Oxular Limited

Clinical Trial Protocol

Clinical Trial Protocol Title:

A Multi-Center, Randomized, Two-Arm, Parallel-Group, Single-masked, 24-week, Clinical Trial to Evaluate Safety and Tolerability of Two Dose Levels of Suprachoroidal Triamcinolone Acetonide Administered with the Oxulumis® Ophthalmic Administration Device in Subjects with Diabetic Macular Edema

Clinical Trial Reference Number:	OXUCT-103
ClinicalTrials.gov Identifier:	NCT05512962
Investigational Product Name:	Triamcinolone acetonide via suprachoroidal delivery with the Oxulumis® device in DME
CT Version:	V3.0
Date:	17 Feb 2023
Sponsor:	Oxular Ltd. Magdalen Centre 1 Robert Robinson Avenue Oxford OX4 4GA, United Kingdom Email: OXUCT-103@oxular.com Telephone: +44 (0)1865 636200
Funding Source:	Oxular Ltd.
Author(s):	PD Dr. med. Friedrich Asmus, MD, Chief Medical Officer

Contact Information for Medical Oversight:

Oxular Medical Monitor - Clinical Development

Oxular Limited, Magdalen Centre, 1 Robert Robinson Avenue Oxford OX4 4GA, United Kingdom

OXUCT-103@oxular.com

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.

Sponsor signatory:

PD Dr. med. Friedrich Asmus, MD
Chief Medical Officer

DocuSigned by:
Friedrich Asmus
Signer Name: Friedrich Asmus
Signing Reason: I am the author of this document
Signing Time: 2/17/2023 | 2:46:06 PM CET
2F7AC61A303E467885F388363F8E8CC47 2/17/2023

Name, Function (print)	*Signature*	*Date*

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

Coordinating Principal Investigator:

Name:	*Signature*	*Date*
Function:		
Organization:		
Address:		
Telephone:		

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

Principal Investigator:

Name:	*Signature*	*Date*
Function:		
Organization:		
Address:		
Telephone:		

Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
Anti-VEGF	Anti-Vascular Growth Factor
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BM	Biomicroscopy
CFP	Color Fundus Photography
CNV	Choroidal Neovascularization
CRF	Case Report Form
CME	Cystoid Macular Edema
CRO	Contract Research Organization
CST	Central Subfield Thickness
CTP	Clinical Trial Protocol
DME	Diabetic Macular Edema
EDC	Electronic Data Capture
EMA	European Medicines Agency
EoS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	High Resolution
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction for Use
IOP	Intraocular Pressure
IRB	Institutional/Independent Review Board
ISO	International Organization for Standards
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
ME	Macular Edema

OCT-A	Optical Coherence Tomography Angiography
OU	Oculus Uterque – Both Eyes
PDR	Proliferative Diabetic Retinopathy
PRP	Panretinal Photocoagulation
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TA	Triamcinolone Acetonide
TEAE	Treatment Emergent Non-Serious Adverse Effect
UADE	Unanticipated Adverse Device Effect
US FDA	United States Food and Drug Administration
VEGF	Vascular Endothelial Growth Factor

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1 Protocol Summary

1.1 Synopsis

Title	A 24-week, Randomized, Two-Arm, Parallel-Group, Single-masked, Clinical Trial to Evaluate Safety and Tolerability of Two Dose Levels of Suprachoroidal Triamcinolone Acetonide Administered with the Oxulumis® Ophthalmic Administration in Subjects with Diabetic Macular Edema
Sponsor Protocol #:	OXUCT-103
Phase:	Exploratory Clinical Trial – Phase 2
Background and Rationale:	There remains a high unmet need for a safe and efficacious treatment for DME in selected patients. Currently approved treatments including intravitreal (IVT) steroid implants or IVT anti-VEGF treatments in DME may not show satisfactory and/or sustained enough improvement of the macular edema and of vision. With existing ophthalmic steroid treatments, visual benefits may be compromised by meaningful side effects, which often trigger additional drug treatments or even ocular surgeries, *e.g.*, intraocular lens replacement surgery. Accordingly, there continue to be significant treatment challenges for the heterogenous population of patients with DME. The current clinical trial evaluates a novel microcatheterization approach for suprachoroidal steroid administration that has the potential to address challenges with respect to critical adverse events, efficacy, and durability of treatment compared to other currently applied treatment options, *e.g.*, subtenon, or IVT administration of the same ophthalmic steroid suspension. The proposed ophthalmic administration device (Oxulumis®) deploys an integrated, highly flexible, soft (atraumatic) microcatheter in the suprachoroidal space through a minimally invasive, short (27G) insertion needle in the region of the pars plana, typically 4-7mm post

limbus corneae. The soft microcatheter incorporates an illuminated shaft. Before administration of the drug product, the illumination allows confirmation of microcatheter positioning in the suprachoroidal space. Drug delivery is achieved via a low-volume administration of the triamcinolone acetonide suspension (Triesence®). The current trial evaluates two different dose levels to initially explore the safety of different administration volumes. The low dose is 2.4mg triamcinolone acetonide (TA, 60µl of a 40mg/ml suspension). The mid-dose is 4.0mg TA (100µl of a 40mg/ml suspension).

In a compassionate use program in Switzerland, both dose levels of 2.4mg and 4.0mg were applied in patients with cystoid macular edema (CME) or post-surgical inflammatory edema refractory to standard treatments. In this limited number of treatments so far, no safety concerns were observed.

The current trial OXUCT-103 is expected to deliver first exploratory data for two randomized dose groups, that both dose levels are safe, and may explore first trends of potential differences in peak efficacy and duration of effect.

It is anticipated that posterior deployment of the drug in the suprachoroidal space will lead to a safer, more tolerable, and effective treatment compared to IVT or subtenon administration. An important success factor for a completed Oxulumis® procedure is a controlled scleral engagement of the insertion needle of the ophthalmic administration device. In a subset of subjects with more limited access to the orbita, enophthalmus, and/or a thick, opaque, hypermobile conjunctivas a small incision of the conjunctiva may be needed to ensure facilitated access and full visibility through the scleral engagement phase of the Oxulumis microcatheterization procedure. Depending on the expert assessment of the investigator at the screening visit, the procedure can either be performed,

	a) in an in-clinic setting first. In case the study treatment cannot be administered in this setting, the investigator can perform the procedural variant with a conjunctival/tenon incision. Activities for Visit 2 need to be completed within 14 days (for details on scheduling see Section 1.3). b) at the discretion of the investigator, the procedure can be performed directly in an operating/procedure room, if the procedural variant with the conjunctival/tenon incision is likely to be needed. An operating/procedure room will allow for the setting for a conjunctival/tenon incision, which is typically not performed in an in-office setting. As eligibility for this trial is based on limited or no response to standard treatments, this trial uses another dose level of TA suspension as a control rather than exposing subjects the same or a similar treatment that they already had failed to respond. The standard dose for IVT injection is 4.0mg. This dose level will be administered in the current trial in the mid-dose group. In addition, 2.4mg TA will be used in the low dose group. In both dose groups, TA is expected to be administered closer to the location of the disease activity compared to other treatment approaches. Local concentrations of TA in the retinal tissues are expected to be higher compared to the same doses administered by IVT or subtenon injection.
Overall Design	Twenty-four (24) week, randomized, two-arm, single-masked, clinical trial to evaluate safety, tolerability, and to explore the efficacy of two dose levels of suprachoroidal triamcinolone acetonide (TA) suspension (Triesence®, 2.4 mg, and 4.0mg) administered using the Oxulumis® ophthalmic administration device in subjects with pre-treated Diabetic Macular Edema.

A focus of this trial is to evaluate the feasibility, safety, and tolerability of the ophthalmic administration of a low and a mid-dose of suprachoroidal triamcinolone acetonide suspension (Triesence®) with the Oxulumis® in DME. In addition, for the two dose groups of the trial, efficacy data on visual and anatomic changes will be collected.

To support the main objectives of this trial, a sample size of 20 treated subjects is estimated to be sufficient to detect common and very common adverse events. This safety information is relevant to inform further trials in the Oxulumis development program with respect to safety considerations including initial safety and feasibility experience with suprachoroidal administration procedure.

After a screening period, approximately 20 eligible DME subjects will be randomized and treated using a 1:1 ratio to receive a single administration of one of two dose levels of TA (low dose, 2.4mg. or mid-dose, 4.0mg, respectively). Subjects in whom the procedure could not be completed, and TA is not injected, will be replaced in order to reach approximately 20 treated subjects.

The follow-up period after treatment administration will be up to twenty-four (24) weeks.

Clinical visits will occur on Day 0, Day 1, Week 1, Week 4, and then every four (4) weeks thereafter for a total of twenty-four (24) weeks. From Week 4 on, subjects will be assessed for their need for follow-on treatment to determine the length of the treatment interval.

Treatment Arm	Intervention	Subjects
1	One treatment with suprachoroidal **low dose (2.4mg**) triamcinolone acetonide	N=10
2	One treatment with suprachoroidal **mid-dose (4.0mg**) triamcinolone acetonide	N=10

	If subjects show a need for the next treatment of DME according to pre-specified criteria, participation in this clinical investigation will end, and an early termination/end of the study visit will be conducted at the respective visit date. In this case, the follow-up period will be shorter than 24 weeks. After completion of participation in this clinical trial, patients will continue treatment with therapeutic options determined by the treating retinal specialists in accordance with current medical practice for their DME. Periodically, the coordinating investigator together with the medical monitor will review individual patient data as well as the totality of the safety data to recommend if the investigation should continue as is, continue with changes, or be terminated. This review can also be performed by a Safety Review Committee, which includes all active investigators in this trial.
Objective(s):	Primary Objective: • To evaluate the safety and tolerability of two dose levels of triamcinolone acetonide administered with the Oxulumis® to the suprachoroidal space in subjects with DME. Exploratory Objective: • To explore the efficacy of two dose levels of triamcinolone acetonide with respect to VA changes, edema control, and durability of the treatment effect of suprachoroidal triamcinolone acetonide suspension (Triesence®) in subjects with DME.
Endpoint(s):	Safety endpoint: The primary endpoint of this study is safety and tolerability as assessed by: 1. Frequency of ocular and systemic adverse events (treatment-emergent serious adverse events [SAEs] and treatment-emergent non-serious adverse events [TEAEs])

2. Frequency of adverse device effects (ADEs, serious ADEs [SADEs])

Exploratory efficacy (and/or safety) endpoints:

1. Mean Change in BCVA (ETDRS) at all study visits through Week 24 compared to baseline
2. Percentage of subjects with vision gain and vision loss of at least 5, at least 10, and at least 15 letters at all study visits through Week 24 compared to baseline
3. Time to subjects requiring follow-on treatment
4. Mean Change in Central subfield thickness (CST) at all study visits through Week 24 compared to baseline.
5. Mean Change in IOP at all study visits through Week 24 compared to baseline

Population Studied:	This study population will consist of adult male and female subjects who: • Have been diagnosed with Type 1 or Type 2 diabetes mellitus. • Have DME involving the center of the fovea with central subfield thickness (CST) in the study eye of: ≥ 320 for males or ≥ 305 for females on Spectralis (Heidelberg) or ≥ 305 for males or ≥ 290 for females with Cirrus (Zeiss) by SD-OCT. • Have BCVA of ≤73 letters (ETDRS, approximate Snellen equivalent of 20/40 or worse) at the screening in the study eye. • Have shown short-lived, limited, or no response to prior therapy with ocular (*e.g.*, IVT, or subtenon) injections of steroids and/ or anti-VEGF agents. Short-lived in the context of this trial is defined as less than 4 weeks.

	• Have no structural deficit of the retina likely correlated to short-lived, limited, or absent therapeutic response. • Study eye suitable for suprachoroidal injection, *i.e.,* no relevant structural abnormalities can be observed like choroidal coloboma, chorioretinal anastomosis, and extreme scleral thinning, or hypotony, amongst others. The study is planned to be conducted in the United States.
Duration of Study:	There will be up to ten (10) clinic visits over 24 weeks (in addition to up to three [3] weeks of Screening, plus up to 14 days to complete the baseline visit activities). Subjects who meet the criteria for follow-on treatment will end study participation with an earlier EoS Visit before week 24.
Number of Subjects:	Approximately 20 subjects will be randomized and treated using a 1:1 ratio to two treatment arms receiving either 2.4mg TA (low dose arm) or 4.0mg TA (mid-dose arm) as a single treatment with triamcinolone acetonide (Triesence®) administered with the Oxulumis® to the suprachoroidal space of one eye, the study eye. Subjects in whom the procedural attempts do not result in administration of TA will be replaced to reach a total of approximately 20 treated subjects.
Eligibility:	Inclusion Criteria: Subjects will be eligible if they meet all the following inclusion criteria: 1. Able to understand and sign an informed consent form. 2. At least 18 years of age. 3. Have been diagnosed with Type 1 or Type 2 diabetes mellitus. 4. Have DME involving the center of the fovea in the study eye with a central subfield thickness (CST) on SD-OCT of: ≥ 320 for males or ≥ 305 for females on Spectralis (Heidelberg) or ≥ 305 for males or ≥ 290 for females with Cirrus (Zeiss).

