Parexel International

Oxular Limited

OXUCT-102

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

Statistical Analysis Plan

Version: 1.0

Parexel Project Number: 269127

SPONSOR SIGNATURE PAGE

Approved by:

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Chief Medical Officer
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Date

Parexel Signature Page

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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SUBJECT: Statistical Analysis Plan

In December 2023, the team were informed that the Sponsor had decided to stop patient enrollment in this study with immediate effect. The Biostatistics team were informed that the planned statistical analyses in the SAP would not be performed, however a new SAP would not be developed for budgetary reasons.

Therefore, the SAP filed in the TMF does not accurately reflect the planned analyses for this study after the cancellation. Instead, the TLF shells filed in the SAP can be used as a reference for the planned analyses.

This document has been signed electronically or on the final page by the following:

Signatory	**Date**
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Approval Signatures

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	Date of last signature	New document

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
$AUC_{0\text{-last}}$	AUC from time zero to the last quantifiable concentration
$AUC_{0\text{-x}}$	AUC from time zero to time x
BCVA	Best Corrected Visual Acuity
BLQ	Below the Limit of Quantification
CD	Cannot Determine
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
C_{max}	Maximum observed concentration
CPMS	Clinical Pharmacology, Modeling and Simulation
cRORA	Complete outer Retinal Pigment Epithel and Atrophy
CST	Central Subfield Thickness
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DRSS	Diabetic Retinopathy Severity Score
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
ENR	Enrolled Analysis Set
FAS	Full Analysis Set
FCS	Fully Conditional Specification
gCV	Geometric Coefficient of Variation
IOP	Intraocular Pressure
IP	Investigational Product
IVT	Intravitreal
LOCF	Last Observation Carried Forwards
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT	Optical Coherence Tomography
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PN	Preferred Name
PPS	Per Protocol Set
PT	Preferred Term

Abbreviation/Acronym	Definition/Expansion
RAN	Randomized Analysis Set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SI	International System of Units
SOC	System Organ Class
SSC	Study Steering Committee
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
T_{max}	Time corresponding to occurrence of C_{max}
VEGF	Vascular Endothelial Growth Factor
WHO-DD	World Health Organization - Drug Dictionary
WNL	WinNonlin

1 INTRODUCTION

There is a great unmet need for diabetic macular edema (DME) therapies, which have a broader spectrum of pharmacological activities and thereby also addressing the strong inflammatory component of DME. In addition, therapies with a long duration of action of more than 6 months would reduce the treatment burden of subjects. Ocular corticosteroids have the potential to address this unmet need, as they have not only shown strong anti-edema effects similar to anti-vascular endothelial growth factor (VEGF) treatments, but also a broad anti-inflammatory effect.

Provided an acceptable safety profile, ocular steroids can deliver visual improvement in treatment-naïve subjects as well as DME subjects who show limited, short-lived, no visual improvement with intravitreal (IVT) administered anti-VEGF drugs. The use of current steroid therapies for DME, including Ozurdex®, is limited by typical and frequent adverse reactions. Due to these safety concerns and the limited durability of only 3-6 months for the most frequently used intravitreal steroid implant, there remains a high unmet medical need for efficacious ocular treatments for DME with a more favorable benefit-risk profile.

OXU-001 is a combination therapy of sustained-release dexamethasone acetate microspheres (DEXAspheres®) administered suprachoroidally with the Oxulumis® ophthalmic illuminated microcatheterization device, an ophthalmic administration device. OXU-001 is expected to have a sustained anti-edema effect and a reduced incidence of steroid-related ocular adverse events (AEs) compared to current standard intraocular steroid treatments.

The current study aims to compare safety, tolerability, efficacy, and durability of two dose levels of suprachoroidal sustained-release OXU-001 using the Oxulumis® ophthalmic illuminated microcatheterization device compared with intravitreal dexamethasone implant (OZURDEX®) in subjects with DME.

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Trial Report (CTR) of Part A of Clinical Trial OXUCT-102, a Phase II randomized trial in subjects with DME recruited into two parts – an open label Part A and a masked Part B. This SAP covers the planned analyses for Part A only.

Data shall be provided in the clinical trial database, except for pharmacokinetic (PK) data, central lab data, and imaging data, which shall be provided separately by external vendors.

The content of this SAP is based on following study documents:

- Clinical Trial OXUCT-102 Protocol, Version 3.0 (24 February 2023)
- Electronic Case Report Form (eCRF), Version 2.0 (16 May 2023)
- Electronic Laboratory Data Transfer Specifications, Version 0.1
- Pharmacokinetic Data Transfer Agreement, Version 1.0 (08 May 2023)
- DARC Imaging Data Dictionary, Version 0.1.

2 CLINICAL TRIAL OBJECTIVES

For the objective of this clinical trial, no estimands are defined per the clinical trial protocol (CTP). Data generated in this clinical trial in previously anti-VEGF treated and treatment-naïve DME subjects for subject-relevant outcomes will inform estimands for subsequent clinical trials. Also, clinical experience with the Oxulumis® ophthalmic procedure will contribute to building estimands for future trials of OXU-001.

The trial objectives for Part A are defined as follows.

2.1 Primary Objective

The primary objective of Part A of this trial is to evaluate the safety, tolerability, and feasibility of suprachoroidal OXU-001 in subjects with DME.

2.2 Exploratory Objectives

The exploratory objectives of the trial relate in addition to efficacy and are defined as follows:

1. To evaluate the durability of suprachoroidal OXU-001 in subjects with DME
2. To explore the efficacy of suprachoroidal OXU-001 determined by change in visual acuity, edema control, and impact on vision-related quality of life in subjects with DME.

2.3 Other Objectives

The other objective of the trial relates to PK and is to assess systemic exposure of dexamethasone after suprachoroidal administration of OXU-001.

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design and Plan

This is a phase two, multi-center, randomized, masked, fifty-two-week parallel-group trial with two parts (A and B).

Part A is an open label, randomized, single dose two treatment group comparison of two dose levels of sustained-release suprachoroidal OXU-001 (DEXAspheres® administered using the Oxulumis® illuminated microcatheterization device, an ophthalmic administration device).

Part B is a randomized, masked, active comparator, single dose, comparison of two dose levels of suprachoroidal OXU-001 and IVT Ozurdex® to evaluate the safety, tolerability, efficacy, and durability in subjects with DME. This SAP covers the Part A analyses only, and further details on Part B will be provided in a separate SAP.

Part A consists of two parallel, randomized treatment groups, administered a suprachoroidal mid dose (Dexamethasone Acetate 1.5mg) OXU-001 (9 subjects) and a suprachoroidal high dose (Dexamethasone Acetate 3.0mg) OXU-001 (9 subjects) in a total of approximately 18 subjects who were previously treated with intravitreal anti-VEGF in the study eye. The treatment will be administered via suprachoroidal microcatheterization.

Subjects will be randomly assigned to receive either the mid-dose (1.5mg) or high dose (3.0mg) OXU-001 in a 1:1 fashion according to a central randomization scheme provided by an interactive voice response system /interactive web response system. Subjects in whom the administration of study treatment could not be completed will be replaced in order to reach the targeted numbers of treated subjects.

Only one eye will be determined as the study eye and only the study eye will receive a single administration of trial treatment on Visit 2, Day 0. Subjects will receive study treatment using either the OXU-001 Standard, or the OXU-001 ConjIncision Variant (see CTP section 4.1). 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 best corrected visual acuity (BCVA) will be selected as the study eye; if both eyes meet the relevant criteria and have the same BCVA, the investigator can select the study eye. If one eye is previously treated, the other eye may still qualify as a treatment naïve study eye if all inclusion criteria and none of the exclusion criteria are met. Subjects' fellow eye may continue to receive non-study treatment following guidelines and standards at the investigational site. Subjects in Part A should not receive steroid treatment in their fellow eye, as this may have an impact on the PK assessment of OXU-001. Treatment of the fellow eye is not considered part of the trial treatment.

This trial will be monitored by an independent data monitoring committee (DMC). The composition, roles, responsibilities, and rules governing the DMC are available in a DMC Charter. This trial's execution will be supervised by a study steering committee (SSC). The composition, roles, responsibilities, and rules governing the SSC are available in the SSC Charter. No interim analyses are planned.

Subjects will be followed for 52 weeks, with a safety analysis at Week 6, and further analysis at Week 24 and Week 52. Randomization will be performed at the baseline visit (Visit 2), followed by

a single administration of trial treatment on Day 0to the study eye within 14 days after the start of Visit 2 activities. Day 0 is defined as the date of completion of administration of trial treatment. Subjects will then enter a 52-week post-baseline follow-up period. See the schedule of activities in section 1.3 of the CTP for further details.

3.2 Endpoints and Associated Variables

3.2.1 Safety Variables

Frequency and severity of

- Ocular and systemic adverse events (serious adverse events, adverse events of special interest, and treatment-emergent adverse events)
- Device adverse effects (serious adverse device effects and treatment-emergent device adverse effects)

3.2.2 Exploratory Efficacy Variables

- Time from baseline (Visit 2) to subjects requiring follow-on treatment (per pre-specified criteria)
- Mean Change BCVA (Early Treatment Diabetic Retinopathy Study (ETDRS)) at Week 24 compared to baseline
- Mean Change in central subfield thickness (CST) on spectral domain optical coherence tomography (SD-OCT) at Week 24 compared to baseline
- Mean Change in BCVA (ETDRS) through Week 52 compared to baseline
- Mean Change in CST on SD-OCT through Week 52 compared to baseline
- Proportion of subjects requiring follow-on treatment at study visits from Week 12 through Week 52
- Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) gain of BCVA from week 4 to week 52 compared to baseline
- Proportion of subjects with 5-, 10-, or 15-letter (ETDRS) loss of BCVA from week 4 to week 52 compared to baseline.
- Proportion of subjects with BCVA >68 letters (ETDRS) at each study visit from week 4 to week 52
- Mean change in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) composite score at Week 24 and Week 52 compared to baseline.

3.2.3 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at time point(s) described in the protocol version 3.0. as follows:

Plasma PK concentrations will be determined at the following nominal times: 0 (predose sample taking during screening visit), Day 0 (60min after administration of the trial treatment), Day 1, Week 1, Week 4, Week 24 and Week 52.

Unless otherwise stated, derivation of PK parameters will be the responsibility of the Clinical Pharmacology, Modeling and Simulation (CPMS) group, Parexel.

If calculable, the following PK parameters listed in Table 3-1 will be determined for dexamethasone in plasma following single suprachoroidal dose administration.

Table 3-1 Plasma Pharmacokinetic Parameters After Single Dose Administration or First Dose Administration of Multiple Dose Study

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration
T_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
$AUC_{0\text{-last}}$	AUClast	AUCLST	Area under curve (AUC) from time zero to the last quantifiable concentration
$AUC_{0\text{-x}}$	$AUC_{0\text{-x}}$	AUCINT	AUC from time zero to time x, e.g. $AUC_{0\text{-60'}}$, $AUC_{0\text{-1d}}$, $AUC_{0\text{-1w}}$, $AUC_{0\text{-4w}}$, $AUC_{0\text{-24w}}$, $AUC_{0\text{-52w}}$

CDISC = Clinical Data Interchange Standards Consortium. WNL = WinNonlin.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Note that this section is not applicable to PK data.

4.2.1 Treatment

For presentations in Part A outputs, 'treatment' refers to the following:

- OXU-001 mid dose (Dexamethasone Acetate 1.5mg)
- OXU-001 high dose (Dexamethasone Acetate 3.0mg).

4.2.2 Study Day

Study days will be numbered relative to the first day of trial drug administration.

