Clinical Trial Protocol:

Protocol Title:	A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of Two Doses of OCS-01 compared to Vehicle in the Treatment of Inflammation and Pain Following Cataract Surgery
IND#	131596
Protocol Number:	DX216
Study Phase:	2
Product Name:	OCS-01 ophthalmic suspension
Indication:	Inflammation and pain following cataract surgery
Investigator:	Multi-center clinical investigation
Sponsor:	Oculis ehf. Álfheimar 74, 6. hæð 104 Reykjavik | Iceland Tel. +354 546 4440
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1 SYNOPSIS

Protocol Title:	A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of Two Doses of OCS-01 compared to Vehicle in the Treatment of Inflammation and Pain Following Cataract Surgery
IND #	131596
Protocol Number:	DX216
Study Drugs:	1. OCS-01 (Dexamethasone Cyclodextrin Nanoparticle Ophthalmic Suspension 1.5%) 2. Placebo (vehicle for OCS-01)
Study Phase:	2
Objective(s):	The primary objective of this study is to evaluate the efficacy and safety of OCS-01 once a day (QD) and twice a day (BID) compared to placebo (vehicle) BID in the treatment of inflammation and pain following cataract surgery. The secondary objective of this study is to evaluate the optimal dosing frequency of OCS-01 (QD versus BID) in the treatment of inflammation and pain following cataract surgery.
Overall Study Design:	
Structure:	Multi-center, randomized, double-masked, placebo (vehicle)-controlled study
Duration:	Approximately 20-52 days
Controls:	Placebo (vehicle for OCS-01)
Dosage/Dose Regimen/ Instillation/ Application/Use:	Subjects will be randomized to one of the following treatment groups in a 1:1:1 fashion: 1. OCS-01 QD + Placebo (vehicle) QD 2. OCS-01 BID 3. Placebo (vehicle) BID Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms: 1. OCS-01 QD + Placebo (vehicle) QD 2. OCS-01 BID 3. Placebo (vehicle) BID

	For masking purposes, each dosing box and the pouches within it will be labeled either "AM" or "PM." Dosing boxes and pouches will be labeled this way regardless of whether the products within the 2 boxes are the same (i.e. OCS-01 BID and placebo treatment arms) or different (i.e. OCS-01 QD). All qualified subjects will dose for 14 days beginning 1 day post-surgery in the operated eye. Doses should be instilled at approximately 8 AM (± 2 hours) and 8 PM (± 2 hours), as close to 12 hours apart as possible.
Summary of Visit Schedule:	Visit 1 (Day -28 to Day -1 [prior to surgery]): Screening, baseline evaluations Visit 2 (Day 1 [18 to 30 hours post-surgery]): Review of inclusion and exclusion criteria, randomization, and dosing and dispensation of study medication Visit 3 (Day 2) Pain assessments (telephone call) Visit 4 (Day 4 ± 1): Inflammation, pain, and safety assessments Visit 5 (Day 8 ± 1): Inflammation, pain, and safety assessments Visit 6 (Day 15 ± 2): Inflammation, pain, and safety assessments Visit 7 (Day 22 ± 2): 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, 150 subjects will be randomized into the following groups: OCS-01 QD: 50 subjects OCS-01 BID: 50 subjects Placebo (vehicle) BID: 50 subjects

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. Be able to comply with the study requirements and visit schedule;
3. Be at least 18 years of age of either sex or any race;
4. Be planning to undergo unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in the study eye;
5. Have an anterior chamber cell score ≥ 2 at Visit 2 (Day 1 [18 to 30 hours post-uncomplicated cataract surgery with no vitreous loss]);
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 (Day -1 to Day -28 [prior to surgery]);
7. Have a negative urine pregnancy test at Visit 1 (Day -1 to Day -28 [prior to surgery]), if female of childbearing potential (i.e. those who have experienced menarche, who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use acceptable effective contraceptive measure throughout the study period. Acceptable effective contraceptive measure is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

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. Be monocular;
3. Have any intraocular inflammation (e.g. white blood cells or flare) present in either eye at the Visit 1 (Day -1 to Day -28 [prior to surgery]) slit lamp examination;
4. Have a score > 0 on the Ocular Pain Assessment at Visit 1 (Day -1 to Day -28 [prior to surgery]) in the study eye;