5. Have BCVA in the study eye of ≤73 ETDRS letters (approximate Snellen equivalent of 20/40 or worse) at the screening visit. The eligibility will be assessed based on the ETDRS BCVA letter score.
6. Short-lived, limited, or no response to prior ocular injection therapy (*e.g.*, IVT or subtenon) of steroids and/or anti-VEGF agents based on the investigator's assessment. Short-lived in this trial is defined as less than 4 weeks.
7. For women who are not postmenopausal (*i.e.*, at least12 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 (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit (D0), if study participation ends before Visit 7, Week 12. 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.
8. Males must agree to use a barrier method of contraception from the treatment visit (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit (D0), if study participation ends before Visit 7, Week 12.
9. 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 the participation in this trial.

Main Exclusion Criteria:

Subjects will be eligible if they do not meet any of the following exclusion criteria:

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 concurrence of the Oxular Medical Monitor, may either put the subject at risk because of participation in the trial, may influence the results of the trial, or the subject's ability to participate in the trial.
2. Macular edema considered due to a cause other than diabetes mellitus in the study 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).
4. Conditions, in the study eye, that may render the 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.
10. History of glaucoma surgery, and or anti-glaucoma therapy with more than two active substances (in separate or a combination preparation) at the screening visit are exclusionary.
11. History of closed-angle glaucoma.
12. IOP <6mmHg (hypotony) in the study eye at screening.
13. Spherical equivalent of the refractive error of −6 diopters of myopia or worse (prior to cataract or refractive surgery) at screening.
14. Cataract or other media opacity that limits the ability to obtain the planned imaging assessments.
15. History of retinal detachment.
16. Subjects who were previously treated for DME in the study eye must not have received:
    a.) an intravitreal anti-VEGF treatment within four (4) weeks before screening. The 4 week interval before screening is used for IVT bevacizumab, ranibizumab, aflibercept, brolucizumab, or faricimab (*i.e.,* a combined Anti-VEGF/anti-Ang2 agent), as also inclusion criterion No. 6 on therapeutic response must be met.
    b.) Prior treatment with SUSVIMO® (Port Delivery System) implant at any time is exclusionary.

c.) Intra- or periocular/subtenon triamcinolone acetonide suspension within 12 weeks before screening.

d.) Intravitreal dexamethasone implant (Ozurdex®) within 24 weeks before screening.

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

f.) Prior treatment with suprachoroidal steroids (commercial, investigational, or off-label) at any time is exclusionary.

17. 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.
18. Treatment with ocriplasmin (Jetrea®) at any time.
19. 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.
20. 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 is exclusionary.
21. Hypersensitivity to triamcinolone acetonide, or any of the excipients in the Triesence® formulation or Oxulumis® device components.
22. Active malignancy or history of malignancy within the past five (5) years.
23. Uncontrolled diabetes with a hemoglobin A1c (HbA1c) > 12% or any other uncontrolled systemic disease at screening.

24. Uncontrolled hypertension, defined as blood pressure with a systolic value of ≥ 160mmHg or a diastolic value of ≥ 100 mmHg upon repeat assessment at screening.
25. History of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure, or any acute coronary event within 90 days before screening.
26. 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.
27. Subjects who were previously randomized in this trial, but in whom administration of study treatment could not be completed.

Investigational Product:	Triamcinolone acetonide injectable suspension 40 mg/mL (Triesence®) administered with the Oxulumis® ophthalmic administration device to the suprachoroidal space. The trial will investigate two dose levels of TA: 1. Low dose arm: the target dose of triamcinolone acetonide suspension is 2.4 mg (*i.e.*, 60µl). 2. Mid dose arm: the target dose of triamcinolone suspension is 4.0mg (*i.e.*, 100µl) The Oxulumis® is a sterile, semi-automatically operated, minimally invasive, single-use device designed to deploy a therapeutic drug via a delivery-guiding illuminated ophthalmic microcatheter into the suprachoroidal space. The illumination confirms that the microcatheter is deployed correctly, prior to administration of the therapeutic drug. Subjects will receive topical anesthetics and/or local injection anesthesia (typically subtenon injections) at the discretion of the investigator to reduce potential pain and discomfort during the

	procedure. The investigator will assess at the baseline visit the expected procedural complexity in categories of low, medium, or high. 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, a variant of the Oxulumis® procedure may be used with an incision of the conjunctiva/tenon. This procedural variant is expected to be carried out after local injection anesthesia in an operating/ procedure room. Locally established procedural practices for conjunctival/tenon incision and closure will be used at the discretion of the investigator. The treatment visit V2, Day 0, can be split to allow for collection of baseline assessments on a different day than the administration of the study drug. If a first attempt of study treatment is made in-clinic and treatment cannot be administered, a second attempt in an operating/procedure room is allowed. Only assessments feasible in an operating/procedure room setting need to be performed on this treatment day (for details see 1.3) The maximum time interval from starting activities of V2 to completion is 14 days. Antiseptic conditions according to global IVT treatment standards and following the current practice at the investigational site must be applied before the Oxulumis® procedure.
Dosing Regimen:	A single suprachoroidal administration of triamcinolone acetonide suspension (Triesence®) (at two different dose levels per treatment arm, 2.4mg and 4.0mg, respectively) will be given at the baseline visit (Visit 2, Day 0) in the study eye.
Reference/Comparator Therapy:	This trial will assess in two randomized parallel groups the safety and exploratory efficacy of triamcinolone acetonide suspension 40mg/ml at dose levels of 2.4mg and 4.0mg.

Need for Follow-On Treatment.

End-of-Study

Subjects will be followed with regular visits (from Week 4 on, at monthly intervals) to assess the safety and the course of visual and anatomic outcomes.

From Week 4 on, subjects will be evaluated against prespecified criteria indicating the need for follow-on treatment (*i.e.*, indicating the end of the current treatment interval). Criteria are as follows:

- At least 75 µm increase in CST on SD-OCT compared to the best-achieved CST value since the baseline visit [Visit 2, day 0].
- A decrease in BCVA of at least 10 ETDRS letters from the best achieved BCVA since the baseline visit [Visit 2, day 0], that in the opinion of the investigator, is due to worsening of DME.

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

If one or both above criteria are met, the subject will be eligible for follow-on treatment and will be managed according to the local standard of care after ending participation in this clinical trial.

If the investigator decides that the subject requires follow-on treatment during a study visit, the respective visit-day procedures will be extended to include the assessments foreseen for the EoS visit. This visit will then be an early termination/EoS visit.

For subjects who decide to discontinue study participation for any reason, the respective visit-day procedures will be extended to include the assessments scheduled for the EoS visit (or an EoS visit will be scheduled for the subject if notification of discontinuation is received outside of a scheduled study visit). This visit will then be an early termination/EoS visit.

If the non-study eye requires management for ME, this shall be carried out according to the local standard of care.

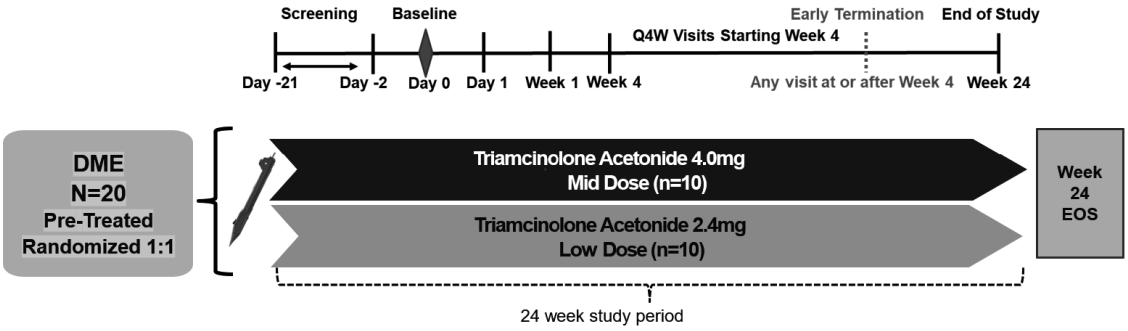
Assessments/Evaluations:	Safety: • Adverse events (AE) and Adverse Device Effects (ADE) will be coded to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA). o Subjects will be monitored for safety throughout the study. o On the injection day, Day 0, Visit 2, subjects will be monitored for at least sixty (60) minutes immediately following the suprachoroidal administration of TA. Additional assessments including efficacy endpoints: • Best-corrected visual acuity (BCVA) using the ETDRS methodology • IOP measurement • Slit-lamp biomicroscopy • Dilated indirect ophthalmoscopy • SD-OCT • OCT Angiography (OCT-A) • Color fundus photography using (UWF) imaging or 4 wide-field (4WF) imaging • (if available at site:) Swept-Source (SS)-OCT or Ultra-widefield (UWF) SD-OCT
Selection of 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 drug at 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. Subjects' fellow eyes may continue to receive non-study treatment following guidelines and standards at the investigational site. Treatment of the fellow eye is not considered part of the study treatment.
Statistical Methods:	Analyses will generally be descriptive in nature. The incidence of AEs and ADEs will be summarized for the study population. Ocular AEs will be summarized for all subjects using descriptive statistics for each eye and per treatment arm. Efficacy endpoints will be summarized for all subjects using descriptive statistics for each eye and per treatment arm. Summary statistics for other safety and efficacy outcomes will be presented. Further details will be provided in a Statistical Analysis Plan (SAP). Descriptive subgroup analysis will be performed and will be defined in a statistical analysis plan (SAP).

1.2 Schema

The study flow diagram is displayed in Figure 1.

Figure 1: Study Flow Diagram



♦ = Suprachoroidal Triamcinolone Administration; all baseline visit activities, *e.g.,* a 2nd treatment attempt in an operating/procedure room, need to be completed within 14 days, Q4W = monthly

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

Study Period	Screening	Baseline	Post-Baseline Follow-Up

Study Visit	1	2		3	4	5	6	7	8	9	10
Days/Week	Day -21 to-2	D0 To be completed within 14 days		D1	W1	W4	W8	W12	W16	W20	W24 ET/EoS
Visit Window (days) [a]		in-clinic [b]	variant with conj./tenon incision [j]	+ 1	± 3	± 5	± 5	± 5	± 5	± 5	± 5
ICF	X										
Eligibility	X	X*	X*								
Randomization		X*	X[k]								
Demographics	X										
Medical History	X										
Concomitant Medication	X	X*	X*	X	X	X	X	X	X	X	X
AEs and ADE	X	X**	X**	X	X	X	X	X	X	X	X
Height, Weight, Vital Signs	X										
Lab Assessment	X										
Pregnancy Test [d]	X	X*	X*	-	X	X	X	X	X	X	X
Slit-lamp BM	OU	OU*	OU[k]	SE	SE	SE	SE	OU	SE	SE	OU
IOP	OU	OU*/SE***,[i]	OU*,[k]/SE**	SE	SE	SE	SE	OU	SE	SE	OU
BCVA[e, f]	OU	OU*	OU*,[k]	SE	SE	SE	SE	OU	SE	SE	OU
Dilated Ophthalmoscopy	OU	OU*/SE**	OU*,[k]/ SE**	SE	SE	SE	SE	OU	SE	SE	OU

Study Visit	1	2		3	4	5	6	7	8	9	10
Days/Week	Day -21 to-2	D0 To be completed within 14 days		D1	W1	W4	W8	W12	W16	W20	W24 ET/EoS
Visit Window (days) [a]		in-clinic [b]	variant with conj./tenon incision [j]	+ 1	± 3	± 5	± 5	± 5	± 5	± 5	± 5
Axial Length[g]	OU										
SD-OCT	OU	SE*/SE**	SE*,k	SE	SE	SE	SE	OU	SE	SE	OU
OCT-A	OU							OU			OU
Swept-Source or UWF OCT [h]	OU	SE***		SE	SE	SE	SE	SE	SE	SE	SE
Color Fundus Photog.	OU	SE**	SE*,k	SE	SE	SE	SE	OU	SE	SE	OU
Overall Assessment of Expected Procedural Complexity	X										
Study Medication Administration		SE	SE								
Procedure Documentation and Assessment		X**	X**								
Subject's Experience Assessment[j]		X***	X***	X	X	X					
Assessment of need for follow-on treatment						SE	SE	SE	SE	SE	SE