Study day = (Date of measurement – Date of trial drug administration)

Per the CTP, the date of trial drug administration is Day 0.

4.2.3 End of Trial

The end of Part A of the trial is defined as the date of the last visit of the last subject in Part A of the trial.

A subject is considered to have completed the trial if the subject has completed all periods of Part A of the trial including the last visit (Week 52/end of study or early termination visit). The date of the last available post-treatment assessment will therefore be considered the end of trial date per subject for Part A.

4.2.4 Baseline

The baseline value is defined as the last non-missing measurement recorded before the first dose of trial drug administration (note that in the case that treatment administration with the standard variant is not completed (i.e. no dose of study treatment adminisered), and treatment with the ConjIncision variant is completed, the completed administration with the ConjIncision variant will be considered the first dose). Per the CTP schedule of activities, baseline values should be assessed on Visit 2, however for some endpoints that are assessed at screening but not at Visit 2 (e.g. NEI-VFQ25, laboratory assessment) the baseline value will be taken from the screening visit.

The baseline measurement for individual domains is defined as the last non-missing measurement recorded before the first (and only) dose of trial drug administration for that domain (e.g. the baseline

vital signs measurements is the last non-missing vital sign measurement recorded before first dose of trial drug).

No imputation will be done for missing baseline value for derivation of change from baseline or summary tables and shift tables, unless otherwise stated.

4.2.5 Study Eye

Only one eye will be determined as the study eye, and only the study eye will receive a single administration of trial treatment on Visit 2, Day 0. If one eye is previously treated, the other eye may still qualify as a treatment-naïve study eye if all inclusion criteria and none of the exclusion criteria are met.

4.2.6 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Unless otherwise specified, the following applies:

- For by visit summaries, the last non missing assessment (including repeat assessments except for BCVA, where repeat assessments are mandatory, see CTP Section 9.3.5 and SAP section 4.10.2.2) recorded at each visit will be summarized, and unscheduled visits will not be included
- For across visit summaries, scheduled, unscheduled and repeated assessments will be included
- Listings will present all visits, including unscheduled ones.

4.2.7 Summary and Representation of Data

Continuous data will be summarized in terms of mean, standard deviation (SD), median, first quartile, third quartile, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data will be summarized in terms of frequency counts and percentages.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. P-values less than 0.001 will be presented as “<0.001”. Confidence intervals (CIs) will be presented to one more decimal place than the raw data.

The term ‘systemic’ includes non-ocular, local and topical events.

4.3 Software

All report outputs will be produced using SAS® software version 9.4 or later in a secure and validated environment.

The PK analyses will be conducted using Phoenix® WinNonlin version 8.2 or later in a secure and validated environment.

4.4 Study Subjects

4.4.1 Analysis Sets

The following analysis sets are defined for Part A of this trial:

Analysis Set	Description
Enrolled Analysis Set (ENR)	The ENR will include all subjects who have signed informed consent.
Randomized Analysis Set (RAN)	The RAN will include all subjects who have signed informed consent and are assigned a randomization number.
Full Analysis Set (FAS)	The FAS will include all randomized subjects who received the trial treatment and have at least one post-baseline efficacy observation or measurement (efficacy endpoints are detailed in section 4.10.2). Subjects will be analyzed according to the trial treatment group to which they were randomized.
Per Protocol Set (PPS)	The PPS will consist of the FAS population with exception of subjects with important protocol violations that could influence the validity of the data for the primary efficacy evaluations. In the analyses based on the PPS, subjects will be analyzed according to their randomized trial treatment group. All criteria to exclude subjects from the PPS will be made based on a review of the data prior to the Week 24 and Week 52 analysis, respectively (note that this will not be a masked review because Part A has no masking).
Safety Analysis Set (SAS)	The SAS will include all subjects for whom administration of trial treatment was started, or the trial procedure was started (according to the field 'Was the procedure started (needle insertion of device/applicator to eye wall)?' on the eCRF). In analyses performed on the Safety Analysis Set, subjects will be analyzed according to their actual treatment received. Note: in Part A no applicator will be used, as this is part of the Ozurdex trial treatment which will only be used in Part B.
Pharmacokinetic Analysis Set (PKAS)	The PKAS will include subjects enrolled in Part A of the trial who have received the trial drug and for whom at least one PK sample has been analyzed and with no major protocol deviations that have PK implications.

All safety and demographic analyses, including the primary analysis of safety endpoints, will be

performed of the SAS. The exploratory efficacy analyses will be performed on the FAS. Efficacy analyses will also be performed on the PPS. All analyses of PK parameters will be performed on the PKAS.

A summary of the number and percentage of subjects in each analysis set (as described above) and the reason for exclusion from the analysis set will be presented by treatment group and overall for all enrolled subjects, with denominators based on the number of subjects enrolled in each treatment group. The percentage will not be presented for the ENR or RAN.

A by subject listing of analysis set details will be presented for all enrolled subjects, including the subject identifier, treatment group, age, sex, race, indication of inclusion/exclusion from each analysis set and reason for exclusion. If subject data has been partially excluded from an analysis set (based on data review meeting discussions), details of the data and visit that has been excluded will appear on this listing.

4.4.2 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the trial will be provided, from randomization to trial completion.

A summary of subject disposition information will be presented for the ENR by treatment group and overall, including the number of subjects enrolled, randomised/not randomised and treated/not treated. The number and percentage of subjects who have completed the trial, are ongoing the trial and have discontinued the trial, along with the reason for discontinuation will be presented. Percentages will be based on the number of treated subjects in each treatment group.

A by subject listing of subject disposition will be presented for the ENR, including the date of informed consent, date of randomization, trial status (ongoing/completed/discontinued) date of trial discontinuation or completion, and reason for trial discontinuation, treatment status (treated/not treated), and date of treatment completion.

A summary of screen failed subjects will be presented for the ENR including the number of screen failed subjects and the reason for screen failure by prior treatment status (pre-treated with intravitreal anti-VEGF/ treatment-naïve) and study eye. Percentages will be based on the number of screen failed subjects.

A listing of screen failed subjects including reason for screen failure and date of screen failure will also be presented for the ENR.

4.4.3 Protocol Deviations

Important protocol deviations are defined as deviations from the protocol likely to have an impact on the evaluation of efficacy and/or safety of trial treatments, and are specified in the project specific Protocol Deviation Specification. Protocol deviations (both important and non-important) and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project specific Protocol Deviation Specification.

Protocol deviations (as in Sections 4.4.3.1 and 4.4.3.2) and analysis sets will be reviewed in a data

review meeting to decide on inclusion or exclusion of subject(s) from analyses sets. Decisions regarding the exclusion of subjects and/or subject data from analyses will be made prior to database lock and will be documented and approved.

A summary of the number and percentage of subjects with an important protocol deviation by type of deviation will be presented for all randomized subjects by treatment group and overall, with percentages based on the number of subjects randomized.

A by subject listing of all protocol deviations (both important and non-important) will also be presented for all randomized patents. including the subject identifier, site, protocol deviation classification, protocol deviation description and details of exclusion from specific analysis sets due to a protocol deviation.

4.4.3.1 Protocol Deviations with Non-PK Implications

Protocol deviations with non-PK implications are specified in the project specific Protocol Deviation Specification.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- Suprachoroidal Sustained-Release administration deviations – interruption of administration resulting in underdose, overdose, partial or complete intravitreal deployment etc.
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol
- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s).

Further details are specified in the project specific Protocol Deviation Specification.

4.5 Demographics and Baseline Characteristics

Descriptive summaries of demographic and other baseline characteristics will be presented for the SAS by treatment group and overall. Percentages will be based on the number of subjects in the SAS in the corresponding treatment group.

Summaries of the following demographic characteristics will be presented:

- Age (in years) at screening as reported on the eCRF
- Sex (male/female)
- Ethnicity (Hispanic or Latino/ Not Hispanic or Latino/ Unknown)
- Race (American Indian or Alaska Native/ Asian/ Black or African American/ Native Hawaiian or Other Pacific Islander/ Caucasian White/ Other/ Multiple/ Not Reported) – subjects who indicate more than one race group will be summarized as ‘Multiple’
- Weight (kg)

- Height (cm)
- Body mass index (kg/m^2)
- Baseline BCVA (letters) by eye
- Baseline intraocular pressure (IOP) (mmHg) by eye
- Baseline CST (µm) by eye
- Baseline NEI VFQ-25 composite score.

Body mass index will be calculated as [weight (kg) / [height (m)]^2].

Demographic and baseline characteristics will also be listed for the SAS.

4.6 Medical and Surgical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.1 or higher and assigned to a System Organ Class (SOC) and Preferred Term (PT). Medical and surgical history will be classed as ocular or systemic according to the eCRF.

Ocular and systemic subject prior and current medical and surgical history will be presented for the SAS separately for the two categories The number and percentage of subjects with medical history findings will be presented by SOC and PT by treatment group and overall, with ocular medical history further broken down by eye. Percentages will be based on the number of subjects in the SAS per treatment group.

Subjects with multiple medical and surgical history findings within the same SOC/PT will be counted once per SOC/PT. The SOCs will be sorted by international order (see Appendix 6.1), and PTs will be sorted by descending overall frequency (within system organ class). PTs with the same frequency will be further sorted by alphabetical order.

Medical and surgical history will be classed as prior or current as follows:

- Prior: if the end date of the medical/surgical event is before the date of first dose of trial treatment.
- Current: if the end date of the medical/surgical event is on or after the date of first dose of trial treatment. Also if medical/surgical history event is marked as ‘ongoing’ on the eCRF.

In the case of missing/partial medical or surgical history end dates, the following imputation rules will be applied to class the event as current or prior:

- If the day is missing but the month and year are present, then the last day of the month is imputed
- If the day and month are missing and the year is present, then the 31st December is imputed
- If the imputed date is later than the date of death or date of trial discontinuation, then impute the maximum of the death and date of trial discontinuation dates
- If the end date is completely missing, then assume the event is ongoing.

A by-subject listing for ocular and systemic medical and surgical history will be provided for the SAS.

4.6.1 Diabetic Medical History

Prior and current diabetic medical history will be summarized for the SAS overall, and by treatment group (overall and for both the study eye and fellow eye, as appropriate). The number and percentage of subjects with a history of the following will be presented with percentages based on the SAS:

- Diabetes mellitus (type 1/ type 2)
- Diabetic macular edema (by eye)
- Diabetic retinopathy (by eye)
- Proliferative diabetic retinopathy (by eye)
- Vitrectomy (by eye)
- Glaucoma surgery (by eye)
- Cataract surgery, including whether the posterior capsule is intact (by eye).

Summary statistics of the duration of DME and time since first DME treatment will also be presented. The duration of DME will be calculated as [date of informed consent - date of onset of DME in the respective eye +1]. At the overall level, the earliest date of onset over both treatment groups will be used. The time since first DME treatment will be calculated as [date of first DME treatment in the respective eye - date of informed consent +1]. At the overall level, the earliest date of onset over both treatment groups will be used. The first DME treatment will be identified as they first medication or procedure with 'Diabetic Macular Edema' indication on the CRF.

Diabetic medical history will be classed as prior or current per the rules in section 4.6.

Prior and current diabetic medical history will also be listed for the SAS.

4.7 Prior and Concomitant Medications and Medical Procedures

Prior and concomitant ocular and systemic medications will be coded according to the World Health Organization - Drug Dictionary (WHO-DD) version 'B3 September 2022' or later. Prior and concomitant medical procedures will be coded according to MedDRA® version 25.1 or higher.