5. 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. Washout periods for medications prior to the day of cataract surgery are as follows:
    a. Topical ocular steroids: 14 days;
    b. Periocular injection of any corticosteroid solution: 28 days;
    c. Intraocular treatment with a corticosteroid including dexamethasone drug delivery systems: 56 days after implantation; fluocinolone acetonide drug delivery systems: 48 months after implantation; any other intravitreal injection: 95 days after injection;

    Note: While it is expected that subjects requiring an intraocular treatment with a corticosteroid will be excluded due to underlying exclusionary conditions, subjects who otherwise meet all eligibility criteria will be required to follow the above-mentioned washout intervals.

    d. Any systemic treatment with a corticosteroid including oral: 14 days; systemic or parenteral sustained/extended release: 180 days;

    Note: Inhaled, intranasal, and topical dermatologic steroids (except on the face and periocular region) are allowed. Topical dermatologic steroids on the face and periocular region require a 7 day washout.

    e. Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs): 7 days;
    f. Systemic analgesics/pain relievers (e.g. gabapentin, pregabalin, and opioids): 14 days;

    Note: Use of an opioid during cataract surgery is allowed;

    g. Systemic acetaminophen, NSAIDs, acetylsalicylic acid, or other anti-inflammatory agents: 7 days;

    Note: Use of up to 81 mg of acetylsalicylic acid dosed once daily is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study.

    h. Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): all current or previous use of BPH medications excludes participation in this study. ;
    i. Cyclosporine: 56 days or immunomodulating or immunosuppressive agents (e.g. calcineurin inhibitors, antiproliferative agents, mammalian target

of rapamycin (mTOR) inhibitors, etc.): 2 months

j. Mast cell stabilizers or antihistamines (e.g. β2-adrenergic agonists. cromoglicic acid, ketotifen, brompheniramine, cetirizine, diphenhydramine): 7 days;

6. Require the use of a contact lens or a collagen shield within 72 hours prior to Visit 2 (Day 1 [18 to 30 hours post-surgery]) or for the remainder of the study period in either eye;
7. Require the use of non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following, which are allowed: mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, prophylactic antibiotics, non-prostaglandin analog intraocular pressure (IOP)-lowering agents, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye (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);
8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). Subjects taking IOP-lowering medication must not be on more than 1 IOP-lowering medication. Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]).

Note: Combination IOP agents count as 2 medications.

9. Currently have or have a history of herpes keratitis in the study eye;
10. Have corneal abrasions or ulcers in the study eye (not including the surgical clear corneal wound from cataract surgery);
11. Have evidence of acute external ocular infections (bacterial, viral, and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva), corneal endothelial dystrophies, intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye;
12. Have uncontrolled and clinically significant dry eye syndrome in the study eye (use of artificial tears is allowed);
13. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in either the fellow eye or the study eye;

14. Have cystoid macular edema, diabetic retinopathy, or diabetic macular edema; compromised macular function; significant macular diseases; or a history of macular edema in the study eye;
15. Have previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye that in the opinion of the Investigator may affect the pharmacokinetics of the study medication, intraocular inflammation, or the normal healing process;
16. Have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation;
17. Have a planned use of femtosecond laser or any other ophthalmic surgical procedure (e.g. MIGS [minimally invasive glaucoma surgery], vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.) in addition to the cataract extraction procedure via phacoemulsification and PCIOL implantation in the study eye;
18. Have a planned use of anterior capsule staining for capsulorhexis (i.e. trypan blue) during cataract surgery;
19. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of Visit 1 (Day -1 to Day -28 [prior to surgery]), or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery);
20. Have surgery planned or scheduled for the contralateral eye during the 3-week study period;
21. Have an immunosuppressive or an autoimmune disease that in the opinion of the Investigator could affect intraocular inflammation or the normal healing process of the eye;
22. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and will likely affect wound healing;
23. Currently have a suspected or known malignancy or be currently receiving anti-neoplastic therapy;
24. Have previously been enrolled in this clinical study, have planned to participate in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation, or be currently in the follow-up period of a previous clinical trial;
25. Be enrolled in the study if the Investigator determines that the subject should not be included for reasons not already specified (e.g. systemic or other ocular disease/abnormality), if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment;
26. Be a female who is currently pregnant, planning a

pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration, or have a positive urine pregnancy test at Visit 1 (Day -1 to Day -28 [prior to surgery]).

