial are summarized in Table 3 for Part A and in Table 4 for Part B. As surgical centers may be in different facilities from investigational sites, not all standard assessments for V2 may be possible. Therefore, specific adaptations for V2 in Alternative No.2 and No.3 are made.

The decision and planning for the sequence of V2 activities and the choice of the alternative schedule No.1-No.3 will be based on an expert assessment of the expected complexity of the OXU-001 procedure following the guidance in Section 12.4.

For Part B, the setting for study treatments is determined before the randomization to IVT Ozurdex® or one of two suprachoroidal OXU-001 treatment arms and will for masking purposes also not be changed, if the unmasked team learns about a masked Ozurdex® treatment scheduled for an operating/surgically equipped procedure room.

The date for calculation of visits following Visit 2, Day 0 will be the date of completion of administration of study treatment, *i.e.*, it can be the date of the 2nd session for treatment administration.

9.1.2 Optional Safety Visit Week 6 – Part B

At the discretion of the investigator, an additional visit can be scheduled for subjects participating in Part B at Week 6 +/- 5 days. This visit is recommended if subjects show in the opinion of the investigator a trend for an IOP increase in the prior visits 3 – 5. The optional safety visit has an abbreviated schedule of assessments compared to other regular visits as provided in Section 1.3.

9.1.3 Early Termination Visit

An early termination (ET) visit shall be performed if subjects decide to stop their participation in the study. Subjects are free to withdraw consent at any time during the study without prejudice. Any subject who withdraws consent should be asked about the reason(s) and the presence of any AEs at the time of withdrawn consent. The actual visit schedule will be extended by the assessments foreseen for the end of study (EoS) visit as laid out in Table 1 (Part A) and Table 2 (Part B). For subjects in whom the study treatment could not be administered, an extra EOS/ET visit is not performed.

9.1.4 Unscheduled Visit

All attempts should be made to keep subjects on the study schedule. However, unscheduled visits may be necessary if abnormal findings or AEs occur to evaluate further or repeat testing following abnormal findings, or for any other reason, as warranted.

9.2 Administrative and General/Baseline Procedures

9.2.1 Consent Form Completion

Following Institutional Review Board/ Ethics Committee (IRB/EC) approval and before any investigation-related procedure, potential subjects will be asked to sign a written informed consent form (ICFs). The subjects will be given sufficient time for the information to be read and understood. The subject will be approached and given the chance to ask any questions that have arisen after reading the ICFs. For more information on the informed consent, process see Section 11.1.3.

9.2.2 Demographic Information and Medical History

At the screening visit, information about the subject's demographics, and medical/surgical history, will be obtained.

Demographics variables to be collected are: age, gender, race, and ethnicity (in accordance with the US FDA guidance document (US FDA 2016).

9.2.3 Eligibility Assessment

At the Screening visit, the potential subjects' eligibility will be assessed based on meeting all the inclusion and none of the exclusion criteria. On, or prior to the baseline visit (Visit 2, Day 0), an additional eligibility review is performed upon review of the laboratory results, urine pregnancy test (UPT), and results of the CRC assessment of CST per inclusion criterion, and any change in concomitant medication or medical history since the screening visit, that may render a subject ineligible for participation. BCVA will be assessed at the baseline visit also, but for the eligibility determination only the assessment from the screening visit is relevant.

9.2.4 Assessment of Expected Procedural Complexity

The treating physician (who is an unmasked investigator in Part B) will assess at the screening visit the expected procedural complexity in categories of low, medium, or high. For the guidance document see Section 12.4. If subject characteristics (*e.g.*, enophthalmos, and/or thick, opaque conjunctiva or similar features) suggest an increased complexity for engaging the Oxulumis® insertion needle into the sclera, the OXU-001 ConjIncision Procedural Variant with an incision of the conjunctiva/tenon may be used. This procedural variant is expected to be carried out after local injection anesthesia in an operating or surgically equipped procedure room. Locally established procedural practices for conjunctival/tenon incision and closure will be used at the discretion of the treating physician. Also in Part B, the procedural setting for the Baseline Visit V2 is already planned as part of the Screening Visit activities. For masking purposes, the investigator decision on *e.g.,* performing the study treatment directly in an operating/room will not be reversed in subjects randomized to receive IVT Ozurdex®.

9.2.5 Pregnancy Test

For women of childbearing potential, a negative serum pregnancy test at screening (Visit 1, Day -30 to Day -2) and urine pregnancy test at baseline (Visit 2, Day 0) is required for eligibility. Additional urine pregnancy tests will be performed on Visits 4-18 (Week 52). For the pregnancy test on Visit 3, Day 1, the interval since prior test on Day 0 is considered too short.

9.2.6 Adverse Event and Adverse Device Effect Collection

At every visit, the investigator (or designee) will assess for and record all AEs and ADEs that occur from the time the informed consent is signed until the end of study. More details are within Section 9.4.1.

9.2.7 Concomitant Medication Review

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject receives at the time of enrolment or receives during the study must be recorded at each visit along with:

1. Reason for use
2. Dates of administration including start and stop dates
3. Start and stop dates for changes in medications and changes in dose

4. Dosage information including the route of administration, dose, and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.2.8 Pharmacokinetic Blood Sampling

In Part A, whole blood samples of approximately [5] mL will be collected for measurement of plasma concentrations of study intervention on Visits 1, 2, 3, 4, 5, 11, and 18 (screening, Days 0 [60min after administration of the study treatment], and Day 1, week 1, 4, 24, and 52, respectively) as specified in the SoA of Part A (Table 1). Further details are available in Section 9.6.

9.2.9 Study Intervention

Details on study interventions can be found in Section 6.

9.2.10 NEI VFQ-25

National Eye Institute 25-item visual function questionnaire (NEI VFQ-25) is a commonly used instrument to determine the vision-related quality of life. The NEI-VFQ25 will be assessed at screening, 24, and week 52 visits (Visits 1, 11, and 18, respectively), as specified in the SoAs (Table 1 - Part A and Table 2 - Part B).

The NEI VFQ-25 will be presented in the local language and administered in a quiet setting, preferably before other study procedures are performed by masked site staff in Part B. Depending on the subject's visual acuity and reading ability, either the interviewer or the self-administered NEI VFQ-25 version will be used. For the self-administered version, the subjects will complete the self-administered NEI VFQ 25. For the interviewer version, trained site staff should perform the interview administered NEI VFQ-25 with the subject. The method of administering the questionnaire should remain the same throughout the study. If a subject's vision deteriorates so that they are not able to self-administer the questionnaire at any time after the screening visit, an interview administered questionnaire will be performed instead. More details are provided in the NEI VFQ-25 manual.

9.2.11 Documentation and Assessment of the Administration Procedure

Shortly after the procedure administration on treatment days of the baseline visit V2 and regardless of completion of study treatment, the treating physician (unmasked investigator in

Part B) will document the procedure details and complete the procedure assessment questions (for details see Section 12.3).

If the Oxulumis® procedure is repeated, *i.e.,* if the OXU-001 administration procedure is performed on two treatment days or in 2 separate sessions on one day, the questionnaire will need to be completed twice. If the variant would be switched within one treatment session (*e.g.*, in an operating room with a first non-completed OXU-001 Standard procedural variant directly followed by an OXU-001 ConjIncision Procedural Variant, only one assessment needs to be completed.

9.2.12 Patient Experience Assessment

Details about the subject's experience during and after the procedure will be collected (by masked site staff in Part B). For details see Sections 12.1 and Section 12.2. It is mandatory to give instructions to the subject at the beginning of the interview to only answer the interview questions. This is specifically in part B intended to avoid sharing of potentially unmasking information about the procedure.

The Patient Experience assessment will only be completed after completion of administration of study treatment. Specifically, in V2 activity alternative No.3 (see Table 3 and Table 4), the assessment will only be performed after completion of treatment on the 2nd treatment day of V2.

9.2.13 Disposition of Samples

Any remaining blood, plasma, serum, or urine samples collected for laboratory testing will be destroyed.

9.3 Ocular Assessments

Planned timepoints for all ocular assessments are provided in the SoAs in Section 1.3.

9.3.1 Axial Length Measurement

Axial length measurement will assess the axial dimensions of the eye to support exploratory imaging of the location of the deployment of study drug in equipped sites only. Axial length will be measured at equipped sites at the screening visit in both eyes using a non-contact optical biometry device (*e.g.,* partial coherence interferometry (PCI) using the IOL Master

(Carl Zeiss Meditec AG), LensStar (Haag-Streit, Switzerland), Pentacam AXL (Oculus Optikgeräte GmbH, Germany)).

If sites are not equipped to measure axial length with one of the indicated devices, the axial length could be retrieved from medical reports, *e.g.*, in subjects who have undergone lens replacement surgery in the past. For such values taken from medical history, the date (at least the year) of the measurement has to be recorded.

9.3.2 IOP Measurement

IOP of the study eye will be assessed at every visit using Goldmann applanation tonometry or the Tono-pen™, as specified in the SoAs in Section 1.3. The same method of IOP measurement used at screening must be used throughout the study for an individual subject.

IOP measurement in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3.

