Clinical Trial Protocol: DX220

Protocol Title:	A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of OCS-01 ophthalmic suspension in the Treatment of Inflammation and Pain Following Cataract Surgery
Protocol Number:	DX-220
Study Phase:	3
Investigational Product Name:	OCS-01 (Dexamethasone Ophthalmic Suspension,1.5% [15 mg/mL])
IND Number:	[redacted]
Indication:	Inflammation and pain following cataract surgery
Investigators:	Multi-center clinical investigation
Sponsor:	OCULIS Operations Sàrl EPFL Innovation Park, Building D 1015 Lausanne | Switzerland (T) +41 21 711 3970
Contract Research Organization:	[redacted]

	Date
Original Protocol:	Version 1.0, 25 September 2023

Confidentiality Statement

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1.0 SYNOPSIS

Protocol Title:	A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of OCS-01 ophthalmic suspension in the Treatment of Inflammation and Pain Following Cataract Surgery
Protocol Number:	DX-220
Investigational Product:	• OCS-01 (Dexamethasone Ophthalmic Suspension,1.5% [15 mg/mL]) • Vehicle of OCS-01
Study Phase:	3
Primary Objective(s):	The primary objective of this study is to evaluate the efficacy and safety of OCS-01 compared to vehicle in the treatment of inflammation and pain following cataract surgery.
Overall Study Design:	
Structure:	Multi-center, randomized, double-masked, vehicle-controlled study
Duration:	[redacted]
Controls:	Vehicle of OCS-01
Dosage/Dose Regimen/ Instillation/Application/Use:	Subjects will be randomized to one of the following treatment groups in a 1:1 fashion: 1. OCS-01 once daily (QD) 2. Vehicle QD All qualified subjects will dose for 14 days beginning 1-day post-surgery in the operated eye. Dose should be instilled at approximately 8 AM (± 2 hours).
Summary of Visit Schedule:	Seven visits over the [redacted]: • Visit 1 ([redacted] [prior to surgery]): Screening. • Visit 2 ([redacted] post-surgery]): Review of inclusion and exclusion criteria, randomization, and dosing and dispensation of study medication. • Visit 3 ([redacted] Pain assessments (telephone call). • Visit 4 [redacted] Inflammation, pain, and safety assessments. • Visit 5 ([redacted] Inflammation, pain, and safety assessments. • Visit 6 ([redacted] Inflammation, pain, and safety assessments. • Visit 7 ([redacted]): Inflammation, pain, and safety assessments and exit visit.

Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Approximately 160 subjects (80 subjects per arm) will be randomized.
Condition/Disease:	Inflammation and pain following cataract surgery
Inclusion Criteria:	Each subject must: 1. Provide written informed consent approved by the appropriate ethics committee; 2. Able to comply with the study requirements and visit schedule; 3. At least 18 years of age of either sex or any race; 4. Will undergo unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in the study eye; [redacted] 6. Have a pin-hole visual acuity (VA) without any other correction > 20 letters (approximately 20/400) in the operative eye and > 35 letters (approximately 20/200) in the fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart at Visit 1 1 ([redacted] [prior to surgery]).
Exclusion Criteria:	Each subject must not: 1. Have a known sensitivity or allergy to dexamethasone, corticosteroids, or any of the study medication's components; 2. Have only one functional eye (monocular); 3. Have any intraocular inflammation (e.g., white blood cells or flare) present in either eye at the Visit 1 ([redacted] [prior to surgery]) slit lamp examination; 4. Have a score > 0 on the Ocular Pain Assessment at Visit 1 [redacted] [prior to surgery]) in the study eye;







	[redacted]
Study Formulations and Formulation Numbers:	• OCS-01 (Dexamethasone Ophthalmic Suspension,1.5% [15 mg/mL]) • Vehicle for OCS-01
Evaluation Criteria:	
Efficacy Measures and Endpoints:	*Hierarchical Primary Efficacy Measures:* 1. Absence of anterior chamber cells (i.e. score of '0') at Visit 6[redacted]; 2. Absence of pain (i.e. score of '0') at Visit 4[redacted]

	[redacted]
Safety Measures:	• Change from baseline of pin-hole VA (without any other correction) as measured on the ETDRS chart; • Change from baseline of IOP; • Adverse event (AE) rates.
[redacted]	[redacted]

General Statistical Methods and Types of Analyses

[redacted]

General Considerations

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. Differences between treatment groups will be calculated as OCS-01 - vehicle) and change from baseline will be calculated as follow-up visit - baseline. Baseline values will be defined as the last non-missing measure prior to initiation of study treatment. All efficacy analyses will use a 2-sided alpha = 0.05 test unless otherwise stated and corresponding 2-sided 95% confidence intervals (CIs) will be presented as applicable.

The unit of analysis in this study will be the study eye for all ocular efficacy and safety summaries and the subject for all non-ocular summaries.

Primary Efficacy Analysis

The hierarchical primary efficacy variables, the absence of anterior chamber cells at Visit 6 ([redacted] and the absence of pain at Visit 4 ([redacted] will be summarized using discrete summary statistics, including 2-sided 95%CIs for each treatment group.

The primary efficacy analyses will first test the difference in proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and vehicle at Visit 6 ([redacted]) using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

If the proportion of study eyes with absence of anterior chamber cells (score of '0') is statistically significantly higher for OCS-01 versus vehicle at a 2-sided alpha = 0.05 at Visit 6 ([redacted]), then the study will be considered a success and the hierarchical hypothesis testing will compare the proportion of study eyes with absence of pain (score of '0') at Visit 4 ([redacted]) between OCS-01 and vehicle using the Pearson chi- squared statistic at a 2-sided alpha=0.05 (Fisher's exact test will be used if any expected cell count is less than 5).

Analyses will be completed primarily on the FAS and secondarily on the PP population.

[redacted]

Safety Analysis:

The primary safety analyses will summarize VA, IOP, and AEs as described below.

VA data will be summarized at each visit, using discrete summaries including mean change from baseline in the number of letters and the proportion of subjects with worsening from previous visit of ≥ 2 lines using the ETDRS scale.

IOP will be summarized at each visit, using continuous and discrete summary statistics, including mean change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.