Evaluation Criteria:

Efficacy Measures:

Hierarchical Primary Efficacy Measures:

1. Absence of anterior chamber cells (i.e. score of '0') at Visit 6 (Day 15);
2. Absence of pain (i.e. score of '0') at Visit 4 (Day 4).

Secondary Efficacy Measures:

- Absence of anterior chamber cells at Visits 4, 5, and 7 (Days 4, 8, and 22);
- Absence of pain at Visits 3, 5, 6, and 7 (Days 2, 8, 15, and 22);
- Absence of flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22);
- Absence of both anterior chamber cells and flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22);
- Use of rescue medication on or prior to each visit and overall.

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.

Rescue Criteria:

- Grade $\geq$ 2 anterior chamber cells at Visit 5 (Day 8) (or after) with topical ocular steroids and/or NSAIDs;
- Severe ocular pain at Visit 4 (Day 4) (or after) with oral acetaminophen.

General Statistical Methods and Types of Analyses:

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 (Day 15) (or who discontinue due to lack of efficacy or receive rescue medication prior to Visit 6 [Day 15]) 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 one 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.

Hypotheses

Primary Endpoint:

H_{011}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.

H_{111}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).

H_{012}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.

H_{112}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Hierarchical Primary Endpoint:

H_{021}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.

H_{121}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).

H_{022}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with vehicle, in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.

H_{122}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with vehicle, in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Multiple comparison adjustments for testing OCS-01 BID and OCS-01 QD versus vehicle in the absence of anterior chamber cells will not be made (i.e. the testing of H_{011} versus H_{111} and H_{012} versus H_{112} will both be completed at a 2-sided alpha = 0.10). A hierarchical testing strategy will be employed for testing absence of pain; statistical inference will only be made on the absence of pain endpoint if the corresponding OCS-01 dose (BID or QD) demonstrated statistical superiority over placebo (vehicle) in the absence of anterior chamber cells.

Sample Size Determination

With a total of 150 subjects (50 subjects per treatment group: OCS-01 BID, OCS-01 QD, and placebo [vehicle] in the FAS [i.e. 1:1:1 randomization]), the study has 85% power to detect a statistically significant treatment difference between OCS-01 BID and placebo and between OCS-01 QD and placebo for the proportion of subjects with absence of cells on post-operative Visit 6 (Day 15), assuming a 2-sided alpha level of 0.10, and the proportion of subjects with absence of cells is 0.45 (active) and 0.20 (placebo [vehicle]).

Additionally, with this sample size, the study has 83% power to detect a statistically significant

treatment difference between OCS-01 (BID or QD) and placebo for the proportion of subjects with absence of ocular pain on post-operative Visit 4 (Day 4), assuming a 2-sided alpha level of 0.10 and the proportion of subjects with absence of ocular pain is 0.50 (active) and 0.25 (placebo [vehicle]).

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 – placebo (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 = 0.10 test unless otherwise stated and corresponding 2-sided 90% and 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.

Handling of Missing Data

The primary analyses of all efficacy data will use last observation carried forward (LOCF) to impute missing data; data for visits after a subject is discontinued for lack of efficacy or receives rescue medication will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints. To check robustness of results, sensitivity analyses of the primary efficacy endpoints will include analyses of observed data only, imputing data from subject visits after discontinuation for lack of efficacy or receipt of rescue medication as failures. Tipping point analysis and multiple imputation methods using monotone methodology will also be used to impute missing data as additional sensitivity analyses. PP analyses will use observed data only, with the exception of subjects who have missing data due to discontinuation for lack of efficacy or for subjects who receive rescue medication; for these subjects, missing data after discontinuation or data after receiving rescue medication will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints.

Demographics

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

Primary Efficacy Analysis

The hierarchical primary efficacy variables, the absence of anterior chamber cells at Visit 6 (Day 15) and the absence of pain at Visit 4 (Day 4), will be summarized using discrete summary statistics, including 2-sided 95% CIs for each treatment group.