After complete or partial treatment administration at the baseline visit, IOP measurement in the study eye must be performed at least twice over the 60 minutes following treatment until normalization. Subjects will only be discharged if the IOP is normal after that follow-up period or if IOP lowering measures have been taken. No IOP monitoring is necessary, neither a complete nor a partial OXU-001 dose has been administered. For specific guidance on scheduling of IOP measurements in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

9.3.3 Slit-Lamp Biomicroscopy

Subjects' anterior ocular structure (including assessment and systematic grading of lens opacities) and ocular adnexa will be examined in the study eye at each study visit using a slit lamp, as specified in the SoA's in Section 1.3. The systematic slit lamp examination will comprise ocular adnexa, ocular surface, aqueous humor and vitreous, iris and pupil, and the lens. Lens opacity assessments will be graded following the scale suggested by the WHO Cataract grading group (Thylefors *et al.*, 2002; The WHO Cataract Grading Group 2002). Grading will comprise the subcategories nuclear cataract, cortical cataract, and posterior subcapsular cataract. Gradings range from grade 0 to grade 9 for each of the categories. Grade 9 means cannot grade. Sites may use a source data sheet to support the lens opacity grading.

Slit-lamp biomicroscopy in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3.

For specific guidance on scheduling of slit-lamp biomicroscopy in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

9.3.4 Dilated Indirect Ophthalmoscopy

Subjects' posterior pole and peripheral retina will be examined by dilated indirect ophthalmoscopy at each study visit in the study eye, as specified in Section 1.3. A post-dose evaluation must be performed after injection.

For specific guidance on scheduling of dilated indirect ophthalmoscopy in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

Dilated indirect ophthalmoscopy in the fellow eye will be performed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3.

9.3.5 Best-Corrected Visual Acuity

Manifest refraction will be conducted prior to the BCVA assessment.

The BCVA assessment will be conducted prior to dilating pupils, using the standard ETDRS protocol at 4 meters with back-illuminated eye charts and before any other ocular procedures/assessments requiring contact with the eye are performed.

BCVA in the study eye will be assessed at all visits by masked site staff in Part B, as specified in the SoAs in Section 1.3. For specific guidance on scheduling of BCVA assessments in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

All BCVA assessments in the study eye need to be performed in duplicate. Both measurements will be entered in the CRF. For eligibility determination at the screening visit, the mean of both BCVA assessments will be calculated, if both ETDRS letters scores do not differ by more than 5 letters. If the difference is greater than 5 letters, the better (higher) ETDRS letter score will be used. Further details on handling duplicate BCVA assessments will be described in the SAP.

Refraction only needs to be performed a single time, if duplicate BCVA assessments are performed sequentially.

BCVA in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3. For BCVA assessments in the fellow eye, only single measurements are needed. BCVA assessment will be performed by a certified visual acuity examiner, who is masked to the study treatment in Part B.

9.3.6 Spectral-Domain Optical Coherence Tomography

Retinal structure and pathological changes will be evaluated at every visit using SD-OCT. SD-OCT images will be captured and transmitted to the CRC via an encrypted secure website. All SD OCTs will be electronically archived at the investigational sites as part of the source documentation.

Acceptable OCT machines are Spectralis (Heidelberg Engineering GmbH) and Cirrus (Carl Zeiss Meditec AG). Other devices need to be approved by the sponsor upon request. The same device should be used for screening, baseline, and the subsequent follow-up assessments for each subject.

SD-OCT will be performed at each visit for the study eye.

For specific guidance on scheduling of SD-OCT assessments in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

For the fellow eye, SD-OCT will be performed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3. Further details are included in the imaging manual including details on 4-Wide-Field Near infrared (IR) Plus imaging at sites equipped with a Heidelberg Spectralis device.

9.3.7 Peripheral Swept-Source OCT or Peripheral Enhanced Depth Imaging (EDI) OCT

The retina, choroid, suprachoroidal space, and sclera over the area of treatment instillation will be assessed using peripheral SS-OCT or peripheral EDI-OCT in the study eye at equipped sites.

At the screening visit, the Week 12, the Week 24, and Week 52/EOS/ET visit, both eyes will be assessed. Study eye will be imaged at all other visits. Further details are included in the imaging manual.

For specific guidance on scheduling of peripheral OCT assessments in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

9.3.8 Anterior Segment OCT (in Part A only)

The choroid, suprachoroidal space, and sclera in the area of insertion site will be explored using AS-OCT in Part A only at equipped sites. At the screening visits, both eyes will be assessed. The study eye will be assessed on Visits 1, 2, 3, 4, and 5 as specified in the SoAs in Section 1.3.

For specific guidance on scheduling of AS-OCTs in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B. Further details are included in the imaging manual.

9.3.9 Color Fundus Photography

Retinal anatomy will be evaluated by Color Fundus Photography (CFP) in Part A and Part B. CFP in the study eye will be captured at all visits, as specified in the SoAs in Section 1.3. CFP in the fellow eye will be captured at the screening, Week12, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3. For specific guidance on scheduling of CFP assessments in the operational alternatives No.1-No.3 see Table 3 for Part A, and Table 4 for Part B.

A CFP must be performed once a subject has met follow-on treatment criteria in the study eye and before follow-on treatment is given. CFP will be captured using either 4WF or UWF imaging methods. If these methodologies are not available, acquisition of a 7-field CFP could be considered with the approval of the sponsor's Medical Monitor. Further details on CFP imaging are included in the imaging manual.

9.3.10 Fluorescein Angiography

The anatomical state of the retinal vasculature will be evaluated by fluorescein angiography (FA). The study eye will be the transit eye. FA will be captured and analyzed for both eyes. FA will be captured using either 4WF or UWF imaging methods.

Fluorescein angiography will be performed at the screening, Week 24, and Week 52 visits, as specified in the SoAs in Section 1.3. Further details are included in the imaging manual.

9.4 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoAs in Section 1.3.

The following assessments will also provide safety-relevant information but are discussed in other sections: IOP assessment (Section 9.3.2), slit-lamp biomicroscopy (Section 9.3.3), dilated indirect ophthalmoscopy (Section 9.3.4), SD-OCT (Section 9.3.6), and pregnancy test (Section 9.2.4).

9.4.1 Adverse Event and Adverse Device Effect Collection

At every visit, the investigator (or designee) will assess and record all AEs and ADEs that occur from the time the informed consent is signed until the end of study. Duration (start and stop dates), severity/grade, outcome, treatment, and relationship to study treatment, administration procedure, and the study device will be recorded. For more details, please refer to Safety Reporting of Adverse Events and Serious Adverse Events within Section 9.5.

9.4.2 Laboratory Testing

Blood samples for routine clinical laboratory tests will be collected at the screening visit (Visit 1, Day -30 to -2), at Visit 11 (Week 24), and Visit 18 (Week 52) or End of Study / Early Termination visit. Screening laboratory tests may be repeated at the discretion of the investigator. Tests to be performed at the screening visit are:

1. Non-fasting chemistry (blood): sodium, potassium, chloride, bicarbonate, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase bilirubin direct, bilirubin indirect, total bilirubin, creatinine, blood urea nitrogen, total protein, calcium, phosphorus, glucose, and hemoglobin A1c
2. Hematology (complete blood count with differential): white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet count, and mean platelet volume
3. Thyroid: thyroid-stimulating hormone

In addition to the laboratory testing at the screening visit, only hemoglobin A1c will be tested at Visit 11 (Week 24) and Visit 18 (Week 52) or End of Study / Early Termination visit.

Laboratory testing will be performed by a certified central laboratory. For details see the study's laboratory manual.

The investigator must review the laboratory report, document the review, and record any clinically significant abnormal findings. Clinically significant abnormal findings from the screening laboratory testing that are explained by known diseases or conditions will be considered medical history and recorded as such on the medical history page of the case report form (CRF). If the screening laboratory assessments detect new, clinically significant abnormal findings, that are not explained by known diseases or conditions, such findings should be recorded as non-treatment-emergent AE. Any clinically significant new or worsened lab findings occurring from the time of study intervention on at Visit 2, Day 0, should be recorded as treatment-emergent AE. The laboratory reports shall be filed with the source documents. The laboratory reports must be filed with the source documents.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (*e.g.,* AE, or serious adverse event [SAE]) then the results must be recorded in the CRF.

9.4.3 Vital Signs, Weight, and Height

Height will only be measured at screening. Weight and vital signs will be assessed at screening, Week 24, and Week 52. Vital signs include measuring body temperature, blood pressure after 5min of sitting in a relaxed position, and heart rate. If blood pressure values would render subjects not eligible per exclusion criterion No. 30 at screening, at the same visit or later (but within the screening window of up to 30 days), repeat assessments could be performed to exclude temporarily exaggerated values. Subjects are asked to refrain from consuming any caffeinated beverages at least 30 minutes prior to blood pressure and pulse measurements.

9.5 Safety Reporting of Adverse Events and Serious Adverse Events

All subjects enrolled in the study treatment will be assessed for safety.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor regarding any event that seems unusual, even if this event may be

considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study.

The definitions of adverse events (AEs) and serious adverse events (SAEs) according to corresponding local regulations can be found in Section 11.2.

The definitions of device-related safety events, adverse device effects (ADEs), and serious adverse device effects (SADEs) can be found in Section 11.2.10 and include requirements of regulations in the US and Europe. Device deficiencies are discussed in Section 11.2.4.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs or ADEs. This includes events reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The method of recording, evaluating, and assessing the causality of AEs, SAEs, ADEs, and SADEs and the procedures for completing and transmitting corresponding reports are provided in Section 11.2.