The number and percentage of subjects who took prior or concomitant ocular and systemic medications will be summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) class (ATC3 will be used) and preferred name (PN) for the SAS by treatment group and overall, for both the study eye and fellow eye for ocular medications. Percentages will be based on the number of subjects in the SAS in the corresponding treatment group. Subjects with multiple prior or concomitant medications within the same ATC class and PN will be counted only once per ATC class and PN. The ATC classes will be sorted by descending overall frequency, and PNs will be sorted by descending overall frequency within ATC class. ATC classes and PNs with the same frequency will be further sorted by alphabetical order.

The above summary will be repeated for medications indicated as follow on treatment (as defined in section 4.10.2.1).

The number and percentage of subjects who had prior or concomitant ocular and systemic medical procedures will be summarized by SOC and PT for the SAS by treatment group and overall.

Percentages will be based on the number of subjects in the SAS in the corresponding treatment group. Subjects with multiple prior or concomitant medical procedures within the same SOC class and PT will be counted only once per SOC class and PT. The SOCs will be sorted by international order (see Appendix 6.1), and PTs will be sorted by descending overall frequency within SOC. PTs with the same frequency will be further sorted by alphabetical order.

Medications and medical procedures that start and stop prior to the date of first dose of trial treatment will be classified as prior only. If a medication/procedure starts before the date of trial treatment and stops on or after the date e of trial treatment, or is marked as ongoing, then the medication/procedure will be classified as both prior and concomitant. Medications/procedures will be classified as concomitant only if they have a start date on or after the date of first dose of trial treatment. If the medication/procedure start and/or stop dates are missing or partial, the classification will be assigned per the rules in Appendix 6.3.

Listings of ocular and systemic prior and concomitant medications will also be presented for the SAS, for both the study and fellow eye for ocular medications. Dose, frequency, route and indication for the medications will be included in the listings. Follow on treatments and DME treatments will be identified in this listing. A separate listing of prior medications identified as anti-VEGF treatments will be provided for the SAS. Note that DME treatments will be identified as any medication or procedure with 'Diabetic Macular Edema' indication on the CRF, and anti-VEGF treatments will be identified as any medication under the S01LA ATC code (class 4).

A listing of prior and concomitant ocular and systemic medical procedures will also be presented for the SAS. Indication for the medical procedure will be included in the listing. DME treatments will be identified in this listing. A separate listing of prior medical procedures identified as anti-VEGF treatments will be provided for the SAS.

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

For Part A of the OXEYE trial the intended compartment for administration is the suprachoroidal space, as only OXU-001 dose levels are tested.

The following summaries of treatment exposure will be presented for the SAS by treatment group separately for the first and second treatment sessions:

The number and percentage of subjects

- Who received each treatment variant (OXU-001 Standard Variant/ OXU-001 ConjIncision Variant/ Combination OXU-001 Standard Variant followed by ConjIncision Variant in one Treatment Session)
- Who completed the trial treatment with administration of the randomized dose of the trial drug to the intended compartment
- Who completed the trial treatment with administration of a dose other than the randomized dose (over- or underdose) to the intended compartment
- Who completed the trial treatment with administration of trial drug partially or fully to another compartment than intended (e.g. intravitreal, when suprachoroidal is intended) by compartment

- In whom the trial treatment could not be completed, along with reason treatment could not be completed.

Percentages will be based on the SAS.

A by subject listing of subject exposure to trial drug (including details of completion of treatment, over or under-dose received, and compartment of the dose administered) will be presented for the SAS.

4.8.2 Compliance

No summaries of treatment compliance will be presented because treatment is only administered once by a treating investigator.

4.9 Analyses Supporting Primary Safety Objective

4.9.1 Primary Endpoints

The primary objective of Part A of the trial is to evaluate the safety, tolerability, and feasibility of suprachoroidal OXU-001 in subjects with DME. The primary endpoints are the frequency and severity of the following types of adverse events:

- Ocular and systemic AEs
- Ocular and systemic serious adverse events (SAEs)
- Adverse events of special interest (AESI), per definition in section 6.5 (ocular only)
- Ocular and systemic treatment emergent adverse events (TEAEs)
- Ocular and systemic ADEs (note that all adverse device effects will be treatment-emergent)
- Ocular and systemic serious device adverse effects (SADEs).

Ocular AEs will be summarized overall and separately for the study eye and fellow eye.

Other adverse event types will be summarized to support the primary objective, as further described in this section.

4.9.2 Statistical Method of Analysis

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

AEs and ADEs that occur from the time that informed consent is signed until the end of trial will be recorded. Adverse events will be coded using MedDRA Version 25.1 or higher. All adverse event summaries will be done on the SAS.

Adverse device effects are defined as any AE that is classed as related to the investigational medical device, and will be identified based on the eCRF field ‘Is this Adverse Event an Adverse device Effect?’. ADEs are a subset of all AEs. Treatment emergent adverse events or adverse device effects are defined as any AE or ADE occurring or worsening (defined as an increase in severity) on or after

the date of the first trial treatment session (including preparatory activities). All ADEs will be treatment emergent because the device is not used prior to treatment.

Missing or incomplete AE start and end dates will be imputed according to the rules specified in Section 6.2. The listings will present original (non-imputed) dates.

For tabular summaries, an AE is considered related to investigational product (IP)/ medical device or trial procedure if the relationship is marked as causally, probably or possibly related as indicated on the eCRF, else it is considered not related if marked as not related on the eCRF. Subjects who experience the same event multiple times will be included in the most related category. For each subject and each AE, the worst severity recorded will be attributed and used in summaries of severity. Subjects who experience the same event multiple times will be included in the most severe category. If severity or relationship is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed in tabular summaries but will be recorded as missing in the listings.

An overall summary of AEs related to the primary safety endpoint will present the number and percentage of subjects and number of events for:

- All AEs
- All ADEs
- Treatment emergent AEs
- SAEs
- SADEs
- AESIs (as defined in Appendix 6.5).

Percentages will be based on the number of subjects in the SAS.

For the following AE types, the number and percentage of subjects as well as the number of events will be presented by SOC and PT by treatment group and overall for the SAS, with percentages based on the number of subjects in the SAS per treatment group:

- All AEs
- All ADEs
- Treatment emergent AEs
- SAEs
- SADEs
- AESIs (as defined in Appendix 6.5).

These AE summaries will be presented separately for ocular and non-ocular AEs where appropriate, and the ocular AEs will be presented overall and separately for the study and fellow eye.

Subjects with multiple AEs within the same SOC and/or PT are counted once per SOC and/or PT. The summaries will be sorted by international order for SOC (see Appendix 6.1), and then by descending frequency of PT (within SOC). SOCs and PTs with the same frequency will be further sorted by alphabetical order.

Listings of the following types of adverse events will be presented for the SAS, with flags for the ocular/non-ocular AEs, study eye/ fellow eye and a flag for subjects who did not receive treatment:

- All AEs
- All ADEs
- Serious AEs, including seriousness criteria met (congenital anomaly or birth defect/disability or permanent damage/death/ hospitalization (initial or prolonged)/life threatening/other serious (important medical events)/other)
- Serious ADEs, including seriousness criteria met (congenital anomaly or birth defect/disability or permanent damage/ chronic disease /death/ hospitalization (initial or prolonged)/life threatening/other serious (important medical events)).

4.9.3 Sensitivity analyses

Not applicable for safety analyses.

4.9.4 Supplementary analyses

To further support the primary safety endpoints, additional adverse event summaries will be presented.

An overall summary of AEs supporting the primary safety endpoint will present the number and percentage of subjects and number of events for:

- TEAEs by maximum severity (mild/moderate/severe)
- ADEs by maximum severity (mild/moderate/severe)
- TEAEs related to the IP
- TEAEs related to trial procedure
- Treatment emergent serious adverse events (TESAEs) related to the IP
- TESAEs related to trial procedure
- TEAEs resulting from device deficiencies
- ADEs resulting from device deficiencies
- TEAEs leading to discontinuation from trial
- ADEs leading to discontinuation from trial
- TEAEs leading to death
- ADEs leading to death
- TEAEs of IOP changes (ocular only)
- TEAEs of cataract and lens opacification (ocular only)
- TEAEs ocular pain and discomfort by maximum severity (mild/moderate/severe) (ocular only).

AEs of IOP changes, cataract and lens opacification, and ocular pain and discomfort are defined per the following SOCs, high level group terms, high level terms and PTs as follows:

AE Group	SOC	High Level Group Term	High Level Term	PT

IOP changes	Investigations	Neurological, special senses and psychiatric investigations	Ophthalmic function diagnostic procedures	• Intraocular pressure fluctuation • Intraocular pressure decreased • Intraocular pressure increased
	Eye disorders	Glaucoma and ocular hypertension	Glaucomas (excl congenital)	All under high level term 'Glaucomas (excl congenital)'
Cataract and lens opacification	Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract conditions	All under high level term 'Cataract conditions'
			Lens structural change, deposit and degeneration (excl cataracts)	Posterior capsule opacification
	Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Eye and ear procedural complications	Posterior capsule opacification
Ocular pain and discomfort	Eye disorders	Eye disorders NEC	Ocular disorders NEC	• Eye pain • Ocular discomfort

Percentages will be based on the number of subjects in the SAS

For the following AE types, the number and percentage of subjects as well as the number of events will be presented by SOC and PT by treatment group and overall for the SAS, with percentages based on the number of subjects in the SAS per treatment group:

- TEAEs by maximum severity (mild/moderate/severe)
- ADEs by maximum severity (mild/moderate/severe)
- TEAEs related to the IP
- TEAEs related to trial procedure
- TESAEs related to the IP
- TESAEs related to trial procedure
- TEAEs resulting from device deficiencies
- ADEs resulting from device deficiencies
- TEAEs leading to discontinuation from trial
- ADEs leading to discontinuation from trial
- TEAEs leading to death
- ADEs leading to death
- TEAEs of IOP changes (ocular only)
- TEAEs of cataract and lens opacification (ocular only)
- TEAEs of ocular pain and discomfort by maximum severity (mild/moderate/severe) (ocular only).

These AE summaries will be presented separately for ocular and non-ocular AEs, and the ocular AEs will be presented overall and separately for the study and fellow eye.

Subjects with multiple AEs within the same SOC and/or PT are counted once per SOC and/or PT. The summaries will be sorted by international order for SOC (see Appendix 6.2), and then by descending frequency of PT (within SOC). SOCs and PTs with the same frequency will be further sorted by alphabetical order.

Listings of the following types of adverse events will be presented for the SAS, with flags for the ocular/non-ocular AEs and study eye/fellow eye:

- AEs leading to discontinuation from trial
- ADEs leading to discontinuation from trial
- AEs resulting from device deficiencies
- ADEs resulting from device deficiencies
- AEs leading to death
- ADEs leading to death
- AEs indicating non-completion of trial treatment
- ADEs indicating non-completion of trial treatment

Note that AEs/ADEs indication non-completion of trial treatment will be identified as subjects where the AE cause discontinuation from trial with reason 'Inability to Administer Treatment'.

Any action taken with the Oxulumis device as a result of an AE will be presented in the listings above.

4.10 Exploratory Efficacy Evaluation

4.10.1 Analysis and Data Conventions

No formal testing of hypotheses has been planned in this trial. Therefore, no formal sample size calculations were performed. Eighteen subjects are considered adequate to analyze the trial objectives.

4.10.1.1 Multi-center Studies

Subjects will be recruited from different sites in the US in Part A of this trial. Adjustment of the primary outcome analysis by site will not be done for Part A due to the small overall sample size and the expected comparable contribution of sites to the Part A recruitment.