Ocular treatment-emergent AEs (TEAEs) in the study eye for all treated subjects will be summarized using discrete variables at the subject and event level by system organ class (SOC) and preferred term (PT) for each treatment group. A TEAE will be defined as any AE that occurs after the treatment is initiated. An additional analysis will examine ocular AEs for the non-study eye. Non-ocular TEAEs will be summarized using discrete summaries at the subject and event level by SOC and PT for each treatment group. Treatment related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized at each visit including shift from baseline (as appropriate) using discrete summary statistics.

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3.0 LIST OF ABBREVIATIONS

γCD	γ-cyclodextrin
AC	Anterior Chamber
AE	Adverse Event
BID	Twice a Day
BPH	Benign Prostatic Hyperplasia
CI	Confidence Interval
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	Glucocorticoids
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUD	Intrauterine Device
LogMAR	Logarithm of the Minimum Angle of Resolution
MIGS	Minimally Invasive Glaucoma Surgery
mTOR	Mammalian Target of Rapamycin
NSAID	Non-Steroidal Anti-Inflammatory Drug
OU	Both Eyes
PCIOL	Posterior Chamber Intraocular Lens
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
QD	Once a Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Study Eye
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events

USV	Unscheduled Visit
VA	Visual Acuity

4.0 INTRODUCTION

4.1 Background

The current preferred treatments for ocular inflammation, including post-surgery, include the use of topical steroids. Glucocorticoids (GCs) are among the most effective and widely prescribed therapies for the treatment of acute and chronic inflammatory diseases, including ocular inflammation (Choi and Bielory 2008).

One of the most powerful GCs currently available in the US for the treatment of various kinds of inflammation affecting the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe is dexamethasone. Dexamethasone is a corticosteroid that has been used in the form of eye drops (Maxidex®, Alcon, USA) to treat inflammation caused by surgery, infections, or injury (Alcon Laboratories 2002). [redacted]

Additionally, a higher proportion of treatment-emergent adverse events (TEAEs), including ocular TEAEs, were reported for the placebo group compared to either OCS-01 group. Results indicate OCS-01 is safe and well tolerated.

[redacted]

The primary objective is to evaluate the efficacy and safety of OCS- 01 compared to vehicle.

4.2 Study Rationale

Current dexamethasone eye drops for the treatment of ocular inflammation, including post- surgery, are dosed every 4-6 hours until symptoms subside. This leaves a medical need for less frequent administration. Phase 2 and Phase 3 studies on OCS-01 have demonstrated favorable safety, and efficacy in reducing the number of subjects with anterior chamber cells and the number of subjects with pain following cataract surgery. Thus, this study aims to further evaluate the efficacy and safety of once daily OCS- 01 for the treatment of post-cataract surgery inflammation.

[redacted]

[redacted]

4.4 Placebo Justification

This justification is based on Oculis's interpretation of the International Conference on Harmonisation (ICH) Topic E10 guideline on the "Choice of control group in clinical trials" (CPMP/ICH/364/96).

4.4.1 Rationale

The inclusion of a placebo (vehicle) group is considered essential to the design of this study as:

- It provides the most rigorous evaluation of the efficacy and safety of OCS-01.
- It is required by the FDA as a negative control in post-cataract inflammation studies.
- It will allow indirect comparisons with Loteprednol and other studies that were recently conducted with a placebo design (Rajpal, Fong et al. 2013, Fong, Silverstein et al. 2018).

The sponsor believes that vehicle can be safely and ethically administered in this study with close monitoring and rescue criteria based on the following rationale:

Guideline 5 of the International Ethical Guidelines for Health-related Research Involving Humans specifies that a placebo-controlled trial is acceptable only if "delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures" (CIOMS 2016).

For this indication, pain and inflammation following cataract surgery, delaying or withholding intervention will not pose substantial risk to the subject. Further, there are rescue criteria defined in the protocol (Section 7.5) if the subject is displaying Grade 2 or greater anterior cells or experiencing severe ocular pain. In addition, several studies have been completed in both Europe and in the US to evaluate a study drug for ocular pain and inflammation using a placebo-controlled trial design.

Some examples include:

NCT00198445: Safety and Efficacy Study of Topical Bromfenac Versus Placebo to Treat Ocular Inflammation After Cataract Surgery

NCT01367249: Efficacy of Bromfenac Ophthalmic Solution in Patients Undergoing Cataract Surgery

NCT01426854: Nepafenac Compared to Placebo for Ocular Pain and Inflammation

NCT01318499: Nepafenac 0.3% Two Study

NCT00405730: Nepafenac 0.1% Eye Drops, Suspension Compared to Ketorolac Trometamol 0.5% Eye Drops, Solution and Placebo

NCT00430092: Difluprednate 0.5% Eye Drops Compared to Placebo for Inflammation Following Ocular Surgery

NCT02208297: Lotemax 0.38% Gel Compared to Placebo for Inflammation and Pain Following Cataract Surgery

4.4.2 Measures to Ensure Safe Participation in the Study

Vehicle-controlled studies may only be ethically conducted when subjects at a controlled risk are included, subjects are fully informed of all the potential risks, subjects are carefully monitored, and adequate protocol safety measures are in place. In this proposed trial, a number of general protective measures are incorporated into the study protocol with the intention to minimize the risk to subjects.

The following specific measures are included in the protocol:

- Subjects at low risk are selected and they will be fully informed of their chances of randomization to the vehicle group during informed consent.
- Subjects are carefully monitored for pain and inflammation following cataract surgery.
- The rescue and withdrawal criteria minimize subject risk and will allow proper medical care.

Based on the above rationale and the measurements for a safe medical supervision for the subjects, Oculis believes that it is scientifically and ethically appropriate to use vehicle control in this study.

5.0 STUDY OBJECTIVES AND HYPOTHESIS

5.1 Study Objective

The primary objective of this study is to evaluate the efficacy and safety of OCS-01 QD compared to vehicle in the treatment of inflammation and pain following cataract surgery.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of OCS-01 to control inflammation and pain in subjects after cataract surgery	Hierarchical Primary Efficacy Measures: • Absence of anterior chamber cells (i.e. score of '0') at Visit 6[redacted] • Absence of pain (i.e. score of '0') at Visit 4 ([redacted]
[redacted]	
[redacted]	[redacted]

Details of the primary estimand can be found in Section 12.6.1 General Statistical Considerations.