9.5.1 Time Period and Frequency of Safety Information

All AEs and SAEs will be collected from the signing of the ICF until the EOS visit (Week 52) at the time points specified in the SoAs (Section 1.3). The AEs and SAEs that begin before the start of study intervention but after obtaining ICF where the severity did not worsen after the start of study intervention will be collected as such, however, considered non-treatment emergent AEs and SAEs. The AEs and SAEs that begin after the start of the study intervention and those existing pre-dose that worsened in severity post-dose will be considered treatment-emergent AEs and SAEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 11.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. For timelines of reporting to regulatory authorities or IRBs/ECs, see Section 11.2.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and the investigator

considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

9.5.2 Method of Detecting Safety Events

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

9.5.3 Follow-up of Safety Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs (as defined in Section 11.2.8) will be followed until resolution, stabilization, the event is otherwise explained, or the subject withdraws the informed consent or is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is provided in Section 11.2.11).

9.5.4 Regulatory Reporting Requirements of Serious Safety Events

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Safety reporting to the regulatory authorities will be performed according to the following regulations applicable to the US and the EU (also described in Section 9.5):

- IND safety reporting Guidance for Industry and Investigators – Safety Reporting Requirements for INDs and BA/BE Studies (US FDA 2012)
- Guidance Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies for Investigators (US FDA 2021a) and Sponsors (US FDA 2021b)
- Detailed guidance on the collection, verification, and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use from the European clinical trials directive (The European Parliament and the Council of the European Union 2011)
- The Clinical Trials Directive 2001/20/EC (The European Parliament and the Council of the European Union 2001)

- From the EU Medical Device Coordination Group: MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (Medical Device Coordination Group (MDCG) 2020) and the European Medical Device Directive (European Parliament/Council (EC) 2017)

The detailed information on safety reporting timelines and processes according to the above regulations will be outlined in Safety Monitoring Plan,

9.5.5 Contraception Guidance

Multiple cohorts and case-control studies in humans suggest that maternal corticosteroid use specifically during the first trimester increases the rate of cleft lip with or without cleft palate from about 1/1000 infants to 3- 5/1000 infants. Two prospective case-control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero. Human and animal studies suggest an increased risk for intrauterine growth restriction and decreased birth weight. An independent overview and discussion of these effects were recently compiled also by Bandoli *et al.* (Bandoli *et al.*, 2017).

Accordingly, and following the guidance on contraception of the Clinical Trial Facilitation Group (Clinical Trials Facilitation and Coordination Group 2020), the following contraception guidance needs to be implemented in this study and is also mentioned in the inclusion criteria in Section 5.

The following methods are considered highly effective as they can achieve a failure rate of less than 1% per year when used consistently and correctly:

1. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
   - oral
   - intravaginal
   - transdermal
2. progestogen-only hormonal contraception associated with inhibition of ovulation
   - oral
   - injectable
3. implantable
4. intrauterine device
5. intrauterine hormone-releasing system

6. bilateral tubal occlusion
7. vasectomized partner
8. sexual abstinence

Women who are not postmenopausal (*i.e.*, at least 12 months of non-therapy-induced amenorrhea or surgically sterile (absence of ovaries and/or uterus)) must agree to remain abstinent or use combined contraceptive methods that result in a failure rate of less than 1% per year from the treatment visit (Visit 2, Day 0) until the end of trial participation, or, if subjects discontinue trial participation before Week 52, for at least 52 weeks from the treatment visit (Visit 2, Day 0).

Some forms of contraception, (*e.g.*, hormonal contraception) need to be started before the treatment visit (Day 0) to have full effect from the time of exposure on.

Males must agree to use a barrier method of contraception starting from the treatment visit (Visit 2, Day 0) until the end of trial participation, or, if subjects discontinue trial participation before Week 52, for at least 52 weeks from the treatment visit (Visit 2, Day 0).

Male subjects must defer from sperm donation for the duration of the study and/or 52 weeks after receiving the study treatment, whichever is longer.

9.5.6 Adverse Events of Special Interest

In this trial, adverse events of special interest (AESIs) are defined and monitored following the same expedited reporting as used for SAEs (see Section 11.2). AESI comprise the following prespecified terms based on general considerations on potential safety risks with suprachoroidal device deployment and treatment.

1. Suprachoroidal hemorrhage
2. Sterile intraocular inflammation
3. Endophthalmitis
4. Choroidal bacterial infection
5. Retinal detachment
6. Retinal perforation
7. Rise of IOP above 30 mmHg*
8. Rise of at least 10 mmHg from baseline IOP*
9. Severe pain or discomfort after administration of IP

An AESI of "severe pain or discomfort after administration of IP" should be reported when a subject indicates severe pain or discomfort after completion of the injection procedure. Pain or discomfort during the procedure are reported separately as AEs. For assessing the occurrence of the AESI of "severe pain or discomfort after administration of IP", the answers in the Subject's Experience Assessment Questionnaires should be considered (see Section 12.1)

To consider an acute IOP rise after the treatment administration procedure, as an AESI, the rise must continue beyond the 60min observation period on Visit 2, Day 0 or require medical intervention, *e.g.*, a paracentesis to lower IOP. A rise of IOP would qualify as an AESI, when it is:

a) newly detected at follow-up visits after Visit 2, D 0,
b) the rise is persistent and,
c) the rise is observed over at least 2 successive scheduled study visits.

9.5.7 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of the study intervention and until the completion of the study.

If pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy. This includes the female subject or female partner of a male subject (after obtaining the necessary signed ICF from the female partner).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (*e.g.,* spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 11.2.

The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate (after obtaining a signature of pregnancy follow-up specific ICF) and the information will be forwarded to the sponsor.

Any female subject who becomes pregnant while participating in the study will not be treated with the study intervention when the pregnancy becomes apparent before treatment administration at V2. If pregnancy is detected after administration of study treatment, the subject will be offered to attend study visits for a safety follow-up with non-invasive assessments only (as standard at the relevant site for the assessment of pregnant patients).

9.5.8 Disease-Related Events and/or Outcomes not Qualifying as Safety Events

No specific disease-related events not qualifying as AEs or SAEs are defined for this clinical trial. A significant and unexpected loss in VA or parameters indicating an increase of macular edema may be reported as AE if the extent is significant or unexpected in the opinion of the investigator or sponsor. Non-improvement or worsening of disease leading to the need for follow-on treatment (as defined in Section 7.5.2) would only qualify as an AE, if significant or unexpected in the opinion of the investigator.

9.5.9 Medical Device Deficiencies

Oxulumis® ophthalmic administration devices are being provided for use in this study to administer DEXAsphere® as part of the study intervention.

Device deficiency is defined in ISO 14155:2020 as any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in the information supplied by the manufacturer.

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

Any device deficiencies observed during the drug administration procedure to clinical trial subjects will be documented by the sponsor, followed-up for root-cause, and included in the device risk assessment with an evaluation for the need to implement additional risk mitigations.

Further definitions regarding device deficiencies as well as processes and time periods for detection, notification, reporting, and follow-up of the medical device deficiencies can be found in Section 11.2.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 11.2.11 of the protocol.

9.6 Pharmacokinetics

PK evaluations in the context of this trial are considered mainly safety parameters to evaluate potential systemic exposure after suprachoroidal administration. PK evaluations are not expected to provide surrogates for therapeutic effects.

Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of study intervention on Visits 1, 2, 3, 4, 5, 11, and 18 (screening, Day 0 [60min after administration of the study treatment], and Day 1, week 1, 4, 24 and 52 visits, respectively) as specified in the SoA (Table 1 – Part A) to assess systemic exposure of dexamethasone after administration of OXU-001 for participants in Part A only. On Visit 2, Day 0, after the administration of study treatment, blood samples may be obtained later than 60min after administration, but the exact time has to be recorded. For subjects receiving follow-on treatment with IVT steroids, PK samples taken from the time of administration of this steroid follow-on treatment will not be considered as reflecting PK of the initial study treatment.

Pharmacokinetic data analysis will be conducted using standard noncompartmental methods of analysis with a PK software program that meets or exceeds minimum system requirements. The version of the software used for the analysis will be documented, and the program will meet the requirements of software validation.

Attempts shall be made to adhere to the scheduled collection times, but it is recognized that situations may arise that may compromise the schedule for sample collections. Parameters will be individually calculated for each subject based on actual collection times and presented by summary statistics.

The design and methods for statistical analyses of the pharmacokinetic data are provided in Section 10.4.4 and will be detailed in the SAP.

10 Statistical Considerations

This is a Phase 2 study designed to primarily assess the safety of the experimental intervention. Descriptive summaries of safety, clinically (*e.g.,* mean BCVA change from baseline), and anatomically (*e.g.,* mean CST change from baseline) relevant outcome measures will be presented. Exploratory analyses will be performed to compare the efficacy of the experimental intervention, *i.e.*, two doses of OXU-001 in Part A, and B of the trial, to in Part B the active comparator, Ozurdex.

The Statistical Analysis Plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section.

10.1 Statistical Hypothesis

As the present trial is primarily designed to assess safety, no formal statistical hypothesis testing will be performed for Part A and Part B.

10.2 Sample Size Determination

For Part A of the sample size of 18 subjects is considered adequate to fulfill the objectives of this initial part of the trial. Eighteen (18) subjects are expected to be sufficient to detect common and very common adverse events (specifically increases of IOP) to provide safety input on the doses for Part B (see also Section 7.5.1). Randomized subjects in whom study treatment cannot be administered will be replaced.

For Part B of this clinical trial, the randomization scheme is 2:2:1. Arm B3, the Ozurdex® arm will only half the number of subjects compared to the OXU-001 Arms B1 and B2, to minimize exposure to the expectedly more frequent steroid side effects associated with Ozurdex®. The sample size was determined primarily based on estimating the treatment effect and safety profile of OXU-001 to obtain informative data for designing further trials with a pivotal intent. Randomized subjects in whom study treatment cannot be administered will be replaced.