For each OCS-01 dose (BID and QD), 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 placebo (vehicle) at Visit 6 (Day 15) 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 placebo (vehicle) at a 2-sided alpha = 0.10 at Visit 6 (Day 15) for either dose of OCS-01 (BID or QD), 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 (Day 4) between the corresponding OCS-01 dose and placebo (vehicle) using the Pearson chi-squared statistic at a 2-sided alpha=0.10 (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.

Secondary Efficacy Analysis:

The secondary efficacy variables, the differences in proportions of study eyes with absence of anterior chamber cells (Visits 4, 5, and 7 [Days 4, 8, and 22]), study eyes with absence of pain (Visits 4, 5, and 6 [Days 8, 15, and 22]), study eyes with absence of flare (Visits 4, 5, 6, and 7 [Days 4, 8, 15, and 22]), and study eyes with absence of both anterior chamber cells and anterior chamber flare (Visits 4, 5, 6, and 7 [Days 4, 8, 15, and 22]) will be summarized and analyzed similarly to the primary efficacy summaries and analyses.

Use of rescue medication on or prior to each visit will be summarized by visit and overall using discrete summary statistics.

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

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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List of Abbreviations

γCD	γ-cyclodextrin
AE	adverse event
BID	twice a day
BPH	benign prostatic hyperplasia
CI	confidence interval
CD	cyclodextrin
CFR	Code of Federal Regulations
eCRF	electronic case report form
EMA	European Medicines Agency
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	full analysis set
FDA	Food and Drug Administration
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
LOCF	last observation carried forward
MIGS	minimally invasive glaucoma surgery
mTOR	mammalian target of rapamycin
NSAID	non-steroidal anti-inflammatory drug
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
SOC	system organ class
TEAE	treatment-emergent adverse events
VA	visual acuity

3 INTRODUCTION

3.1 Background

An estimated 95 million people worldwide are affected by cataracts, with cataract surgery being the most commonly performed surgical procedure in many countries (Liu, Wilkins et al. 2017). The current preferred treatments for ocular inflammation include the use of topical corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs), which may be contraindicated in some populations. Corticosteroids, which are considered the mainstay treatment for ocular inflammation, can be associated with adverse events (AEs), especially when frequent or prolonged dosing is needed, such as in patients where post-operative inflammation is severe and/or prolonged (Weber, Kodjikian et al. 2013).

In general, drug penetration from the ocular surface via topical administration into the eye encounters multiple barriers. This results in a bioavailability inside the eye that is generally well below 5%. In spite of this very low topical bioavailability, aqueous eye drops are the patient-preferred dosage form, especially in treatment of diseases of the anterior eye tissues, accounting for over 90% of the market (Loftsson and Stefansson 2017).

Dexamethasone is a corticosteroid that has been used in the form of eye drops (Maxidex®, Alcon, United States of America) to treat inflammation caused by surgery, infections, or injury (Alcon Laboratories 2002). Dexamethasone has limited solubility in water and does not readily permeate from the eye's aqueous exterior into the eye. Studies have shown that cyclodextrins (CDs) are able to enhance topical bioavailability of dexamethasone from aqueous eye drops (Usayapant, Karara et al. 1991, Kristinsson, Fridriksdottir et al. 1996, Sigurdsson, Konraethsdottir et al. 2007, Loftsson and Stefansson 2017). CDs have also been incorporated into other Food and Drug Administration (FDA) approved ophthalmic drops to increase drug solubility (Alcon Laboratories 2000). Oculis is developing a novel drug delivery platform composed of the active ingredient, dexamethasone, and CD nanoparticles (OCS-01, previously called DexNP), which aid in delivery of the active pharmaceutical ingredient from the ocular surface to both the anterior and posterior segments of the eye. CD-based dexamethasone eye drop solutions have been tested in human patients and show excellent penetration into the anterior segment of the eye (Kristinsson, Fridriksdottir et al. 1996, Saari, Nelimarkka et al. 2006, Tanito, Hara et al. 2011). Some of the earliest formulations of dexamethasone CD solutions (0.32 or 0.67% dexamethasone, 2-hydroxypropyl-β-cyclodextrin), were tested in a clinical trial conducted in Iceland 20 years ago (Kristinsson, Fridriksdottir et al. 1996). In 125 patients undergoing cataract surgery, concentrations of dexamethasone were significantly higher after application of dexamethasone CD suspension compared to Maxidex® ($P < 0.001$), indicating that the CD-based drug delivery system enhances both the solubility and permeability of dexamethasone to the anterior segment of the human eye. Notably, no toxic effects were observed with the use of dexamethasone CD suspension.

