Wemedoo
Clinical Information Specialists

OXUCT-103 “CAPE”
Clinical Trial
Statistical Analysis Plan v1.0

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

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1. List of Abbreviations

Term	Definition / Description
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
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
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
SAP	Statistical Analysis Plan

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

2. Administrative Trial Information

2.1. Clinical Trial

The purpose of this 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.

2.1.1. Document Description

This document describes the Statistical Analysis Plan (SAP) for the OXUCT-103 "OXEYE" clinical trial "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".

The purpose of this SAP is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from the OXUCT-103 clinical trial. This document is based on the OXUCT-103 Clinical Trial Protocol v3.0 17 Feb 2023.

2.2. Clinical Trial Registration Information

Branded Name:	CAPE
Protocol Number:	OXUCT-103
Protocol Version:	3.0
Protocol Date:	17 Feb 2023
ClinicalTrials.gov Identifier:	NCT05512962
EudraCT No.:	2022-001533-37
Clinical Phase:	II
Sponsor:	Oxular Ltd.

2.3. SAP Version

Version:	1.0
Date:	22 Jan 2024

2.3.1. SAP Revision History

2.3.1.1. SAP Version

This is the first version of the OXUCT-103 SAP and as such no revisions to this version of the SAP have been made.

2.4. Roles and Responsibilities

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Lead Statistician:	Ivan Soldatovic, MD, PhD Lead Statistician Wemedoo AG
Sponsor's Representative and Clinical Lead:	PD Dr. med. Friedrich Asmus, MD Chief Medical Officer Oxular Ltd.

2.5. Document Approval

The Statistical Analysis Plan for the OXUCT-103 Clinical Trial has been approved by:

Date: 1/23/2024

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3. Introduction

The OXUCT-103 "CAPE" clinical trial is 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 (Triesence®) administered with the Oxulumis® ophthalmic administration device in subjects with previously treated diabetic macular edema.

3.1. Study 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 (Wilkins et al., 2021; Ehlers et al. 2022). 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 (Boyer et al., 2014; Ehlers et al., 2022). Accordingly, there continue to be significant treatment challenges for the heterogenous population of patients with DME (Udaondo et al., 2021; Zur, Iglicki, and Loewenstein, 2019).

The current clinical trial evaluates a novel microcatheterization approach for steroid administration to the posterior suprachoroidal space. This approach 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. Drug delivery is achieved via a low-volume (60µl, or 100µl) administration of 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 (60µl of the 40mg/ml suspension). The mid-dose is 4.0mg TA (100µl of the 40mg/ml suspension).

It is anticipated that posterior deployment of the drug in the suprachoroidal space, closer to the location of the disease activity compared to other treatment approaches, will show advantages in respect to safety, tolerability and therapeutic effects compared to IVT or subtenon administration. Local concentrations of TA in the retinal tissues are expected to be higher with posterior suprachoroidal administration compared to the same doses administered by IVT or subtenon injection.

3.2. Investigational Product

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 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 subtenon anesthetic injections) 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. Details about the Oxulumis® device and the ophthalmic administration are available in the Instruction for Use (IFU) manual.

3.2.1. Risks / Benefits

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.

The combination of the Oxulumis® plus triamcinolone acetonide suspension (Triesence®) used in the current trial is expected to address high 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.

Theoretical class risks associated with the suprachoroidal administration procedure include: endophthalmitis, choroidal hemorrhages, choroidal effusion, retinal penetration, and retinal detachment, amongst others. The atraumatic design, a tangential angle of approach for device insertion (not perpendicular to the sclera 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.

3.3. Objectives

As per protocol, the OXUCT-103 “CAPE” clinical trial has defined a primary objective and a series of exploratory objectives.

3.3.1. Primary Objective and Endpoints

The primary objective of the OXUCT-103 “CAPE” clinical trial is 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.

The primary outcome will be assessed by observing the frequency of ocular and systemic adverse events (treatment-emergent serious adverse events [SAEs] and treatment-emergent non-serious adverse events [TEAEs]), as well as the frequency of adverse device effects (ADEs, serious ADEs [SADEs]).

3.3.2. Exploratory Objectives and Endpoints

The exploratory objectives for the OXUCT-103 “CAPE” clinical trial include:

- exploring the efficacy of two dose levels of triamcinolone acetonide with respect to changes in best-corrected visual acuity BCVA, edema control, and durability of the treatment effect of suprachoroidal triamcinolone acetonide suspension (Triesence®) In subjects with DME.
- performing exploratory device evaluation in terms of device administration and IOP change safety issues.

The exploratory objective will be assessed by the following endpoints:

Efficacy:

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 SAP defined endpoints:

6. Time to improvement of BCVA from baseline by at least 5, at least 10, and at least 15 letters.
7. Duration of maintained improvement of BCVA of at least 5, at least 10, or at least 15 letters, where maintained improvement is defined as improvement over at least 4 weeks (= 2 consecutive visits with a 4-week interval).
8. Percentage of subjects with improvement from baseline CST by at least 10%, by at least 25µm, by at least 50µm, and by at least 75µm.
9. Percentage of subjects with increase of intraocular pressure of at least 5mmHg, at least 10mmHg, and at least 30 mmHg, at all study visits through Week 24 compared to baseline.
10. Course of IOP through the first 60 minutes after administration of study drug and percentage of subjects with normal IOP at the end of the baseline visit.
11. Percentage of subject with elevated IOP from baseline by at least 10mmHg at timepoints of more than 60min after completion of study treatment.
12. Course of pain and discomfort scores after completion of study administration, as assessed in the Subject Experience Assessment questionnaires for Pain and Discomfort.
13. Overview of the Physician Experience in Administration of Study Treatment based on the Retinal Physician's Documentation and Assessment of Administration questionnaire.

4. Study Methods

4.1. Trial Design

The OXUCT-103 trial is a phase II, twenty-four (24) week, randomized, two-arm, single-masked, clinical trial. The 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. The clinical trial was conducted by retinal specialists in clinics or academic hospitals in the United States at 6 investigational sites.

With protocol amendment no. 2 (protocol version 3.0, dated 17 Feb 2023) a 2nd variant for the Oxulumis® procedure was introduced. The initial choice of the procedural variant is based 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
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.