IVT administration of Ozurdex® results in peak effects (in terms of both increased visual acuity and reduced CST) about 2 months after treatment with a return to levels near baseline by month 6. Under this profile and the follow-on treatment criteria defined in Section 7.5.2, clinical experience based on outcomes with clinical trials using the approved 6-month treatment interval (Boyer *et al.*, 2014) or shorter intervals like 16 weeks (Fraser-Bell *et al.*,

2016; Augustin *et al*., 2021) suggest that a large proportion of patients in the Ozurdex® arm will require follow-on treatment by month 6 (estimated at 75%, 80%, and 85% in Table 12).

Pre-clinical data suggest that suprachoroidal administration of OXU-001 leads to similar peaks at Month 2. Assuming that the treatment effect for OXU-0001 is stable for at least 6 months, the proportion of patients requiring follow-on treatment by 6 months in the OXU 001 arms is expected to be smaller than that in the Ozurdex® arm. Table 12 shows the maximum parameter values of 24-week follow-on treatment probabilities in an OXU-001 arm that yield 80% power to reject the null hypothesis (of equal 6-month follow-on treatment probabilities) with Fisher's exact test (2-sided, Type 1 error controlled at 10% and sample sizes of 22 and 44 for the Ozurdex® and OXU-001 arms, respectively).

Table 12 Probability of follow-on treatment by Week 24 for Ozurdex®

	Probability of follow-on treatment by Week 24 for Ozurdex®		
*	75%	80%	85%
Maximum probability for OXU-001 that yields at least 80% power	41%	46%	52%

*(Range of parameter values (probability of follow-on treatment by Week 24) for an OXU-001 dose that yields> 80% power for a 2-sample comparison of proportions (2-sided Fisher's exact test, $\alpha = 0.1$, sample sizes 22 and 44 for Ozurdex® and OXU-001 arms respectively).

Analogously, for an exploratory analysis comparing the frequency of safety events in one of the OXU-001 arms to the Ozurdex® arm, Table 13 shows the maximum probability of events in the OXU-001 arm that will yield 80% power using a 2-sided Fisher's Exact Test (Type 1 error controlled at 10%) to reject the null hypothesis that the frequency with which adverse safety events occur is equal in both arms.

Table 13 Probability of Adverse Safety Event for Ozurdex®

	Probability of Adverse Safety Event for Ozurdex®		
*	25%	30%	35%
Maximum probability for OXU-001 that yields at least 80% power	2.5%	4.6%	7.2%

*Range of parameter values (probability of adverse safety event) for an OXU-001 dose that yields> 80% power for a 2-sample comparison of proportions (2-sided Fisher's exact test, $\alpha = 0.1$, sample sizes 22 and 44 for Ozurdex® and OXU-001 arms respectively)

10.3 Analysis Sets

10.3.1 Full Analysis Set

The Full Analysis Set (FAS) population will include all randomized subjects who received the study treatment and have at least one post-baseline efficacy observation or measurement. Subjects will be analyzed according to the study treatment group to which they were randomized.

10.3.2 Per Protocol Set

The Per Protocol Set (PPS) consists of the FAS population with exception of subjects with important protocol violations that could influence the validity of the data for the primary efficacy evaluations. In the analyses based on PPS, subjects will be analyzed according to the randomized study treatment group. All criteria to exclude subjects from the PPS will be made based on a masked review of the data prior to the unmasking of the trial for the Week 24 analysis.

10.3.3 Safety Analysis Set

The Safety Analysis Set (SAS) will include all subjects in whom the administration of study treatment was started (regardless of whether the subjects were recruited in Part A or Part B). In analyses performed on the Safety Analysis Set, subjects will be analyzed according to their actual treatment received.

10.3.4 Pharmacokinetics (PK) Analysis Set

PK Analysis Set (PKS) population will include subjects enrolled in Part A of the study who have received study drug and for whom at least one PK sample has been analyzed and with no major protocol deviations that have PK implications.

10.4 Statistical Analyses

10.4.1 General Considerations

All statistical analyses will be outlined in detail in an SAP which will be prepared and signed prior to database lock or any study-specific analyses. Summary statistics from investigator findings will be tabulated and summarized descriptively. All continuous measures will be summarized descriptively, including the number of available values, minimum, 1st quartile, median, mean, standard deviation, 3rd quartile, maximum, and 95% confidence interval for the mean, if appropriate. Categorical data will be presented by frequency and percentage. Ordinal ratings may be handled as continuous data if appropriate or presented as categorical if the number of categories is small.

10.4.2 Safety Analysis

All safety analyses will be performed on the SAS population.

The treatment-emergent AEs/ADEs (defined as any AE occurring or worsening with the same date or later than that of the first application of study treatment) will be encoded using the MedDRA dictionary.

The treatment-emergent AEs or ADEs will use the system organ class (SOC) and preferred term (PT) codes. The treatment-emergent AEs or ADEs will be summarized by SOC and PT. Both the number and percentage of subjects who experience the event and the number of events will be summarized.

TEAEs, study drug-related AEs, AEs of Special Interest (AESIs), AEs leading to withdrawal from the study, SAEs, and serious ADEs will be summarized similarly. AEs will be presented categorized as ocular and non-ocular AEs. Ocular AEs will be presented separately for the study eye and the non-study eye.

10.4.3 Exploratory Efficacy and Safety Analyses

The following main exploratory endpoints will be described on efficacy evaluable population and per-protocol efficacy population (if different) for each part of the trial separately, *i.e.*, one analysis for each part:

1. Time from baseline (Visit 2) to subjects requiring follow-on treatment (per pre-specified criteria).
2. Mean Change BCVA (ETDRS) at Week 24 compared to baseline.
3. Mean Change in central subfield thickness (CST on SD-OCT) at Week 24 compared to baseline.
4. Mean Change in BCVA (ETDRS) through Week 52 compared to baseline.
5. Mean Change in CST on SD-OCT through Week 52 compared to baseline.
6. Proportion of subjects requiring follow-on treatment at study visits from Week 12 through Week 52.
7. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) gain of BCVA from week 4 to week 52 compared to baseline.
8. Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) loss of BCVA from week 4 to week 52 compared to baseline.
9. Proportion of subjects with BCVA >68 letters (ETDRS) at each study visit from week 4 to week 52.
10. Mean change in NEI VFQ-25 Total Score Week 24, and Week 52 compared to baseline.

Further exploratory endpoints for Part A and Part B derived from the assessments of this trial will be summarized in detail in the SAP.

All continuous measures will be summarized descriptively, including the number of available values, minimum, 1st quartile, median, mean, standard deviation, 3rd quartile, maximum, and 95% confidence interval for the mean, if appropriate. Categorical data will be presented by frequency and percentage. Ordinal ratings may be handled as continuous data if appropriate or presented as categorical if the number of categories is small.

10.4.4 Pharmacokinetics Analyses

Based on PK evaluation for other suprachoroidal, or intravitreal steroids as well as PK data from testing of DMA and DXM systemic exposure following suprachoroidal administration of DMA microsphere formulations in animal models, it is expected that the majority of data points reflect minimal systemic exposure or are below the lower level of quantitation. If observed plasma dexamethasone concentrations allow, they will be used to calculate several PK parameters, including time to maximum observed drug concentration (tmax), maximum observed drug concentration (Cmax), area under the curve (AUC) from time zero (pre-dose) to time t, where t is the last time point with a measurable concentration [AUC(0-tlast)], AUC from time zero to 60min [AUC(0-60min)], AUC from time zero to one day [AUC(0-1d)], AUC from time zero to one week [AUC(0-1w)], and AUC from time zero to each of the remaining time points. For the Day 0 sample, the exact time of sampling after study treatment will be recorded and this time interval will be used for calculations, as it may not be exactly 60min.

Pharmacokinetics analyses will be described in detail in the SAP.

10.4.5 Important Protocol Violations

Protocol violations will be collected and reviewed during the trial.

Important protocol violations are defined as those violations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

Examples of important protocol violations include:

1. Not meeting the inclusion criteria or meeting the exclusion criteria, respectively
2. Missing study visits or out of window study visits (depending on the type of visit and on the time interval).
3. Intake of non-authorized concomitant treatment
4. Missing important safety data points (IOP measurements, dilated fundus examinations, BCVA measurement, SD-OCT measurement, etc.)

10.4.6 Other Analyses

10.4.6.1 Subject Disposition and Baseline Characteristics

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment. Demographics and baseline characteristics, including age, gender, and race will be summarized using descriptive statistics for the SAF population.

10.4.6.2 Medical History

Medical history findings will be presented by count, frequency, and percentage of findings.

10.4.6.3 Other Safety

Laboratory test results, and vital signs will be presented by count, frequency, and percentage of findings.

10.4.6.4 Concomitant Medications

For prior and concomitant medications, the original terms will be recorded on the Study Subjects' eCRF by the investigator. Prior and concomitant medications will be coded using WHO-DD, and verbatim original terms recorded on the eCRF will be presented as data listings and summary tables.

10.4.6.5 Physician Procedure Assessment

Analyses of the Physician Procedure Assessment will be described in the SAP.

10.4.6.6 Patient Experience Assessment

Analyses of the Patient Experience Assessment will be described in the SAP.

10.4.7 Missing Data and Imputation Methods

In case the start date for an AE/ADE is missing or incomplete, so that it is not possible to evaluate if it has occurred pre- or post-treatment, this AE/ADE will be classified conservatively as treatment-emergent.