5.2 Study Hypothesis

It is hypothesized that the planned QD dose of OCS-01 via topical ophthalmic administration will be safe, well tolerated and effective in treating inflammation and pain in subjects following cataract surgery.

6.0 OVERALL STUDY DESIGN

This is a multi-center, randomized, double-masked, vehicle-controlled study, designed to evaluate the efficacy and safety of OCS-01 compared to vehicle in treating inflammation and pain following cataract surgery.

Subjects will be randomized 1:1 to receive OCS-01 or vehicle QD. Subjects will dose 1 drop in the study eye QD for 14 days, beginning 1-day post-surgery in the operated eye (administration of first dose will be performed in the clinic on Day 1). The study will last up to 52 days, including screening at Visit 1 ([redacted] [prior to surgery]).

7.0 STUDY POPULATION

7.1 Number of Subjects (approximate)

It is estimated that approximately 160 subjects will be randomized in a 1: 1 ratio to OCS-01 or vehicle. This is a multi-center study in the US only.

7.2 Study Population Characteristics

Subjects may be of either sex or any race and must be at least 18 years of age at Visit 1 ([redacted] [prior to surgery]). Subjects must be planning to undergo unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in the study eye and must meet all of the inclusion criteria and none of the exclusion criteria.

7.3 Inclusion Criteria

Each subject must:

1. Provide written informed consent, approved by the appropriate ethics committee;
2. Able to comply with the study requirements and visit schedule;
3. At least 18 years of age of either sex or any race;
4. Will undergo unilateral cataract extraction via phacoemulsification and PCIOL implantation in the study eye;

[redacted]

6. Have a pin-hole visual acuity (VA) without any other correction > 20 letters (approximately 20/400) in the operative eye and > 35 letters (approximately 20/200) in the fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart at Visit 1 ([redacted] [prior to surgery]);

7.4 Exclusion Criteria

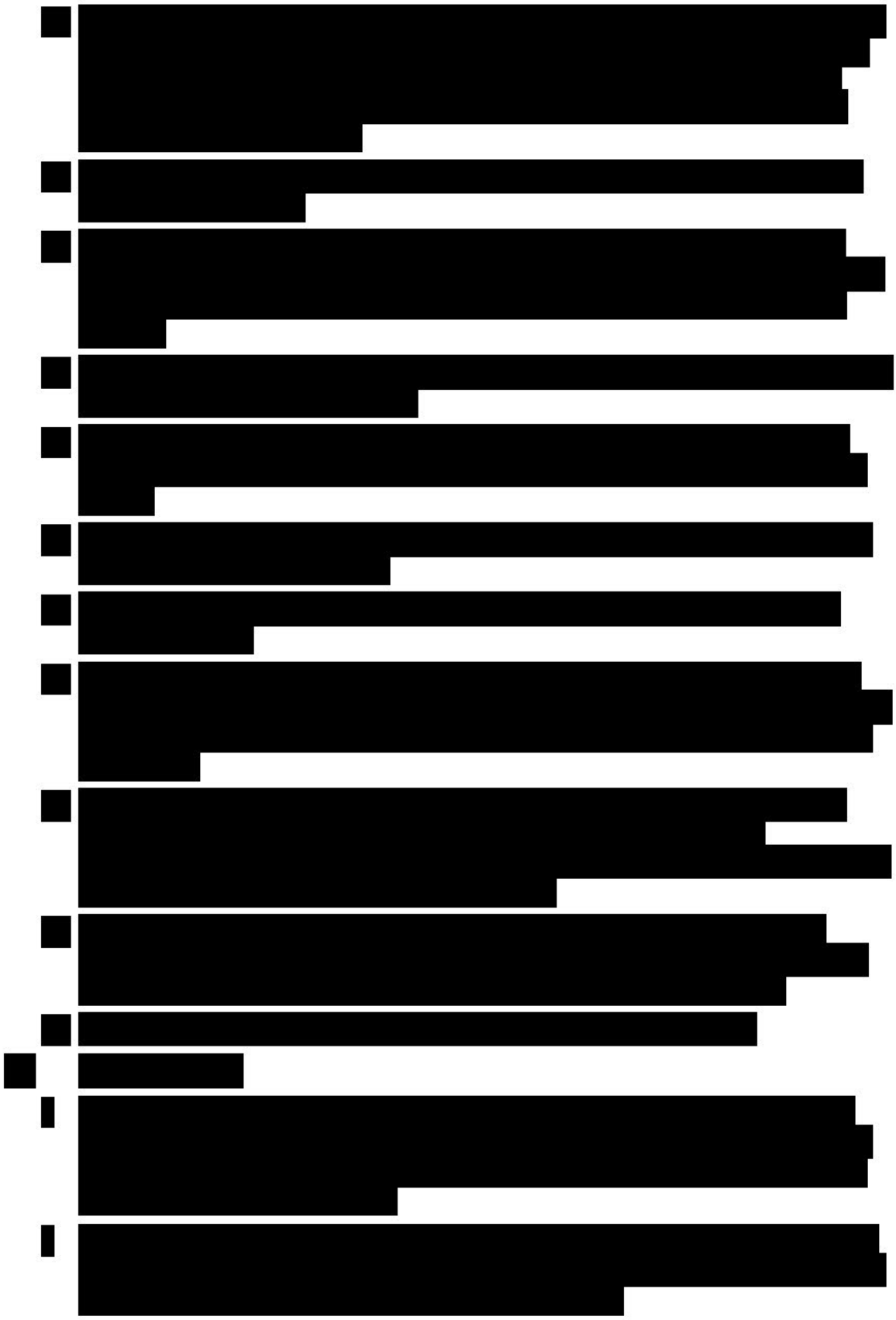
Each subject must not:

1. Have a known sensitivity or allergy to dexamethasone, corticosteroids, or any of the study medication's components;
2. Have only one functional eye (monocular);

3. Have any intraocular inflammation (e.g., white blood cells or flare) present in either eye at the Visit 1 [redacted] [prior to surgery]) slit-lamp examination;
4. Have a score > 0 on the Ocular Pain Assessment at Visit 1 ([redacted] [prior to surgery]) in the study eye;

[redacted]

[redacted]



- [redacted]

7.6 Withdrawal Criteria (if applicable)

Subjects may be discontinued prior to their completion of the study due to the following:

- Adverse event (AE)
- Lost to follow-up
- Withdrawal of consent by subject
- Investigator discretion
- Death
- Subject not adequately following required study procedures
- Study terminated by the Sponsor
- Other

Note: In addition, any subject may be discontinued for any sound medical reason.