AEs = adverse events; ADEs = adverse device effects; BCVA = best corrected visual acuity; BM = biomicroscopy; CFP = color fundus photography, CMs = concomitant medications; EoS = end of study; ET = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; ICF = informed consent form; OCT-A (Ocular Coherence Tomography Angiography); OU = both eyes; SD-OCT = Spectral-Domain Ocular Coherence Tomography; SE = study eye; Tx = treatment. (*) Pre-treatment, (**) Post-Attempt or Post-treatment, (***) Post Treatment.

a. Visit dates and visit windows are calculated for the screening visit from the day of the first procedural attempt and for post baseline visits from the date of the completed study treatment administration. Between the maximum interval from start of activities for Visit 2 and the completion is 14 days including a potential 2nd treatment attempt in an operating/procedure room, see also footnote b. and c.

b. Column shows the schedule of assessments for a study treatment carried out in a setting with access to devices for ophthalmic assessment or imaging.
c. The treatment day can be primarily performed in an operating/procedure room or be split between a first in-clinic attempt followed by another attempt in an operating/procedure room in case of non-completion of administration of the study treatment in the clinic. If the operating/procedure room is not fully equipped with ophthalmic assessment and imaging devices, this assessment schedule is the minimum to be performed.
d. Females of childbearing potential only. A urine pregnancy test will be performed at screening. A pregnancy test on D0 (urine) shall be negative for the subject to receive study treatment. Additional pregnancy tests will be performed at monthly intervals throughout study participation.
e. BCVA assessments need to be performed in duplicates for the eyes that should be assessed at visits.
f. BCVA eligibility will be assessed at the screening visit.
g. Axial length measurement to assess the axial dimensions of the eye to support exploratory imaging of the location of the deployment of study drug in equipped sites only.
h. SS-OCT or UWF SD-OCT to visualize the site of deployment will be obtained at sites in which the equipment is available.
i. On Day 0, subjects will be monitored for at least sixty (60) minutes immediately following study treatment with at least 2 IOP measurements.
j. If the Oxulumis® procedure is attempted first in-clinic and then another procedural attempt in an operating/procedure room, the subject's experience questionnaire will only be completed for the completed procedure, *i.e.,* the procedure when study drug is administered.
k. In case the study procedure is only performed in an operating/procedure room setting, the mandatory baseline assessments would have to be performed still at the investigational site, if not available in the operating/procedure room facility. This may be done prior to or on the same day of treatment administration. All baseline visit activities have to be completed within 14 days after their start.

2 Introduction

2.1 Study Rationale

Oxular Limited is developing a novel investigational ophthalmic administration device, called the Oxulumis®, which can be used for semi-automated microcatheterization of the suprachoroidal space.

The Oxulumis® deploys an integrated, highly flexible, atraumatic 7mm microcatheter in the suprachoroidal space through a minimally invasive, short (27G) needle insertion in the area of the pars plana. The typical distance of the insertion site to the limbus cornea is between 4--7mm. Through the microcatheter of 7mm length, triamcinolone acetonide suspension (Triesence®) can be delivered in proximity to the posterior retina. The soft microcatheter incorporates an illuminated shaft. The illumination is used to visualize the catheter and to confirm positioning of the microcatheter and the atraumatic tip in the posterior region before administration of the drug product. Drug delivery is performed as low-volume administration.

Triamcinolone acetonide suspension (Triesence®) disperses slowly in the suprachoroidal space following deployment. It is anticipated that the posterior positioning of the drug will reduce diffusion of Triesence® and steroid exposure of anterior ocular tissues, including the ciliary body and the lens, which are relevant structures for main adverse effects of ocular steroid treatment.

Another clinical advantage of suprachoroidal administration compared to IVT injections is the absence of penetration of the vitreous cavity. The risk of IVT bacterial contamination leading to *e.g.*, endophthalmitis is expected to be reduced.

Overall, a combination of the Oxulumis® with a US FDA approved ophthalmic steroid such as triamcinolone acetonide suspension (Triesence®) is expected to have the following benefits:

1. Reduction of the risk of steroid-induced complications and adverse events
2. Enhanced efficacy of triamcinolone acetonide suspension compared to IVT and other forms of steroid delivery due to an expected higher steroid concentration in the posterior choroid and retina.
3. Prolonged efficacy compared to IVT delivery of triamcinolone acetonide suspension
4. No penetration of the vitreous cavity with the suprachoroidal administration procedure of triamcinolone acetonide suspension

Oxular Limited is conducting the OXUCT-103 clinical trial as a 24-week randomized, two-arm, parallel-Group, single-masked, clinical trial to evaluate safety and tolerability of two dose levels of suprachoroidal triamcinolone acetonide administered with the Oxulumis® ophthalmic administration in approximately 20 subjects with diabetic macular edema.

2.2 Background

There remains a high unmet need for a safe and efficacious treatment for DME in selected patients. Currently approved treatments may neither show satisfactory peak efficacy nor sustained improvement of vision (Wilkins *et al.,* 2021; Ehlers et al. 2022). In addition, steroid treatment-related side effects occur frequently and may trigger additional drug treatments or even ocular surgeries The major treatment challenges are summarized below:

For DME, registered intravitreal (IVT) anti-VEGF treatments (*e.g.*, Lucentis® or Eylea®) are the current standard of care (Ehlers *et al.,* 2022). However, a sizeable proportion of DME patients experiences very limited vision gains and short-lived or insufficient edema control due to additional inflammatory factors contributing to chronic DME (Udaondo *et al.,* 2021; Zur, Iglicki, and Loewenstein, 2019). Administration of ocular steroids in DME may result in adequate disease control, however current formulations and their side effect profiles remain challenging. For topical or subtenon steroid administration, treatment effects may not last sufficiently long with need for early re-treatment (Shah *et al.*, 2020; Qi *et al.*, 2012). For both subtenon and IVT administration, a high incidence of steroid-related adverse events, such as cataract formation and increased intraocular pressure (IOP), substantially complicate treatment and thereby even limit the use of ocular steroids in a relevant number of patients (Boyer *et al.,* 2014; Ehlers *et al.*, 2022).

To overcome these therapeutic challenges, an innovative approach for ophthalmic drug administration is needed, which has the potential to reduce the rate and extent of complications with IVT steroid administration and maximizes the benefit/risk ratio by providing sufficiently high, local steroid concentrations to control DME.

In recent clinical trials assessing a device with a microinjection needle for suprachoroidal steroid administration, first trends of reducing side effects could be observed (Barakat *et al.*, 2021; Campochiaro *et al.*, 2018; Yeh *et al.,* 2020). However, the microneedle device typically punctures the eyewall at the pars plana and injects the steroid at this anterior location. A more posterior administration of steroids using an insertion point at 4-7mm post the limbus corneae in combination with deployment of a7mm- microcatheter is expected to further reduce the risk for IOP increases by reducing exposure to steroids of the more anterior parts of the eye. In

addition, by steroid administration to the posterior suprachoroidal space, higher local concentrations of steroids in the targeted macular region are expected.

2.3 Preclinical Testing of the Oxulumis® Ophthalmic Administration Device

The tissue contact portion of the Oxulumis® was tested per the requirements of ISO 10993 for devices with limited use (<24 hrs.), and the results of this testing demonstrated biocompatibility suitable for transient tissue contact with breached or compromised tissue. All testing was conducted in accordance with FDA 21 CFR Part 58 Good Laboratory Practice (GLP) Regulations. The results of testing showed that the patient-contacting materials used in the Oxulumis® passed all the applicable biocompatibility requirements contained in ISO 10993-1. Results of the toxicological risk assessment indicate that the patient contacting, and fluid pathway materials do not pose an unacceptable level of risk to the target patient population. Additionally, extractable and leaching testing to evaluate impurities that could potentially be conferred to the drug product resulted in levels of extracted elements that were safe based on their relationship with ICH Q3D guidelines for elemental impurities (parenteral route of administration).

The Oxulumis® has also undergone a battery of testing in acute pig and rabbit studies for the purpose of evaluating the device design with regard to the microcatheter formulation, structure, and length. In addition, in these studies, the feasibility of dose volumes and the effectiveness of training procedures for ocular disease specialists were evaluated. The current Oxulumis® design has been optimized for safety and efficacy of delivery to the suprachoroidal space based on outcomes from these preclinical animal studies.

2.4 Previous clinical experience

The efficacy and safety of IVT steroids in the management of DME is well documented.

In their recent Cochrane review, Rittiphairoj *et al.* reported findings from 10 clinical trials involving 4505 eyes with DME of 4348 subjects treated with IVT steroids compared to other treatments (Rittiphairoj *et al.*, 2020). Despite potential efficacy on visual acuity (VA) and reduction of ME, 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.

To overcome these potential side effects (IOP elevation and cataract progression), several groups have tried to deliver TA via the suprachoroidal space. By changing the site of administration from the vitreous cavity to the suprachoroidal space, 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 develop these side effects.

Suprachoroidal drug administration has been proposed as an approach to ophthalmic drug administration resulting in higher concentrations of medication to target tissues (*i.e.*, in choroid, and retina) and lower concentrations of medication to anterior segment structures (Pearce, Hsu, and Yeh, 2015). Although already proposed in the late 1970s by Russian ophthalmic surgeons, suprachoroidal drug administration was only picked up again three decades later with technical advances in microsurgical techniques including the use of a microsurgical cannula (Olsen *et al.*, 2006) or a hollow microneedle (Patel *et al.*, 2012) to target the suprachoroidal space. These animal studies in non-human primates and rabbits demonstrated detailed drug distribution following suprachoroidal delivery.

2.4.1 Diabetic Macular Edema:

Experience with subtenon TA treatment

For the subtenon treatment of DME with TA, clinical data are summarized in a review and meta-analysis (Qi *et al.*, 2012).

The review compared IVT administration of TA and subtenon TA injections. Overall, these clinical data demonstrate that both administration methods may initially improve VA and reduce ME. However, the subtenon administration of TA in DME has a significantly shorter duration, as visual and anatomic benefits already decline at the 3 months follow-up assessments. As expected, the IOP increase with subtenon TA was lower at 3 months compared to IVT TA. These systematic review data also suggest that subtenon TA in DME has limitations in respect to maximum efficacy, durability, and steroid-induced IOP increases. Of note, the subtenon dose of TA is generally substantially higher (40 mg, 1.0 mL) compared to the IVT administered dose (4.0 mg, 100 µl) (Qamar, Saleem, and Saleem, 2013). Also, the posterior subtenon administration may have some relevant safety complications like an accidental direct injection of TA into the choroidal or retinal circulation, perforation of the globe, occlusion of the central retinal artery, cataract formation, orbital fat atrophy, strabismus, and conjunctival necrosis.

Experience with suprachoroidal microneedle TA injections

Recently, clinical trials (Wykoff *et al*., 2018; Barakat *et al.*, 2021) investigating microinjection techniques in the area of the pars plana, suggested the clinical feasibility of suprachoroidal administration with an acceptable safety profile and meaningful clinical efficacy.

In the HULK trial (Wykoff *et al*., 2018), an open-label, 20 subjects study evaluating the use of TA applied to the suprachoroidal space with a microinjector in the management of DME, treatment naïve subjects (n=10) had 8.5 ETDRS letters improvement at month 6, while those previously treated (n=10) improved only by 1.1 letters. Ten percent (10%) of the subjects (n=2 of 20) experienced a ≥ 10 mmHg increase in IOP during the trial. There were three cases of cataract progression. Notably, there was injection site pain (1 of 20 subjects) and inadvertent IVT drug deposit (1 of 20 subjects).

In the TYBEE Phase 2 trial, 71 subjects with DME were randomized to receive either: *i*) 4 monthly doses of aflibercept (Day 0, Weeks 4, 8, and 12) with additional as-needed aflibercept doses at Weeks 16 and/or 20), or *ii*) 2 TA injections (4 mg) administered to the suprachoroidal space (Day 0 and week 12) with the option for aflibercept at weeks 4, 8, 16 and 20 as needed (Barakat *et al.*, 2021). 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 mono arm (-176.1 µm), the mean 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, logrank test, two-sided significance level of 0.10). An IOP increase of more than 30mmHg occurred in 3 subjects in the active group and 0 subjects in the control group. Intraocular pressure increases of more than 10mmHg occurred in 5 and 0 subjects in the active and control groups, respectively (Barakat *et a*l., 2021).

2.4.2 Suprachoroidal Administration of TA via Microcatheterization

There has been rapid and substantial progress in medical technology since Penkov's conceptualization of suprachoroidal drug administration in the 1960s. This has resulted in the technical development and exploration of the feasibility of medical devices that use microcatheters to administer drugs to the suprachoroidal space.

For the use of microcatheters to reach the suprachoroidal space, more recent smaller studies showed substantial progress of the device technique resulting in therapeutic benefits in advanced retinal disease unresponsive to conventional treatments.

The subsequent publications demonstrate the feasibility and principal safety of suprachoroidal administration via microcatheterization. The knowledge around the choice of agents for the respective forms of ME, specifically for neovascular AMD, has further matured over the last decade.