After a screening period, approximately 20 eligible DME subjects will be randomized and treated (updated with protocol version 3.0) 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). Only one (1) eye will be determined as the study eye and only the study eye will receive a single administration of study drug.

Study eyes need to meet all inclusion criteria and none of the exclusion criteria. Treatment of the fellow eye is not considered part of the study treatment. 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.

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.

4.1.1. Trial Flow Chart

The trial has been planned with up to 10 study visits, including the screening and baseline visit, over a period of 24 weeks (in addition to up to three weeks of screening). If administration of study treatment requires two treatment sessions, i.e. administration cannot be completed in the 1st session "in-clinic" and a 2nd treatment session for a conjincision procedure is scheduled, baseline visit activities need to be completed within 14 days.

The screening visit (Visit 1) is planned to take place -21 to -2 days prior to the baseline visit (Visit 2), which is also when suprachoroidal triamcinolone is administered. Another eight follow-up visits are planned. The baseline visit is followed by Visit 3 the next day, and Visit 4 one week later, and then subsequently every four weeks until Visit 10 after 24 weeks.

The flow chart of the OXUCT-103 clinical trial is shown in Figure 1, below.

Figure 1. OXUCT-103 Clinical Trial Flow Chart (based on protocol version 3.0)

<table>
<tr><td rowspan="2">Screening</td><td rowspan="2">Baseline and Randomization</td><td colspan="8">Triamcinolone Acetonide 2.4mg (N=10)</td></tr>
<tr><td colspan="8">Triamcinolone Acetonide 4.0mg (N=10)</td></tr>
<tr><td>Visit 1
Day -21 to -2</td><td>Visit 2
D0
To be completed within 14 days</td><td>Visit 3
D1 (+1)</td><td>Visit 4
W1
(±3)</td><td>Visit 5
W4
(±5)</td><td>Visit 6
W8
(±5)</td><td>Visit 7
W12
(±5)</td><td>Visit 8
W16
(±5)</td><td>Visit 9
W20
(±5)</td><td>Visit 10
W24
(±5)</td></tr>
</table>

4.2. Methods to Minimize Bias

4.2.1. Randomization

The OXUCT-103 clinical trial is designed as a two-arm, parallel-group, single-masked, randomized trial. Approximately 20 subjects will be treated using a 1:1 ratio to two treatment arms receiving either:

1. Low Dose – 2.4mg dose of triamcinolone acetonide (low-dose arm)
2. Mid Dose – 4.0mg dose of triamcinolone acetonide (mid-dose arm)

as a single treatment with triamcinolone acetonide (Triesence®) administered with the Oxulumis® to the posterior suprachoroidal space of one eye, the study eye. This type of randomization method will provide a sufficiently balanced distribution of participants at the interim analysis time points, as well as for the final analysis arms. If study treatments cannot be completed in up to two treatment sessions, further subjects will be randomized to meet the target subject number of approximately 20.

4.2.2. Masking Procedures

This is a single masked trial. The trial 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 trial.

4.2.3. Unmasking Procedures

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.

4.3. Sample Size

A total of approximately 20 subjects will receive a single treatment with Triesence® administered with the Oxulumis® to one eye, the study eye. Based on protocol version 3.0, dated 17 Feb. 2023, additional subjects will be enrolled, if the study treatment cannot be completed in randomized subjects, to target a total of approximately 20 treated subjects.

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.

4.4. Timing of Final Analysis

Once all subjects have completed the full course of the trial and their data has been entered into eCRF in the Oomnia EDC/CTMS, and source data verification has been performed as outlined in the trial protocol, all data queries have been reconciled and closed, and all instances of the eCRF have been locked, the trial database will be locked upon the written authorization of the sponsor's representative.

Upon database lock, the sponsor's representative will give written authorization for database exported from the Oomnia EDC/CTMS system for forwarding to the Lead Statistician for analysis.

5. Trial Subjects

5.1. Subject Disposition

A summary figure (CONSORT flow diagram, see Appendix 3, section 13) will be generated for the OXUCT-103 "CAPE" clinical trial at the subject level, including reasons for being excluded from the next analysis population (see section 6 for more details) for the populations listed below:

- Screened subjects (SP)
- Safety population (SAF)
- Efficacy evaluable population (EEP)
- Per protocol population (PP)

The CONSORT flow diagram will give an overview of the subject disposition, while the additional tables and listings will provide more detailed information (e.g. primary reason for discontinuation and proportions).

5.2. Definition of Compliance and Assessment

5.3. Definition of Protocol Deviation

For the purpose of the OXUCT-103 "CAPE" clinical trial, protocol deviations will be collected and reviewed during the trial. Important protocol deviations are deviations including those defined as violations in the protocol (Section 9.5), which are likely to have an impact on the efficacy and/or safety of trial treatments. In practice, in the protocol deviation documents the terms "major" are used for "important" (in the ICH classification) and the term "minor" for "non-important" (in the ICH classification) protocol deviations.

5.3.1. Protocol Deviations

Protocol deviations (both categorized as major and minor) and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the following sections.

5.3.1.1. Major Protocol Deviations

Major ("important") protocol deviations are defined as follows:

- Not meeting the inclusion criteria or meeting the exclusion criteria, respectively
- Missing trial visits or out of window study visits (depending on type of visit and on the time interval). A more detailed breakdown is available in the Protocol Deviation Specification document.
- Intake of non-authorized concomitant treatment impacting subject safety and potentially efficacy outcomes, e.g. concomitant medication increaing the risk of AEs or additional non-authorized treatments for study-specific disease or their compliacionts.
- Missing important safety data points (IOP measurements, dilated fundus examinations, BCVA measurement, SD-OCT measurement, etc.)

In specific situations, the sponsor can issue indivudal waivers on meeting certain eligibilty criteria, if the overall clinical assessment of the investigator in accordance with Oxular's medical monitor suggests no altered risk/benefit for trial participation.

Major ("important") protocols deviations will be summarized in tables by treatment dose group.