Subjects who will require the need for therapy of DR complications will be imputed as those requiring follow-on treatment. Further categorizations for imputations may be explored as sensitivity analyses.

More details can be found in the study SAP.

11 Supporting Documentation and Operational Considerations

11.1 Regulatory, Ethical, And Study Oversight Considerations

11.1.1 Regulatory and Ethical Considerations

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements. The sponsor or the sponsor's representatives will obtain regulatory approval from the competent authority prior to the clinical trial start. The sponsor will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtaining approval are amended, the sponsor or the sponsor's representatives will submit these documents for review and subsequent approval to the competent authority.

An annual safety/progress report will be provided by the sponsor or the sponsor's representatives to the competent regulatory authority as required by applicable regulations.

The sponsor or the sponsor's representatives will obtain ethical approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the clinical trial start. The sponsor will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtaining approval is amended, the sponsor or the sponsor's representatives will submit these documents for review and subsequent approval to the IRB/IEC.

The investigator is responsible for the accuracy and completeness of all data recorded in the patient medical charts and CRFs. All data recorded in the CRF are derived from source data unless specifically exempted. Source data will be defined prior to the start of the clinical trial but consists in general of the information documented in the patient medical chart. Corrections to data should be made in a way so that the originally recorded data is still legible and traceable. Any changes should be initialed and dated by the person correcting them. The

investigator will maintain a file of essential documents of the trial as defined by the regulatory requirements, ICH, and the sponsor.

11.1.2 Financial Disclosure

Financial compensation of the investigator and/or his/her institution will be regulated in a financial agreement established between the sponsor or the sponsor's representative and the investigator and/or his/her institution.

11.1.3 Informed Consent Process

Following IRB/IEC approval and before any investigation-related procedure, potential subjects will be asked to sign a written ICF. The subjects will be given sufficient time for the information to be read and understood. The subject will be approached and given the chance to ask any questions that have arisen after reading the ICF.

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The sponsor or its designee must review and approve any proposed deviations from the sponsor's sample ICFs before IRB/IEC submission. The final IRB/IEC approved Consent Forms must be provided to the sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the subject before his or her participation in the study. The case history or clinical records for each subject shall document the ICF process and that written ICF was obtained prior to participation in the study.

Subjects unable to give consent personally will only be consented in those countries where national law/regulations permit.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to participate. The final revised IRB/IEC-approved Consent Forms must be provided to the sponsor for health authority submission purposes.

Subjects must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the ICF process

and that written ICF was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the subject. All signed and dated Consent Forms must remain in each subject's study file or the site file and must be available for verification by study monitors at any time.

11.1.4 Recruitment Strategy

Subjects in this clinical trial will be recruited from the pool of patients at the participating investigational sites and by referrals from general ophthalmologists or optometrists to the investigational centers.

11.1.5 Data Protection

11.1.5.1 Organizational and Technical Arrangements

In the following organizational and technical arrangements are summarized that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of information, and personal data processed.

Processing of personal data shall be carried out on behalf of the Sponsor by each clinical investigation site, governed by a contract and strictly according and subject to compliance with each country's data privacy laws, including the United States' (US) Health Insurance Portability and Accountability Act of 1996 (HIPAA), the European Union (EU) General Data Protection Regulation Article 6(1)(f) and Article 9(2)(j), the United Kingdom's (UK) Data Protection Act of 2018, and any subsequent amendments to these regulations or local law equivalent that is later adopted ("Regulation") as well as the privacy and confidentiality requirements of ICH Good Clinical Practice (GCP).

All personal data shall be treated as confidential by the clinical trial sites. When collecting personal data and healthcare information, the clinical site shall be the Controller for this data. The clinical site shall utilize pseudonymization whereby a unique subject identification number is assigned to each subject enrolled in the study. This means that subject names are not included in data sets that are transmitted to any sponsor location. The clinical site will maintain the key linking the unique subject identifier to personal identifying information associated with each patient ("Pseudonymized Data Controller"). The sponsor shall only be Controller of anonymized data ("Anonymized Data Controller") that is created during the clinical trial, which

the clinical trial site shall process on the sponsor's behalf as a Processor. When serving as Controller or Processor, the clinical site shall act in accordance with the applicable data protection laws.

11.1.5.2 Confidentiality Measures

Each clinical trial site shall implement appropriate technical and organizational measures to ensure a level of security appropriate to the risk, taking into account the state of the art, the costs of implementation and the nature, scope, context, and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons. Any access to personal data information contained within databases and binders shall be carefully restricted and only viewable by appropriate clinical trial staff for legitimate purposes. Security procedures shall be in place to protect against unauthorized access or loss of personal data to ensure that personal data is kept safe and treated in accordance with privacy policies and data protection and privacy laws.

In accordance with data privacy laws and good practice, each clinical site shall obtain consent from study subjects to collect, use and disclose their data consistent with good clinical practice and the laws on confidentiality and data privacy regulations.

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

Data generated by this study must be available for inspection upon request by representatives of applicable national and local health authorities, sponsor monitors, representatives, and collaborators, and the IRB/IEC for each study site, as appropriate.

All reasonable precautions within the constraints of the applicable regulatory requirement(s) will be taken to maintain the confidentiality of subjects' identities and sponsor's proprietary information by any party (*e.g.*, domestic and foreign regulatory authorities, sponsor's monitors, and auditors) with direct access to subject medical information.

11.1.5.3 Mitigation Measures in Case of Data Security Breach

The data protection officer of the clinical trial site shall be informed about the project before the start of a clinical study. The data protection officer is obligated to monitor compliance with the requirements of all data protection regulations. The data protection officer must, therefore,

not only be informed but all necessary information must be provided so that the data protection officer can fulfill his or her inspection obligations.

In case of a data security breach, the data protection officer shall be informed. The data protection officer is required to report the breach immediately (within 72h) to the responsible data protection supervisory authority. Subjects who are personally concerned and potentially endangered by a data protection breach will be informed immediately. Any possible measure to remedy the data protection breach will be arranged. Appropriate technical and organizational measures are implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, destruction, or accidental loss, in particular where the processing involves the transmission.

11.1.6 Committees Structure

11.1.6.1 Data Monitoring Committee

This trial will be monitored by an independent data monitoring committee (DMC). The composition, roles, responsibilities, and rules governing the DMC are available in a DMC Charter.

11.1.6.2 Study Steering Committee

This trial's execution will be supervised by a study steering committee (SSC). The composition, roles, responsibilities, and rules governing the SSC are available in the SSC Charter.

11.1.7 Dissemination of Clinical Study Data

Investigators and their staff shall hold confidential and not disclose directly or indirectly to a third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Sponsor's products or research programs that is provided to the Investigator. All such persons must be instructed not to further disseminate this information to others. Investigators shall not use the confidential information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by the Investigator shall not apply to (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than disclosure by or through the Investigator; (c) information which, as evidenced by the Investigator's written records, was

known by the Investigator prior to Oxular Limited's disclosure; (d) information which is lawfully disclosed to the Investigator by a third party, not under any obligation of confidence to Oxular Limited; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Oxular Limited.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Oxular Limited. Oxular Limited reserves the right of prior review of any publication or presentation of information related to the study. Oxular Limited reserves the right of prior review of any publication or presentation of information related to this study. Oxular Limited may use these data now or in the future for presentation or publication at Oxular Limited's discretion or submission to Regulatory Authorities.

11.1.8 Data Quality Assurance

All subject data relating to the study will be recorded on electronic CRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The sponsor is responsible for the data management compliance of this study, including quality checking of the data, and assumes accountability for actions delegated to other individuals. Authorized representatives of the sponsor may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, and GCP guidelines of the ICH, and any applicable local regulatory requirements. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time and in a reasonable manner. The Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection.

Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Additionally, the investigational site shall provide direct access to all trial-related sites, source data/documents, and reports for the purpose of inspection by local and regulatory authorities. In the event of this latter, the Investigator shall contact the sponsor immediately if contacted by a regulatory agency about an inspection.

QC procedures shall be implemented beginning with the data entry system, and data QC checks that will be run on the database shall be generated. Any missing data or data anomalies shall be communicated to the site(s) for clarification/resolution. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Clinical study records shall be retained according to the following requirements unless local regulations or institutional policies require a longer retention period than summarized:

1. US regulations (21 CFR Part 312.62) require that records and documents pertaining to the conduct of this study and the distribution of investigational products (including medical records, eCRFs, ICFs, test results, and investigational product records) be kept on file by the Investigator for 2 years after a marketing application is approved for the investigational product for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified.
2. ICH-GCP requires that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

No clinical trial records shall be destroyed or transferred to another location or party without prior notification and authorization from the Sponsor.

11.1.9 Source Documents

An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the clinical trial on each subject enrolled. Case histories include the CRFs and supporting source documents. Source documents include subject signed ICFs, and subject medical records with dates and details of the trial procedures (screening, laboratory and other test results, study treatments, AEs, subject status, etc.). The source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. These source documents shall be filed at the investigator's site.

The sponsor will provide the study sites with eCRFs that will be completed for each study subject based on the source documentation. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Data reported on the CRF or entered in the eCRF that are transcribed from source documents shall be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records shall be available.

The Investigator, or designated representative, shall complete the eCRF pages as soon as possible after information is collected during an examination, treatment, or any other clinical trial procedure. Any outstanding entries shall be completed immediately after each subject completes the clinical trial. An explanation shall be provided for all missing data.

The sponsor's representative will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements (see Section 11.1).