4.10.1.2 Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons is needed, as the comparisons between groups performed as part of the efficacy analyses are exploratory only.

4.10.2 Exploratory Efficacy Variables

4.10.2.1 Follow-On Treatment

Starting at the Week 12 visit, subjects will be evaluated against prespecified criteria indicating the need for follow-on treatment (i.e., indicating the end of the current treatment interval). The criteria are as follows:

1. At least 75µm thickening in CST on SD-OCT compared to best CST value since the baseline visit, Visit 2, or.
2. A decrease in BCVA of > 10 letters (ETDRS) from the best achieved BCVA since the baseline visit, Visit 2, that, in the opinion of the investigator, is due to the worsening of DME.

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

Subjects who will require the need for therapy of diabetic retinopathy complications will be imputed as those requiring follow-on treatment.

Note that there is a distinction between a subject requiring follow on treatment, and the subject actually receiving it. The assessment of whether the subject requires follow-on treatment will be taken directly from the eCRF field 'Is the subject eligible for follow-on treatment?', and subjects who actually receive follow on treatment will be identified via the eCRF field 'Will the subject be receiving follow-on treatment?'.

The time to subjects requiring follow on-treatment (in weeks) will be calculated as follows:

- For subjects who are eligible for follow on treatment:
  - date subject first eligible to receive follow on treatment on the eCRF - date of treatment administration + 1
- For subjects who are not eligible for follow on treatment:
  - date of censoring - date of treatment administration + 1.

The date of censoring is calculated as the latest of the following dates from the eCRF:

- Latest visit date
- Date of trial discontinuation/loss to follow up
- Date of death (note that for subjects who are lost to follow up and then subsequently die, the subject will be censored at the date of discontinuation/loss to follow up (the last date they are known to be alive)).

However, if none of these occurred and the subject has not died, they will be censored at Week 52 (the end of the follow up period). Note that the time of origin of the survival analyses will be baseline, as defined in section 4.2.4.

The survival probability of subjects requiring follow-on treatment at all visits starting from Week 20 to Week 52 with 95% CI will be presented for the FAS, along with the median survival probability of subjects requiring follow-on treatment and the corresponding 95% CI. The survival probability of subjects requiring follow-on treatment will be calculated using the Kaplan Meier method and 95%

CIs will be calculated using the Greenwood method (CONFTYPE=LINEAR option). The survival curves will be compared between the treatment groups using a logrank test, and the p-value of this test will be presented. The number of events and number of subjects censored at each time point will also be included from Week 12 to 52.

Further, a Kaplan Meier plot of the survival probability of subjects requiring follow-on treatment over time will be presented for the FAS. The number of subjects at risk will also be presented on the plot.

The number and percentage of subjects requiring follow-on treatment will be presented for the FAS cumulatively by visit and treatment group (from Week 12 to Week 52). The number and percentage of subjects requiring diabetic retinopathy treatment will also be presented for the FAS cumulatively by visit and treatment group (from Week 12 to Week 52) Percentages will be based on the FAS per treatment group. Note that diabetic retinopathy treatments will be identified as any medication or procedure with 'Diabetic Retinopathy', 'Diabetic Retinopathy Complication' or 'Proliferative Diabetic Retinopathy' indication on the eCRF.

As a sensitivity analysis, the above summaries will be repeated (on the FAS and PPS) for time to subjects receiving follow on treatment (rather than requiring follow on treatment, per the definition above) for the subset of subjects who required the follow on treatment.

The time to subjects receiving follow on-treatment (in weeks) will be calculated as follows:

- For subjects who receive follow on treatment:
  - date of administration of first follow-on treatment on the eCRF - date of treatment administration + 1
- For subjects who do not receive follow on treatment:
  - date of censoring - date of treatment administration + 1.

The date of censoring is calculated as the latest of the following dates from the eCRF:

- Latest visit date
- Date of trial discontinuation/loss to follow up
- Date of death (note that for subjects who are lost to follow up and then subsequently die, the subject will be censored at the date of discontinuation/loss to follow up (the last date they are known to be alive)).

The above analyses will be repeated on the PPS.

A listing of the follow-on treatment assessments and follow on treatment received will also be presented for the FAS.

4.10.2.2 Best Corrected Visual Acuity

BCVA in the study eye will be assessed at all visits, as specified in the schedule of activities, using the standard ETDRS protocol at 4 meters. BCVA scores will be obtained directly from the eCRF data.

Per the CTP, all BCVA assessments in the study eye will be performed in duplicate, and both measurements will be entered in the eCRF. If both ETDRS letters scores do not differ by more than 5 letters, then the mean of both BCVA assessments will be used for summaries. If the difference is greater than 5 letters, the better (higher) ETDRS letter score will be used. All BCVA measurements will be presented individually in the listings, and the measurement used in the analysis will be identified in the listing.

For example, if subject A has BCVA measurements of 60 letters and 62 letters at a particular visit, then since these measurements do not differ by more than 5 letters then, mean of the two measurements (61) will be used in any analyses as the sole measurement for that subject for that visit. If a subject has BCVA measurements of 50 letters and 60 letters at a particular measurement, then since these measurements do differ by more than 5 letters then the higher measurement (60) will be used in any analyses as the sole measurement for that subject for that visit.

BCVA in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the schedule of activities, and only single measurements will be taken for the fellow eye.

The following summaries will be presented for the FAS for the study eye by treatment group:

- Descriptive summaries of the at-visit value and change from baseline at all post-baseline visits to Week 52 (this includes the at-visit value and change from baseline to Week 24) in BCVA. This analysis will be performed with no imputation, with missing BCVA values imputed using last observation carried forwards (LOCF), and with missing BCVA values imputed using multiple imputation (see Appendix 6.9 for details)
- Comparison between the treatment groups via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36, and Week 52 with the corresponding p-values from a hypothesis test of no difference between the treatment groups. An analysis of covariance (ANCOVA) model of the difference in mean change from baseline in BCVA at Week 4, 12, 24, 36 and Week 52 will assess the main effect of treatment, adjusting for the baseline BCVA value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline BCVA value may be removed). This analysis will be performed with no imputation, with missing BCVA values imputed using LOCF, and with missing BCVA values imputed using multiple imputation (see Appendix 6.9 for details)
- Line plots of the mean ± SD of the at-visit value and change from baseline in BCVA over time by treatment group. These plots will be generated with no imputation, with missing BCVA values imputed using LOCF, and with missing BCVA values imputed using multiple imputation (see Appendix 6.9 for details)
- Spaghetti plots of individual at-visit value and change from baseline in BCVA over time (with all subjects on the same plot) by treatment group
- The number and percentage of subjects with a gain of >=5, >=10, or >=15 letters in BCVA from week 4 to week 52 compared to baseline by visit
- Time to subjects gaining at least >=5, >=10, or >=15 letters in BCVA after baseline (in weeks). For subjects who achieve letter gain, this will be calculated as [earliest date of letter gain – date of baseline BCVA measurement + 1]. For subjects who do not achieve letter gain, this will be calculated as [date of censoring - date of baseline BCVA measurement + 1]. Date of censoring is as defined in section 4.10.2.1, and this endpoint will be analyzed using the

same statistical methods as described in section 4.10.2.1 (Kaplan Meier plots will not be included).

- The number and percentage of subjects with a loss of >=5, >=10, or >=15 letters in BCVA from week 4 to week 52 compared to baseline by visit
- The number and percentage of subjects with a sustained gain (defined as a gain in BCVA from baseline that is present on at least two consecutive post-baseline study visits) of >=5, >=10, or >=15 letters in BCVA from week 4 to week 52 compared to baseline by visit
- The number and percentage of subjects with BCVA >68 letters and >70 letters at each study visit from week 4 to week 52
- The number and percentage of subjects with BCVA >68 letters at each study visit from week 4 to week 52 for the subset of subjects who had <=68 letters at baseline
- The number and percentage of subjects with BCVA >70 letters at each study visit from week 4 to week 52 for the subset of subjects who had <=70 letters at baseline
- Bubble plots of the mean change from baseline in BCVA over time with the size of the bubble proportional to the area of the medication bleb (μm^2) measured through peripheral optical coherence tomography (OCT) at the corresponding visit.

For the above summaries, percentages will be based on the analysis set per treatment group.

A sensitivity analysis will be conducted where only BCVA data up to the time of the subject requiring follow on treatment (as defined in section 4.10.2.1) will be used in the above analyses of the at-visit value and change from baseline over time in BCVA and the corresponding treatment comparisons (subjects will be censored after requiring follow on treatment in the analyses). The records not included in the sensitivity analyses shall be identified in the listings. Imputation methods shall not be used to impute missing data that occurs after censoring.

A subgroup analysis will be performed on subjects treated with the Oxulumis standard variant, ConjIncision variant or combination variant. Descriptive summaries of the at-visit value and change from baseline to Week 24 and all post-baseline visits to Week 52 in BCVA will be presented by treatment and subgroup. A comparison between the treatment groups via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36 and Week 52, with the corresponding p-values from a hypothesis test of no difference between the treatment groups will be presented for the FAS by treatment and subgroup. An ANCOVA model of the difference in mean change from baseline in BCVA will assess the main effect of treatment, adjusting for the baseline BCVA value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline BCVA value may be removed). The effect of subgroup will not be included in the ANCOVA model due to small sample size.

The above analyses will be repeated on the PPS.

BCVA measurements will also be listed for both the study eye and fellow eye for the FAS. The BCVA measurements where the duplicate measurement (study eye only) exceeded the 5 letter threshold to be considered the better measurement will be flagged in this listing.

4.10.2.3 Central Subfield Thickness (On Spectral Domain Optical Coherence Tomography)

Retinal structure and pathological changes will be evaluated at every visit using SD-OCT. SD-OCT will be performed at each visit for the study eye. For the fellow eye, SD-OCT will be performed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the schedule of activities.

The following summaries will be presented for the FAS for the study eye by treatment group:

- Descriptive summaries of the at-visit value and change from baseline at all post-baseline visits to Week 52 (this includes the at-visit value and change from baseline to Week 24) in CST (µm). This analysis will be performed with no imputation, with missing CST values imputed using LOCF, and with missing CST values imputed using multiple imputation (see Appendix 6.9 for details)
- Comparison between the treatment groups via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36 and Week 52 with the corresponding p-values from a hypothesis test of no difference between the treatment groups. An ANCOVA model of the difference in mean change from baseline in CST at Week 4, 12, 24, 36 and Week 52 will assess the main effect of treatment, adjusting for the baseline CST value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline CST value may be removed). This analysis will be performed with no imputation, with missing CST values imputed using last observation carried forwards (LOCF), and with missing CST values imputed using multiple imputation (see Appendix 6.9 for details)
- Line plots of the mean ± SD of the at-visit value and change from baseline in CST over time by treatment group. These plots will be generated with no imputation, with missing CSTA values imputed using LOCF, and with missing CST values imputed using multiple imputation (see Appendix 6.9 for details)
- Spaghetti plots of individual at-visit value and change from baseline in CST over time (with all subjects on the same plot) by treatment group
- Bubble plots of the mean change from baseline in BCVA over time with the size of the bubble proportional to the area of the medication bleb (μm^2) measured through peripheral optical coherence tomography (OCT) at the corresponding visit.

A sensitivity analysis will be conducted where only CST data up to the time of the subject requiring follow on treatment (as defined in section 4.10.2.1) will be used in the above analyses of the at-visit value and change from baseline over time in CST and the corresponding treatment comparisons (subjects will be censored after requiring follow on treatment in the analyses). The records not included in the sensitivity analyses shall be identified in the listings. Imputation methods shall not be used to impute missing data that occurs after censoring.