6. Analysis Populations

Subjects suitable for study participation include individuals over 18 years of age, diagnosed with Type 1 or Type 2 diabetes mellitus, with DME with short-lived, limited or no therapeutic response with prior therapy with ocular injections of steroids and/ or anti-VEGF agents.

For the purpose of the trial, outcomes will be assessed on two population groups:

- Safety Analysis population
- Exploratory Analysis population

6.1. Safety Analysis Population

The safety population (SAF) will include all subjects in whom the administration of study treatment was started, defined as at least one (1) time inserting the insertion needle of the device in the sclera, regardless of whether the treatment was completed.

6.2. Exploratory Analysis Population

The exploratory efficacy analysis will be performed on two populations:

- Efficacy Evaluable Population (EEP): All subjects who received the study treatment and have at least one post baseline visit efficacy observation or measurement in the study eye.
  Efficacy assessments after a 1st treatment session or as part of a 2nd treatment session count as assessment of the baseline visit and not as post baseline efficacy observation. In addition, those subjects to whom the drug was partially administered to compartments that are not the suprachoroidal space will be considered EEP population.
- Per Protocol (PP) Population: Efficacy Evaluable Population with exception of subjects with major (important) protocol deviations and with exception of those subjects to whom the drug was partially administered to compartments that are not the suprachoroidal space.

6.3. Eligibility and Withdrawal Criteria

6.3.1. Inclusion Criteria

Patients must meet all of the following criteria in order to be eligible for this study:

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 for the entire participation in this clinical trial. 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 starting from treatment administration through the end of participation in this clinical trial.
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.

6.3.2. 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 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 four-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 (added per OXUCT-103 “CAPE” protocol version 3.0).

6.3.3. Study Discontinuation

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.

6.3.3.1. Discontinuation of Study Intervention

Discontinuation of the study intervention on a subject level 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.

6.3.3.2. Subject Discontinuation/Withdrawal from Study

A subject's participation in the trial may be discontinued at any time. Subjects will be asked to specify the reason for the termination but have the right not to answer.

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.

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'

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.

6.3.4. Assessment for Follow-On Treatment and End of Study

From Week 4 on, each subject will be evaluated against prespecified criteria indicating the need for follow-on treatment (i.e., indicating the end of the current treatment interval and the end of study participation).
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.

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.

7. Statistical Methods and Analysis

7.1. Hypothesis

No formal statistical hypothesis was developed for the OXUCT-103 "CAPE" trial.

7.2. Safety Analyses

7.2.1. Primary Endpoint

The primary endpoints supporting the primary objective of evaluating the safety and tolerability of two dose levels of triamcinolone acetonide administered with the Oxulumis® are:

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])

7.2.1.1. Analytical Procedures for the Primary Endpoint

The safety endpoint analysis will be performed on the SAF population. The primary endpoint analysis of ocular adverse events that occurred in the study eye will be split in two groups related to the two different device presentations used in the study:

- **First device lot** (21120801), in use through end of October 2022
- **Second device lots** (22110812, 23011214), in use from January to August 2023.

Data will be summarized separately for each treatment arm, as well as according to non-ocular and ocular AE occurrences. Adverse events will be summarized using frequencies and percentages per adverse event (as multi-response), as well as per subject.

Treatment-emergent serious and non-serious adverse events (TEAEs) and serious and non-serious adverse device effects (ADEs) will be coded to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. MedDRA -coded AEs will be presented as sheet tables while verbatim entries will be presented as data listings.

7.3. Exploratory Analysis

Exploratory analysis will include the following assessments:

- Best-corrected visual acuity (BCVA) using the ETDRS methodology
- IOP measurement
- SD-OCT
- Retinal Physician's Documentation Assessment of Administration
- Subject Experience Assessment

These assessments will be evaluated through exploratory endpoints.

7.3.1. Exploratory Efficacy (and/or Safety) Endpoints

The exploratory efficacy (and/or safety) endpoints include the following:

Mentioned in the study protocol:

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 pre-treatment IOP.

Additional exploratory endpoints as defined in this SAP:

6. Time to improvement of BCVA from baseline by at least 5, at least 10, or at least 15 letters.
7. Duration of maintained improvement of BCVA of at least 5, at least 10, or at least 15 letters, where maintained improvement is defined as improvement over at least 4 weeks (=-2-consecutive visits with a 4-week interval)
8. Percentage of subjects with improvement from baseline CST by at least 10%, by at least 25µm, by at least 50µm, and by at least 75µm.
9. Percentage of subjects with increase of intraocular pressure of at least 5mmHg, at least 10mmHg, and at least 30 mmHg, at all study visits through Week 24 compared to baseline.
10. Course of IOP through the first 60 minutes after administration of study drug and percentage of subjects with normal IOP at the end of the baseline visit.
11. Percentage of subject with elevated IOP from baseline by at least 10mmHg at timepoints of more than 60min after completion of study treatment.
12. Course of pain and discomfort scores after completion of study administration, as assessed in the Subject Experience Assessment questionnaires for Pain and Discomfort.
13. Overview of the Physician Experience in Administration of Study Treatment based on the Retinal Physician's Documentation and Assessment of Administration questionnaire.

7.3.2. Analytical Procedures for the Exploratory Efficacy (and/or Safety) Endpoints

In addition to an overall analysis, the exploratory efficacy endpoint analysis will be split will be split in two groups related to the two different device presentations used in the study :

- First device lot (21120801), in use through end of October 2022
- Second device lots (22110812, 23011214), in use from January to August 2023.

Exploratory safety endpoints includes the course in pre- and post-treatment IOP over the initial 60 minutes post treatment and over the time of study participation. IOP changes will be evaluated, overall and per dose group of 2.4mg and 4.0mg (different volume administration).

The subject's experience in respect to pain and discomfort will be evaluated based on subject reported scores assessed with the Subject Experience Assessment questionnaires.

All exploratory efficacy endpoint variables will be presented using descriptive statistical methods. Nominal endpoint variables will be presented using frequency count and percent for each arm separately. Numerical (continuous) endpoint variables will be presented as mean, 95% CI for mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

Nominal endpoint variables will be presented using a bar chart with 95% CI error bars while continuous variables will be presented using line graphs with 95% CI and boxplots.