The use of microcatheter drug administration to the suprachoroidal space was reported in 11 subjects (eyes) with advanced neovascular AMD that failed to respond to conventional therapy (Chang, 2009). Treatment consisted of a single dose of bevacizumab (Avastin) and/or TA administered by suprachoroidal catheterization. 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 in this small group of subjects 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, with 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 TA 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 CSFT 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 RVO, 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 was administered to the submacular suprachoroidal space via a microcatheter.

BCVA improved by 2+ lines in 4 eyes and remained stable in 2 eyes. At 1 to 2 months, the hard exudates had almost completely resolved in all eyes. There were no complications observed.

In compassionate use cases in Switzerland, as of December 2021, Oxulumis® was used to deliver Triesence® in a total of 4 patients with 6 treatments (2 repeat treatments of the initially treated eye) with refractory ME of different etiologies (post-surgical ME, and non-infectious inflammatory cystoid ME). In contrast to their pre-treatment, these patients showed, after suprachoroidal administration of TA, a robust anatomical response with a quick onset, as well as visual improvements. No device-related AEs were described and no challenges with IOP rises after TA administration were encountered.

Compared to the administration of TA using a microneedle device at the pars plana, Oxulumis® is specifically designed to administer the drug via microcatheterization more posteriorly, potentially allowing for effective, higher concentrations of drug in the macular region and lower exposure of the anterior segment tissues to TA. This is expected to translate into better benefit/risk based on greater efficacy and a better safety profile for triamcinolone acetonide suspension (Triesence®) delivered to the suprachoroidal space using the Oxulumis®.

2.5 Benefit/Risk Assessment

To date, only a limited number of patients with ME have been treated with Triesence® administered with the Oxulumis®, limiting the ability to establish a robust benefit/risk profile. However, so far, no severe, serious adverse events or serious adverse device effects have been reported.

Suprachoroidal administration of triamcinolone acetonide suspension with Oxulumis®, in contrast to IVT injection, does not penetrate the vitreous cavity, and reaches more posterior sections of the retina, towards the macula, through the suprachoroidal space. The suprachoroidal route of administration is, therefore, expected to result in improved safety and tolerability, particularly with regard to complications, such as increased IOP in addition to potential improvement in efficacy due to the expected higher concentration of triamcinolone acetonide suspension in the retina and choroid. For repeat treatments over a longer period of time, the cataract risk would be expected to be smaller, although the duration of the current clinical trial with a single administration and follow-up of up to 24 weeks may not be long enough to provide definitive data on cataract progression.

Similarly, two recent 24-week studies with suprachoroidal TA and a microinjection device for the suprachoroidal space could not detect differences in cataract progression in DME (TYBEE trial) and ME due to non-infectious uveitis (PEACHTREE trial) (Price, Albini, and Yeh, 2020; Barakat *et al.,* 2021).

The combination of the Oxulumis® plus triamcinolone acetonide suspension (Triesence®) used in the current trial is expected to satisfy an unmet medical need to:

1. Reduce the risk of steroid-induced complications and adverse events
2. Enhance the efficacy of triamcinolone acetonide suspension compared to IVT administration
3. Prolong the efficacy of triamcinolone acetonide suspension compared to IVT administration
4. Ensure non-penetration of the vitreous cavity with the suprachoroidal administration.

Theoretical class risks associated with the suprachoroidal administration procedure include: endophthalmitis, choroidal hemorrhages, 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) to further reduce any potential procedural risks. The atraumatic design, a tangential angle of approach for device insertion (not perpendicular to the sclera once the sclera is reached in the insertion phase and not pointing to the vitreous cavity), and the 7mm length of the microcatheter, together with the rounded ball-like catheter tip, as well as control over the speed of the microcatheter deployment by adjustment of the Oxulumis® are design elements expected to prevent or substantially limit the risk of the adverse events summarized above. 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 optimize detection of any adverse events and other unforeseen risks and to potentially initiate countermeasures in a timely fashion, subjects will be monitored closely for at least 60 minutes after administration of triamcinolone acetonide suspension (Triesence®) to the suprachoroidal space. This monitoring includes an ophthalmoscopy, IOP measurements, and post-treatment retinal imaging. Additionally, visits following treatment, on day 1, week 1,

week 4, and every 4 weeks thereafter, will include multiple safety evaluations to ensure the detection and management of any emerging adverse events.

3 Objectives and Endpoints

3.1 Objectives

The objectives of this exploratory clinical trial are summarized in detail below.

3.1.1 Primary Objective

- To evaluate the safety and tolerability of two dose levels of triamcinolone acetonide administered with the Oxulumis® to the suprachoroidal space in subjects with DME.

3.1.2 Explorative Objective

- To explore the efficacy of two dose levels of triamcinolone acetonide with respect to VA changes, edema control, and durability of the treatment effect of suprachoroidal triamcinolone acetonide suspension (Triesence®) in subjects with DME.

3.2 Endpoints

3.2.1 Primary (Safety) Endpoints

The primary endpoint of this study is safety and tolerability as assessed by:

1. Frequency of ocular and systemic adverse events (treatment-emergent serious adverse events [SAEs] and treatment-emergent non-serious adverse events [TEAEs])
2. Frequency of adverse device effects (ADEs, serious ADEs [SADEs])

3.2.2 Exploratory Efficacy (and/or Safety) Endpoints

1. Mean Change in BCVA (ETDRS) at all study visits through Week 24 compared to baseline.
2. Percentage of subjects with vision gain and vision loss of at least 5, at least 10, and at least 15 letters at all study visits through Week 24 compared to baseline.
3. Time to subjects meeting criteria for follow-on treatment (per pre-specified criteria).
4. Mean Change in Central subfield thickness (CST) at study visits through Week 24 compared to baseline.
5. Mean Change in IOP at all study visits through Week 24 compared to baseline.

4 Clinical Trial Design

4.1 Overall Trial Design

This is a 24-week, randomized, two-arm, parallel-group, single-masked, clinical trial to evaluate safety and tolerability of two dose levels of suprachoroidal triamcinolone acetonide administered with the Oxulumis® ophthalmic administration in 20 subjects with DME. Triamcinolone acetonide suspension (Triesence®) will be administered to the suprachoroidal space in subjects with DME showing short-lived, limited, or no response to prior anti-VEGF or steroid therapy.

A focus of this trial is to evaluate the feasibility, safety, and tolerability of the ophthalmic administration of a low and a mid-dose of suprachoroidal triamcinolone acetonide suspension (Triesence®) with the Oxulumis® in DME. In addition, for the two dose groups of the trial, efficacy data on visual and anatomic changes will be collected.

To support the main objectives of this trial, a sample size of 20 treated subjects is estimated to be sufficient to detect common and very common adverse events. This safety information is relevant to inform further trials in the Oxulumis development program with respect to safety considerations including initial safety and feasibility experience with suprachoroidal administration procedure.

After a screening period, approximately 20 eligible DME subjects will be randomized using a 1:1 ratio to receive a single administration of one of two dose levels of TA (low dose, 2.4mg. or mid-dose, 4.0mg, respectively). Subjects in whom the study treatment cannot be administered will be replaced. Randomization will limit bias in assignment to one of the two dose levels.

The study will be conducted by retinal specialists in clinics or academic hospitals in the United States at up to 10 investigational sites.

Table 2 Treatment groups of two dose levels of triamcinolone acetonide suspension

Treatment Arm	Intervention	Subjects
1	One treatment with suprachoroidal **low dose (2.4mg)** triamcinolone acetonide	N=10
2	One treatment with suprachoroidal **mid-dose (4.0mg)** triamcinolone acetonide	N=10

Clinical visits will occur on Screening Day, Day 0, Day 1, Week 1, Week 4, and then every four (4) weeks thereafter for a total of twenty-four (24) weeks. From Week 4 on, subjects will be assessed for their need for follow-on treatment to determine the length of the treatment interval. The treatment visit V2, Day 0, can be split to allow for collection of baseline assessments on a different day than the administration of the study treatment. If a first attempt of study treatment is made in-clinic and treatment cannot be administered, a second attempt in an operating/procedure room is allowed. Only assessments feasible in an operating/procedure room setting need to be performed for this 2nd treatment attempt (for details see 1.3). The maximum time interval from starting activities of V2 to completion is 14 days. If the investigator decides to perform the Oxulumis procedure directly in an operating/procedure room, some assessments, as indicated in Section 1.3, need to be performed before the administration of study treatment. The follow-up period after a completed treatment administration will be up to twenty-four (24) weeks.

If subjects show a need for the next treatment of DME according to pre-specified criteria (for details see Section 6.1.8), participation in this clinical investigation will end, and an early termination/end of the study visit will be conducted at the respective visit date. In this case, the follow-up period will be shorter than 24 weeks.

For subjects who decide to discontinue study participation for any reason, the respective visit-day procedures will be extended to include the assessments scheduled for the EoS visit (or an EoS visit will be scheduled for the subject if notification of discontinuation is received outside of a scheduled study visit). For subjects in whom the treatment administration could not be completed on the respective treatment day(s), only a CFP and a SD-OCT need to be acquired. This visit will then be an early termination/end-of-study visit.

After completion of participation in this clinical trial, patients will continue treatment with therapeutic options determined by the treating retinal specialists in accordance with current medical practice for their DME.

Periodically, the coordinating investigator together with the medical monitor will review individual patient data as well as the totality of the safety data to recommend if the investigation should continue as is, continue with changes, or be terminated.

Study eyes shall 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.

Subjects' fellow eyes may continue to receive non-study treatment following guidelines and standards at the investigational site. Treatment of the fellow eye is not considered a study treatment. If the non-study eye requires management for DME, this should be carried out according to the local standards of care. Treatment of non-study eyes is not considered a study treatment.

4.2 Scientific Rationale for Study Design

4.2.1 Target Indication

The OXUCT-103 exploratory clinical trial will evaluate safety, tolerability, and the efficacy of administering Triesence® (2.4 mg) to the suprachoroidal space using the Oxulumis® in subjects with DME with short-lived, limited or no therapeutic response with prior therapy with ocular injections of steroids and/ or anti-VEGF agents. For details on the eligibility criteria see Section 5.1 and Section 5.2.

4.3 Justification of Dose

The current trial evaluates two different dose levels. The low dose is 2.4mg TA (60µl of a 40mg/ml TA suspension). The mid dose is 4.0mg TA (100µl of a 40mg/ml TA suspension). In a compassionate use program in Switzerland, both dose levels, 2.4mg and 4.0mg, were applied in patients with cystoid macular edema (CME) or post-surgical inflammatory edema refractory to standard treatments.

The current trial OXUCT-103 is expected to deliver safety and first exploratory data for two randomized dose groups. Trends for potential differences of the dose levels in peak efficacy and duration of effect will be explored.

It is anticipated that posterior deployment of the drug in the suprachoroidal space will lead to a safer, more tolerable, and effective treatment compared to IVT or subtenon administration. As eligibility for this trial is based on limited or no response to standard treatments, this trial uses another dose level of TA suspension as a control rather than exposing subjects the same or a similar treatment that they already had failed to respond.

The standard dose for IVT injection is 4.0mg. This dose level will be administered in the current trial in the mid dose group. In addition, 2.4mg TA will be used in the low dose group, Using the Oxulumis® device in both treatment groups, TA is expected to be administered closer to the location of the disease activity compared to other treatment approaches. Local concentrations of TA in the retinal tissues are expected to be higher compared to the same doses administered by IVT or subtenon injection.

4.4 End-of-Study Definition

The end of the study is defined as the time at which all subjects have either:

- Received the study drug and have been followed for 24 weeks; or
- Met criteria for follow-on treatment, or
- Have withdrawn consent, or
- Are lost to follow-up

A subject is considered to have completed the study if the subject has received the study drug and has completed the 8 study visits over the 24-week follow-up period, which includes the final EoS visit.

5 Study Population

5.1 Inclusion Criteria

Subjects will be eligible if they meet all the following inclusion criteria:

1. Able to understand and sign an informed consent form.
2. At least 18 years of age.
3. Have been diagnosed with Type 1 or Type 2 diabetes mellitus.
4. Have DME involving the center of the fovea in the study eye with central subfield thickness (CST) on SD-OCT of:

≥ 320 for males or ≥ 305 for females on Spectralis (Heidelberg) or

≥ 305 for males or ≥ 290 for females with Cirrus (Zeiss).

5. Have BCVA in the study eye of ≤73 ETDRS letters (approximate Snellen equivalent of 20/40 or worse) at the screening visit. The eligibility will be assessed based on the ETDRS BCVA letter score.
6. Short-lived, limited, or no response to prior ocular injection therapy (*e.g.*, IVT or subtenon) of steroids and/or anti-VEGF agents based on the investigator's assessment. Short-lived in this trial is defined as less than 4 weeks.
7. For women who are not postmenopausal (*i.e.*, at least12 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 (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit (Day 0), if study

participation ends before visit 7, Week 12. 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.