A subgroup analysis will be performed on subjects treated with the Oxulumis standard variant, ConjIncision variant or combination variant. Descriptive summaries of the at-visit value and change from baseline to Week 24 and all post-baseline visits to Week 52 in CST will be presented by treatment and subgroup. A comparison between the treatment groups via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36 and Week 52, with the corresponding p-values from a hypothesis test of no difference between the treatment groups will be presented for the FAS by treatment and subgroup. An ANCOVA model of the difference in mean change from baseline in CST will assess the main effect of treatment, adjusting for the baseline CST value (in the case of

model convergence issues due to a low amount of available data, the adjustment for baseline CST value may be removed). The effect of subgroup will not be included in the ANCOVA model due to small sample size.

The above analyses will be repeated on the PPS.

CST measurements will also be listed for both the study eye and fellow eye for the FAS. The highest CST value post-visit 2 will be flagged in the listing, and any CST measurements which have a decrease of ≥75µm from this highest value will also be flagged.

4.10.2.4 NEI VFQ-25

The NEI VFQ-25 is a commonly used instrument to determine the vision-related quality of life. The NEI VFQ25 will be assessed at screening, 24, and week 52 visits (Visits 1, 11, and 18, respectively), as specified in the schedule of activities.

The NEI VFQ-25 consists of a base set of 25 vision targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The NEI VFQ-25 generates the following subscales:

- General health
- General vision
- Ocular pain
- Near activities
- Distance activities
- Social functioning
- Mental health
- Role difficulties
- Dependency
- Driving
- Color vision
- Peripheral vision.

Further details on the questions, responses and subscales can be found in appendix 6.6. The responses from individual subscales will be used to calculate the NEI VFQ-25 composite score per Appendix 6.7.

Descriptive summaries of the at-visit value and change from baseline to Week 24 and Week 52 of the NEI VFQ-25 composite score, near activities subscale score and distance activities subscale score will be presented by treatment group for the FAS. The treatment groups will be compared via the difference in mean change from baseline of the scores with 95% CI at Week 24 and Week 52, with the corresponding p-values from a hypothesis test of no difference between the treatment groups. An ANCOVA model of the difference in mean change from baseline in the scores at Week 24 and Week 52 will assess the main effect of treatment, adjusting for the baseline scores (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline score may be removed).

As a supportive analysis, a summary of the number and percentage of subjects whose

- Fellow eye is able to see better than their study eye
- Study eye is able to see better than their fellow eye
- Study eye and fellow have similar BCVA (≤±5 letters difference).

at baseline, Week 24 and Week 52 will be presented for the FAS. The fellow eye will be classed as 'better seeing' if the BCVA result of the fellow eye is 5 letters or more greater than the BCVA result of the study eye (otherwise the study eye is classed as 'better seeing'). This will help to inform which eye is dominating the NEI VFQ-25 assessment. These results will also be included in the listing of NEI VFQ-25 data.

The above analyses will be repeated on the FAS for the sub-populations of subjects requiring follow on treatment and subjects not requiring follow on treatment (as defined in section 4.10.2.1), and will also be repeated on the PPS.

The results of the responses to the NEI VFQ-25 questions, the calculated subscale score and calculated composite score will be listed for the FAS.

4.11 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

4.11.1 Pharmacokinetic Concentrations

Concentration Listings:
Pharmacokinetic concentration data for dexamethasone, will be listed by subject for the PKAS. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and considered excluded from PK analysis.

Concentration Summary Tables:
Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of subjects who received treatment), n (number of subjects with non-missing values), and n(BLQ) (the number of subjects with BLQ samples).

Concentration for dexamethasone will be summarized by treatment and nominal timepoint for the PKAS. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (gCV%) (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as non-calculable.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of subject level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

For geometric mean linear/linear graphs, all BLQ values will be substituted with ½ the LLOQ for calculation of geometric mean and for log/linear graphs the log transformed geometric mean will be displayed.

For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero (except for intravenous administration when these BLQs should not be displayed). When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

To visualize subject level concentrations and the comparison between treatment groups, the descriptive PK graphs (including LLOQ line) listed below will be generated.

- Individual subject profiles for Dexamethasone Plasma Concentration-Time Data – (Linear Scale and Semi-Logarithmic Scale) (SAS)
- Overlaid individual subject profiles for Dexamethasone Plasma Concentration-Time Data – (Linear Scale and Semi-Logarithmic Scale) (SAS)
- Mean (± SD) Dexamethasone Plasma Concentration-Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKAS).

Figures will be generated in black and white using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.11.2 Pharmacokinetic Parameters

PK parameters will be provided by CPMS group. PK parameters will be calculated by noncompartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® Version 8.2 or higher following these guidelines:

- Actual time from dose will be used in the calculation of all derived pharmacokinetic parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Handling of BLQ samples for derivation of blood/serum/plasma/cerebrospinal fluid PK parameters after single dose administration
    - BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 4-1.

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, T_{max}	Obtained directly from the observed concentration-time data
AUC_{last}	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The $AUC_{0\text{-}last}$ is the sum of areas up to the time of the last quantifiable sample: $AUC_{0\text{-}last} = \int_0^t C_{last} * dt$
$AUC_{0\text{-}x}$	The AUC from zero time to the specific time x is the sum of areas up to the specific time x sample: $AUC_{0\text{-}x} = AUC_{0-x} = \int_0^x Cx * dx$

PK Parameters Listings:

PK parameters will be listed by subject for the PKAS. PK parameters that will be flagged and/or excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for flagging/exclusion.

PK Parameter Summary Tables:
The biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by treatment group for the PKAS. Tabular summaries for PK parameters will report N (number of subjects who received treatment) and n (number of subjects with non-missing values).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For T_{max}, only N, n, median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of subject level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g. ratios)	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
T_{max} individuals and min/max	2 d.p
T_{max} median only	2 d.p

s.f = significant figures, d.p. = decimal place

4.11.3 Statistical Analysis of Pharmacokinetic Parameters

No statistical analyses of PK parameters are planned

4.12 Safety Evaluation

All safety summaries and analyses will be based upon the SAS as defined in Section 4.4.1 unless otherwise specified.

4.12.1 Adverse Events

Analyses of adverse events are described in Section 4.9, as these form the primary endpoint for the trial.

4.12.2 Deaths

A summary of the number of subject deaths and the cause of death will be provided for the SAS by treatment group. All deaths will also be listed for the SAS.

4.12.3 Clinical Laboratory Evaluation

The analyses of laboratory data will be descriptive in nature. All analyses will be based on (International System of Units) SI units after conversion by means of standard conversion factors. Results from the central laboratory will be included in the reporting of this trial for the following laboratory groups/parameters at the following time points:

Laboratory Group	Laboratory Parameter	Assessment Time Points
Chemistry	• Sodium • Potassium • Chloride • Bicarbonate • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Gamma-glutamyl transferase bilirubin direct • Bilirubin indirect • Total bilirubin • Creatinine • Blood urea nitrogen • Total protein • Calcium • Phosphorus • Glucose • Hemoglobin A1c	• Screening
Chemistry	• Hemoglobin A1c	• Visit 11 (Week 24) • Visit 18 (Week 52) • End of Study / End of Treatment visit
Hematology	• White blood cell count • Red blood cell count • Hemoglobin • Hematocrit • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration	• Screening

	• Red cell distribution width • Platelet count • Mean platelet volume	
Thyroid	• Thyroid-stimulating hormone	• Screening

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g. <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

At each visit, laboratory measurements will be compared with the laboratory supplied reference ranges and categorized as abnormal (low/high) or normal:

- Low: below the lower limit of the laboratory reference range
- Normal: within the laboratory reference range (upper and lower limit included)
- High: above the upper limit of the laboratory reference range.

Laboratory abnormalities that are considered by the investigator as clinically significant (CS) are per protocol recorded in the database as AEs. Therefore, no tabulation of laboratory values meeting any CS criteria will be presented as all relevant information will be presented in the AE summaries.

Where possible, Hemoglobin A1c measurements will be graded according to CTCAE version 5.0.

For each laboratory parameter, descriptive summaries of the results at each visit will be presented by treatment group for the SAS. For hemoglobin A1c post-baseline visits, the number and percentage of subjects with an improvement since baseline of 0.5% and 1.0% and with a worsening since screening of 0.5% and 1.0% will be presented. Percentages will be based on the SAS in the corresponding treatment group

A summary of the number and percentage of subjects with normal/abnormal laboratory values (both low and high per the definition above) at each visit will be presented by laboratory parameter and treatment group for the SAS. Percentages will be based on the SAS in the corresponding treatment group.

For Hemoglobin A1c, shift tables comparing the baseline Common Terminology Criteria for Adverse Events (CTCAE) grade to the worst post baseline CTCAE grade will be presented by treatment group. Percentages will be based on the number of subjects with each grade at baseline.

All laboratory data (chemistry, hematology, and thyroid) will be displayed in listings for the SAS.

The results of urine pregnancy tests and serum pregnancy tests (females only) will be listed only for the SAS.

4.12.4 Vital Signs

The following vital signs parameters will be assessed for this trial:

- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2), as defined in section 4.5
- Body temperature (degrees Celsius)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min).

Height will only be measured at screening. The other vital signs parameters will be assessed at screening, Week 24, and Week 52.

Summary statistics will be presented for each vital sign parameter by visit and treatment group for the SAS.

A by subject listing of vital signs measurements will be presented by treatment group for the SAS.

4.13 Ophthalmologic Examinations

4.13.1 Axial Length

Axial length measurements will be listed per eye for the FAS.

4.13.2 Slit-Lamp Biomicroscopy

Subjects' anterior ocular structure and ocular adnexa will be examined in the study eye at each study visit using a slit-lamp, as specified in the schedule of activities. Slit-lamp biomicroscopy in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the schedule of activities.

The following parameters will be assessed via slit-lamp biomicroscopy, and the findings will be classified as normal, abnormal not clinically significant, or abnormal clinically significant:

- Ocular Adnexa
  - Eyelid
  - Eyelashes
- Ocular Surface
  - Cornea
  - Conjunctiva
  - Sclera
- Pupil, Iris and Lens
  - Pupil
  - Iris
  - Lens (if lens is 'phakic', then it will also be graded according to Nuclear Lens Opacity grade, Cortical Lens Opacity grade, and Posterior subcapsular cataract grade (0/ 1/ 2/ 3/ 9 – cannot grade))
- Aqueous Humour and Vitreous

- Aqueous humour
- Vitreous cells and haze.

A shift table of the nuclear lens opacity grade, cortical lens opacity grade and posterior subcapsular cataract grade from baseline to the worst post-baseline value on or prior to Week 24 and Week 52 will be presented for the SAS for the study eye by treatment group. The number and percentage of subjects will be presented for each shift combination, and percentages will be based on the total number of subjects with each result at baseline per parameter.

All slit-lamp biomicroscopy findings will be listed for both the study eye and fellow eye for the SAS.

4.13.3 Intraocular Pressure

IOP of the study eye will be assessed at every visit, as specified in the schedule of activities. IOP measurement in the fellow eye will be assessed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the schedule of activities. After administration of trial treatment at a treatment session of the baseline visit, IOP measurement in the study eye must be repeated at least twice over 60 minutes after treatment until normalization.