7.4. Confidence Intervals

All results regarding the primary and exploratory endpoints will be presented with point estimate (proportion, mean, median) and a 95% confidence interval, as applicable.

7.5. Other Analyses and Statistical Considerations

7.5.1. Calculations or Transformations Used to Derive the Outcome

Appropriate transformation(s) (logarithmic, square root, reciprocity, etc.) will not be used to obtain normal distributions. Outcome variables, mean change in BCVA, central subfield thickness (CST), and IOP will be calculated as the difference between the value at Visit 3 through EoS and baseline.

7.5.2. Alternative Methods for Distributional Assumptions

Alternative methods for distributional assumptions will not be applied in this study.

7.5.3. Sensitivity Analysis Plan

No sensitivity analysis is planned for this study.

7.5.4. Interim Statistical Analysis

No interim analysis is to be performed for this study.

7.6. Missing Data

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.

7.7. Adjustment for Multiplicity and Type 1 Error Control

The adjustment for multiplicity and type 1 error is not applicable for this study.

7.8. Non-Standard Statistical Methods

Non-standard statistical methods are not planned for statistical analyses for the OXUCT-103 clinical trial.

7.9. Statistical Software

SAS version 9.4 will be used for statistical analysis of the OXUCT-103 “CAPE” clinical trial.

8. Presentation of Patient Data and Other Evaluations

8.1. Screening Data

Screening data will be presented for the SP population as subject data listings.

8.2. Screening and Baseline Patient Characteristics

The following patient characteristics will be obtained during the Screening Visit 1:

- Demographic data
- Medical history

- Concomitant medication
- Pre-treatment AEs collection
- Height, weight, and vital signs (body temperature, blood pressure, and heart rate)
- Lab assessment
- Urine pregnancy test for females of childbearing potential

Screening and baseline characteristics will be summarized for the SAF population in with respect to allocation to treatment.

Numerical variables will be presented as mean ± SD or median (25-75th percentile), depending on data distribution. Categorical (nominal) data will be presented as count (percent).

8.3. Medical History

All medical history and concurrent medical conditions will be presented as entered by the investigator. in data listings. Also, non-ophthalmic and ophthalmic medical history and concurrent medical conditions will be listed separately. In case of missing dates/partial dates, no imputation of missing data will be performed.

8.4. Concomitant Medication or Procedure

Systemic and ocular concurrent medications or procedures will be presented separately as subject data listings. In case of missing dates/partial dates, no imputation of missing data will be performed.

8.5. Physical Examination and Vital Signs

Descriptive statistics will be presented for physical examination and vital signs data as mean ± SD or median (25-75th percentile), depending on data distribution. Categorical (nominal) data will be presented as count (percent).

8.6. Laboratory Tests

8.6.1. Non-fasting Chemistry, Hematology and Thyroid Parameters

In this trial laboratory testing is only done for assessing factors impacting safety and eligibility for participating. Accordingly, any abnormal findings are recorded in medical history or if newly occurred as AEs. No separate statistical analysis of laboratory values is performed.

8.7. Reasons, Details and Timing of Withdrawal/Lost to Follow-Up Data

Early termination will be tabulated by analysis population (SAF, EEP, and PP) along with the reasons for discontinuation. The time point of withdrawal will also be presented (ie. date of discontinuation and last visit completed). In this protocol, termination/end-of-study related to meeting follow-on treatment criteria does not fall under the category of early termination.

9. Data Management and Other Procedures

9.1.1. Clinical Data Management Plan and Data Quality Assurance

The CDMP will enforce appropriate handling of data at all steps of the project to assure a high-quality ready for analysis database at the end of the study. The Lead Data Manager and Project Lead (delegated by sponsor) is responsible for the oversight and knowledge of the data management process as well as review of the CDMP. Together with them, a Data Manager from the Wemedoo AG team suggests and prepares the system for all needs as defined by the sponsor. The purpose of electronic Case Report Forms (eCRF) is to capture all clinical and workflow data as defined by the protocol. The data is necessary for statistical analysis and for GCP verification purposes. The type, number, and form of the data capture elements (DCEs) are defined by the protocol and statistical analysis plan.

DCEs and data flow will be simulated within the Oomnia EDC/CTMS system prior to the initiation of the data capture process. The simulation will be presented to the Project Lead designated by the sponsor. If any discrepancies are detected, the Wemedoo AG data manager will correct and revise the data flow with the Project Lead. Upon addressing all issues detected during the simulation, the Wemedoo AG data manager will finalize and sign the document.

The Trial Manager and Trial Statistician provide input to, and review of, updates and changes to the Data Management Plan, if needed, during the project. If required, the CDMP can be modified during a trial. The sponsor or his designee must request the CDMP in written form. Any changes must also be verified by the Wemedoo AG data team and sponsor, or his designee.

The Clinical Data Management Plan for the OXUCT-103 trial is described in the file, OXUCT-103 CDMP v2.0 19 May 2023.docx.

9.1.2. Other Standard Operating Procedures and/or Documents

For more details regarding the Oxuct-103 clinical trial, please refer to the finalized trial protocol, Oxuct-103 Clinical Trial Protocol v2.0 24May2022 clean, dated 24 May 2022.

10. References

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Wilkins, C. S., E. K. Sobol, G. M. Lema, J. G. Lee, R. B. Rosen, and A. Deobhakta. 2021. 'Intravitreal dexamethasone insert in diabetic macular edema super-refractory to antivascular endothelial growth factor therapy', Eur J Ophthalmol: 11206721211004391.

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11. Appendix 1 – Study Schedule (Assessments and Procedures)

	Screening	Baseline		Post-Baseline Follow-Up							
Days / weeks	Day –21 to -2	D0 To be completed within 14 days		D1	W1	W4	W8	W12	W16	W20	W24 ET/EoS
Visit	1	2		3	4	5	6	7	8	9	10
Visit Window		in-clinic[b]	variant with conj./tenon incision[j]	+1 days	±3 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
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 [b,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
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	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		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, (**) 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.