8. Males must agree to use a barrier method of contraception from the treatment visit (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit (Day 0), if study participation ends before visit 7, Week 12.
9. 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 the participation in this trial.

5.2 Exclusion Criteria

Subjects will be eligible if they do not meet any of the following exclusion criteria:

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 concurrence of the Oxular Medical Monitor, may either put the subject at risk because of participation in the trial, may influence the results of the trial, or the subject's ability to participate in the trial.
2. Macular edema considered due to a cause other than diabetes mellitus in the study 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).
4. Conditions, in the study eye, that may render the suprachoroidal microcatheter insertion and deployment difficult or subject the patient to excessive risk of complications. Examples include but are not limited to ocular surface diseases 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 diseases 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.
10. History of glaucoma surgery, and or anti-glaucoma therapy with more than two active substances (in separate or a combination preparation) at the screening visit are exclusionary.
11. History of closed-angle glaucoma.
12. IOP <6mmHg (hypotony) in the study eye at screening.
13. Spherical equivalent of the refractive error of −6 diopters of myopia or worse (prior to cataract or refractive surgery) at screening.
14. Cataract or other media opacity that limits the ability to obtain the planned imaging assessments.
15. History of retinal detachment.
16. Subjects who were previously treated for DME in the study eye must not have received:
    a.) an intravitreal anti-VEGF treatment within four (4) weeks before screening. The 4-week interval before screening is used for IVT bevacizumab, ranibizumab, aflibercept, brolucizumab, or faricimab (*i.e.,* a combined Anti-VEGF/anti-Ang2 agent), as also inclusion criterion No. 6 on therapeutic response must be met.
    b.) Prior treatment with SUSVIMO® (Port Delivery System) implant at any time is exclusionary.
    c.) Intra- or periocular/subtenon triamcinolone acetonide suspension within 12 weeks before screening.
    d.) Intravitreal dexamethasone implant (Ozurdex®) within 24 weeks before screening.

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

f.) Prior treatment with suprachoroidal steroids (commercial, investigational, or off-label) at any time is exclusionary.

17. 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.
18. Treatment with ocriplasmin (Jetrea®) at any time.
19. 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.
20. 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.
21. Hypersensitivity to triamcinolone acetonide, or any of the excipients in the Triesence® formulation or Oxulumis® device components.
22. Active malignancy or history of malignancy within the past five (5) years.
23. Uncontrolled diabetes with a hemoglobin A1c (HbA1c) > 12% or any other uncontrolled systemic disease at screening.
24. Uncontrolled hypertension, defined as blood pressure with a systolic value of ≥ 160mmHg or a diastolic value of ≥ 100 mmHg upon repeat assessment at screening.
25. History of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure, or any acute coronary event within 90 days before screening.
26. 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.
27. Subjects who were previously randomized in this trial, but in whom administration of study treatment could not be completed.

5.3 Lifestyle Considerations

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

5.4 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently enrolled in the study. 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.

Individuals who do not meet the criteria for participation in this study (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 shall be assigned a new subject number and sign a new ICF for each screening/rescreening event.

6 Study Intervention and Concomitant Therapies

6.1 Study Intervention Administered

In the OXUCT-103 clinical trial, Triesence® will be administered with the Oxulumis® Ophthalmic Administration Device to the suprachoroidal space of study eyes.

6.1.1 Oxulumis® Ophthalmic Administration Device

The Oxulumis® ophthalmic administration device is a sterile, semi-automatically operated, minimally invasive, single-use device. It is designed to deploy a therapeutic drug via a delivery-guiding illuminated ophthalmic microcatheter to ophthalmic compartments, *e.g.*, to the suprachoroidal space. The illumination provides confirmation that the microcatheter is inserted and deployed correctly, prior to administration of the therapeutic drug. With a 27G insertion needle and an 7mm microcatheter, the Oxulumis® administration device is well suited to administer suspensions of drugs like Triesence® to the posterior retina.

For the Oxulumis® administration procedure, subjects may receive topical anesthetics (*e.g.*, anesthetic eye drops, gels, local subconjunctival, or anesthetic injections, typically subtenon administrations) to reduce potential pain and discomfort during the procedure.

As for IVT injections, antiseptic conditions shall be applied following the standard procedures at the investigational site. Colorless disinfectants for ophthalmic use, *e.g.,* chlorhexidine or application of PVP iodine followed by sterile rinsing with saline, are recommended. Details about the Oxulumis® device and the ophthalmic administration are available in the Instruction for Use (IFU) manual.

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 Triamcinolone acetonide (Triesence®)

Triesence® (Triamcinolone acetonide [TA] 40 mg/mL; Novartis Pharmaceutical Corporation [former subsidiary: Alcon Laboratories, Inc.]) is a synthetic corticosteroid with anti-inflammatory action approved by the United States Food and Drug Administration (US FDA) for IVT administration for the treatment of ophthalmic diseases including sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. The suprachoroidal microcatheterization with the Oxulumis® is an investigational route of administration for Triesence®. In the context of other development programs, clinical data on the generally favorable safety of other forms of suprachoroidal administration of TA have been generated (see Section 2.4.2).

Hypersensitivity reactions may occur to triamcinolone acetonide or any of the excipients in the Triesence® formulation. Per the US prescribing information of Triesence®, each mL of the sterile, aqueous suspension provides 40 mg of triamcinolone acetonide, with sodium chloride for isotonicity, 0.5% (w/v) carboxymethylcellulose sodium and 0.015% polysorbate 80. It also contains potassium chloride, calcium chloride (dihydrate), magnesium chloride (hexahydrate), sodium acetate (trihydrate), sodium citrate (dihydrate) and water for injection. Sodium hydroxide and hydrochloric acid may be present to adjust pH to a target value 6 – 7.5.

6.1.3 Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate conditions (*e.g.*, temperature) have been maintained during transit for all study interventions received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only subjects enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study interventions 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.

4. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (*i.e.*, receipt, reconciliation, and final disposition records).
5. 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.

6.1.4 Assignment to Study Intervention

This is a double-arm study in which all enrolled subjects will be randomized at a 1:1 ratio to receive either low (2.4mg) or mid (4mg) dose of TA in a single-masked manner. Accordingly, approximately 10 subjects will be treated at each of the two dose levels. 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 are randomized but the study treatment cannot be administered, these subjects will be replaced, targeting approximately 20 treated subjects total.

6.1.5 Masking

This is a single masked study. The study subjects will be masked for the treatment dose allocation. No masking of treatment assignment nor the dose is foreseen for the Investigator, the site staff nor the Sponsor team involved in the trial. Subjects will only be able to receive information about their treatment assignment after the end of the study. No impact on masking is expected from the potential repeat of procedural attempts in an operating/procedure room. In case of any emergency, the treating site investigator can share the dose level upon request and needs to document all details regarding this procedure.

6.1.6 Study Intervention Compliance

The investigator will administer the study intervention after the subject had been randomized to one of the two treatment arms. The date and time of each dose administered will be recorded in the source documents. The study intervention, the allocated treatment dose and study subject identification will be confirmed at the time of dosing by a member of the study site staff taking all the necessary measures to maintain subject's masking.

6.1.7 Dose Modification

There is no planned dose modification in this study.

6.1.8 Follow-on Treatment

Subjects will be followed with regular visits (from Week 4 on with monthly intervals) to assess the safety and the course of visual and anatomic outcomes. From Week 4 on, subjects

will be evaluated against prespecified criteria indicating the need for follow-on treatment (*i.e.*, indicating the end of the current treatment interval).

Criteria are as follows:

- At least 75 μm increase in CSFT on SD-OCT compared to the best-achieved CST value since the baseline visit [Visit 2, day 0].
- A decrease in BCVA of at least 10 ETDRS letters from the best achieved BCVA since the baseline visit [Visit 2, day 0], that in the opinion of the investigator, is due to worsening of DME.

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

If one or both of the above criteria are met, the subject will be eligible for follow-on treatment and will be managed according to local standard of care.

If subjects meet the criteria for follow-on treatment in the study, the visit will be considered EoS visit, and the assessment scheduled for EoS visit will be performed.

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

6.1.9 Treatment for Complications of the Underlying Disease

A subject may receive other treatment for complications of the underlying diseases at any time if they experience any complications other than recurrence or progression of ME that require urgent management (*e.g.*, progression to high-risk PDR, intraocular lens replacement for visually significant cataract, neovascularization, etc.).

Any ocular or systemic treatments already clinically indicated or planned at the time of patient referral to this study, should be performed before further consideration of study participation. After such treatments, the post intervention intervals defined in the exclusion criteria must be met to consider participation or rescreening, respectively. The date and time of medication administered to treat complications as well as the name and dosage regimen of the medication shall be recorded. If the treatment administered has an effect on DME, *e.g.*, intravitreal anti-VEGF injections, the study participation for this subject ends with the visit, where the decision on the need for the treatment of a complication has been recorded and an early termination/end-of-study visit will be performed.

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

There will be no continued access to the study intervention, specifically not to the investigational Oxulumis® ophthalmic administration device after the end of the study.

6.1.11 Treatment Overdose

The study includes a single administration of one of two dose levels of the study drug assigned by a central randomization procedure. The risk of overdose from receiving study intervention is very low, with overdose defined as administration of a dose greater than 4.0mg TA. Overdose resulting from a device malfunction will be captured as an Adverse Device Effect (ADE). In the event of an accidental overdose of triamcinolone acetonide suspension (Triesence®), 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.

6.2 Prior and Concomitant Therapy

6.2.1 Permitted Medications and/or Treatments

Any treatment that the subject receives at the time of enrollment or receives during the investigation shall be recorded along with:

- Reason for use
- Dates of administration including start and stop dates
- Start and stop dates for changes in medications and changes in dose
- Dosage information including dose and frequency

Intranasal, inhaled, and topical glucocorticoid medications or stable systemic steroids are allowed. For further guidance see also Table 3.

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

6.2.2 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 administered with the Oxulumis® prior to screening (see the exclusion criteria in Section 5.2 or during the trial as specified in Table 3 in this section. This includes medications for DME administered locally (*e.g.*, IVT, suprachoroidal, topical, juxtascleral, or periorbital routes).

If the investigator determines that any of these treatments is needed because of worsening of DME, based on follow-on criteria ins Section 6.1.8, the procedures foreseen for the respective

visit-day will be extended to include the assessments mandatory for an EoS visit. This visit will then be an early termination/end-of-study visit.

The treatments in Table 3 render a subject not eligible for this study and are considered a "follow-on" treatment triggering the end of study participation when intended to be administered to a subject participating in this trial.

Table 3 Time Intervals of ME Medication before Screening and Qualification as Follow-on Treatment

Therapy	Forbidden interval before screening	Qualifies as Follow-on Treatment
Ranibizumab or bevacizumab (IVT)	≤ 4 weeks	Yes
Aflibercept (IVT)	≤ 4 weeks	Yes
Faricimab or brolucizumab (IVT)	≤ 4 weeks	Yes
Intra- or periocular/subtenon injection of triamcinolone acetonide	≤ 12 weeks	Yes
IVT dexamethasone implant (Ozurdex®)	≤ 24 weeks	Yes
IVT fluocinolone implant	At any time	Yes
IVT Port Delivery System	At any time	Yes
Suprachoroidal Steroids	At any time	Yes
Vitrectomy	≤ 12 weeks	Yes
Focal (Macular) Laser Photocoagulation	≤ 16 weeks	Yes
Panretinal Laser Photocoagulation (PRP)	≤ 16 weeks	Yes
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	Yes

6.2.3 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 not be coded, and verbatim original terms recorded on the eCRF will be presented as data listings.

6.3 COVID-Related Measures

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

The US 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 evaluates a single suprachoroidal administration of TA in ME. The following measures will be taken:

- Assessment of 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.
- 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.
- If restrictions would not allow travel of treated subjects to the investigation site, safety follow-ups could be performed by a local ophthalmologist.

7 Discontinuation of Study, the Study Intervention and Subject Discontinuation/Withdrawal

7.1 Discontinuation of the Trial

This trial will be subject to continuous safety assessment by the investigators and the Medical Monitor with periodic, at least monthly meetings or distribution of safety update communications, to discuss individual and aggregate subject data. If any important safety concerns (*e.g.*, SAEs, SADE, AESIs) arise, dosing of further subjects could be temporarily halted or stopped. If further dosing is stopped, study visits of enrolled subjects with *e.g.*, follow-up visits including safety evaluations will still be performed as foreseen. If the Sponsor, Medical Monitor or designee, study center monitor, or appropriate regulatory officials discover conditions arising during the trial that indicate that the study should be halted, this action may be taken after appropriate consultation.