If at any time during the study the Investigator deems that the subject's safety has been compromised or the subject has been non-compliant, the subject may be withdrawn from the study.

Notification of a subject's discontinuation and the reason for discontinuation will be made to Ora and/or the Sponsor and will be clearly documented on the Electronic Case Report (eCRF).

Any subject who discontinues study drug or who is administered rescue therapy will remain enrolled in the study and continue to participate in all subsequent visits for safety and efficacy assessments. Such a subject will be included in the sensitivity analyses but not analyzed for primary endpoint efficacy. If a subject discontinues participation in the study early, every attempt will be made to complete the exit procedures required at the final study visit (Visit 8).

8.0 STUDY PARAMETERS

8.1 Efficacy Measures

8.1.1 Primary Efficacy Measure

Hierarchical Primary Efficacy Measures:

- Absence of anterior chamber cells (i.e., score of '0') at Visit 6 [redacted];
- Absence of pain (i.e., score of '0') at Visit 4 ([redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

8.1.3 Primary Efficacy Analyses

The hierarchical primary efficacy analyses are as follows:

- Difference between the two treatment arms in the proportion of study eyes with absence of anterior chamber cells (i.e., score of '0') at Visit 6 [redacted]

If the proportion of study eyes with absence of anterior chamber cells (score of '0') is statistically significantly higher for OCS-01 versus vehicle at a 2-sided alpha = 0.05 at Visit 6 ([redacted] for OCS-01, then the study will be considered a success and the next hierarchical hypothesis will be tested.

Assessment for absence of anterior chamber cells will be done prior to dilation of pupils, which can result in cells in the anterior chamber.

- Difference in the proportion of study eyes with absence of pain (score of '0') at Visit 4 ([redacted] between OCS-01 and vehicle.

[redacted]

8.2 Safety Measures

Safety will be assessed by the following measures:

- Change from baseline of pin-hole VA (without any other correction) as measured on the ETDRS chart;
- Change from baseline of IOP.
- AE rates

9.0 STUDY MATERIALS

9.1 Study Treatment(s)

9.1.1 Study Treatment(s)

- OCS-01 (Dexamethasone Ophthalmic Suspension, 1.5% [15 mg/mL]) (QD)
- Vehicle ophthalmic suspension (QD)

9.1.2 Instructions for Use and Administration

Each subject will receive a dosing kit containing aluminum pouches with single-use vials. For more specific information about the numbers of vials, pouches and kits please refer to the study pharmacy manual. The kit contents will be as follows for subjects randomized to each of the respective treatment arms:

- OCS-01 QD
- Vehicle QD

All qualified subjects will dose for 14 days beginning 1-day post-surgery in the operated eye. On Day 1, after all ophthalmic examinations are completed, the first dose will be instilled at the study visit under the supervision of the study staff (this dosing may be out of the 8 AM [± 2 hours] dosing window).

For all other study visits, subjects should continue to dose according to their established schedule. The dose should be instilled at approximately 8 AM (± 2 hours). If the visit is scheduled during the time of normal dosing, the subject should bring their dose with them to the visit for administration during the visit. Every effort should be made to maintain dosing schedule/ frequency.

A patient diary with dosing instructions will be provided to the subject and reviewed at the in-clinic visits.

9.2 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

9.2.1 Labeling/Packaging

Study drug will be packed in single-use vials, within aluminum pouches which will be contained in kits. Refer to the IP manual for the specific number of vials in pouches, pouches in kits and number of kits. All study drugs will be labeled according to applicable regulatory requirements.

9.2.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the Investigator and his/her designees. The study drug will be dispensed only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

Undispensed study drug should be stored at room temperature (15-25°C).

Once dispensed to subjects, study drug should be stored at ambient temperature.

9.2.3 Accountability of Study Drug

The study drug is to only be prescribed by the PI or his/her named sub-Investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects eligible under this protocol to receive study drug.

The Investigator or his/her designee must keep an accurate accounting of the study drug received from the supplier. This includes the amount of study drug dispensed to subjects, amount of study drug returned to the Investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

9.2.4 Return or Disposal of Study Drug

At the end of the study, all study drugs will be returned to the Sponsor or their designee or destroyed at the study site. The return or disposal of study drug will be specified in writing.

10.0 STUDY METHODS AND PROCEDURES

10.1 Subject Entry Procedures

10.1.1 Overview

Subjects as defined by the criteria in Sections 7.2, 7.3, and 7.4 will be considered for entry into this study.

10.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give informed consent (and/or assent) using an informed consent form (ICF).

The ICF must be the most recent version that has received approval/favorable review by a properly constituted institutional review board (IRB).

See Section 13.1.1 for additional information about the Informed Consent.

10.1.3 Washout Intervals

Washout periods are outlined in exclusion criteria in Section 7.4.

10.1.4 Procedures for Final Study Entry

Subjects must satisfy all inclusion and none of the exclusion criteria in order to be randomized into the study.

10.1.5 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a screening number. Screening numbers will be assigned in sequential order at each site beginning with [redacted] and will follow the two-digit site number (e.g., subject [redacted] at Site 99 will have Screening Number [redacted]). No subjects should be rescreened except in special circumstances in which sites should obtain approval to re-rescreen. Inclusion and exclusion criteria will be reviewed, and qualifying subjects will be enrolled into the study. Each subject who qualifies for entry will be assigned a randomization number and corresponding treatment according to the randomization code. Study drug will be randomly assigned using a 1:1 assignment ratio, stratified by site, via an interactive response system.

10.2 Concurrent Therapies

The use of any concurrent/concomitant medication, prescription, or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

The use of artificial tears is allowed during the study, but must be instilled at least 30 minutes before or after test article dosing.