Descriptive summaries of the at-visit value and change from baseline at all post-baseline visits to Week 52 (this includes the at-visit value and change from baseline to Week 24) in IOP will be presented for the FAS for the study eye. A comparison between the treatment groups will be presented via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36 and Week 52, with the corresponding p-values from a hypothesis test of no difference between the treatment groups. An ANCOVA model of the difference in mean change from baseline in IOP will assess the main effect of treatment, adjusting for the baseline IOP value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline IOP value may be removed). This analysis will be performed with no imputation, with missing IOP values imputed using LOCF, and with missing IOP values imputed using multiple imputation (see Appendix 6.9 for details).

A summary of the number and percentage of subjects with the following will be presented by visit (and time point if multiple time points are collected) by treatment group for the study eye for the FAS:

- An IOP increase of 10mmHg or more from baseline
- An IOP measurement of 30mmHg or more
- A sustained IOP increase of 10mmHg or more from baseline (defined as an increase of 10mmHg or more over two consecutive post-baseline study visits)
- A sustained IOP measurement of 30mmHg or more (defined as a measurement of 30 mmHg or more over two consecutive post-baseline study visits).

Further, line plots of the mean ± SD of the at-visit value and change from baseline in IOP over time by treatment group and spaghetti plots of individual at-visit value and change from baseline in IOP over time (with all subjects on the same plot) by treatment group will be presented for the FAS for the study eye. The line plots will be generated with no imputation, with missing IOP values imputed using LOCF, and with missing IOP values imputed using multiple imputation (see Appendix 6.9 for details).

The latest pre-treatment measurement will be taken as the baseline IOP. For IOP that measurements are performed more than once post-treatment on Day 0, all measurements will be included in tables and listings.

A sensitivity analysis will be conducted where only IOP data up to the time of the subject requiring follow on treatment (as defined in section 4.10.2.1) will be used in the above analysis of the at-visit value and change from baseline over time in IOP and the corresponding treatment comparisons (subjects will be censored after requiring follow on treatment in the analyses). The records not included in the sensitivity analyses shall be identified in the listings. Imputation methods shall not be used to impute missing data that occurs after censoring.

A subgroup analysis will be performed on subjects treated with the Oxulumis standard variant, ConjIncision variant or combination variant. Descriptive summaries of the at-visit value and change from baseline to Week 24 and all post-baseline visits to Week 52 will be presented by treatment and subgroup. A comparison between the treatment groups via the difference in mean change from baseline with 95% CI at Week 4, 12, 24, 36 and Week 52, with the corresponding p-values from a hypothesis test of no difference between the treatment groups will be presented for the FAS by treatment and subgroup. An ANCOVA model of the difference in mean change from baseline in IOP will assess the main effect of treatment, adjusting for the baseline IOP value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline IOP value may be removed). The effect of subgroup will not be included in the ANCOVA model due to small sample size.

The above analyses will be repeated on the PPS.

IOP measurements will be listed for both the study eye and fellow eye for the FAS.

4.13.4 Refraction

The results of refraction will be listed only for the SAS for both the study eye and fellow eye.

4.13.5 Dilated Indirect Ophthalmoscopy

Subjects' posterior pole and peripheral retina will be examined by dilated indirect ophthalmoscopy at each study visit in the study eye. Dilated indirect ophthalmoscopy in the fellow eye will be performed at the screening, baseline, Week 12, Week 24, and Week 52 visits, as specified in the schedule of activities.

The following ocular areas will be assessed, and the results of the examination will be recorded per the eCRF as normal, abnormal – clinically significant, or abnormal – not clinically significant:

- Vitreous
- Optic nerve
- Macula
- Peripheral retina.

A shift table of the dilated indirect ophthalmoscopy findings (normal/ abnormal – not clinically significant/ abnormal – clinically significant) from baseline to the worst post-baseline value on or

prior to Week 24 and Week 52 will be presented for the SAS for the study eye by area (as above) and treatment group. The number and percentage of subjects will be presented for each shift combination, and percentages will be based on the total number of subjects with each result at baseline.

Dilated indirect ophthalmoscopy findings will be listed for both the study eye and fellow eye for the SAS.

4.13.6 Optical Coherence Tomography (Spectral Domain/Peripheral/Anterior)

4.13.6.1 SD-OCT

Retinal structure and pathological changes will be evaluated at every visit using SD-OCT. SD-OCT will be performed at each visit for the study eye. For the fellow eye, SD-OCT will be performed at the screening, baseline, Week 12, Week 24, and Week 52 visits.

The following ocular parameters will be summarized:

- Central subfield thickness (µm)
- Total macular volume (µm)
- Central retinal lesion thickness (µm)
- Central retinal thickness (µm)
- Foveal sub retinal fluid thickness (µm)
- Choroidal thickness (µm)
- Total retinal thickness (µm)
- Maximum sub retinal fluid thickness (µm)
- Pigment epithelial detachment thickness (µm)
- Posterior hyaloid presence (yes visible only in the raster / yes visible in the cube / no-hyaloid visible but fully detached / no)
- Vitreomacular traction presence (within central 1mm subfield / outside central 1mm subfield / none / cannot determine (CD))
- Epiretinal membrane presence (yes affecting the foveal contour / yes, but not affecting the fovea / no / CD)
- Presence of intraretinal fluid within the central 1mm subfield at baseline (yes / no / CD)
- Presence of intraretinal fluid within the central 1mm subfield relative to baseline (increased / decreased / stable / resolved / CD)
- Presence of intraretinal fluid outside the central 1mm subfield (yes / no / CD)
- Presence of ellipsoid zone disruption within the central 1mm subfield at baseline (yes / no / CD)
- Presence of ellipsoid zone disruption within the central 1mm subfield relative to baseline (increased / decreased / stable / resolved / CD)
- Presence of complete outer retinal pigment epithel and atrophy (cRORA) [no / under umbo / >0 but <=200 µm ./ >200 µm / CD).

Summary statistics of the at-visit value and change from baseline will be presented for each continuous parameter by visit and treatment group for the SAS for the study eye. The number and percentage of subjects will be presented for each categorical parameter by visit and treatment group for the SAS for the study eye.

SD-OCT findings will be listed for both the study eye and fellow eye for the SAS.

4.13.6.2 Peripheral OCT

The retina, choroid, suprachoroidal space, and sclera over the area of treatment instillation will be assessed using peripheral swept-source OCT or peripheral enhanced depth imaging OCT in the study eye at equipped sites. At the screening visit, the Week 12, the Week 24, and Week 52/EOS/EOT visit, both eyes will be imaged. The study eye will be imaged at all other visits.

The following ocular parameters will be summarized:

- Area of medication bleb (μm^2)
- Maximum height of medication bleb (µm)
- Maximum width of medication bleb (µm)
- Presence of changes along the microcatheter path and/or delivery site relative to baseline (yes / no / CD).

Summary statistics of the at-visit value and change from baseline will be presented for each continuous parameter by visit and treatment group for the SAS for the study eye. The number and percentage of subjects will be presented for each categorical parameter by visit and treatment group for the SAS for the study eye.

Peripheral OCT findings will be listed for both the study eye and fellow eye for the SAS.

4.13.6.3 Anterior OCT

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

The following ocular parameters will be summarized:

- Presence of changes along the microcatheter path and/or delivery site relative to baseline (yes / no / CD)
- Entry zone of the needle visible (yes / no / CD)
- Presence of changes in the suprachoroidal space and/or site of scleral penetration relative to baseline (yes / no / CD).
- Scleral thickness measured at approximately 1mm distance from the distal end of the pars plana (evaluated at screening).

The number and percentage of subjects will be presented for each parameter by visit, total and per treatment group for the SAS for the study eye.

Anterior OCT findings will be listed for the study eye and fellow eye (screening visit only) for the SAS.

4.13.7 Color Fundus Photography

Color fundus photography in the study eye will be captured at all visits, as specified in the schedule of activities. Color fundus photography in the fellow eye will be captured at the screening, Week12, Week 24, and Week 52 visits, as specified in the schedule of activities.

The following ocular parameters will be summarized:

- Diabetic Retinopathy Severity Score (DRSS) (derived from reader's assessment) as described in Appendix 6.8 (10 / 20 / 34 / 43 / 47 / 53 / 61 / 65 / 71-75 / 81-85 / 90)
- At least 2-step improvement of DRSS from baseline (as defined in Appendix 6.8) (yes / no)
- At least 3-step improvement of DRSS from baseline (as defined in Appendix 6.8) (yes / no)
- At least 2-step worsening of DRSS from baseline (as defined in Appendix 6.8) (yes / no)
- Presence of active inflammatory disease (yes / no / CD)
- Newly occurred proliferative diabetic retinopathy (summarized as any of the following newly occurred changes: progression to DRSS level 60 or higher, presence of neovascularization of the disc, presence of neovascularization elsewhere, presence of intraretinal heme (occurring from Week 8 on) (yes / no)
- Presence of neovascularization of the disc (yes / no / CD)
- Presence of cotton wools spots in ETDRS grid quadrants (yes / no / CD)
- Presence of neovascularization elsewhere in each of the posterior retina quadrants (yes / no / CD)
- Presence of cotton wool spots in each of the posterior retina quadrants (yes / no / CD).

The number and percentage of subjects will be presented for each categorical parameter by visit and treatment group for the SAS for the study eye. The treatment groups will be compared via an odds ratio with 95% CI at Week 4, 12, 24, 36, and Week 52 with the corresponding p-values from a hypothesis test of no difference in odds between the treatment groups. A logistic regression model (or multinomial logistic regression model in the case of multinomial variables) will be used assess the main effect of treatment.

All color fundus photography findings will be listed for both the study eye and fellow eye for the SAS.

4.13.8 Fluorescein Angiography

The anatomical state of the retinal vasculature will be evaluated by fluorescein angiography (FA). Fluorescein angiography will be performed at the screening, Week 24, and Week 52 visits, as specified in the schedule of activities, for the study eye and fellow eye.

The following ocular parameters will be summarized:

- Evidence of active inflammatory disease (yes / no / CD)
- Presence of neovascularization of the disk at baseline (yes / no / CD)
- Presence of neovascularization of the disk relative to baseline (increased / decreased / stable / resolved / CD)

- Foveal avascular zone status (regular / irregular / CD)
- Presence of leakage in the macula (none / focal / diffuse / CD)
- Presence of cystoid edema (yes / no / CD)
- Presence of neovascularization elsewhere (yes / no / CD)
- Total area of well defined neovascularization elsewhere (mm^2)
- Presence of vascular staining in each of the posterior retina quadrants relative to baseline (increased / decreased / resolved / CD)
- Presence of capillary non perfusion in each of the posterior retina quadrants at baseline (yes / no / CD)
- Presence of capillary non perfusion in each of the posterior retina quadrants relative to baseline (increased / decreased / resolved / stable / CD)
- Presence of newly occurred proliferative diabetic retinopathy (summarized as any of the following newly occurred changes: presence of increased neovascularization of the disk relative to baseline, presence of neovascularization elsewhere, presence of increased vascular staining in each of the posterior retina quadrants relative to baseline) .

Summary statistics of the at-visit value and change from baseline will be presented for each continuous parameter by visit and treatment group for the SAS for the study eye. The number and percentage of subjects will be presented for each categorical parameter by visit and treatment group for the SAS for the study eye.

Treatment groups will be compared via the difference in mean change from baseline for continuous parameters. An ANCOVA model of the difference in mean change from baseline at Week 4, 12 24, 36 and Week 52 will assess the main effect of treatment, adjusting for the baseline value (in the case of model convergence issues due to a low amount of available data, the adjustment for baseline value may be removed).

For categorical parameters the treatment groups will be compared via an odds ratio with 95% CI at Week 4, 12, 24, 36, and Week 52 with the corresponding p-values from a hypothesis test of no difference in odds between the treatment groups. A logistic regression model (or multinomial logistic regression model in the case of multinomial variables) will be used assess the main effect of treatment.