In a more recent study (Johannesson, Moya-Ortega et al. 2014), levels of dexamethasone were assessed in the tear fluid of healthy subjects treated with a topical application of 1.5% DexNP or Maxidex®. Six (6) subjects received DexNP in one eye and Maxidex® in the contralateral eye. Results reveal that treatment with DexNP results in a 19-fold higher concentration of dexamethasone compared to treatment with Maxidex®. Notably, 4 hours post-instillation, the

concentration of dexamethasone from DexNP treatment was still 10-times higher than what was observed with Maxidex® treatment. These results demonstrate that dexamethasone, complexed with CD nanoparticles, elicits a higher concentration and longer duration of action in the tear fluid than the currently available product, Maxidex®. Importantly, DexNP was well tolerated by the subjects and no serious adverse events (SAEs) were observed.

A study conducted by Saari et al. (Saari, Nelimarkka et al. 2006) evaluated the efficacy of an eye drop containing 0.7% dexamethasone-CD suspension, applied once daily, compared to a 0.1% dexamethasone sodium phosphate eye drops, applied three times daily for the treatment of post-operative inflammation after cataract surgery. The dexamethasone-CD suspension was shown to be safe and more effective in treating post-operative inflammation, after once daily dosing, than 0.1% dexamethasone sodium phosphate eye drops applied three times daily.

In the human studies with DexNP to date, DexNP was well tolerated and the only AE reported has been a modest rise in intraocular pressure (IOP), a known side effect of dexamethasone use, which subsided following discontinuation of DexNP in all cases (Kristinsson, Fridriksdottir et al. 1996) (Johannesson, Moya-Ortega et al. 2014) (Saari, Nelimarkka et al. 2006) (Tanito, Hara et al. 2011) (Ohira, Hara et al. 2015) (Krag and Hessellund 2014) (Shulman, Johannesson et al. 2015).

Building on the enhanced ocular penetration of DexNP, as well as its favorable efficacy results and safety profile, Oculis has developed an updated formulation, OCS-01, consisting of water soluble 1.5% Dexamethasone-γCD complexes to treat post-surgical inflammation.

3.2 Study Rationale

The trial outlined here is a randomized, double-masked, placebo (vehicle)-controlled study evaluating the efficacy and safety of two doses of OCS-01 compared to vehicle in the treatment of inflammation and pain following cataract surgery. The primary objective is to evaluate the efficacy and safety of OCS-01 compared to placebo and the secondary objective is to evaluate the optimal dosing frequency (once a day [QD] or twice a day [BID]).

3.3 Dosage

OCS-01 is a 1.5% w/v suspension that is equivalent to 1.5 g dexamethasone per 100 mL suspension. A single drop from an eye drop bottle is approximately 30 µL, and, therefore, a single drop of OCS-01 would contain approximately 0.45 mg of dexamethasone. Subjects in this study will receive either QD or BID dosing and, therefore, may receive 0.45 mg or 0.90 mg of dexamethasone per day.

As a comparison, Maxidex 0.1% dexamethasone suspension is an FDA approved ophthalmic suspension for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, including inflammation post-cataract surgery. In severe disease, 1-2 drops may be dosed hourly. A 0.1% suspension would contain 0.03 mg of dexamethasone per drop. If the maximum daily dose is applied, this would equate to 2 drops per hour, up to 48 drops. This could result in a maximum daily dose of 1.44 mg.

Further, the 0.45 mg of dexamethasone per 30 µL drop for OCS-01 is also assuming that the entire drop is absorbed into the eye. The maximum capacity of the conjunctival sac is up to 30 µL and a drop of larger volume applied to a human eye will have its excess overflowed. Thus, a maximum 0.45 mg of dexamethasone per drop will reach the eye.