Concurrent enrollment in another study drug or device study is not permitted.

10.2.1 Prohibited Medications/Treatments

Prohibited medications and washout periods are summarized in Table 1.

- Ocular surgical intervention scheduled on the contralateral eye within 3 weeks post- cataract surgery; or corneal or retinal surgery (laser or incisional) in the study eye within 6 months of Visit 1 ([redacted] [prior to surgery]); or laser or incisional surgery during the study period in the study eye (other than cataract surgery);
- Use of a contact lens or a collagen shield 72 hours prior to Visit 2 ([redacted] post-surgery]) and for the remainder of the study period in either eye;
- Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, and other pain medications), or immunomodulating agents, systemically or in either eye, and/or currently using or have any historic use of medications for benign prostatic hyperplasia (BPH) from the washout period through the duration of the study;
- Non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, prophylactic antibiotics, non-prostaglandin analog IOP lowering agents, lid scrubs, or artificial tears (allowed topical medication should not be instilled at the same time as the study drug. Study medication should be instilled at least 30 minutes after any prior allowed topical medication. In addition, any other allowed topical medication should not be instilled within 2 hours following instillation of study medication);
- Planned use of anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery;

- Concurrent enrollment or enrollment within the follow-up period in another study drug or device study is not allowed.

[redacted]

10.2.3 Special Diet or Activities

There are no special diet restrictions for this study.

The use of contact lens 72 hours prior Visit 2 ([redacted] post-surgery]) and for the remainder of the study period in either eye is prohibited.

10.3 Examination Procedures

Procedures to be performed at each study visit are detailed in the Appendix 1: Schedule of Visits and Measurements and additional details for select assessments are located in Appendix 2: Examination Procedures, Tests, Equipment, and Techniques.

Visit 1 - Screening [redacted] prior to surgery)

- Informed consent/assent
- Demographic data
- Medical and medication history
  - Current underlying conditions, including those that began within the last 30 days, which may have been resolved before Visit 1 ([redacted] [prior to surgery]), must be recorded.
  - Any medications the subject is taking, as well as those the subject may have taken but discontinued within 30 days prior to Visit 1 ([redacted] [prior to surgery]) must be recorded.
- Urine pregnancy test (if applicable)
- Inclusion/exclusion criteria
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)
- IOP
- Dilated indirect ophthalmoscopy

Visit 2 - [redacted] post-surgery)

- Review inclusion/exclusion criteria
- Medical and medications update
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)

- Randomization
- Dose and dispense study medication and dosing diary
- Query for AEs (Time of AE [before or after dosing] will be collected)

Visit 3 - [redacted]

- Ocular pain (study eye only)
- Query for AEs

Visit 4 – [redacted]

- Medical and medications update
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)
- IOP
- Query for AE

Visit 5 – [redacted]

- Medical and medications update
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)
- IOP
- Query for AEs

Visit 6 – [redacted]

- Medical and medications update
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)
- IOP

- Query for AEs

Visit 7 – [redacted]

- Urine pregnancy test (if applicable)
- Medical and medications update
- Ocular pain (study eye only)
- Pin-hole VA
- Slit lamp biomicroscopy
- Ocular inflammation assessment of the anterior chamber cell and flare (study eye only)
- IOP
- Dilated indirect ophthalmoscopy
- Query for AEs
- Exit from study

AEs (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness. All AEs will be documented on the appropriate eCRF.

If a female has a positive pregnancy test during the study, then the Investigator will notify the site's monitor immediately. The Investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The Investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to the site's monitor.

10.4 Schedule of Visits, Measurements and Dosing

10.4.1 Scheduled Visits

Refer to Appendix 1: Schedule of Visits and Measurements for a schedule of visits and measurements.

10.4.2 Unscheduled Visits

In the case of an AE or suspicion of inflammation or increased pain in between scheduled study visits, an unscheduled visit (USV) may occur. The Investigator may perform additional assessments at their discretion. All additional assessments will be documented in the subject's source document and eCRF. If the subject meets a rescue criteria at the USV, then see Section 10.2.2 for rescue medications.

10.5 Compliance with Protocol

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (European Medicines Agency [EMA]/ Committee for Medicinal Products for Human Use/ICH/135/1995).

10.6 Subject Disposition

10.6.1 Completed Subjects

A completed subject is defined as having completed the study and exited the study at Day 22 (including subjects that discontinued study therapy, received rescue therapy, and exited the study at [redacted]). Subjects who have early discontinued from the study or withdrawn consent/assent will not be considered completed subjects.

10.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to the following:

- AEs
- Protocol deviations
- Subject's decision (e.g. withdrawal of consent)
- Administrative reasons (e.g. inability to continue, lost to follow up)
- Sponsor termination of study
- Principal Investigator's (PI) decision
- Other

Note: In addition, any subject may be discontinued for any sound medical reason.

If at any time during the study the Investigator deems that the subject's safety has been compromised or the subject has been non-compliant, the subject may be withdrawn from the study. See Section 7.6 Withdrawn Criteria.

Any subject who wishes to withdraw from the study for any reason is entitled to do so at any time without obligation.

Notification of a subject's discontinuation and the reason for discontinuation will be made to Ora and/or the Sponsor and will be clearly documented on the eCRF.

Any subject who discontinues study drug or who is administered rescue therapy will remain enrolled in the study and continue to participate in all subsequent visits for safety and efficacy assessments.

If a subject discontinues participation in the study early, every attempt will be made to complete the exit procedures as required at the final study visit.

10.7 Study Termination

The study may be stopped at any time by the Sponsor for any reason.

10.8 Study Duration

The study will involve 7 visits including a screening visit at Visit 1 ([redacted]). Subjects may be screened from [redacted] prior to surgery. [redacted] including the earliest screening visit and latest exit visit.

10.9 Monitoring and Quality Assurance

During the course of the study an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess test article accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner to ensure that data protection and subject confidentiality rights are adequately maintained. Further details of the study monitoring will be outlined in a Monitoring Plan.

Regulatory authorities of domestic and foreign agencies, Ora Quality Assurance, and/or its designees may carry out on-site inspections and/or audits that may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and/or audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, national, and international laws apply.