In addition, both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Sponsor will timely notify the US FDA and respective IRB following applicable regulations, *e.g.*, 21 CFR 312.56(d) (drugs); 21 CFR 812.150 (devices), and other regulatory authorities as applicable in writing of the trial's early termination.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) guidelines (ICHE6 R2), and local regulatory requirements.

7.2 Discontinuation of Study Intervention

Discontinuation of the study intervention is not foreseen, as this is a one-time ophthalmic administration 2.4 mg or 4mg dose of Triesence® to the suprachoroidal space at the baseline visit. See Section 7.3 below for discontinuation in case of inability to administer the study medication.

7.3 Subject Discontinuation/Withdrawal from the Study

Each subject should remain in the clinical trial until completion of the required follow-up period; however, a subject's participation in the trial may be discontinued at any time. Should this occur, the reason for discontinuation shall be documented in the withdrawal form. Reasons for discontinuation include the inability to administer trial medication with the Oxulumis® device.

Subjects shall be informed about their right to withdraw from the trial at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical trial 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 defects 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, *e.g.*, lack of improvement or clinically meaningful deterioration of DME after administration of Triesence® with the Oxulumis® device.

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 trial until the completion of the trial.

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

- Subject refuses to continue participating in the trial
- Subject's non-compliance

- Subject's participation is terminated by the PI or investigator, although the subject consented since participation is no longer medically appropriate
- Subject is 'lost to follow up' (for details see Section 7.4).

If a subject withdraws from the clinical trial, the site will record the subject's reasons for withdrawal on a Withdrawal Case Report Form (CRF). When subject withdrawal from the clinical trial is due to an adverse event the subject will be followed until 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.

7.4 Lost to Follow-up

A subject is considered "lost-to-follow-up" if the subject does not adhere to the scheduled follow-up visits but has not explicitly requested to be withdrawn from the clinical trial (this does not apply to missed visits). Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:

1. A subject will be considered 'Lost to Follow Up' after a minimum of two phone calls of a physician or delegate at the investigational site to the subject or contact. These two phone calls need to be documented in the subject's records.
2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner and a copy of this letter should be maintained in the subject's records.

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

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the schedule of activities (SoA, see Section 1.3). Adherence to the study design requirements, including those specified in the SoA in Section 1.3, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. 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.

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.

8.1 Evaluations Performed During Investigational Visits

8.1.1 Screening Visit (Visit 1, Days -21 through -2)

- (Informed) Consenting
- Eligibility criteria review
- Obtaining demographic data and medical history
- Concomitant medication review
- AEs and ADEs collection
- Height, weight, vital signs (body temperature, blood pressure, and heart rate)
- Lab assessment
- Urine pregnancy test for females of childbearing potential
- Slit-lamp BM (OU)
- IOP measurement (OU)
- Best-corrected visual acuity using ETDRS protocol (OU), duplicate assessments for either eye
- Dilated indirect ophthalmoscopy (OU)
- Overall assessment of expected procedural complexity (Categories: Low, Medium, High)
- Axial length measurement when available (OU)
- SD-OCT (OU)
- OCT-A (OU)
- Peripheral SS-OCT or UWF SD-OCT when available (OU)
- Color fundus photographs (OU)

8.1.2 Baseline visit (Visit 2, Day 0)

Activities of the baseline visit can spread over up to 14 days. As facilities with the operating/procedure room may not have the full spectrum of ophthalmic assessment or imaging devices, the visit schedule varies for an in-clinic baseline visit and a baseline visit in

an operating/procedure room. If treatment administration in an operating/procedure room is intended, some assessments need to be performed before, as the respective equipment may not be present in an operating/procedure room. If the investigator decides for a 2nd treatment attempt in an operating/procedure room only a selected number of assessments need to be repeated.

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 attempt for treatment administration.

8.1.2.1 In-Clinic baseline visit (Visit 2, Day 0)

Some assessments only need to be completed after administration of study treatment (denoted as "only post treatment) but not after an unsuccessful treatment attempt as indicated in brackets below ("post attempt")

Pre-treatment:

- Eligibility criteria review, partial: only lab results and updates since screening visit
- Randomization
- Concomitant medication review
- AEs and ADEs collection
- Urine pregnancy test for females of childbearing age
- Slit-lamp BM in both eyes (OU)
- IOP measurement in both eyes (OU)
- Best-corrected visual acuity using ETDRS protocol (OU)
- Dilated indirect ophthalmoscopy (OU)
- SD-OCT (SE)

Treatment

- Administration of study medication in study eye (SE)

Post-treatment:

- AEs and ADEs collection (post attempt and post-treatment)
- IOP measurement in the SE (repeat measurements, at least 2 over a period of 60min, only post-treatment)
- Dilated indirect ophthalmoscopy (SE) (post attempt and post treatment)

- SD-OCT (SE) (post attempt and post treatment)
- Peripheral SS-OCT or UWF SD-OCT when available (SE) (only post treatment)
- Color fundus photographs (SE) (post attempt and post treatment)
- Retinal Physician's documentation and assessment of administration procedure (post treatment attempt partially filled in).
- Subject's experience assessment (only post treatment)

8.1.2.2 Operating/Procedure Room baseline visit (Visit 2, time window for start of V2 activities to completion: 14 days)

All listed assessments need to be completed.

This visit variant will be used in case the investigator:

- Decides directly to perform the treatment in an operating/procedure room ("direct to OR/PR")
- Decides for a 2nd treatment attempt in an operating/procedure room after a first in-clinic Visit 2, which did not result in administration of study treatment. In this case, some assessment do not need to be repeated as indicated in brackets below)

The day of completion of administration of study treatment will be used for calculation of further visit dates and windows.

Pre-treatment:

- Eligibility criteria review, partial: (for direct to OR/PR: only lab results and updates since screening visit), for 2nd treatment attempt: only updates since first attempt)
- Randomization (for direct to OR/PR mandatory, may be done prior to OR/PR session)
- Concomitant medication review (mandatory, may be done prior to OR/PR session)
- AEs and ADEs collection (mandatory)
- Urine pregnancy test for females of childbearing age (to be performed 1x on the day of the treatment attempt)
- Slit-lamp BM in both eyes (OU, for direct to OR/PR mandatory; may be done prior to OR/PR session; no repeat for 2nd treatment attempt)
- IOP measurement in both eyes (OU, mandatory)
- Best-corrected visual acuity using ETDRS protocol (OU, for direct to OR/PR mandatory, may be done prior to OR/PR session; no repeat for 2nd treatment attempt)
- Dilated indirect ophthalmoscopy (OU, mandatory)

- SD-OCT (SE, for direct to OR/PR mandatory, may be done prior to OR/PR session, no repeat for 2nd treatment attempt)

Treatment

- Administration of study medication in study eye (SE)

Post-treatment:

- AEs and ADEs collection (mandatory)
- IOP measurement in the SE (repeat measurements, at least 2 over a period of 60min post-treatment, mandatory)
- Dilated indirect ophthalmoscopy (SE, mandatory)
- Retinal Physician's documentation and assessment of administration procedure (for direct to OR/PR to be completely filled; completion of previously started version, if 2nd treatment attempt, mandatory).
- Subject's experience assessment (post treatment, mandatory)

8.1.3 Visits 3 through 9 (Day 1 – Week 20)

The following visits have evaluations to be performed as listed below: Visit 3 (Day 1 +1), Visit 4 (Week 1 ± 3 days), Visit 5 (Week 4 ± 5 days), Visit 6 (Week 8 ± 5 days), Visit 7 (Week 12 ± 5 days), Visit 8 (Week 16 ± 5 days), and Visit 9 (Week 20 ± 5 days)

- Concomitant medication review
- AEs and ADEs collection
- Urine pregnancy test for females of childbearing age (except for visit 2, Day1).
- Slit-lamp BM (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)
- IOP measurement (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)
- Best-corrected visual acuity using ETDRS protocol (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)
- Dilated indirect ophthalmoscopy (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)
- SD-OCT (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)
- OCT-A (OU) on Visit 7 (Week 12 ± 5 days)
- Peripheral SS-OCT or UWF SD-OCT when available (SE)
- Color fundus photographs (SE), for both eyes (OU) on visit 7 (Week 12 ± 5 days)

- Subject experience assessment on visits 3 (Day 1 + 1 day), 4 (Week 1 ± 3 days), and 5 (Week 4 ± 5 days)
- Follow-on treatment administration if prespecified criteria are met from Visit 5, Week 4 onward

8.1.4 End of study visit (Visit 10, Week 24± 5 days)

- Concomitant medication review
- AEs and ADEs collection
- Urine pregnancy test for females of childbearing age.
- Slit-lamp BM (OU)
- IOP measurement (OU)
- Best-corrected visual acuity using ETDRS protocol (OU)
- Dilated indirect ophthalmoscopy (OU)
- SD-OCT (OU)
- OCT-A (OU)
- Peripheral SS-OCT or UWF SD-OCT using accessory lenses (SE)
- Color fundus photographs (OU)
- Follow-on treatment administration if prespecified criteria are met

8.1.5 Early termination (ET) visit

Visits in which subjects meet follow-on treatment criteria as defined in Section 6.1.8 will be considered early termination (ET) visits. The actual visit schedule will be extended by the assessments foreseen for the end of study (EoS)/Week 24 visit as defined in Section 8.1.4.

8.1.6 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.

8.2 Administrative and General/Baseline Procedures

8.2.1 Consent form completion

Following Institutional Review Board (IRB) approval and before any study-related procedure, potential subjects will be asked to sign a written informed consent form (ICF) by the investigator or the study staff. 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. Additional guidance on the informed consent process can be found in Section 10.3.

8.2.2 Demographic information and medical history

The screening visit will obtain information about the subject's demographics, medical/surgical history, and factors pertaining to the use of Oxulumis® to administer Triesence® to the suprachoroidal space.

8.2.3 Urine pregnancy test

For women of childbearing potential, a negative urine pregnancy test at screening and baseline visits is required for eligibility, and then every 4 weeks through the end of study participation (Visit 5-9).

8.2.4 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 enrollment or receives during the study shall be recorded at each visit along with:

- Reason for use
- Dates of administration including start and stop dates
- Start and stop dates for changes in medications and changes in dose
- Dosage information including dose and frequency

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

8.2.5 Weight, Height, Vital Signs

At the screening visits the subject's weight, height, and vital signs will be assessed. Vital signs include measuring of body temperature, of blood pressure after 5min of sitting in a relaxed position, and of heart rate. If blood pressure values would render subjects not eligible per exclusion criterion No. 24, at the same visit, 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.

8.2.6 Oxulumis® use to administer Triesence®

Details about the use of Oxulumis® to administer Triesence® are available in the Oxulumis® IFU manual.

8.2.7 Subject Experience Assessment

Details about the subject's experience during and after the procedure will be collected in interview form (for details see Section 13.1 for the questionnaire for Visit 2, Day 0, and Section 13.2 for Visits 3 through 5).

If the Oxulumis® procedure is repeated after a first in-clinic attempt with an attempt in an operating/procedure room, the subject's experience questionnaire will only be completed on with completion of administration of the study treatment.

8.2.8 Retinal physician's Documentation and Assessment of the Administration procedure

The retinal physician will document the procedure details and complete the procedure assessment questions in the source data using the questionnaire provided in Section 13.3.

If the treatment administration attempts are repeated after a first unsuccessful in-clinic attempt followed by performance of the Oxulumis® procedure in an operating/procedure room setting, only one "Retinal Physician's Documentation and Assessment of the Administration Procedure" will be completed with the final procedure reflecting experiences for all procedural attempts and treatment.

8.2.9 Follow-on Treatment

For details on the assessment of the need for follow-on treatment see Section 6.1.8.

8.2.10 Disposition of samples

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

8.3 Ocular Assessments

8.3.1 Best Corrected Visual Acuity (BCVA)

Manifest refraction will be conducted prior to BCVA assessment at every visit.

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, as specified in the Schedule of Activities, (Section 1.3). All BCVA assessments 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 differences are 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 per visit, if duplicate BCVA assessments are performed sequentially, *i.e.*, no other study assessment in between the 1st and the 2nd BCVA assessment.

BCVA assessment will be performed by a certified VA examiner.

8.3.2 Axial length measurement

Axial length will be measured at the screening visit 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). 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.

8.3.3 Slit-lamp biomicroscopy

Subjects' anterior ocular structure (including the assessment and grading of the 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 (Section 1.3). Slit-lamp biomicroscopy in the fellow eye will be performed at screening, baseline, Week 12, and Week 24/ET, as specified in the SoA (Section 1.3). The exact method for assessing and grading lens opacities/cataracts is described in the study procedure manual.

8.3.4 IOP measurement

Intraocular pressure (IOP) of the study eye will be measured at every visit using Goldmann applanation tonometry or Tono-pen™, as specified in the SoA (Section 1.3). The same method of IOP measurement as chosen at the screening visit must be used throughout the study for each individual subject to allow for comparability of assessments. After the treatment intervention on the baseline visit, IOP measurement in the study eye must be repeated at least twice over a period of 60 minutes after treatment.