The dexamethasone formulation to be tested here contains natural γ-cyclodextrin (γCD). γCD has been evaluated previously in other dexamethasone based eye drops (DexNP) in several indications in clinical trials (Tanito, Hara et al. 2011, Johannesson, Hallberg et al. 2014, Ohira, Hara et al. 2015, Shulman, Johannesson et al. 2015). The eye drops were well tolerated and displayed no signs of irritation or redness.

3.4 Placebo Justification

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

3.4.1 Rationale

The inclusion of a placebo group is considered essential to the design of the DX216 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 placebo 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 if the subject is displaying Grade 2 or greater anterior cells or experiencing severe ocular pain.

Protocol Section 6.5: Rescue Criteria:

- Grade ≥ 2 anterior chamber cells (i.e. ≥ 11 cells on the Anterior Chamber Cells grading scale [see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques]) at Visit 5 (Day 8 ± 1) (or after) may be treated with topical ocular steroids and/or topical NSAIDs;
- Severe ocular pain (i.e. 7 to 10 on the Ocular Pain Grading scale (see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques) at Visit 4 (Day 4 ± 1) (or after) may be treated with oral acetaminophen.

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

3.4.2 Measures To Ensure Safe Participation in the Study

Placebo-controlled studies may only be ethically conducted when patients at a controlled risk are included, patients are fully informed of all the potential risks, patients 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 patients.

The following specific measures are included in the protocol:

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

Based on the above rationale and the measurements for a safe medical supervision for the patients, Oculis believes that it is scientifically and ethically appropriate to use placebo control in the study DX216.

4 STUDY OBJECTIVES AND HYPOTHESIS

4.1 Study Objective

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

The secondary objective of this study is to evaluate the optimal dosing frequency of OCS-01 (QD versus BID) in the treatment of inflammation and pain following cataract surgery.

4.2 Study Hypothesis

It is hypothesized that the planned QD and BID doses of OCS-01 via topical ophthalmic administration will be safe, effective, and well tolerated in subjects post-cataract surgery.

5 OVERALL STUDY DESIGN

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

Subjects will be randomized 1:1:1 to receive OCS-01 QD, OCS-01 BID, or placebo BID. Subjects will dose 1 drop in the study eye BID for 14 days, beginning 1 day post-surgery in the operated eye. The study will last 20-52 days, including screening and a follow-up visit at Visit 7 (Day 22 ± 2).

6 STUDY POPULATION

6.1 Number of Subjects (approximate)

Approximately 150 subjects will be enrolled in the study.

This is a multi-center study.

6.2 Study Population Characteristics

Subjects may be of either sex or any race and must be at least 18 years of age at Visit 1 (Day -1 to Day -28 [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.

6.3 Inclusion Criteria

Each subject must:

1. Provide written informed consent, approved by the appropriate ethics committee;
2. Be able to comply with the study requirements and visit schedule;
3. Be at least 18 years of age of either sex or any race;
4. Be planning to undergo unilateral cataract extraction via phacoemulsification and PCIOL implantation in the study eye;
5. Have an anterior chamber cell score ≥ 2 at Visit 2 (Day 1 [18 to 30 hours post-uncomplicated cataract surgery without vitreous loss]);
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 (Day -1 to Day -28 [prior to surgery]);
7. Have a negative urine pregnancy test at Visit 1 (Day -1 to Day -28 [prior to surgery]), if female of childbearing potential (i.e. those who have experienced menarche, who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use acceptable effective contraceptive measure throughout the study period. Acceptable effective contraceptive measure is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

6.4 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. Be monocular;
3. Have any intraocular inflammation (e.g. white blood cells or flare) present in either eye at the Visit 1 (Day -1 to Day -28 [prior to surgery]) slit lamp examination;
4. Have a score > 0 on the Ocular Pain Assessment at Visit 1 (Day -1 to Day -28 [prior to surgery]) in the study eye;

5. 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 history of use of medications for benign prostatic hyperplasia (BPH) from the washout period through the duration of the study. Washout periods for medications prior to the day of cataract surgery are as follows:

    a. Topical ocular steroids: 14 days;

    b. Periocular injection of any corticosteroid solution: 28 days;

    c. Intraocular treatment with a corticosteroid including dexamethasone drug delivery systems: 56 days after implantation; fluocinolone acetonide drug delivery systems: 48 months after implantation; any other intravitreal injection: 95 days after injection;