11.0 ADVERSE EVENTS

11.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new AE. Study drug includes the study drug under evaluation (OCS-01) and any comparator drug, vehicle, or any other medications required by the protocol given during any stage of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

11.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of the relationship to study drug or the seriousness of the event and should be evaluated according to the following scale:

- *Mild:* AE is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: AE is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe:* AE is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

11.1.2 Relationship to Study Drug

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Suspected:* A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected:* A reasonable possibility does not exist that the study drug caused the AE.

"Suspected adverse reaction" means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. Types of evidence that would suggest a causal relationship between the study drug and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

11.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* an AE that is listed in the IB at the specificity and severity that has been observed.

AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

Preliminary determination of classification of an AE as unexpected is the responsibility of the Investigator and subject to the Medical Monitor's final determination.

11.2 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Note: A Serious Adverse Event (SAEs) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the study Sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

11.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the study Sponsor, and the IRB as required by the IRB, regional and local regulations, and governing health authorities.

11.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of their relationship to the study drug, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate case report forms. The Investigator is obligated to pursue and obtain information requested by Ora and/or the Sponsor in addition to that information reported on the case report form. All subjects experiencing an SAE must be followed-up with and the outcome reported.

In the event of an SAE, the Investigator must notify Ora and the Sponsor upon becoming aware of a SAE; obtain and maintain in his/her files including all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the AE within their guidelines for reporting SAEs.

Investigators are to contact the study's Medical Monitor or designee upon becoming aware of a SAE.

11.4 Procedures for Unmasking of Study Drug

The randomization code should be broken only in the event of a medical emergency, or when knowing the treatment assignment is absolutely necessary for the medical management of the study subject. When possible (i.e. in non-emergency situations), the study Sponsor or representative should be notified prior to unmasking study drug. In emergency situations, the Investigator must notify the Sponsor within 24 hours after determining that it is necessary to unmask the treatment assignment.

The Investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

11.5 Type and Duration of the Follow-up of Subjects after Adverse Events

AEs will be followed until the condition is resolved or stabilized.

12.0 STATISTICAL METHODS

A complete detailed description of the statistical methods will be provided in the SAP.

[redacted]

[redacted]

12.3 Analysis Populations

The following analysis populations will be defined, although additional populations and further refinement of the below populations may be specified in the SAP, prior to unmasking study data:

- *Full Analysis Set:* The full analysis set (FAS) will consist of all randomized subjects, analyzing subjects under the treatment to which they were randomized.
- *Per Protocol Population:* The per protocol (PP) population is a subset of the FAS and includes subjects who remain in the study through Visit 6 ([redacted] (or who discontinue due to adverse event or lack of efficacy or receive rescue medication prior to Visit 6 [redacted] with no major protocol violations that would affect the assessment of the primary efficacy endpoints of the study, analyzing subjects under the treatment received. Major protocol violations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be identified prior to unmasking treatment.
- *Safety Population:* The safety population includes all randomized subjects who receive at least 1 dose of study medication. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

[redacted]

12.5 Interim Analysis

Interim analyses will not be performed.

12.6 Efficacy Analysis

12.6.1 General Statistical Considerations

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. Differences between treatment groups will be calculated as OCS-01 - vehicle, and change from baseline will be calculated as follow-up visit - baseline. Baseline values will be defined as the last non-missing measure prior to initiation of study treatment. All efficacy analyses will use a 2-sided alpha = 0.05 test unless otherwise stated and corresponding 2-sided 95% confidence intervals (CIs) will be presented as applicable.

The unit of analysis in this study will be the study eye for all ocular efficacy and safety summaries and the subject for all non-ocular summaries.

[redacted]

[redacted]

Statistical comparison between treatment groups will be one-sided using an a of 0.025.

In addition to the primary analysis, supplementary analyses are proposed under different assumptions for the estimand to assess efficacy in subjects who have missing data.

Sensitivity analyses on the primary efficacy variables will be performed as described below.

Sensitivity Analysis I

The hypothetical strategy will be used for the intercurrent event. All missing data will be imputed assuming missing not at random (imputing from the vehicle treatment arm). [redacted]



Sensitivity Analysis II

The hypothetical strategy will be used for the intercurrent event. All missing data will be imputed assuming missing at random (imputing from the same treatment arm as the subject with missing data) using similar code as provided above for the primary efficacy analysis.

Sensitivity Analysis III

The primary efficacy analysis will be performed using the PP set with observed data only. Treatment comparisons will also be made using the difference of proportion test and Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five as an additional sensitivity analysis.

Sensitivity Analysis IV

The primary efficacy analysis will be performed using the FAS set with observed data only. Treatment comparisons will also be made using the difference of proportion test and Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five as an additional sensitivity analysis.

Sensitivity Analysis V

The hypothetical strategy will be used for the intercurrent event. All missing data will be imputed as failure. Treatment comparisons will also be made using the difference of proportion test and Pearson's chi-squared test or Fisher's exact test if any of the expected cell counts are less than five as an additional sensitivity analysis.

12.6.2 Primary Efficacy Analysis

Primary Efficacy Measure: The hierarchical primary efficacy measures are the absence of anterior chamber cells (i.e. score of '0') at Visit 6 [redacted] and the absence of pain (i.e. score of '0') at Visit 4 ([redacted]

Primary Efficacy Analysis: The primary efficacy variables, the absence of anterior chamber cells at Visit 6 ([redacted] and the absence of pain at Visit 4 ([redacted] will be summarized using discrete summary statistics, including 2-sided 95% CIs for each treatment group.

The primary efficacy analyses will first test the difference in the proportion of study eyes with absence of anterior chamber cells (score of '0') between OCS-01 and vehicle at Visit 6 ([redacted]) using the Pearson chi-squared statistic (Fisher's exact test will be used if any expected cell count is less than 5).

If the proportion of study eyes with absence of anterior chamber cells (score of '0') is statistically significantly higher for OCS-01 versus vehicle at a 2-sided alpha = 0.05 at Visit 6 ([redacted] then the study will be considered a success. The hierarchical hypothesis testing the proportion of study eyes with absence of pain (score of '0') at Visit 4 [redacted] between OCS- 01 and vehicle will be performed using the Pearson chi-squared statistic at a 2-sided alpha=0.05 (Fisher's exact test will be used if any expected cell count is less than 5).