All fluorescein angiography findings will be listed for both the study eye and fellow eye for the SAS.

4.14 Other Analyses

4.14.1.1 Procedure Documentation and Assessment

During the baseline visit and shortly after the procedure administration, the treating investigator will document the procedure details, and complete the procedure assessment questions. Note that multiple treatment sessions are entered as separate eCRF entries.

The treating investigator responses to the assessment will be summarized for the SAS overall and by treatment group, and further by treatment session and across both treatment sessions for the following questions (note that responses listed as ‘other’ may be further presented by the specific responses recorded on the eCRF):

Setting of the Oxulumis Procedure:

- Clinic
- Procedure Room
- Surgically Equipped Procedure Room
- Operating Room.

OXU-001 Procedural Variant:

- Standard
- ConjIncision (with incision of Conjunctiva/Tenons)
- Combined (Standard followed by ConjIncision).

Type of Anesthesia given

- Topical anesthesia:
  - Topical Tetracaine eye drops
  - Lidocaine Gel
  - Lidocaine Pledgets
- Injection anesthesia:
  - Subtenon Lidocaine
- Other.

Execution of the Oxulumis Procedure

- Procedure was performed successfully in the first attempt (yes / no)
  - (If no) Number of attempts needed in total until a complete procedure with administration of the study drug was performed (analysed as total number of attempts needed to complete the procedure, and in case of two treatment sessions number of attempts per session)
  - Reason attempt did not result in administration of study drug:
    - Could not or only insufficiently engage sclera with the bevel
    - Could engage the sclera, but the catheter did not deploy
    - The catheter deployed subconjunctivally
    - The catheter deployed intravitreally
    - Other
  - Number of different devices used until successful completion of the procedure.

Location of the Insertion Point

- Location of insertion point (following 12 sections of clock dial) (12:00 / 01:00 / 02:00 / 03:00 / 04:00 / 05:00 / 06:00 / 07:00 / 08:00 / 09:00 / 10:00 / 11:00)
- Distance from the limbus that the trocar was inserted (4mm / 5mm / other).

Insertion

- Difficulty (very easy / easy / somewhat easy / difficult / very difficult)
- Complications (no complications / insertion needle could hardly pass the sclera / catheter directly deployed when trigger pressed (no further advancement necessary) / other).

Deployment

- Deployment of the catheter to the suprachoroidal was space completed as intended (yes / no)

- From deployed microcatheter: the light was visible as expected and sufficiently bright (yes / no)
- Speed of deployment during procedure was as initially set (yes / no)
- There was a kink in the tubing (yes / no).

Injection of drug via the drug line

- Injection was completed as expected (yes / no)
- Reason injection was not completed as expected (microcatheter clogged by drug and injection could not be completed / other)
- 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)
- 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)
- Subject felt pain during the injection (yes / no)
    - (If yes) point when pain started:
        - With the trocar's tip insertion into the sclera
        - With trocar advancement into the sclera
        - With catheter deployment
        - With medication injection
        - With catheter withdrawal
        - After procedure completion
        - Other
    - Duration of pain (minutes)
- Reflux experienced (yes / no)
    - (If yes) severity (very mild <10% / mild 10 to <20% / somewhat 20-<40% / marked, 40-<60% / very marked 60% or more)
- Difficulty to inject the trial drug (very easy / easy / somewhat easy / difficult / very difficult)
- Complications experienced while injecting the trial drug? (yes / no)
    - Type of complication:
        - Intravitreal drug deposit
        - Conjunctival drug deposit
        - Disconnect of Merit syringe
        - Catheter clogged by OXU-001
        - Other (specify).

Bleeding

- Intraocular bleeding experienced (yes / no)
    - (If yes) localization of the bleeding (vitreous / retinal / subretinal / choroidal or suprachoroidal)
- Scleral damage experienced (yes / no)
    - Details of scleral damage
- Clinically relevant conjunctival hemorrhage experienced (yes / no)
    - Details of clinically relevant conjunctival hemorrhage
- Other damage experienced:
    - Traumatic cataract
    - Retinal detachment
    - Retinal break

- Other.

Summary statistics of the at-visit value and change from baseline will be presented for each continuous parameter by visit and treatment group for the SAS. The number and percentage of subjects will be presented for each categorical parameter by visit and treatment group for the SAS. Percentages will be based on the number of treatment sessions per treatment group.

The results of the procedure assessment questions will be listed for the SAS per treatment session.

4.14.1.2 Subject Experience Assessment

Details about the subject's experience during and after the procedure will be collected at visits 2, 3 4 and 5.

The subject responses to the assessment will be summarized for the SAS overall and by treatment group and visit, including the number and percentage of subjects with each answer to the following questions:

- Currently experiencing pain in the procedure eye (yes/no)
- Current level of pain in the procedure eye on a scale of 1 – 5 (1 [no pain]/ 2 [minimal pain] / 3 [mild pain]/ 4 [moderate pain]/ 5 [severe pain])
- Rating of 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])
- Rating of 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])
- Currently experiencing discomfort in the procedure eye (yes/no)
- Current level of discomfort in the procedure eye on a scale of 1 – 5 (1 [no discomfort]/ 2 [minimal discomfort] / 3 [mild discomfort]/ 4 [moderate discomfort]/ 5 [severe discomfort])
- Rating of 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])
- Rating of 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]).

A subgroup analysis will be performed on subjects treated with the Oxulumis standard variant, ConjIncision variant or combination variant, and on subjects who received topical or injection anesthesia. The above analysis will be repeated by subgroup level for each subgroup to be analyzed.

The interaction between subjects' pain and discomfort ratings will also be examined. The number and percentage of subjects will be presented overall and by treatment group and visit for:

- Whether currently experiencing pain in the procedure eye (yes/no) by whether currently experiencing discomfort in the procedure eye (yes/no)
- The current level of pain in the procedure eye on a scale of 1 – 5 by the current level of discomfort in the procedure eye on a scale of 1 – 5
- The rating of pain during the procedure on a scale of 1 –5 by the rating of discomfort during the procedure on a scale of 1 – 5

- The rating of pain after completion of the procedure on a scale of 1 –5 by the rating of discomfort after completion of the procedure on a scale of 1 – 5.

Percentages will be based on the analysis set per treatment group.

The results of the subject experience assessment questions will be listed for the SAS.

4.14.1.3 Device Deficiencies

A summary of device deficiencies observed for subjects in the SAS will be presented by treatment group with percentages based on the SAS. The following will be summarized:

- Device status
- Device components concerned
- Reason for rejection / determination of device deficiency.

A listing of device deficiencies will also be provided for subjects in the SAS.

4.14.2 Data Monitoring Committee

This trial will be monitored by an independent DMC. The DMC's main responsibility is to periodically, review the trial data in an unmasked fashion and provide recommendations regarding the trial to the Sponsor based on unmasked benefit/risk assessment.

The composition, roles, responsibilities, and rules governing the DMC are available in the DMC Charter.

The trial DMC, based on a review of the Part A Week 6 safety data, will give a recommendation for the start of Part B, including a recommendation if the 1.5mg and 3.0mg OXU-001 should be tested in Part B, or if the 3.0mg dose should be adjusted to 0.75mg (for details see Section 7.5.1 of the CTP):

Part A of this trial is open label, so there will be no consideration of maintaining the trial masking. Details of how the trial masking will be maintained for Part B can be found in the Masking Maintenance Plan for the trial.

Details pertaining to the scope of analyses for DMC review are provided in the corresponding mock table, listing, and figure shells document.

4.15 Adjustments for Covariates

Adjustments for covariates are not planned due to the small overall sample size in this trial.

4.16 Handling of Dropouts or Missing Data

Unless otherwise stated, missing values will not be imputed and will be excluded from all relevant analyses.

Missing values will be imputed for main efficacy analyses including BCVA, CST and IOP – see sections 4.10.2.2, 4.10.2.3 and 4.13.3 for details.

4.17 Subgroup Analysis

Subgroup analyses on the Oxulumis variant will be presented for the main analyses of BCVA, CST and IOP (see sections 4.10.2.2, 4.10.2.3, and 4.13.3 for details).

Subgroup analyses Oxulumis variant and the type of anesthesia will be presented for the subject experience assessment (see section 4.14.1.2 for details).

The subgroup levels will be identified as follows from the 'Procedure Assessment' eCRF form:

Subgroup	Levels	Derivation
Oxulumis Variant	Standard Variant	'Standard' OXU-001 procedural variant selected on the eCRF
	ConjIncision Variant	'ConjIncision (with incision of Conjunctiva/Tenons)' OXU-001 procedural variant selected on the eCRF
	Combination Variant	'Combination OXU-001 Standard Variant followed by ConjIncision Variant in one Treatment Session' OXU-001 procedural variant selected on the eCRF
Type of Anesthesia	Topical	'Topical Tetracaine Eye Drops', 'Lidocaine Gel' or 'Lidocaine Pledgets' type of Anesthesia given selected on the CRF
	Injection	'Subtenon Lidocaine' type of Anesthesia given selected on the CRF
	Other	'Other' type of Anesthesia given selected on the CRF, or both topical and injection types given

4.18 Planned Analyses

Key analyses will be conducted using all subject data up to Week 24 and Week 52 (end of study). A DMC analysis is also planned based on subject data up to Week 6.

No interim analyses are planned for Part A of this trial.

4.19 Determination of Sample Size

For Part A of the trial, a sample size of 18 subjects is considered adequate to fulfill the objectives of this initial part of the trial. Eighteen subjects are expected to be sufficient to detect common and very common adverse events (specifically increases of IOP) to provide safety input on the doses for Part B.

Any statistical test for comparisons between the treatments in part A are not for confirmatory purposes and have not been powered accordingly.

4.20 Changes in the Conduct of the Trial or Planned Analysis

The definition of the SAS has been changed from the definition in the protocol based on sponsor request. Subjects who started the trial procedure (but did not necessarily start the trial treatment) will be included in the SAS.

5 REFERENCES

There are no sources in the current document.

6 APPENDICES

6.1 International Sort Order for System Organ Class

1. Infections and infestations
2. Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3. Blood and lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic and mediastinal disorders
14. Gastrointestinal disorders
15. Hepatobiliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal and connective tissue disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital, familial and genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury, poisoning and procedural complications
25. Surgical and medical procedures
26. Social circumstances
27. Product issues.

6.2 Imputation Rules for Adverse Events

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 via the imputation rules below.

Missing/Partial Adverse Event Start Date

If the start date of an adverse event is partially missing, the following imputation rules will be used:

- If the day is missing but the month and year are present, then:
  - If the AE start month and year are the same as the month and year of first dose of trial treatment, then the earliest of the day-component of first dose of trial treatment or the day-component of the AE end date is imputed.
  - If the AE start month and year are not the same as the month and year of the first dose of trial treatment, the then the first day of the month is imputed.

- If the day and month are missing and the year is present, then:
  - If the AE start year is the same as the year of first dose of trial treatment, then if the AE end date is prior to the date of first dose of trial treatment then impute the day and month of the AE end date, else impute the day and month of the first dose of trial treatment.
  - If the AE start year is different from the year of first dose of trial treatment, then impute the 1st January.

If the AE start date is completely missing, then impute the date of first dose of trial treatment.

Partial or missing AE start times will not be imputed.

Missing/Partial Adverse Event End Date

If the end date of an adverse event is partially missing, the following imputation rules will be used:

- If the day is missing but the month and year are present, then the last day of the month is imputed
- If the day and month are missing and the year is present, then the 31st December is imputed
- If the imputed date is later than the date of death or date of trial discontinuation, then impute the maximum of the death and date of trial discontinuation dates.