    Note: While it is expected that subjects requiring an intraocular treatment with a corticosteroid will be excluded due to underlying exclusionary conditions, subjects who otherwise meet all eligibility criteria will be required to follow the above-mentioned washout intervals.

    d. Any systemic treatment with a corticosteroid including oral: 14 days; systemic or parenteral sustained/extended release: 180 days;

    Note: Inhaled, intranasal, and topical dermatologic steroids (except on the face and periocular region) are allowed. Topical dermatologic steroids on the face and periocular region require a 7 day washout.

    e. Topical ocular NSAIDs: 7 days;

    f. Systemic analgesics/pain relievers (e.g. gabapentin, pregabalin, and opioids): 14 days;

    Note: Use of an opioid during cataract surgery is allowed;

    g. Systemic acetaminophen, NSAIDs, acetylsalicylic acid, or other anti-inflammatory agents: 7 days;

    Note: Use of up to 81 mg of acetylsalicylic acid dosed once daily is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study.

    h. Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): all current or previous use of BPH medications excludes participation in this study. ;

    i. Cyclosporine: 56 days or immunomodulating or immunosuppressive agents (e.g. calcineurin inhibitors, antiproliferative agents, mammalian target of rapamycin (mTOR) inhibitors, etc.): 2 months

    j. Mast cell stabilizers or anti-histamines (e.g. β2-adrenergic agonists. cromoglicic acid, ketotifen, brompheniramine, cetirizine, diphenhydramine): 7 days;

6. Require the use of a contact lens or a collagen shield within 72 hours prior to Visit 2 (Day 1 [18 to 30 hours post-surgery]) or for the remainder of the study period in either eye;

7. Require use of non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following, which are allowed: mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, prophylactic antibiotics, non-prostaglandin analog IOP-lowering agents, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye (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);
8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). Subjects taking IOP-lowering medication must not be on more than 1 IOP-lowering medication. Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]).

   Note: Combination IOP agents count as 2 medications.
9. Currently have or have a history of herpes keratitis in the study eye;
10. Have corneal abrasions or ulcers in the study eye (not including the surgical clear corneal wound from cataract surgery);
11. Have evidence of acute external ocular infections (bacterial, viral, and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva), corneal endothelial dystrophies, intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye;
12. Have uncontrolled and clinically significant dry eye syndrome in the study eye (use of artificial tears is allowed);
13. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in either the fellow eye or the study eye;
14. Have cystoid macular edema, diabetic retinopathy, or diabetic macular edema; compromised macular function; significant macular diseases; or a history of macular edema in the study eye;
15. Have previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye that in the opinion of the Investigator may affect the pharmacokinetics of the study medication, intraocular inflammation, or the normal healing process;
16. Have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation;
17. Have a planned use of femtosecond laser or any other ophthalmic surgical procedure (e.g. minimally invasive glaucoma surgery [MIGS], vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.) in addition to the cataract extraction procedure via phacoemulsification and PCIOL implantation in the study eye;
18. Have a planned use of anterior capsule staining for capsulorhexis (i.e. trypan blue) during cataract surgery;

19. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of Visit 1 (Day -1 to Day -28 [prior to surgery]), or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery);
20. Have surgery planned or scheduled for the contralateral eye during the 3-week study period;
21. Have an immunosuppressive or an autoimmune disease that in the opinion of the Investigator could affect intraocular inflammation or the normal healing process of the eye;
22. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and will likely affect wound healing;
23. Currently have a suspected or known malignancy or be currently receiving anti-neoplastic therapy;
24. Have previously been enrolled in this clinical study, have planned to participate in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation, or be currently in the follow-up period of a previous clinical trial;
25. Be enrolled in the study if the Investigator determines that the subject should not be included for reasons not already specified (e.g. systemic or other ocular disease/abnormality), if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment;
26. Be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration, or have a positive urine pregnancy test at Visit 1 (Day -1 to Day -28 [prior to surgery]).

6.5 Rescue Criteria

- Grade ≥ 2 anterior chamber cells (i.e. ≥ 11 cells on the Anterior Chamber Cells grading scale [see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques]) at Visit 5 (Day 8 ± 1) (or after) may be treated with topical ocular steroids and/or topical NSAIDs;

- Severe ocular pain (i.e. 7 to 10 on the Ocular Pain Grading Scale [see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques]) at Visit 4 (Day 4 ± 1) (or after) may be treated with oral acetaminophen.