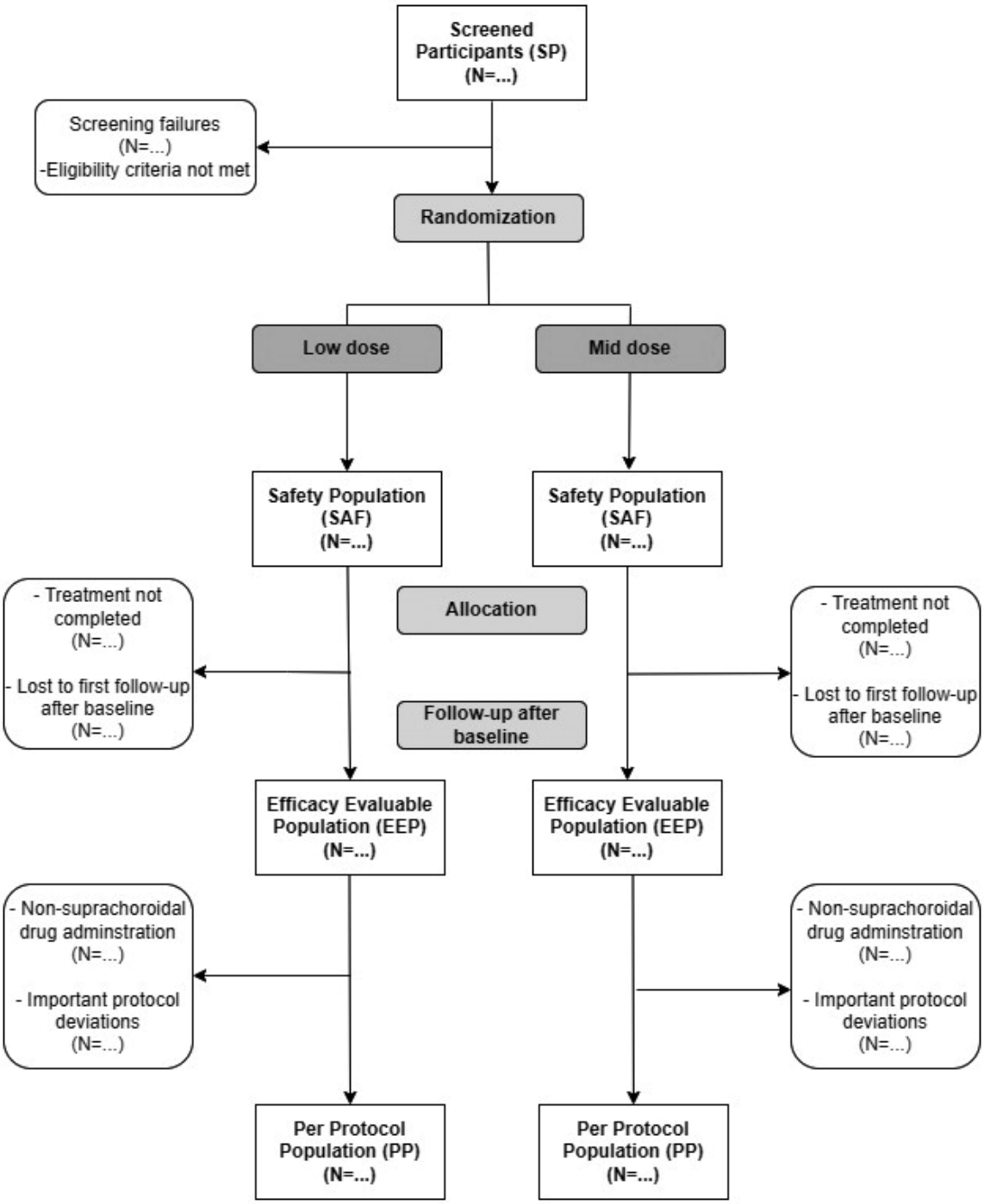
k. In case the study procedure is only performed in an operating/procedure room setting, the mandatory baseline assessments would have to be performed still at the investigational site, if not available in the operating/procedure room facility. This may be done prior to or on the same day of treatment administration. All baseline visit activities have to be completed within 14 days after their start.

12. Appendix 2 – General Conventions

This section details general conventions to be followed while presenting the tables, listings, and figures. The following conventions will be applied to all data presentations and analyses.

- All tables and listings will be displayed in Calibri or Segoe UI Light 10 pt font (where possible).
- All tables, listings and figures will have header sections.
- If needed, some of the tables, listings and figures could have footnote sections.
- The outputs have to be created as per the templates that will be provided along with this analysis plan in case no changes are needed.
- Summary tables and figures will contain a footnote that references any data listings or tables associated with the table (e.g., Source: Listing XX.X.XX).
- The footnotes of tables and listings will be displayed in a separate line of the table, figures, or listing, respectively.
- All arithmetic mean, median, standard deviation, minimum and maximum values will be formatted to one decimal place. More than one decimal place will be represented for results where one decimal place does not render useful information.
- All p-values will be formatted to three decimal places. More than three decimal places will be used for results where three decimal places do not render useful information.
- Confidence intervals will be formatted to one decimal place, where appropriate.
- The number and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses.
- All listings will be ordered by study period (day) and time points (if applicable).
- Date variables will be formatted as DD/MMM/YYYY for presentation, if available.
- Tables, figures, and listings will be presented both in landscape and portrait orientation depending on the data displayed.

13. Appendix 3 – CONSORT Flow Diagram



14. Appendix 4 – Tables, Figures and Graphs

The numbering of the tables, figures, listings is prepared to meet the requirements of the ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice.