Analyses will be completed primarily on the FAS and secondarily on the PP population.

[redacted]

[redacted]

12.7 Safety Analysis

The primary safety analyses will summarize VA, IOP, and AEs, as described below.

VA data will be summarized at each visit, using discrete summaries including mean change from baseline in the number of letters and the proportion of subjects with worsening from previous visit of ≥ 2 lines using the ETDRS scale. The pin-hole VA procedure is detailed in Appendix 2: Examination Procedures, Tests, Equipment, and Techniques.

IOP will be summarized for each visit, using continuous and discrete summary statistics, including mean change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more. The IOP procedure is summarized in Appendix 2: Examination Procedures, Tests, Equipment, and Techniques.

Ocular treatment-emergent AEs (TEAEs) in the study eye for all treated subjects will be summarized using discrete variables at the subject and event level by system organ class (SOC) and preferred term (PT) for each treatment group. A TEAE will be defined as any AE that occurs after the treatment is initiated. An additional analysis will examine ocular AEs for the non-study eye. Non-ocular TEAEs will be summarized using discrete summaries at the subject and event level by SOC and PT for each treatment group. Treatment related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized at each visit including shift from baseline (as appropriate) using discrete summary statistics.

12.8 Handling of Missing Data

[redacted]

12.9 Demographics and Medical History

Subject demographics comprising age, gender, race, and ethnicity will be presented using discrete or continuous summary statistics as appropriate.

13.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, with GCPs including ICH Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

13.1 Protection of Human Subjects

13.1.1 Subject Informed Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study.

All ICFs must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

13.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB approved version of the ICF will be used.

13.1.3 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

13.2 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the Sponsor, the IRB approving this study, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

13.3 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as laboratory tests. The Investigator's copy of the eCRF serves as the Investigator's record of a subject's study-related data.

13.3.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of case report forms should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

13.4 Recording of Data on Source Documents and Case Report Forms

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff who have been trained on the system and have access to the system. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

13.5 Handling of Biological Specimens

Not applicable.

13.6 Publications

Authorship and manuscript composition will reflect joint cooperation among all parties involved in the study. Authorship will be established prior to the writing of the manuscript. The study Sponsor will have the final decision regarding the manuscript and publication.

14.0 REFERENCES

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[redacted]

[redacted]

APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

Pin-hole Visual Acuity

Slit-lamp Evaluation

During Slit Lamp Biomicroscopy: Ocular Inflammation Assessment of the Anterior Chamber Cell and Flare

Ocular Pain Grading Scale (Study Eye Only)

Intraocular Pressure Procedures

Dilated Indirect Ophthalmoscopy

Pin-hole Visual Acuity

Pin-hole, logarithm of the minimum angle of resolution (LogMAR) visual acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Pin-hole visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Pin-hole visual acuity testing should be done with a pin-hole occluder.

Equipment

The visual acuity chart to be used is the ETDRS chart. The subject viewing distance should be 4 meters. If less than 20 letters are read at 4 meters the subject should be moved to a viewing distance of 1 meter and the visual acuity test re-started.

In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use Chart 1 for the right eye (Weber, Kodjikian et al. 2013) and Chart 2 for the left eye (OS).

The right eye (Weber, Kodjikian et al. 2013) should be tested first.

Measurement Technique

The chart should be at a comfortable viewing angle. A pin-hole occluder should be applied to the right eye which should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number.

The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (e.g., "that was a 'C' not an 'O'") before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

Visual Acuity Calculations

- The examiner records each letter identified correctly by circling the corresponding letter on the pin-hole VA Worksheet (Example worksheet for Chart 1 is below).
- Letters read incorrectly or not read at all are NOT marked on the form. Each letter read correctly is scored as one point.

- For each row, write the total number of letters read correctly in the column to the right.
- If line is attempted, but NO letters are read correctly-please enter the number zero (0).
- If line is NOT attempted, please enter a dash (-)

Letters read correctly at 4.0 meters						
Acuity Equivalent	**Chart 1 letters**					**Number Correct**
20/200	**N**	**C**	**K**	**Z**	**O**	
20/160	**R**	**H**	**S**	**D**	**K**	
20/125	**D**	**O**	**V**	**H**	**R**	
20/100	**C**	**Z**	**R**	**H**	**S**	
20/80	**O**	**N**	**H**	**R**	**C**	
20/63	**D**	**K**	**S**	**N**	**V**	
20/50	**Z**	**S**	**O**	**K**	**N**	
20/40	**C**	**K**	**D**	**N**	**R**	
20/32	**S**	**R**	**Z**	**K**	**D**	
20/25	**H**	**Z**	**O**	**V**	**C**	
20/20	**N**	**V**	**D**	**O**	**K**	
20/16	**V**	**H**	**C**	**N**	**O**	
20/12.5	**S**	**V**	**H**	**C**	**Z**	
20/10	**O**	**Z**	**D**	**V**	**K**	
Total Number Correct at 4 meters:						

Letters read correctly at 1.0 meter **(Subject must be sitting for 1 meter test)**						
Acuity Equivalent	**Chart 1 letters**					**Number Correct**
20/800	**N**	**C**	**K**	**Z**	**O**	
20/640	**R**	**H**	**S**	**D**	**K**	
20/500	**D**	**O**	**V**	**H**	**R**	
20/400	**C**	**Z**	**R**	**H**	**S**	
20/320	**O**	**N**	**H**	**R**	**C**	
20/250	**D**	**K**	**S**	**N**	**V**	
Total Number Correct at 1 meter:						

If less than 20 letters at 4 meters, add Total Number Correct at 4 meters plus Total Number Correct at 1 meter to calculate pin-hole VA.