IOP measurement in the fellow eye will be measured at screening, baseline, Week 12, and Week 24/ET, as specified in the SoA (Section 1.3).

8.3.5 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 the SoA (Section 1.3). A

post-dose evaluation shall be performed immediately after the administration of the study treatment.

Dilated indirect ophthalmoscopy in the fellow eye will be performed at screening, baseline, Week 12, and Week 24/ET, as specified in the SoA (Section 1.3).

8.3.6 SD-OCT, and Peripheral OCT assessments

Retinal characteristics will be evaluated at every visit using SD-OCT. Key imaging parameters are described below but may be adapted and if necessary extended to fulfill the objectives of this trial. More details will be described in more detail in the trial's imaging manual. All OCT images will be captured and uploaded to a central repository at a central reading center (CRC) via an encrypted secure website. All OCTs images will be electronically archived at the investigational sites as part of the source documentation.

Acceptable SD-OCT machines are Spectralis (Heidelberg Engineering GmbH) and Cirrus (Carl Zeiss Meditec AG). Other devices would need to be approved by the sponsor upon request. In this case, device specific CST values for eligibility assessment will be provided as for the devices mentioned in inclusion criterion No.4. The same device should be used for screening and the subsequent follow-up assessments for each subject.

For Spectralis devices the below parameters should be used to acquire two scans:

- Volume Scan (centered on the fovea): 20° x 20°, 97 Section with ART set to 16 and High-Resolution mode (HR)
- Volume Scan (centered on the fovea): 30° x 5°, 7 Section with ART set to 25 and HR)

For Cirrus devices the below parameters should be used to acquire two scans:

- 512x128 Macular Cube
- HD 5 Line Raster

Peripheral SS-OCT (will be assessed in sites with available capabilities using appropriate imaging parameters).

OCT imaging, *i.e.*, SD-OCT and, when available peripheral OCT, will be performed at each visit for the study eye. Exceptions are:

- If the Oxulumis® procedure is not completed, only a post treatment attempt SD-OCT is required. The optional peripheral OCT is not assessed, as its main purpose is to visualize the suprachoroidal drug bleb post study treatment.

- If the Oxulumis® procedure is completed in an operating/procedure room with neither access to an SD-OCT nor Peripheral OCT in this facility on Day 0, Visit 2, these are not required to be performed post treatment. Assessments on Day 1 will be sufficient.

For the non-study eye, SD-OCT and, when available.

8.3.7 OCT-Angiography

The anatomical state of the retinal vasculature will be evaluated by optical coherence tomography angiography (OCT-A). Key imaging parameters are described below but may be adapted and if necessary extended to fulfill the objectives of this trial. More details will be described in more detail in the trial's imaging manual. OCT-A images will be captured and uploaded to a central repository at a CRC via an encrypted secure website. All OCT-As will be electronically archived at the investigational sites as part of the source documentation.

The preferred OCT-A machine for retinal vascular diseases is the ZEISS PlexElite. The Optovue can also be used but may have fewer wide-angle choices. The same device should be used for screening and the subsequent follow-up assessments for each patient. The preferred scan acquisition protocols for retinal vasculopathies are 3x3 and 9x9 scans.

OCT-A imaging, will be performed at screening, Week 12, and Week 24/EOS visits, as specified in the SoA (Section 1.3).

8.3.8 Color fundus photography

Retinal anatomy will be evaluated by Color Fundus Photography (CFP). In case of non-completion of the procedure in the clinic, a CFP is required to be acquired in the study eye. Key imaging parameters are described below but may be adapted and if necessary extended to fulfill the objectives of this trial. More details will be described in more detail in the trial's imaging manual. Fundus photography will be captured and uploaded to a central repository at a CRC via an encrypted secure website. All CFPs will be archived at the site as part of the source documentation.

CFP in the study eye will be captured at all visits, as specified in the SoA (Section 1.3). If the Oxulumis® procedure is completed in an operating/procedure room with no access to a CFP in this facility on Day 0, Visit 2, it is sufficient to perform the CFP foreseen for Day 1, Visit 3.

CFP in the fellow eye will be captured at screening, Week 12, and Week 24/ET, as specified in the SoA (Section 1.3).

A CFP shall 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 (see Table 4). Additional images to document the site of drug deployment using infra-red imaging will be taken.

4 Wide Field imaging (4WF): Take one FR (Fundus Reflex) and stereo pairs of F1W and F2W, and single images F4W and F5W of each eye for a minimum of 7 images per eye, 14 total images OU. In addition, infra-red images of the site of deployment will be taken.

Ultrawide Field (UWF) imaging: Perform 2 Central Wide Field single images. In addition, infra-red images of the site of deployment will be taken.

Table 4 Overview of Imaging Systems and Required Field of View for Wide-Field Color Funds Photographs

Imaging System	Required Image Field of View (FOV)
Clarus	Take all images at 133-degree capture mode
Optos	Take all images at 200-degree capture mode
Spectralis	Take all images using a 102-degree lens using ART 15

8.4 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 8.3.4), slit-lamp biomicroscopy (Section 8.3.3), dilated indirect ophthalmoscopy (Section 8.3.5), SD-OCT (Section 8.3.6). and pregnancy test (Section 8.2.3).

8.4.1 Adverse Events and Adverse Device Effect collection

At every visit, the investigator (or designee) will assess for and record all adverse events (AEs) and adverse device effects (ADEs) that occur from the time the informed consent is signed until the end of the study.

8.4.2 Safety laboratory tests

Blood samples for routine clinical laboratory tests will be collected at the screening visit (Visit 1, D -21 to -2). Screening laboratory tests will be performed in local CLIA certified laboratories. Tests may be repeated once at the discretion of the investigator. The minimum tests to be performed include the following:

- Non-fasting chemistry (blood): sodium, potassium, chloride, bicarbonate, albumin, alkaline phosphatase, aspartate amino transferase, alanine amino transferase, bilirubin direct, bilirubin indirect, total bilirubin, creatinine, blood urea nitrogen, total protein, calcium, phosphorus, and hemoglobin A1c
- 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
- Thyroid: thyroid-stimulating hormone

The investigator shall review the laboratory report, document the review, and record any clinically significantly 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. The laboratory reports shall 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 subject management or are considered clinically significant by the investigator, then the results shall be recorded in the CRF.

8.4.3 Height, Weight, Vital Signs, and Blood Pressure

Blood pressure and heart rate will be measured after 5min of sitting in a relaxed position. If blood pressure values would render subjects not eligible per exclusion criterion No. 24, at the same visit, 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. Height and Weight will be used calculate the BMI (kg/m^2).

8.5 Safety Reporting, Adverse Events (AEs), and Serious Adverse Events (SAEs)

All subjects enrolled to 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) considering the definitions also of 21 CFR 312.31(a) can be found in Section 11.

The definitions of device-related safety events including adverse device effects (ADEs), device deficiencies, and serious adverse device effects (SADEs) can be found in Section 11.3, Section 11.4, and Section 11.6.

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 all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study (see Section 7). 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 causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.7.

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the signing the ICF until EoS/ET visit (Week 24) at the timepoints specified in the SoA (see Section 1.3).

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. The AEs and SAEs that begin between obtaining the signed ICF and the start of study intervention will be categorized as non-treatment emergent AEs/SAEs. This also includes AEs/SAEs, which continue after the start of study intervention but do not worsen in severity.

The AEs and SAEs that begin after start of the study intervention, and those existing pre-dose that worsened in severity post-dose will be considered treatment-emergent AEs and SAEs.

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").

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. 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 see Section 12.

Investigators are not obligated to actively seek information on AEs or SAEs after 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.

8.5.2 Method of Detecting AEs and SAEs

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. To limit bias in safety reporting, subjects are masked to their dose level. The study team must not disclose the dose level received until after the end of the study except for emergency situations.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 11.7.4.

8.5.4 Disease-related events and/or Disease-related outcomes not qualifying as AEs or SAEs

No specific disease-related events not qualifying as AEs or SAEs are defined for this clinical trial. 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 need for follow-on treatment (as defined in Section 6.1.8) would only qualify as an AE, if significant or unexpected in the opinion of the investigator.

8.5.5 Regulatory Reporting Requirements for 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:

- 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)

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

8.5.6 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 8.5.1). AESIs comprise the following prespecified terms based on general considerations on potential safety risks with suprachoroidal device deployment and treatment.

- Suprachoroidal hemorrhage
- Sterile intraocular inflammation
- Endophthalmitis
- Choroidal bacterial infection
- Retinal detachment
- Retinal perforation
- Rise of intraocular pressure above 30 mmHg
- Rise of at least 10 mmHg from baseline IOP
- Severe pain or discomfort after administration of IP

To consider an acute IOP rise after the treatment administration procedure as an AESI, the rise must continue beyond the 60min observation period on Day 0, Visit 2, or require medical intervention, *e.g.*, a paracentesis to lower IOP. For a persistent rise of the IOP detected upon the follow-up visits, to consider it as meeting AESI criteria, the rise must be maintained over 2 successive visits.

8.5.7 Device Deficiencies

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

The definition of a medical device deficiency as well as processes and time periods for detection, notification, reporting, and follow-up of the medical device deficiencies can be found in Section 11.4.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Sections 8.5 of this protocol.

8.5.8 Contraception Guidance

According to the USPI for Triesence®, (Alcon Laboratories Inc., 2007), administration in pregnancy can cause fetal harm with first trimester use. Multiple cohorts and case-control studies in humans suggest that maternal corticosteroid use 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 5.1.

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.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
- implantable
- intrauterine device

- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

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.

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 (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit (Day 0), if study participation ends before visit 7, Week 12.

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.

Male participants must agree to use a barrier method of contraception from the treatment visit (Day 0) until the end of trial participation, or for at least 12 weeks from the treatment visit Day 0, if study participation ends before visit 7, Week 12.

8.5.9 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 a 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 8.5 and Section 8.5.1.

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 Visit 2. If the pregnancy is detected after administration of study treatment, the patient 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 Statistical Considerations

This is a 24-week, randomized, two-arm, parallel-group, single-masked, clinical trial to evaluate safety and tolerability of two dose levels of suprachoroidal triamcinolone Acetonide Administered with the Oxulumis® ophthalmic administration in subjects with Diabetic Macular Edema.

9.1 Statistical Hypothesis

The present clinical trial is a single-masked, two-arm study to evaluate safety and tolerability of two dose levels, therefore no formal statistical hypothesis was developed.

9.2 Sample Size Determination

A total of approximately 20 subjects will receive a single treatment with Triesence® administered with the Oxulumis® to one eye, the study eye. Subjects in whom study treatment cannot be administered will be replaced.

The sample size is not based on power calculations. It is chosen based on clinical experience and considered to be adequate to fulfill the objectives of the clinical trial. A sample size of 20 subjects is estimated to detect common and very common adverse events, which is key to inform further trials in the Oxulumis® development program in respect to safety considerations.

9.3 Analysis Sets

In this clinical trial, the following definitions for analysis sets will apply.

9.3.1 Safety Population

The safety population (SAF) will include all subjects in whom the administration of study treatment was started.

9.3.2 Efficacy Evaluable Population

The efficacy evaluable population will include all subjects who received the study treatment and have at least one post baseline efficacy observation or measurement in the study eye (*i.e.,* either BCVA or CST).

9.3.3 Per Protocol Efficacy Population

The per protocol efficacy population (PP) consists of the Efficacy Evaluable Population with the exception of subjects with important protocol violations.

9.4 Statistical Analyses

9.4.1 General Considerations

All statistical analyses will be outlined in detail in a Statistical Analysis Plan (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. Where applicable, treatment arms of 2.4mg and 4.0mg will be compared with descriptive statistics. 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.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF 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 version 24.1. This version will be used throughout the entire study. If available, updates of the MedDRA dictionary will not be applied afterwards.

The treatment-emergent AEs or ADEs will use the system organ class (SOC) and preferred term (PT) codes.

TEAEs, study drug-related AEs, AEs of Special Interest (AESIS), AEs leading to withdrawal from the study and SAEs will be summarized in a similar manner. 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.

9.4.3 Exploratory Efficacy and Safety Endpoint Analysis

The following main exploratory endpoints will be described on efficacy evaluable population and per protocol efficacy population (if different):

1. Mean Change in BCVA (ETDRS) at all study visits through Week 24 compared to baseline
2. Percentage of subjects with vision gain and vision loss of at least 5, at least 10, and at least 15 letters at all study visits through Week 24 compared to baseline
3. Time to subjects requiring follow-on treatment
4. Mean Change in Central subfield thickness (CST) at all study visits through Week 24 compared to baseline.
5. Mean Change in IOP at all study visits through Week 24 compared to baseline

Further exploratory endpoints 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.