14.1. Populations and Demographic Data

14.1.1. Disposition of Subjects

14.1.1.1 CONSORT Flow Diagram
14.1.1.2 Eligibility Criteria Violations (n, %)
14.1.1.3 Study Discontinuations and Reasons by Treatment Dose (n, %)
14.1.1.4 Follow-On Treatment Received (n, %)

14.1.2. Study Populations

14.1.2.1. SAF, EEP, and PP Populations Overall and by Study Eye Laterality (n, %)
14.1.2.2. Major and Minor Protocol Deviations by Treatment Dose Group and Study Eye Laterality (n, %)

14.1.3. Demographics: Overall and by Treatment Dose for the SAF Population

14.1.3.1 Subject Age, Gender, Racial Designation, and Ethnicity (descriptive; n, (%))

14.1.4. Vital Signs and Anthropometry by Treatment Dose for the SAF population

14.1.4.1 Body Temperature, SBP, DBP, and Heart Rate at Screening (descriptive)
14.1.4.2 Height, Weight, and BMI at Screening (descriptive)

14.2. Medical History

14.2.1. Non-Ophthalmic Medical History by Treatment Dose for the SAF Population

14.2.1.1 Relevant and Ongoing Non-Ophthalmic Medical Conditions per Patient (n, %)
14.2.1.2 Relevant Non-Ophthalmic Medical Conditions or Events by MedDRA SOC and PT (n, %; multi-response)

14.2.2. Ophthalmic Medical History by Treatment Dose for the SAF Population

14.2.2.1 Relevant and Ongoing Ophthalmic Medical Conditions per Patient (n, %)
14.2.2.2 Relevant Ophthalmic Medical Conditions or Events by MedDRA SOC and PT (n, %; multi-response)

14.3. Concomitant Medication and Concomitant Procedure by Treatment Dose for the SAF Population

14.3.1. Non-Ocular Concomitant Medications and Procedures by Treatment Dose

14.3.1.1 Non-Ocular Concomitant Medications and Procedures (% n; multi-response)
14.3.1.2 Reason for Non-Ocular Concomitant Medication and Procedure (n, %)
14.3.1.3 Number of Non-Ocular Concomitant Medications and Procedures per Patient (n, %)

14.3.2. Ocular Concomitant Medications and Procedures by Treatment Dose and by Eye

14.3.2.1 Ongoing and Non-Ongoing Ocular Concomitant Medications and Procedures (% n; multi-response)
14.3.2.2 Reason for Ocular Concomitant Medication and Procedure (n, %)
14.3.2.3 Number of Ocular Concomitant Medications and Procedures per Patient (n, %)

14.4. Ocular Examination for the SAF Population

14.4.1. Lens Examination by Treatment Dose and by Visit

14.4.1.1 Lens and Psudophakic Type/Status (n, %, multi-response)
14.4.1.2 Phakic Lens Nuclear Lens Opacity (NUC) Grade by Eye (n, %)
14.4.1.3 Phakic Lens Cortical (Cor) Grade by Eye (n, %)
14.4.1.4 Cortical Central 3mm Zone (CEN) Present by Eye (Y/N) (n, %)
14.4.1.5 Phakic Lens Posterior Subcapsular Cataract (PSC) Grade by Eye (n, %)

14.4.2. IOP Measurement by Treatment Dose and by Visit

14.4.2.1 IOP by Eye (descriptive)
14.5.2.2 IOP – Study Eye (boxplot)
14.4.2.3 IOP – Study Eye (line chart)
14.4.2.4 IOP – Fellow Eye (boxplot)
14.4.2.5 IOP – Fellow Eye (line chart

14.5. Study Medication Administration by Treatment Dose

14.5.1. For the SAF Population

14.5.1.1 Study Medication Administration Quadrant (n, %)
14.5.1.2 Location of Insertion Point (n, %, multi-response)
14.5.1.3 Trocar Insertion Distance from the Limbus (n, %)

14.5.2. For the EEP Population

14.5.2.1 Study Medication Administration Quadrant (n, %)
14.5.2.2 Location of Insertion Point (n, %, multi-response)
14.5.2.3 Trocar Insertion Distance from the Limbus (n, %)

14.5.3. For the PP Population

14.5.3.1 Study Medication Administration Quadrant (n, %)
14.5.3.2 Location of Insertion Point (n, %, multi-response)
14.5.3.3 Trocar Insertion Distance from the Limbus (n, %)

14.6. Retinal Physician's Documentation and Assessment of Administration – SAF Population

14.6.1. Operative Assessment

14.6.1.1 Antiseptic Applied for Disinfection (n, %)

14.6.2. Type of Anesthesia Given

14.6.2.1 Forms of Anesthesia Administered (n, %, multi-response)
14.6.2.2 Quadrant of Application for Subconjunctival Lidocaine (n, %, multi-response)
14.6.2.3 Quadrant of Application for Subtenon Lidocaine (n, %, multi-response)

14.6.3. Execution of Oxulumis® Procedure

14.6.3.1 First Attempt Success Rate (Y/N) (n, %)
14.6.3.2 Reason for First Attempt Failure (n, %, multi-response)
14.6.3.3 Study Medication Administration Failure with Reasons by Eye Laterality and Overall (n, %)
14.6.3.4 Number of Devices Used (n, %)

14.6.4. Insertion Point

14.6.4.1 Angle of Trocar Insertion Relative to the Sclera Surface and Bevel Orientation (n, %)
14.6.4.2 Insertion Completed Through the Sclera (Y/N) (n, %)
14.6.4.3 Insertion Difficulty and Complications (n, %, multi-response)

14.6.5. Deployment

14.6.5.1 Deployment Summary (Completion, Light Visibility, Speed and Kink Present) (Y/N) (n, %)

14.6.6. Injection of Drug Via the Drug Line

14.6.6.1 Injection Completed as Expected by Eye Laterality (Y/N) (n, %)
14.6.6.2 Drug Injection Duration and Residence Time of the Catheter (n, %)
14.6.6.3 Pain Experienced During the Injection, Intervention Performed and Pain Start Time (n, %)
14.6.6.4 Duration of Experienced Pain (Descriptive)
14.6.6.5 Study Drug Injection Difficulty and Complications (n, %, multi-response)

14.6.7. Bleeding

14.6.7.1 Intraocular Bleeding and Localization (n, %)
14.6.7.2 Scleral and Other Damage (n, %, multi-response)

14.7. Retinal Physician's Documentation and Assessment of Administration – EEP Population

14.7.1. Operative Assessment

14.7.1.1 Antiseptic Applied for Disinfection (n, %)

14.7.2. Type of Anesthesia Given

14.7.2.1 Forms of Anesthesia Administered (n, %, multi-response)
14.7.2.2 Quadrant of Application for Subconjunctival Lidocaine (n, %, multi-response)
14.7.2.3 Quadrant of Application for Subtenon Lidocaine (n, %, multi-response)