Calculated pin-hole VA Score at 1m: =

____

(Total Number Correct at 4m + Total Number Correct at 1m)

Is total number correct at 4-meters 20 letters or more? **□ Yes □ No** • **If No, test at 1 meter** • **If Yes, add 30 to Total Number Correct at 4-meters to calculate pin-hole VA** **Calculated pin-hole VA Score at 4m =** ____ (Total Number Correct at 4m +30)	

Slit-lamp Evaluation

Slit lamp biomicroscopy will be performed at each visit during the study. Magnification, slit beam and examination procedure will be consistent with Investigator's standard practice. The slit beam observations should be assessed in a dark room using a slit beam of 1.0 mm height and 1.0 mm width with maximum luminance, with 16x magnification and 1x1mm oblique high intensity beam.

The Investigator will note any findings present and whether the findings are clinically significant or not clinically significant. Findings which are clinically significant will be described. All findings will be documented on each subject's source document and corresponding electronic case report form. The following ocular structures will be examined:

- Eyelid
- Cornea
- Conjunctiva
- Anterior Chamber (see below)
- Iris
- Lens

During Slit Lamp Biomicroscopy: Ocular Inflammation Assessment of the Anterior Chamber Cell and Flare

Anterior Chamber Cells and Flare

This procedure will be done prior to any other procedure that requires dilation of the pupil, such as dilated indirect ophthalmoscopy, to avoid cells from being introduced into the anterior chamber. The anterior chamber cell count will be recorded as the actual number of cells observed if : S10 cells are seen (only white blood cells should be counted; red blood cells and pigment cells should not be counted). Anterior chamber flare will also be graded per the table below.

Anterior Chamber Cells		Anterior Chamber Flare	
Grade	**Cell Count**	**Grade**	**Flare Count**
0	0	0	None
1	1-10	1	Faint
2	11-25	2	Moderate (iris and lens details clear)
3	26-50	3	Marked (iris and lens details hazy)
4	>50	4	Intense (fibrin or plasmoid aqueous)

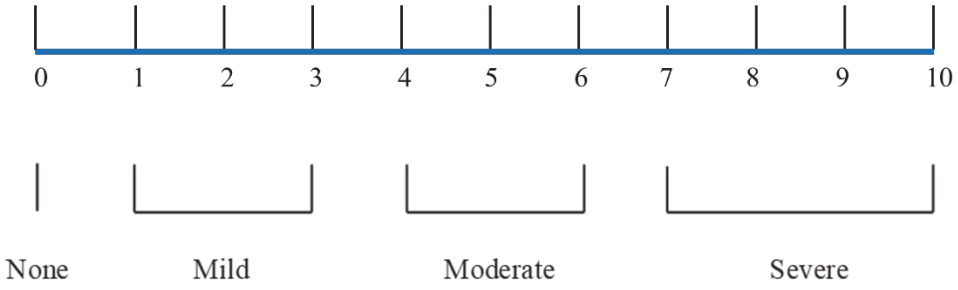
Scale based on (Jabs, Nussenblatt et al. 2005).

Ocular Pain Grading Scale (Study Eye Only)

Ocular pain will be assessed by the subject self-reporting at screening and at each follow-up visit, utilizing a numerical pain rating scale graded from 0 to 10 (McCaffery and Beebe 1994). Subjects will assess the level of pain they are experiencing in the study eye at the time of the assessment.

The examiner will ask the subject the following question:

On a scale of 0 to 10, in which 0 is no pain and 10 is the worst possible or unbearable pain, please mark on the scale the number that best describes the pain or discomfort you are feeling in the operated eye at this time. The middle of the scale (around 5) can be used to describe "moderate pain". Only whole number scores are allowed.*



*At the screening assessment visit, the subject will be asked about the eye scheduled for surgery. The examiner will record the number selected by the subject on the appropriate eCRF.

Intraocular Pressure Procedures

Intraocular pressure will be taken by qualified study site personnel (Investigator or his/her designee, technician) using a calibrated tonometer. The same instrument should be used at every study visit, if possible.

The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest. Both eyes will be tested, with the right eye preceding the left eye. The tension knob is pre-set at a low pressure value (4-6 mmHg) before and after each measurement.

The technician will look through the binocular viewer of the slit lamp at low power and follow the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the technician then takes his/her fingers off the tension knob and records the IOP reading in the source document. The procedure will be repeated on the same eye twice consecutively.

If the measurements are within 2 mmHg or less of each other, the mean of the 2 readings will be calculated and recorded. If the 2 readings differ by more than 2 mmHg, a third (consecutive) reading will be taken and the median (middle) IOP will be recorded.

Rounding of the mean IOP result is not allowed (i.e. a mean of 25.5 mmHg does not qualify as 26 mmHg for meeting eligibility criteria, or a mean of 35.5 mmHg does not qualify as 36 mmHg).

Dilated Indirect Ophthalmoscopy

Dilated indirect ophthalmoscopic examination will be performed after pin-hole visual acuity, slit-lamp biomicroscopy, and tonometry have been assessed. The examination will not be performed until the subject's eyes are deemed sufficiently dilated in the opinion of the Investigator. The Investigator will note any findings present and whether the findings are clinically significant or not clinically significant. Findings which are clinically significant will be described. All findings will be documented on each subject's source document and corresponding electronic case report form.

The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

APPENDIX 3: APPROVALS

Protocol Title: A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of OCS-01 Ophthalmic Suspension in the Treatment of Inflammation and Pain Following Cataract Surgery

Protocol Number: DX220

Final Date: 25 Sep 2023

Signed: [redacted] Date: 26-SEP-2023

Chief Executive Officer
Oculis Operations Sàrl

Signed: [redacted] Date: 26-SEP-2023

Oculis Operations Sàrl

Signed: [redacted] Date: 25-SEP-2023

Signed: [redacted] Date: 25-SEP-2023

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of OCS-01 Ophthalmic Suspension in the Treatment of Inflammation and Pain Following Cataract Surgery
Protocol Number:	DX220
Final Date:	25 September 2023

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name:
Title:
Affiliation:
Address:
Telephone number:

signNow

Document History

SignNow E-Signature Audit Log

All dates expressed in MM/DD/YYYY (US)

Document name: DX220-Protocol
Document created: 09/25/2023 16:16:41
Document pages: 57
Document ID: 6871d0f34cdf43a18d57f70cbd9ff5135a208b33
Document Sent: 09/25/2023 16:22:09 UTC
Document Status: Signed
09/26/2023 15:55:18UTC

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