If the end date of the AE is completely missing, then assume the AE is ongoing.

Partial or missing AE end times will not be imputed.

6.3 Imputation of Missing or Partial Dates for Prior and Concomitant Medications and Procedures

The following details the imputation rules to be used for prior and concomitant medications and medical procedures for which either the start or end date of the medication/procedure is missing or partial. Dates will not be directly imputed, but the medication/procedure will be classified as either prior or concomitant or both depending on the available date information.

Medications and procedures for which the start date is missing or partial should be classified as follows:

- If the day is missing but the month and year are present, then:
  - If the medication/procedure start month and year are the same as the month and year of first dose of trial treatment, then classify as prior and concomitant, unless the day component of the first dose of trial treatment is the first day of the month, then class as concomitant, unless the medication/procedure end date is before the first dose of trial treatment in which case class as prior.
  - If the medication/procedure start month and/or year are greater than the month and year of first dose of trial treatment, then classify as concomitant
  - If the medication/procedure start month and/or year are less than the month and year of first dose of trial treatment, then classify as prior unless the medication/procedure end date is after the first dose of trial treatment in which case class as both prior and concomitant.

- If the day and month are missing and the year is present,
  - If the medication/procedure start year is the same as the year of first dose of trial treatment, then classify as prior and concomitant unless the medication/procedure end date is before the first dose of trial treatment in which case class as prior
  - If the medication/procedure start year is greater than the year of first dose of trial treatment, then classify as concomitant
  - If the medication/procedure start year is less than the year of first dose of trial treatment, then classify as prior unless the medication/procedure end date is after the first dose of trial treatment in which case class as both prior and concomitant.

- If the start date is completely missing, then classify the medication/procedure as both prior and concomitant unless the end date is before the first dose of trial treatment in which case class as prior

If the end date is partial or missing, then assume the latest end date possible for the purpose of applying the classification rules above. If the day component is missing, assume the last day of the month, if the month is missing assume December, and if the whole date is missing assume it is ongoing.
If both the start and end dates are missing, then class as both prior and concomitant.

6.4 Visit Windowing

Visit windows are defined per the CTP as follows:

Visit	Study Day/Week	Visit Window (Days)
1	Day -30 to -2	N/A
2	Day 0*	0-14
3	Day 1	±1
4	Week 1	±3
5	Week 4	±5
6	Week 6	±5
7	Week 8	±5
8	Week 12	±7
9	Week 16	±7
10	Week 20	±7
11	Week 24	±7
12	Week 28	±7
13	Week 32	±7
14	Week 36	±7
15	Week 40	±7
16	Week 44	±7
17	Week 48	±7
18	Week 52 (End of Study)	±7

6.5 Adverse Events of Special Interest

The following AEs of special interest are defined for this study:

- Suprachoroidal hemorrhage
- Sterile intraocular inflammation
- Endophthalmitis
- Choroidal bacterial infection
- Retinal detachment
- Retinal perforation
- Rise of IOP above 30 mmHg
- Rise of at least 10 mmHg from baseline IOP
- Rise of IOP above 30 mmHg and 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 Visit 2, Day 0 or require medical intervention, e.g., a paracentesis to lower IOP. A rise of IOP would qualify as an AESI, when it is:

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

6.6 NEI VFQ-25 Questions, Subscales and Responses

Note that the optional questions in the appendices of the NEI VFQ-25 will not be collected in this trial, and will not be considered in any of the below calculations. The NEI VFQ-25 is comprised of the questions in Table 6-1 - the subscale each question belongs to as well as the categorial and numeric responses to the questions are also shown.

Table 6-1 NEI VFQ-25 Response Recoding

Subscale	Question Number	Question with Response (Numerical Response)
General Health	1	In general, would you say your overall health is: • Excellent (1) • Very Good (2) • Good (3) • Fair (4) • Poor (5)
General Vision	2	At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind? • Excellent (1) • Good (2) • Fair (3) • Poor (4) • Very Poor (5) • Completely Blind (6)
Mental Health	3	How much of the time do you worry about your eyesight? • None of the time (1) • A little of the time (2) • Some of the time (3) • Most of the time (4) • All of the time (5)
Ocular Pain	4	How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is: • None (1) • Mild (2) • Moderate (3) • Severe (4) • Very severe (5)
Near Activities	5	How much difficulty do you have reading ordinary print in newspapers? Would you say you have: • No difficulty at all (1)

		• A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Near Activities	6	How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say: • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Near Activities	7	Because of your eyesight, how much difficulty do you have finding something on a crowded shelf? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Distance Activities	8	How much difficulty do you have reading street signs or the names of stores? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Distance Activities	9	Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)

Peripheral Vision	10	Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Social Functioning	11	Because of your eyesight, how much difficulty do you have seeing how people react to things you say? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Color Vision	12	Because of your eyesight, how much difficulty do you have picking out and matching your own clothes? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Social Functioning	13	Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Distance Activities	14	Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events? • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5)

		• Stopped doing this for other reasons or not interested in doing this (6)
Driving	15	Are you currently driving, at least once in a while? • Yes (1) • No (2)
Driving	15a	If no: have you never driven a car or have you given up driving? • Never drove (1) • Gave up (2)
Driving	15b	If you gave up driving: was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons? • Mainly eyesight (1) • Mainly other reasons (2) • Both eyesight and other reasons (3)
Driving	15c	If currently driving: how much difficulty do you have driving during the daytime in familiar places? Would you say you have: • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4)
Driving	16	How much difficulty do you have driving at night? Would you say you have: • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Driving	16a	How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have: • No difficulty at all (1) • A little difficulty (2) • Moderate difficulty (3) • Extreme difficulty (4) • Stopped doing this because of your eyesight (5) • Stopped doing this for other reasons or not interested in doing this (6)
Role Difficulties	17	Do you accomplish less than you would like because of your vision? • All of the time (1) • Most of the time (2) • Some of the time (3)

		• A little of the time (4) • None of the time (5)
Role Difficulties	18	Are you limited in how long you can work or do other activities because of your vision? • All of the time (1) • Most of the time (2) • Some of the time (3) • A little of the time (4) • None of the time (5)
Ocular Pain	19	How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say: • All of the time (1) • Most of the time (2) • Some of the time (3) • A little of the time (4) • None of the time (5)
Dependency	20	I stay home most of the time because of my eyesight • Definitely True (1) • Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)
Mental Health	21	I feel frustrated a lot of the time because of my eyesight • Definitely True (1) • Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)
Mental Health	22	I have much less control over what I do, because of my eyesight • Definitely True (1) • Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)
Dependency	23	Because of my eyesight, I have to rely too much on what other people tell me • Definitely True (1) • Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)
Dependency	24	I need a lot of help from others because of my eyesight • Definitely True (1)

		• Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)
Mental Health	25	I worry about doing things that will embarrass myself or others, because of my eyesight • Definitely True (1) • Mostly True (2) • Not Sure (3) • Mostly False (4) • Definitely False (5)

6.7 NEI VFQ-25 Composite Score Calculation

The composite score gives an overall measure of vision-targeted health related quality of life. The first step to calculating the composite score is to re-code the original numeric values obtained from the questionnaire (see Appendix 6.6) per Table 6-2.

Table 6-2 NEI VFQ-25 Response Recoding

Question Number	Original Response Category	Recoded Value
1, 3, 4, 15c[1]	1 2 3 4 5	100 75 50 25 0
2	1 2 3 4 5 6	100 80 60 40 20 0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1 2 3 4 5 6	100 75 50 25 0 Missing[2]
17, 18, 19, 20, 21, 22, 23, 24, 25	1 2 3 4 5	0 25 50 75 100
[1] Item 15c has four-response levels, but is expanded to a five-levels using item 15b. Note: If 15b=1, then 15c should be recoded to "0" If 15b=2, then 15c should be recoded to missing. If 15b=3, then 15c should be recoded to missing.		

[2] Response choice "6" indicates that the person does not perform the activity because of non-vision-related problems. If this choice is selected, the item is coded as "missing."

All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

Next, items within each sub-scale are averaged together to create the 12 sub-scale scores per Table 6-3.

Table 6-3 NEI VFQ-25 Subscale Score Calculation

Scale	Number of Items	Question Numbers to be Averaged (After Recoding)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

Finally, to calculate the overall composite score, take the unweighted mean of the subscale scores, excluding the general health subscale. By averaging the sub-scale scores rather than the individual items, equal weight is given to each sub-scale, whereas averaging the items would give more weight to scales with more items.

6.8 Diabetic Retinopathy Severity Score

Table 6-4 Diabetic Retinopathy Severity Score

Score	Disease Severity
10	No retinopathy
20	Very mild non-proliferative diabetic retinopathy
35	Mild non-proliferative diabetic retinopathy
43	Moderate non-proliferative diabetic retinopathy

47	Moderate non-proliferative diabetic retinopathy
53	Severe non-proliferative diabetic retinopathy
61	Mild proliferative diabetic retinopathy
65	Moderate proliferative diabetic retinopathy
71-75	High-Risk proliferative diabetic retinopathy
81-85	Advanced proliferative diabetic retinopathy
90	Cannot grade

An improvement in the DRSS is defined as a shift from a disease severity rating in the table above to a less serious severity (e.g. from 'very mild non-proliferative diabetic retinopathy' to 'no retinopathy'). A worsening in the DRSS is defined as a shift from a disease severity rating in the table above to a more serious severity (e.g. from 'moderate non-proliferative diabetic retinopathy' to 'high-Risk proliferative diabetic retinopathy').

An n-step improvement in DRSS is defined as a shift from a row of the table above to the previous n^{th} row (e.g. a 2-step improvement could be a shift from 'mild proliferative diabetic retinopathy' to 'moderate non-proliferative diabetic retinopathy'. An n-step worsening is defined similarly as a shift to the next n^{th} row (e.g. a 2-step worsening could be a shift from 'no retinopathy' to 'mild non-proliferative diabetic retinopathy'.). A DRSS of 'cannot grade' will not be considered in the calculation of a step improvement.

6.9 Multiple Imputation

The following steps will be performed to impute missing data using multiple imputation:

Step 1 - Preparation

A dataset of subjects with observed values and those needing estimation by multiple imputation will be created.

Step 2 - Imputation

Imputation is the generation of multiple copies of the original dataset by replacing missing values by using an appropriate stochastic model. The missing data will be imputed using the Fully Conditional Specification (FCS) method. The FCS method is based on an iterative algorithm; at each iteration and for each variable of the prediction model, there is a prediction step and an imputation step. The models used for prediction and imputation will be linear regression models. A total of 50 imputations will be performed using a seed of 95285. Imputations will be performed under the missing-at-random assumption (that missing data is systematically related to the observed but not the unobserved data)

The imputation model will include the treatment group, baseline value (of the endpoint in question), and the value at each previous post-baseline visit (of the endpoint in question).

Step 3 - Analysis

For each of the imputed datasets, the endpoint is analyzed using the same statistical methods that would have been used had the data been complete, to yield 50 parameter estimates. The specific

statistical methods for the analysis of each endpoint for which multiple imputation will be performed can be found in sections 4.10.2.2, 4.10.2.3 and 4.13.3.

Step 4 - Pooling

The last step is to pool the 50 parameter estimates into one estimate, and to estimate the corresponding variance. Pooling will be performed based on Rubin's rules to produce a unique point estimate and standard error, taking into account the uncertainty of the imputation process. These pooled estimates can then be used to calculate the necessary confidence intervals and p-values as required in sections 4.10.2.2, 4.10.2.3 and 4.13.3.