14.7.3. Execution of Oxulumis® Procedure

14.7.3.1 First Attempt Success Rate (Y/N) (n, %)
14.7.3.2 Reason for First Attempt Failure (n, %, multi-response)
14.7.3.3 Number of Devices Used (n, %)

14.7.4. Insertion Point

14.7.4.1 Angle of Trocar Insertion Relative to the Sclera Surface and Bevel Orientation (n, %)
14.7.4.2 Insertion Difficulty and Complications (n, %, multi-response)

14.7.5. Deployment

14.7.5.1 Deployment Summary (Completion, Light Visibility, Speed and Kink Present) (Y/N) (n, %)

14.7.6. Injection of Drug Via the Drug Line

14.7.6.1 Injection Completed as Expected by Eye Laterality (Y/N) (n, %)
14.7.6.2 Drug Injection Duration and Residence Time of the Catheter (n, %)
14.7.6.3 Pain Experienced During the Injection, Intervention Performed and Pain Start Time (n, %)
14.7.6.4 Duration of Experienced Pain (Descriptive)
14.7.6.5 Injection Location in Relation to Major Retinal Landmarks (n, %, multi-response)
14.7.6.6 Experienced Reflux and Severity (n, %)
14.7.6.7 Study Drug Injection Difficulty and Complications (n, %, multi-response)

14.7.7. Bleeding

14.7.7.1 Intraocular Bleeding and Localization (n, %)
14.7.7.2 Scleral and Other Damage (n, %, multi-response)

14.8. Retinal Physician's Documentation and Assessment of Administration – PP Population

14.8.1. Operative Assessment

14.8.1.1 Antiseptic Applied for Disinfection (n, %)

14.8.2. Type of Anesthesia Given

14.8.2.1 Forms of Anesthesia Administered (n, %, multi-response)
14.8.2.2 Quadrant of Application for Subconjunctival Lidocaine (n, %, multi-response)
14.8.2.3 Quadrant of Application for Subtenon Lidocaine (n, %, multi-response)

14.8.3. Execution of Oxulumis® Procedure

14.8.3.1 First Attempt Success Rate (Y/N) (n, %)
14.8.3.2 Reason for First Attempt Failure (n, %, multi-response)
14.8.3.3 Number of Devices Used (n, %)

14.8.4. Insertion Point

14.8.4.1 Angle of Trocar Insertion Relative to the Sclera Surface and Bevel Orientation (n, %)
14.8.4.2 Insertion Difficulty and Complications (n, %, multi-response)

14.8.5. Deployment

14.8.5.1 Deployment Summary (Completion, Light Visibility, Speed and Kink Present) (Y/N) (n, %)

14.8.6. Injection of Drug Via the Drug Line

14.8.6.1 Drug Injection Duration and Residence Time of the Catheter (n, %)
14.8.6.2 Pain Experienced During the Injection, Intervention Performed and Pain Start Time (n, %)
14.8.6.3 Duration of Experienced Pain (Descriptive)
14.8.6.4 Injection Location in Relation to Major Retinal Landmarks (n, %, multi-response)
14.8.6.5 Experienced Reflux and Severity (n, %)
14.8.6.6 Study Drug Injection Difficulty and Complications (n, %, multi-response)

14.8.7. Bleeding

14.8.7.1 Intraocular Bleeding and Localization (n, %)
14.8.7.2 Scleral and Other Damage (n, %, multi-response)

14.9. Patient Experience Assessment by Treatment Dose and by Visit for the SAF Population

14.9.1 Current Level of Pain in the Study Eye (n, %)
14.9.2 Pain and Discomfort During the Procedure (n, %)
14.9.3 Current Level Of Discomfort in the Study Eye (n, %)

14.10. Safety Data

14.10.1. Non-ocular Adverse Events for the SAF Population

14.10.1.1 Non-ocular – AE Ongoing, Frequency, Outcome and Severity per Patient (n, %)
14.10.1.2 Non-ocular – AE Ongoing, Frequency, Outcome and Severity per Event (n, %, multi-response)
14.10.1.3 Non-ocular – AE Relatedness to Investigational Device, Investigational Product, and Investigational Procedure per Patient (n, %)

14.10.1.4 Non-ocular – Non-Treatment AEs by MedDRA SOC / PT per Patient (n, %)
14.10.1.5 Non-ocular – TEAEs by MedDRA SOC / PT per Patient (n, %)
14.10.1.6 Non-ocular – TEAEs by MedDRA SOC / PT per Event (n, %, multi-response)

14.10.1.7 Non-ocular – SAEs Frequency and Outcome per Patient (n, %)
14.10.1.8 Non-ocular – SAE Seriousness Criteria per Patient (n, %, multi-response)
14.10.1.9 Non-ocular – SAEs by MedDRA SOC / PT per Patient (n, %)
14.10.1.10 Non-ocular – SAEs by MedDRA SOC / PT per Event (n, %, multi-response)

14.10.2. Ocular Adverse Events by Treatment Dose and Device Lots for the SAF Population

14.10.2.1 AE Frequency, Outcome and Severity per Patient (n, %)
14.10.2.2 AE Relatedness to Investigational Device, Investigational Product, and Investigational Procedure, and Intervention per Patient (n, %)

14.10.2.3 AEs of Special Interest per Patient – Study Eye (n, %)
14.10.2.4 AEs of Special Interest per Event – Study Eye (n, %)

14.10.2.5 TEAEs by MedDRA SOC / PT per Patient (n, %)
14.10.2.6 TEAEs by MedDRA SOC / PT per Event (n, %)
14.10.2.7 TEAEs by Severity and MedDRA SOC / PT (n, %)

14.10.2.8 Adverse Device Effects (ADEs) by MedDRA SOC / PT – Study Eye (n, %)
14.10.2.9 AE-Related Investigational Product and Device Intervention per Patient – Study Eye (n, %)
14.10.2.10 AE-Related Investigational Product and Device Intervention per Event – Study Eye (n, %, multi-response)
14.10.2.11 Other AE Related Action Taken per Event (n, %, multi-response)