11.1.10 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for the recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Further to regulations outlined in Section 8, reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

1. Discontinuation of further study intervention development.

For site termination:

1. Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
2. Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
3. Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and shall ensure appropriate subject therapy and/or follow-up.

11.1.11 Publication Policy

The data resulting from this clinical trial will be proprietary information of the sponsor. None of the data resulting from this clinical trial will be allowed to be presented or published in any form, by the investigator or any other person, without the prior approval of the sponsor. The sponsor shall not unreasonably refuse, or delay publications based on the trial. The sponsor will publish data from this clinical trial also in case of negative results.

The sponsor may request, and the investigators shall not unreasonably refuse, the deletion of confidential information from a proposed publication. The parties will use their best efforts to provide scientifically meaningful equivalent information for such deleted confidential information.

11.2 Safety: Events, Definitions, and Procedures

11.2.1 Emergency Contacts for Investigator Reporting of Safety Events

The primary mechanism for reporting an SAE/SADE/AESI to Sponsor will be the electronic data capture system (EDC). The site will enter the SAE/SADE/AESI data into the electronic system as soon as it becomes available. If the EDC system is unavailable for a period of time expected not to allow reporting within 24 hours, the (paper) SAE/SADE/AESI forms will be

sent by fax to report the event within 24 hours. Contacts for SAE reporting can be found in the Investigator Site File.

11.2.2 Adverse Events Definition

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention and does not imply any judgment of causality.

An adverse event can arise with any use of the drug (*e.g.,* off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

11.2.3 Device Adverse Events and Device Adverse Effects Definitions

The AE definition provided in Section 11.2 includes Medical Device AEs.

In addition, according to position paper of the Medical Device Coordination Group on safety reporting for medical devices, (Medical Device Coordination Group (MDCG) 2020) an AE is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

This definition includes events:

a. that are anticipated as well as unanticipated events
b. occurring in the context of a clinical investigation related to the investigational device, the comparator, or the procedures involved

For safety reporting, all activities related to the use of a medical device may be considered procedures.

An adverse device effect (ADE) is an adverse event related to the use of an investigational device.

This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational

medical device as well as any event resulting from use error or intentional misuse of the investigational medical device.

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event (for detailed information, refer to Section 11.2.8).

A device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in the information supplied by the manufacturer. The safety reporting of device deficiencies follows the guidance of these regulations as applicable (European Parliament/Council (EC) 2017).

11.2.4 Time Period for Detecting Device Deficiencies

Medical device deficiencies that result in an incident will be detected and documented during the period of the study in which the medical device is used.

Thereafter, if the investigator learns of any device deficiency at any time after a subject has received drug administration with the device, or has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

11.2.5 Follow-up Period of Device Deficiencies

The following principles for follow-up will be applied for device deficiencies:

1. Follow-up applies to all subjects, including those who discontinue study intervention.
2. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
3. New or updated information will be recorded on the original completed form with all changes signed and dated by the investigator.

11.2.6 Reporting Requirements of Device Deficiencies

The sponsor will report to the Regulatory Authorities:

1. Device deficiency-related SAEs and SADEs, observed either during the drug administration procedure or subsequently reported by investigators (see below) as expedited safety reports following the guidelines in Section 9.5.4.

2. Non-serious AEs due to device deficiencies (including but not limited to "failure to treat" with the device) will be reported in the annual DSUR as part of the IND annual reporting requirements of 21 CFR 312.33.
3. Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate will be reported by the sponsor without delay to the concerned Regulatory Authorities.
4. Any new findings to any event referred to in points (1), (2) and (3).

The following regulations apply for **reporting of Device Deficiencies to the Sponsor**:

1. Any device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
2. The medical device deficiency without any related AE or related to non-serious AE will be recorded in the corresponding EDC chapters. The investigator has to notify the Sponsor about a newly recorded medical device deficiency via email or a telephone call. The medical device deficiencies related to SAEs, SADEs and AESIs will be recorded in the EDC based SAE form. If the EDC is unavailable, then the procedure described in Section 11.2.1 must be applied.
3. The sponsor will be the contact for the receipt of device deficiency reports.

The investigator will promptly report all SAEs or AEs suspected to be device deficiency-related occurring post-treatment with any medical device provided for use in the study for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of SAEs or SADEs determined to be device deficiency-related to the IRB/IEC.

11.2.7 Regulatory Reporting Requirements (Serious Safety Events, Safety Reporting in Clinical Investigations of Medical Devices, and DSUR).

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies (as applicable) about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRBs/IECs, and investigators according to the regulations listed in Section 11.2. The specific reportability criteria, reporting timelines and procedures for expedited reporting, cross-reporting for the investigational medicinal product and medical device, and submission of the Drug Safety Update Report (DSUR) will be outlined in the Safety Management Plan and in accordance with the regulations listed in the Section 11.2.

11.2.8 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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

   The term life-threatening in the definition of serious refers to an event in which the subject was at (immediate) risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

3. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.,* sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other important medical events:

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

11.2.9 Suspected Unexpected Serious Adverse Reaction Definition

For an event to be qualified as a suspected unexpected serious adverse reaction (SUSAR), the AE must meet three (3) criteria:

- the event is serious,
- there is a reasonable possibility for the event to establish a causal relationship to the study drug being researched (*i.e.*, it qualifies adverse reaction), and
- the nature and severity of the reaction are not in agreement with the product information and the safety information in the IB (*i.e.,* the reaction is unexpected as per the reference safety information, *i.e.*, the event is unexpected).

All SUSARs will be reported as required to the Competent Authorities and the Ethics Committee (EC)/Institutional Review Boards (IRBs) as required by applicable regulations.

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in or not listed at the specificity or severity that has been observed in the IB’s Reference Safety Information for the investigational medicinal product and/or investigational device.

For the comparator Ozurdex®, the RSI from the US Prescribing Information will be used. Investigator guidance for reporting of Ozurdex® events is still provided in the Investigator Brochure.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.2.10 Device Serious Adverse Event, Serious Adverse Device Effect, and Unexpected Serious Adverse Device Effect Definitions

To allow for comparability of safety reporting across trials in the development program of Oxular on the Oxulumis device, also a categorization of Device SAEs following the medical device regulations outlined in the Section 11.2.11 will be performed. The criteria for seriousness assessment for the Medical Device Adverse Event are slightly different from the SAE criteria outlined in Section 11.2.8.

A Device SAE is an adverse event that led to

1. **Death**
2. **Serious deterioration in the health of the subject, that either resulted in:**
   - Life-threatening illness or injury.
   - Permanent impairment of a body structure or a body function.
   - Hospitalization or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
   - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
   - Chronic disease (as per MDR 2017/745).
3. **Fetal distress, fetal death, or a congenital abnormality or birth defect**

A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

For the reportability assessment purposes the following events are also discussed in this section based on the regulatory guidelines listed in the Section 11.2.11, shall be reported, without delay to corresponding authorities as per local regulations:

a) any serious adverse event that has a causal relationship with the investigational device, the comparator, or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, the intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

An unexpected serious adverse device effect USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report for the device.

11.2.11 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events (Drug or Device)

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (*e.g.,* hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the investigator to send photocopies/digital copies of the subject's medical records to Oxular Ltd. or its delegates instead of completing the SAE report form.

There may be instances when copies of medical records for certain cases are requested by Oxular Ltd or its delegates. In this case, all subject identifiers, except for the subject number, must be redacted on the copies of the medical records before sharing with Oxular Ltd. or its delegates.

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

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF and/or SAE form. Colloquialisms and abbreviations should be avoided. Serious AEs must also be recorded on the AE eCRF. Only 1 medical concept should be recorded in the event field on the AE eCRF and SAE form (if applicable).

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (*e.g.,* cascade events or clinical sequelae) should also be entered as separate AEs. For example, if severe diarrhea is known to have resulted in dehydration, both diarrhea and dehydration should be entered as AEs on the eCRF, and if also serious, on the SAE form.

Persistent or Recurrent Adverse Events

A persistent AE extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe or its sign or symptoms occur more frequently, the change in the severity grading, the date when the severity change was reported, and any new action taken shall be recorded in the eCRF.

A recurrent AE occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the AE eCRF.

Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF and SAE form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the eCRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.5.1), regardless of attribution, will be recorded on the AE eCRF and SAE form and reported to the Sponsor within 24 hours of event knowledge.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept. For example, if death resulted from respiratory failure, the AE recorded should be "Respiratory Failure", and the outcome of the AE would be "Death". If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death" on the AE eCRF and SAE form.

Preexisting Medical Conditions

A preexisting medical condition is one that had been already present at the start of the study (at the time of the signature of the ICF). Such conditions should be recorded on the Medical and Surgical History eCRF (see also Section 11.1.9).

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

Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in the protocol.

Special Situations Reporting

Medication errors and uses outside what is foreseen in the protocol, including overdose and occupational exposure must be reported to the Sponsor on an AE eCRF and an SAE form for tracking purposes and will be considered a protocol deviation. Additional instructions for reporting special situation information will be provided by the Sponsor at the time of notification.

Assessment of Intensity

The investigator will assess the intensity for each AE and SAE reported during the study and assign it to one of the following categories:

1. Mild:
   A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with the usual activities of daily living.
2. Moderate:
   A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
3. Severe:
   A type of adverse event that interrupts usual activities of daily living significantly affects clinical status or may require intensive therapeutic intervention.