9.4.4 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.
As important protocol violations are considered:

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

9.4.5 Other Analyses

9.4.5.1 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. The frequency and percentage of subjects who discontinue from the study, along with the reason for discontinuation, will be summarized. Demographics and baseline characteristics, including age, gender, and race will be summarized using descriptive statistics for the SAF population.

9.4.5.2 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 not be coded, and verbatim original terms recorded on the eCRF will be presented as data listings.

9.4.5.3 Physician Procedure Assessment

Physician procedure assessment will be described on the Safety Population (SAF).

9.4.5.4 Patient Experience Assessment

Patient experience assessment will be described on the Safety Population (SAF) at study visits.

9.4.6 Missing Data and Imputation Methods

No imputation of missing data will be performed.

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.

9.5 Deviations from the clinical study protocol

The investigator is not allowed to deviate from the clinical trial protocol, except under emergency circumstances.

In some cases, failure to comply with the protocol may be considered a failure to protect the rights, safety, and well-being of subjects, since non-compliance exposes subjects to unreasonable risks. Investigators should seek minimization of such risks by adhering to the protocol. Simultaneously, if adhering to the protocol might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety, and well-being of the subject by intentionally deviating from the requirements of the clinical trial protocol, so that subjects are not exposed to unreasonable risks.

Observable and data-driven protocol deviations will be recorded and categorized in a central protocol deviation log.

Relevant information for each protocol deviation will be documented on a deviation form.

Protocol deviations shall be reported to regulatory authorities in specified timelines as appropriate.

9.6 Interim Analysis

To compile data on the safety of the Oxulumis® device, Oxular Ltd. intends to perform an analysis on clinical data up to Week 4 of the trial. The focus will be on safety events and feedback on administration from the investigator and the subjects. The exact details of this analysis will be laid out in the SAP.

10 Supporting Documentation and Operational Considerations.

10.1 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) 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 IRB.

The investigator is responsible for accuracy and completeness of all data recorded in 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 making the correction. The investigator will maintain a file of essential documents of the trial as defined by the regulatory requirements, ICH, and the sponsor.

10.2 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.

10.3 Informed Consent Process

Following IRB 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 submission. The final IRB 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 patient before his or her participation in the study. The case history or clinical records for each patient shall document the ICF process and that written ICF was obtained prior to participation in the study.

Patients 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 patient to participate. The final revised IRB-approved Consent Forms must be provided to the sponsor for health authority submission purposes.

Patients 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 policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient 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 patient. All signed and dated Consent Forms must remain in each patient’s study file or in the site file and must be available for verification by study monitors at any time.

10.4 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. Recruitment is expected to be completed in 9 months after the initiation of the clinical trial.

10.5 Data Protection

The sponsor maintains confidentiality standards by coding each patient enrolled in the study through the assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient'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 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 patient medical information.

The data protection officer of the clinical study site and the sponsor must 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 needs to 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.

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

The subject must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

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

10.5.1 Committee Structure

10.5.1.1 Safety Committee

Periodically, the coordinating investigator together with the medical monitor will review individual patient data as well as the totality of the safety data to recommend if the investigation should continue as is, continue with changes, or be terminated.

10.5.1.2 Study Steering Committee

The study will use the services of a study steering committee (SSC). The composition, roles, responsibilities, and rules governing the SSC are available in the SSC Charter.

10.5.2 Dissemination of Clinical Trial 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 a 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 to prior review of any publication or presentation of information related to the study. Oxular Limited reserves the right to 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 for submission to Regulatory Authorities.

10.5.3 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, 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:

- 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.
- 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.

10.5.4 Source Documents

The 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, subject medical records with dates and details of the trial procedures (screening, laboratory and other test results, study treatments, AEs, and 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.

10.6 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 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.

10.7 Study and Site Start up and Closure

10.7.1 First Act of Recruitment

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

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

10.7.2 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 7, reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, 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 assure appropriate subject therapy and/or follow-up.

11 Safety: Events, Definitions and Procedures

11.1 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 which will not 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 Adverse Event (AE)

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.

11.3 Device Adverse Event (AE) and Adverse Device Effect (ADE)

The AE definition provided in Section 11.2 includes Medical Device AEs. In addition, AEs will be assessed, if they qualify as adverse device effects (ADE), which is defined as an AE related to the use of an investigational medical 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 from intentional misuse of the investigational medical device.

11.4 Device Deficiency

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. 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. Device deficiencies resulting in SAEs or SADEs will be reported according to regulatory reporting requirements described in Section 11.4.3.

11.4.1 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.

11.4.2 Follow-up of Device Deficiencies

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

- Follow-up applies to all subjects, including those who discontinue study intervention.
- 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.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

11.4.3 Regulatory Reporting Requirements of for Device Deficiencies

The sponsor will report:

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 8.5.5.
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.

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 11.1 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.

11.5 Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed (for the US CFR 312.32(a) applies):

a. Results in death

b. 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.

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

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

d. 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.

e. Is a congenital anomaly/birth defect

f. 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 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.

According to the US FDA guidance, the determination of the categorization of an event, *e.g.*, as serious or life-threatening, can be based on the opinion of either the investigator or sponsor (US FDA, 2012).

11.6 Device SAE, SADE and USADE

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 European MDR will be performed (European Parliament/Council (EC) 2017). The seriousness criteria here are slightly different from the SAE criteria outlined in Section 11.5.

A Medical Device SAE is any serious adverse event that led to

a. death

b. serious deterioration in the health of the subject, that either resulted in:

- A life-threatening illness or injury.
- A 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 (European Parliament/Council (EC) 2017).

c. Led to 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.

Any device deficiency that might have led to an SAE if appropriate action had not been taken, the intervention had not occurred, or circumstances had been less fortunate.

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.

11.7 AE and SAE Recording

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 in lieu of completion of 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 8.5.1), 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.

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.

11.7.1 Assessment of Intensity

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

- 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 usual activities of daily living.

- 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.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status or may require intensive therapeutic intervention.

11.7.2 Assessment of Causality

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.

The relationship will be determined by the Investigator according to the following criteria (Medical Device Coordination Group (MDCG), 2020):

- **Not related**: The relationship to the intervention can be excluded.
- **Possibly related**: The relationship with the intervention is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probably related**: The relationship with the intervention seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causally related**: The serious event is associated with the intervention beyond reasonable doubt.

11.7.3 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).

11.7.4 Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental assessments 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.

12 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, and investigators according to the regulations listed in Section 8.5.5. 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 8.5.5.

12.1 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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 to the Institutional Review Boards (IRBs). In the US, this follows the requirements laid out in the US FDA guidance on safety reporting (US FDA, 2012).

Following the definitions in 21 CFR 312.32(a), an adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure, or the SmPC of Triesence (US Version; (Alcon Laboratories Inc., 2007) or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure 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.

13 Outcome Assessments and Questionnaires

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

Subject's Experience Assessment:
Current and Procedure Pain & Discomfort

To be completed by the Site Interviewer

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

Instructions for the site interviewer: Ask the study to subject the questions below after the 60 minutes post-procedure observation period.

Questions should be asked at any time after the 60 minutes post-procedure observation period 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 the subject (to be read to the subject by the interviewer): Please answer the following questions about your experience of the procedure with the Oxulumis® device.

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	

13.2 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: Ask the study to 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 : 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	

13.3 Retinal physician's documentation and assessment of administration procedure

Retinal physician's documentation and

Assessment of the Oxulumis® Administration Procedure

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).

1. Operative Assessment

1.1. Antiseptic applied for Disinfection

Please select which antiseptic agent has been used:

Povidone Iodine

Chlorhexidine

Other

If other, please specify

_____

2. Type of Anesthesia given

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

Topical Tetracaine eye drops

Lidocaine Gel

Subconjunctival Lidocaine

Subtenon Lidocaine

Other (allow more than one entry in field other)

If other, please specify the distance in mm (enter number)

_____

2.1.1 If subconjunctival, please specify quadrant where applied (more than 1 selection possible)

superior – temporal

superior - nasal

inferior - temporal

inferior - nasal

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

superior – temporal

superior - nasal

inferior - temporal

inferior - nasal

3. **Execution of the Oxulumis® Procedure**

3.1 Was the procedure performed successfully in the first attempt?

Yes

No

3.1.1 If **No**, please tick all applicable

Could not or only insufficiently engage sclera with the bevel

I could engage the sclera, but the catheter did not deploy

The catheter deployed subconjunctivally

The catheter deployed intravitreally

Other

If other, please specify:

_____

3.1.2 How many different devices needed to be used until successful completion of the procedure?

1

2

3

3.1.2.1 If 2 or 3 is ticked, please briefly summarize:

_____

3.1.2.2 Provide a reason for exchanging Device 1

_____

3.1.2.3 Provide a reason for exchanging Device 2

_____

4. **Location of the Insertion Point**

4.1 Which Quadrant was chosen?

superior – temporal

superior - nasal

inferior - temporal

inferior - nasal

4.2 At which distance from the limbus was the trocar inserted?

Please tick the right category

5mm

7mm

Other

If other, please specify the distance in mm (enter number)

_____

5. **Insertion**

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

- o <10°
- o 10-15°
- o 16-30°
- o >30°

5.2 Bevel orientation

- Up
- Sideways left
- Sideways right
- Down

5.3 Insertion completed through the sclera

Yes

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)

No complications

Insertion needle could hardly pass the sclera

Catheter directly deployed when trigger pressed (no further advancement necessary)

Other

If other, please specify

_____

6. Deployment

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

Yes

No

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

Yes

No

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

Yes

No

6.4 Any kink in the tubing?

Yes

No

6.4.1. If **'**Any kink in the tubing' is ticked '**Yes**,' please provide details and presumed reason?

_____

7. <u>Injection of drug via the drug line</u>

7,1 Was the injection completed as expected?

Yes

No

7.1.1 If **No**, please tick as appropriate:

Microcatheter clogged by drug and injection could not be completed

Other (please specify)

_____

7.2 What was the time interval for the drug injection?

Less than 10 sec

10-14 sec

15-19 sec

20-24 sec

25-30 sec

Longer than 30 sec

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

Less than 10 sec

10-14 sec

15-19 sec

20-24 sec

25-30 sec

Longer than 30 sec

7,4 Did the patient feel pain during the injection?

Yes

No

7.4.1 If **Yes**, when did the pain start

With the insertion needle's tip inserted into the sclera

With the insertion needle's advancement into the sclera

With catheter deployment

With medication injection

With catheter withdrawal

After procedure completion

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?

Yes

No

7.6.1 If **Yes**, specify

_____

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

insertion point

arcades

anterior to equator

equator

posterior to equator

optic nerve

Other, please specify

7.8 Any reflux?

Yes

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 Complications:
Yes

No

7.10.1 If 'Complications' is equal to '**Yes**' answer this question:

Tick all Complications, that apply:

Intravitreal drug deposit

Conjunctival drug deposit

Disconnect of Merit syringe

Catheter clogged by Triesence

Other

If other, please specify.

7.11 Bleeding

7.11.1 Any intraocular bleeding?

Yes

No

7.11.2 If 'Any intraocular bleeding' is equal to '**Yes**' answer this question:

7.11.3 Localization of the bleeding:

vitreous

retinal

subretinal

Choroidal/suprachoroidal

If 'Any intraocular bleeding' occurred, please provide details

_____

7.11.4 Any scleral damage?

Yes

No

If 'Any scleral damage' occurred, please provide details:

_____

Please comment:

7.11.5 Any other damage, please tick the ones that apply

Traumatic cataract

Retinal detachment

Retinal hole

Other

If other, please specify

_____

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

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

In subjects with factors indicating a potentially high expected complexity of performing the Oxulumis® procedure, the investigator may decide to preemptively perform the procedure directly in an operating/procedure room with the procedural variant including a conjunctival/tenon incision to potentially facilitate scleral engagement.

This subjective investigator assessment has to be performed at screening.
Note: Significant scleral abnormalities need to be assessed for potentially leading 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 Conj/Tenon? Opacity? Mobility?	Low	Medium	High
• Medical History of Conj./Tenon abnormalities, *e.g.,* Chronic blepharitis? Toxic conjunctivitis (*e.g.*, due to	Low	Medium	High

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.			
• 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

Medium

High

Complexity

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

In an in-clinic setting. Only if not completed, a treatment attempt with a conjunctival/tenon incision is planned (in an □ operating/□ procedure room setting)

In a procedure room. Only if not completed, a treatment attempt with a conjunctival/tenon incision is planned (operating room setting).

In an □ operating/□ procedure room with a setting allowing a conjunctival/tenon incision, if needed.

*depending on the location of the investigational site, procedure rooms may also be sufficiently equipped to perform procedures like conjunctival/tenon incisions and their closure by surgical (*e.g.,* fibrin) glue or suturing.

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