14.10.2.12 SAE Seriousness Criteria per Patient (n, %, multi-response)
14.10.2.13 SAE Outcome per Patient (n, %)
14.10.2.14 Serious Treatment-Emergent AEs (TEAEs) – Study Eye (listing)
14.10.2.15 Serious ADEs (SADEs) by MedDRA SOC / PT per Patient – Study Eye (n, %)
14.10.2.16 Serious ADEs (SADEs) by MedDRA SOC / PT per Event – Study Eye (n, %)
14.10.2.17 SADE Seriousness Criteria per Patient – Study Eye (n, %, multi-response)

14.11. Exploratory Data by Treatment Dose and by Visit

14.11.1. Exploratory Data for the EEP Population – Efficacy/Safety

14.11.1.1 BCVA Values per Patient – Study Eye (line chart)
14.11.1.2 BCVA Values per Patient – Fellow Eye (line chart)
14.11.1.3 Overall Mean and Mean Change in BCVA from Baseline – Study Eye (descriptive)
14.11.1.4 Overall Mean and Mean Change in BCVA from Baseline – Fellow Eye (descriptive)
14.11.1.5 Overall Mean and Mean Change in BCVA from Baseline (boxplot)
14.11.1.6 Percentage of Subjects with Vision Gain and Vision Loss of at Least 5, 10, and 15 Letters from Baseline (n, %)
14.11.1.7 Percentage of Subjects with Vision Gain and Vision Loss (histogram)
14.11.1.8 Time to Subjects Meeting Criteria for Follow-on Treatment (days) (descriptive)
14.11.1.9 Central Subfield Thickness (CST) Values per Patient – Study Eye (line chart)
14.11.1.10 Central Subfield Thickness (CST) Values per Patient – Fellow Eye (line chart)
14.11.1.11 Overall Mean and Mean Change in CST from Baseline – Study Eye (descriptive)
14.11.1.12 Overall Mean and Mean Change in CST from Baseline – Fellow Eye (descriptive)
14.11.1.13 Overall Mean and Mean Change in CST from Baseline (boxplot)

14.11.1.14 Mean Change in IOP from Baseline (descriptive)
14.11.1.15 Mean Change in IOP from Baseline (boxplot)
14.11.1.16 Time to Improvement of Baseline BCVA by at Least 5, 10, and 15 Letters (days) (descriptive)
14.11.1.17 Duration of Maintained Improvement of Baseline BCVA by at Least 5, 10, and 15 Letters (days) (descriptive)
14.11.1.18 Percentage of Subjects with Improvement from Baseline CST by at Least 10% (descriptive)
14.11.1.19 Percentage of Subjects with Improvement from Baseline CST by at Least 20, 50, and 75µm (descriptive)
14.11.1.20 Percentage of Subjects with Increase of IOP of at Least 5, 10, and 30 mmHg from Baseline (n, %)
14.11.1.21 Percentage of Subjects with Increase of IOP of at Least 5, 10, and 30 mmHg from Baseline (bar chart)
14.11.1.22 Course of IOP through the First 60 Minutes After Administration of Study Drug (descriptive)
14.11.1.23 Course of IOP through the First 60 Minutes After Administration of Study Drug (dot plot)
14.11.1.24 Percentage of Subjects with Elevated IOP by at Least 10mmHg at Over 60 Minutes After Administration (descriptive)

14.11.2. Exploratory Data for the PP Population – Efficacy/Safety

14.11.2.1 BCVA Values per Patient – Study Eye (line chart)
14.11.2.2 BCVA Values per Patient – Fellow Eye (line chart)
14.11.2.3 Overall Mean and Mean Change in BCVA from Baseline – Study Eye (descriptive)
14.11.2.4 Overall Mean and Mean Change in BCVA from Baseline – Fellow Eye (descriptive)
14.11.2.5 Overall Mean and Mean Change in BCVA from Baseline (boxplot)
14.11.2.6 Percentage of Subjects with Vision Gain and Vision Loss of at Least 5, 10, and 15 Letters from Baseline (n, %)
14.11.2.7 Percentage of Subjects with Vision Gain and Vision Loss (histogram)
14.11.2.8 Time to Subjects Meeting Criteria for Follow-on Treatment (days) (descriptive)
14.11.2.9 Central Subfield Thickness (CST) Values per Patient – Study Eye (line chart)
14.11.2.10 Central Subfield Thickness (CST) Values per Patient – Fellow Eye (line chart)
14.11.2.11 Overall Mean and Mean Change in CST from Baseline – Study Eye (descriptive)
14.11.2.12 Overall Mean and Mean Change in CST from Baseline – Fellow Eye (descriptive)
14.11.2.13 Overall Mean and Mean Change in CST from Baseline (boxplot)
14.11.2.14 Mean Change in IOP from Baseline (descriptive)
14.11.2.15 Mean Change in IOP from Baseline (boxplot)
14.11.2.16 Time to Improvement of Baseline BCVA by at Least 5, 10, and 15 Letters (days) (descriptive)
14.11.2.17 Duration of Maintained Improvement of Baseline BCVA by at Least 5, 10, and 15 Letters (days) (descriptive)
14.11.2.18 Percentage of Subjects with Improvement from Baseline CST by at Least 10% (descriptive)
14.11.2.19 Percentage of Subjects with Improvement from Baseline CST by at Least 20, 50, and 75µm (descriptive)
14.11.2.20 Percentage of Subjects with Increase of IOP of at Least 5, 10, and 30 mmHg from Baseline (n, %)
14.11.2.21 Percentage of Subjects with Increase of IOP of at Least 5, 10, and 30 mmHg from Baseline (bar chart)
14.11.2.22 Course of IOP through the First 60 Minutes After Administration of Study Drug (descriptive)
14.11.2.23 Course of IOP through the First 60 Minutes After Administration of Study Drug (dot plot)
14.11.2.24 Percentage of Subjects with Elevated IOP by at Least 10mmHg at Over 60 Minutes After Administration (descriptive)

14.12. Follow-On by Treatment Dose by Visit for the SAF Population

14.12.1 Follow-On Treatment Eligibility Measurements (n, %)