Assessment of Causality

1. The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
2. The relationship will be determined by the Investigator according to the following criteria (Medical Device Coordination Group (MDCG) 2020):
   1. **Not related**: The relationship to the intervention can be excluded.
   2. **Possibly related**: The relationship with the intervention is weak but cannot be ruled out completely. Alternative causes are also possible.
   3. **Probably related**: The relationship with the intervention seems relevant and/or the event cannot reasonably be explained by another cause.
   4. **Causally related**: The serious event is associated with the intervention beyond reasonable doubt.

Assessment of the Outcome of Adverse Events

The Investigator will record the outcome of AEs and SAEs using the following criteria:

Recovered/resolved: The subject has fully recovered from the event, with no residual effects observable.

Recovered/resolved with sequelae: The subject has recovered from the event, but with residual sequelae effects observable.

Not recovered/resolved: Effects of the event are still present.

Recovering/resolving: The subject has improved but has not fully recovered from the event.

Fatal: The death is related to the event.

Unknown: The outcome of the event is unknown to the reporter (*e.g.*, the subject was lost to follow-up).

Follow-up of AEs and SAEs

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

SAEs unrelated to study treatment and non-serious AEs are to be followed until the last scheduled study visit (EOS visit), with the outcome at that point of time to be recorded in the eCRF. SAEs related to study treatment are to be followed up until resolution or until they return to baseline, stabilize, or the subject is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and SAE form (if applicable) and in the subject's medical record to facilitate source data verification. For some SAEs, the Sponsor or its designee may follow up by telephone, facsimile, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (*e.g.,* hospital discharge summary, consultant report, or autopsy report).

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or sponsor's designee with a copy of any postmortem findings including histopathology.

Emergency unmasking procedure

In the event of a medical emergency, when knowledge of treatment assignment is needed for immediate medical management of the subject's health, Investigators can obtain unmasked treatment assignments through the centralized randomization system at any time. Thorough documentation of the rationale for unmasking is required. Consultation of the Sponsor Medical Monitor is recommended for all unmasking requests.

12 Outcome Assessments and Questionnaires

12.1 Subject's Experience Assessment – Visit 2, Day 0

Subject's Experience Assessment:

Current and Procedure Pain & Discomfort

To be completed by the Site Interviewer

Site Number	
Subject number	
Date	
Visit number	Visit 2, Day 0
Interviewer / completed by (print name)	

Instructions for the site interviewer:

Instruct subjects only to answer the questions on procedural pain and discomfort. This is of great importance specifically in Part B) to avoid sharing of any potentially unmasking information by the subject.

Ask the study subject the questions below after the post-procedure observation period.

Questions should be asked at any time after 60 minutes post-treatment but should not be asked within five minutes from the completion of any post-treatment measurement (*e.g.,* OCT, IOP, etc.). Indicate the study subject's response by checking one response for each question.

Instructions for the subject (to be read to the subject by the interviewer): Please answer the following questions about your experience of the procedure.

Question 1: Are you currently experiencing pain in the procedure eye?

☐ Yes

☐ No

Question 2: Rate your **current** level of pain in your procedure eye on a scale of 1 – 5

☐ (1) No Pain

☐ (2) Minimal Pain

☐ (3) Mild Pain

☐ (4) Moderate Pain

☐ (5) Severe Pain

Question 3: Rate your pain **during** the procedure on a scale of 1 – 5

☐ (1) No Pain

☐ (2) Minimal Pain

☐ (3) Mild Pain

☐ (4) Moderate Pain

☐ (5) Severe Pain

Question 4 Rate your pain **after completion**, of the procedure on a scale of 1 – 5

☐ (1) No Pain

☐ (2) Minimal Pain

☐ (3) Mild Pain

☐ (4) Moderate Pain

☐ (5) Severe Pain

Question 5: Are you currently experiencing discomfort in the procedure eye?

☐ Yes

☐ No

Question 6: Rate your **current** level of discomfort in your procedure eye on a scale of 1 – 5

☐ (1) No Discomfort

☐ (2) Minimal Discomfort

☐ (3) Mild Discomfort

☐ (4) Moderate Discomfort

☐ (5) Severe Discomfort

Question 7: Rate your discomfort **during** the procedure on a scale of 1 – 5

☐ (1) No Discomfort

☐ (2) Minimal Discomfort

☐ (3) Mild Discomfort

☐ (4) Moderate Discomfort

☐ (5) Severe Discomfort

Question 8: Rate your discomfort **after completion**, of the procedure on a scale of 1 – 5

☐ (1) No Discomfort

☐ (2) Minimal Discomfort

☐ (3) Mild Discomfort

☐ (4) Moderate Discomfort

☐ (5) Severe Discomfort

Signature of site-interviewer	
Date	

12.2 Subject's Experience Assessment – Day 1, Visit 3 through Week 4, Visit 5

Subject's Experience Assessment:

Current and Procedure Pain & Discomfort

To be completed by the Site Interviewer

Site Number	
Subject number	
Date	
Visit number (circle one)	☐ Day 1 (Visit 3) ☐ Day 7 (Visit 4) ☐ Day 30 (Visit 5)
Interviewer / completed by (print name)	

Instructions for site interviewer:

Instruct subjects only to answer the questions on procedural pain and discomfort. This is of great importance specifically in Part B) to avoid sharing of any potentially unmasking information by the subject.

Ask the study subject the questions below. Questions can be asked at any time during the study visit and separated by at least five minutes from the completion of any post-treatment measurement (*e.g.,* OCT, IOP, etc.). Indicate the study subject's response by checking one response for each question.

Instructions for study subject (to be read to the subject by the interviewer): Please answer the following questions about your current level of pain and discomfort in the eye which received the study treatment.

*Question **1:*** Are you currently experiencing pain in the procedure eye?

☐ Yes

☐ No

Question 2: Rate your **current** level of pain in your procedure eye on a scale of 1 – 5

☐ (1) No Pain

☐ (2) Minimal Pain

☐ (3) Mild Pain

☐ (4) Moderate Pain

☐ (5) Severe Pain

Question 3: Are you **currently** experiencing discomfort in the procedure eye?

☐ Yes

☐ No

Question 4: Rate your **current** level of discomfort in your procedure eye on a scale of 1 – 5

☐ (1) No Discomfort

☐ (2) Minimal Discomfort

☐ (3) Mild Discomfort

☐ (4) Moderate Discomfort

☐ (5) Severe Discomfort

Signature of site-interviewer	
Date	

12.3 Retinal Physician's Assessment of the Administration Procedure

Retinal physician's documentation and

Assessment of the Treatment Administration Procedure

This questionnaire should be completed by the treating physician (unmasked investigator in Part B) for all subjects, regardless of treatment assignment. For subjects assigned to Ozurdex in Part B, only questions under 1. and 2. are applicable. The remaining questions are related to the OXU-001 administration procedure using the Oxulumis® device and therefore do not have to be completed for subjects assigned to Ozurdex.

If the Oxulumis® procedure is repeated, *i.e.,* if the OXU-001 administration procedure is performed on two treatment days or in 2 separate sessions on one day, the questionnaire will need to be completed twice. If the variant would be switched within one treatment session (*e.g.,* in an operating room with a first non-completed OXU-001 Standard procedural variant directly followed by an OXU-001 ConjIncision Procedural Variant, only one assessment needs to be completed.

Introduction:

Note that any difficulty or challenge with the device noted below may qualify as an adverse event (AE) or as an adverse device effect (ADE) and needs to be recorded as such in the study documentation (source and CRF).

Date of Assessment: _____(dd/mmm/yyyy)

Setting:

- ☐ Clinic
- ☐ Procedure Room
- ☐ Surgically equipped Procedure Room
- ☐ Operating Room

Procedural Variant

- ☐ OXU-001 Standard Variant
- ☐ OXU001ConjIncision Variant (with incision of Conjunctiva/Tenons)
- ☐ Combination Standard Variant followed by ConjIncision Variant in one Treatment Session
- ☐ IVT Ozurdex

1. Antiseptic applied for Disinfection

1.1 Please select which antiseptic agent has been used:

1. Povidone Iodine
2. Chlorhexidine
3. Other
4. If other, please specify:

_____

2. Type of Anesthesia given

2.1 Which forms of anesthesia were administered: (more than 1 choice possible)

1. Topical Tetracaine eye drops
2. Lidocaine Gel
3. Lidocaine Pledgets
4. Subtenon Lidocaine
5. Other

If other, please specify the other anesthetic(s) or forms of anesthesia including location of injection (*e.g.,* quadrant for injection anesthesia):

_____

2.1.1 If pledgets, was there a repeat administration of pledgets?

1. Yes;

   If yes, please specify the total number of repeat administrations of pledgets:

   _____
2. No

2.1.2 If pledgets, please specify quadrant where applied (more than 1 selection possible)

1. superior – temporal
2. superior - nasal
3. inferior – temporal
4. inferior – nasal

2.1.3 If subtenon, please specify quadrant where applied (more than 1 selection possible

1. superior – temporal
2. superior - nasal
3. inferior - temporal
4. inferior - nasal

3. Execution of the Oxulumis Procedure

3.1 Was the procedure, during this session, performed successfully in the first attempt?

1. Yes
2. No

3.1.1 If "No", how many attempts did you need in total until you performed a complete procedure with administration of the trial drug: _____

3.1.2 If "No", select all that apply for the different attempts that did not result in administration of the trial drug:

1. Could not or only insufficiently engage sclera with the bevel
2. I could engage the sclera, but the catheter did not deploy
3. The catheter deployed subconjunctivally
4. The catheter deployed intravitreally
5. Other

If other, please specify the "Other" reason(s) the procedure was not performed successfully on the first attempt:

_____

3.1.3 How many different devices were opened for the procedure?

1. 1
2. 2
3. 3
4. Other, please specify number: _____

3.1.4 How many different devices were used (*i.e.*, the device touched the subjects eye during a procedural attempt) until successful completion of the procedure.

1. 1
2. 2
3. 3
4. Other, please specify number:

3.1.4.1 If 2, 3, or others is ticked, please briefly summarize:

_____

3.1.4.2 Provide a reason for exchanging Device 1

_____

3.1.4.2.1 Kit number

_____

3.1.4.3 Provide a reason for exchanging Device 2

_____

3.1.4.3.1 Kit number

_____

3.1.4.4 Provide a reason for exchanging further devices

_____

3.1.4.4.1 Please provide further Kit numbers

_____

4. Location of the Insertion Point

4.1 Which Quadrant was chosen for the drug administration

1. superior – temporal
2. superior - nasal
3. inferior - temporal
4. inferior – nasal

4.2 In which sector following the 12 sectors of a clock or watch dial, was the insertion point located

☐	12:00
☐	1:00
☐	2:00
☐	3:00
☐	4:00
☐	5:00
☐	6:00
☐	7:00
☐	8:00
☐	9:00
☐	10:00
☐	11:00

4.3 Was an incision of the conjunctiva/tenon(s) performed

1. Yes
2. No

If yes, briefly described the incision technique and the size of the opening:

_____

4.4 At which distance from the limbus was the trocar inserted:

Please tick the right category

1. 4mm
2. 5mm
3. Other

If other, please specify the distance from the limbus was the trocar inserted in mm

_____

5. Insertion *(to be completed for completed procedures)*

5.1 At which angle relative to the base of the eye was the trocar inserted into the sclera?

1. <10°
2. 10-15°
3. 16-30°
4. >30°

5.2 Insertion completed through the sclera

1. Yes
2. No

5.4 Difficulty (tick as appropriate (or dropdown)

1. very easy
2. easy
3. somewhat easy
4. difficult
5. very difficult

5.5 Complications (tick as applicable)

1. No complications
2. Insertion needle could hardly pass the sclera
3. Catheter directly deployed when trigger pressed (no further advancement necessary)
4. Other

If other, please specify

_____

6. Deployment *(to be completed for completed procedures)*

6.1 Was the deployment of the catheter to the suprachoroidal space completed as intended?

1. Yes
2. No

6.2 From deployed microcatheter: Was the light visible as expected and sufficiently bright?

1. Yes
2. No

6.3 Was the speed of deployment during the procedure as initially set?

1. Yes
2. No

6.4 Any kink in the tubing?

1. Yes
2. No

6.4.1. If 'Yes', please specify details and presumed reason(s) for the kink in the tubing?

_____

7. Injection of drug via the drug line *(to be completed for completed procedures)*

7.1 Was the injection completed as expected?

1. Yes
2. No

7.1.1 If No, indicate why the injection was not completed as expected:

1. Microcatheter clogged by drug and injection could not be completed
2. Other (please specify)

_____

7.2 What was the time interval for the drug injection:

1. Less than 10 sec
2. 10-14 sec
3. 15-19 sec
4. 20-24 sec
5. 25-30 sec
6. Longer than 30 sec

7.3 What was the residence time of the catheter in the suprachoroidal space after completion of the injection?

1. Less than 10 sec
2. 10-14 sec
3. 15-19 sec
4. 20-24 sec
5. 25-30 sec
6. Longer than 30 sec

7.4 Did the patient feel pain during the injection

1.Yes
2.No

7.4.1 If Yes, when did the pain start

1. With the trocar's tip insertion into the sclera
2. With trocar advancement into the sclera
3. With catheter deployment

4. With medication injection
5. With catheter withdrawal
6. After procedure completion
7. Other, please specify

_____

7.5 How long did the pain last? Enter duration in minutes

_____

7.6 Was any medication or intervention performed to alleviate pain?

1. Yes
2. No

7.6.1 If yes, please specify any medication or intervention that was performed to alleviate pain. *(Please report on Prior and Concomitant Medication CRF)*

_____

7.7 Where is the injection located in relation to the major retinal landmarks (please tick all that apply)

1. insertion point
2. arcades
3. anterior to equator
4. equator
5. posterior to equator
6. optic nerve
7. Other, please specify

_____

7.8 Any reflux?

1. Yes
2. No

7.8.1 If yes. Specify:

1. very mild, <10%
2. mild 10 to <20%
3. somewhat 20-<40%
4. Marked, 40-<60%
5. Very Marked 60 and more %

7.9 Difficulty to inject the study drug

1. very easy,
2. easy,
3. somewhat easy,
4. difficult,
5. very difficult

7.10 Were there any complications while injecting the study drug?

6. Yes
7. No

7.10.1 If 'Complications' is equal to 'Yes' , select all complications, that apply:

1. Intravitreal drug deposit
2. Conjunctival drug deposit
3. Disconnect of Merit syringe
4. Catheter clogged by OXU-001
5. Other

If other, please specify:

_____

7.11 Bleeding

7.11.1 Any intraocular bleeding

1. Yes
2. No

7.11.2 If 'Yes', localization of the bleeding:

1. vitreous

2. retinal
3. subretinal
4. Choroidal/suprachoroidal

If 'Any intraocular bleeding' occurred, please provide details: *(Please report as an Adverse Event)*

_____

7.11.4 Any scleral damage

1. Yes
2. No

If 'Any scleral damage' occurred, please provide details: *(Please report as an Adverse Event)*

_____

7.11.5 Any clinically relevant conjunctival hemorrhage

1. Yes
2. No

If 'Any clinically relevant conjunctival hemorrhage occurred, please provide details: *(Please report as an Adverse Event)*

_____

7.11.6 Any other damage, please select the ones that apply: *(Please report as an Adverse Event)*

1. Traumatic cataract
2. Retinal detachment
3. Retinal break
4. Other

If other, please specify:

12.4 Guidance on Factors to Consider for Assessment of Expected Procedural Complexity

Guidance on Factors to Consider for Assessment of Expected Procedural Complexity

Individual subject factors may vary widely between subjects impacting the procedural complexity of the Oxulumis® illuminated microcatheterization.

In subjects with factors indicating a potentially high expected complexity of performing the Oxulumis® procedure, the treating physician (unmasked investigator in Part B) may decide to directly perform the study treatment in an operating/surgically equipped procedure room with using the ConjIncision Procedural Variant, which uses a conjunctival/tenon incision to increase visualization and to potentially facilitate scleral engagement.

This subjective investigator assessment has to be performed at screening and has to be shared as part of the eligibility assessment with the sponsor.

Note: Significant scleral abnormalities may be considered and may lead to non-eligibility per exclusion criterion No. 4.

Also note that with an assessment of expected high procedural complexity, exclusion criterion No.4 must not be met, *i.e.,* neither conditions in the study eye, that may render the suprachoroidal microcatheter insertion and deployment difficult (even with scleral incision) should be present nor the risks of complications for a patient should be excessive.

Factor/History/ Medication	**Complexity**		
Facial Skull Anatomy			
• Configuration of the orbita? Access?	☐ Low	☐ Medium	☐ High
• Configuration of forehead? Prominence of the brow ridge?	☐ Low	☐ Medium	☐ High
• Blepharoptosis? Excessive eyelid skin (dermatochalasis)?	☐ Low	☐ Medium	☐ High

• Other, please specify	☐ Low	☐ Medium	☐ High
Conjunctiva / Tenon			
• Age? (note: higher age may be correlated with thinner conj./tenon)	☐ Low	☐ Medium	☐ High
• Thickness of Conjunctiva/Tenons? Opacity? Mobility?	☐ Low	☐ Medium	☐ High
• Medical History of Conj./Tenon abnormalities, *e.g.,* Chronic blepharitis? Toxic conjunctivitis (*e.g.*, due to chronic use of eyedrops)? Allergic conjunctivitis? Severe dry eye disease? Ocular pemphigoid? Note: per exclusion criterion No.4, ocular surface diseases with significant conjunctival edema and/or inflammation are exclusionary.	☐ Low	☐ Medium	☐ High
• Medication with impact on conj./tenon thickness (note: medications with conj. thinning long term effects may allow better scleral visualization, while those causing increased thickness due to chronic inflammation, increased vascularization or chemosis worsens visualization.)	☐ Low	☐ Medium	☐ High
• Other, please specify	☐ Low	☐ Medium	☐ High
Surgical history			
• Incisional glaucoma surgery? Access in superior temporal quadrant? Scarring?)	☐ Low	☐ Medium	☐ High
• Extracapsular cataract surgery? Access in superior temporal quadrant? Scarring?)	☐ Low	☐ Medium	☐ High

• Other ocular surgeries (*e.g.*, squint surgery or conjunctival peritomy) with potential impact on scleral access in the superior temporal quadrant, please specify	□ Low	□ Medium	□ High

Conclusion:

Overall Assessment of Expected Procedural Complexity (Expert Judgment)

The Oxulumis Procedure in the current subjects is expected to have

- ☐ Low complexity
- ☐ Medium complexity
- ☐ High complexity

The procedure is therefore planned to be performed (please tick as applicable):*

- ☐ In-clinic
- ☐ a Procedure Room
- ☐ a Surgically Equipped Procedure Room
- ☐ an Operating Room

The planned initial procedural variant, if the subject is in a OXU-001 treatment arm is:

- ☐ Standard Variant
- ☐ ConjIncision Variant

If a 2nd treatment session would be needed, the subject would be treated in

- ☐ a Surgically Equipped Procedure Room
- ☐ an Operating Room

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