6.6 Withdrawal Criteria (if applicable)

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

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 required at the final study visit (Visit 7).

7 STUDY PARAMETERS

7.1 Efficacy Measures

7.1.1 Primary Efficacy Measure

Hierarchical Primary Efficacy Measures:

1. Absence of anterior chamber cells (i.e. score of '0') at Visit 6 (Day 15);
2. Absence of pain (i.e. score of '0') at Visit 4 (Day 4).

7.1.2 Secondary Efficacy Measure

Secondary Efficacy Measures:

- Absence of anterior chamber cells at Visits 4, 5, and 7 (Days 4, 8, and 22);
- Absence of pain at Visits 3, 5, 6, and 7 (Days 2, 8, 15, and 22);
- Absence of flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22);
- Absence of both anterior chamber cells and flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22);
- Use of rescue medication on or prior to each visit and overall.

7.1.3 Primary Efficacy Analyses

The hierarchical primary efficacy analyses are as follows:

1. 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 (Day 15).

If the proportion of study eyes with absence of anterior chamber cells (score of '0') is statistically significantly higher for OCS-01 versus placebo (vehicle) at a 2-sided alpha = 0.10 at Visit 6 (Day 15) for either dose of OCS-01 (BID or QD), then the study will be considered a success and the next hierarchical hypothesis will be tested.

2. Difference in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) between the corresponding OCS-01 dose and placebo (vehicle).

7.1.4 Secondary Efficacy Analyses

- Difference in the proportion of study eyes with absence of anterior chamber cells at Visits 4, 5, and 7 (Days 4, 8, and 22).
- Difference in the proportion of study eyes with absence of pain at Visits 5, 6, and 7 (Days 8, 15, and 22).
- Difference in the proportion of study eyes with absence of flare Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22).

- Difference in the proportion of study eyes with absence of both anterior chamber cells and anterior chamber flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22).
- Use of rescue medication on or prior to each visit and overall.

Efficacy measures will be further described in the Statistical Analysis Plan (SAP).

7.2 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

8 STUDY MATERIALS

8.1 Study Treatment(s)

8.1.1 Study treatment(s)

- OCS-01 ophthalmic suspension (QD) + Placebo (vehicle) (QD)
- OCS-01 ophthalmic suspension (BID)
- Placebo (vehicle) ophthalmic suspension (BID)

8.1.2 Instructions for Use and Administration

Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms:

- OCS-01 QD + Placebo (vehicle) QD
- OCS-01 BID
- Placebo (vehicle) BID

For masking purposes, each dosing box and the pouches within it will be labeled either "AM" or "PM." Dosing boxes and pouches will be labeled this way regardless of whether the product within the 2 boxes is the same (i.e. OCS-01 BID and placebo treatment arms) or different (i.e. OCS-01 QD). All qualified subjects will dose for 14 days beginning 1 day post-surgery in the operated eye. Doses should be instilled at approximately 8 AM (± 2 hours) and 8 PM (± 2 hours), as close to 12 hours apart as possible.

For Visit 2, 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). The second dose should be instilled into the operated eye during the PM dosing window (8 PM [± 2 hours]), regardless of

when dose 1 was instilled (subjects should then have instilled 2 doses on Day 1 post-cataract surgery).

For all other study visits, subjects should continue to dose according to their established schedule. If the visit is scheduled during the time of normal dosing, the subject should bring their dose with them to the visit for administration. Every effort should be made to maintain dosing schedule/ frequency.

9 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in Sections 6.2, 6.3, and 6.4 will be considered for entry into this study.

9.1.2 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).

9.1.3 Washout Intervals

Washout periods are outlined in exclusion criteria in Section0.

9.1.4 Procedures for Final Study Entry

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

9.1.5 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 001 and will follow the two-digit site number (e.g. subject 077 at Site 99 will have Screening Number 99-077). 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 1:1:1 assignment ratio, stratified by site, via an interactive response system.

9.2 Concurrent Therapies

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

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

9.2.1 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 (Day -1 to Day -28 [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 (Day 1 [18 to 30 hours 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.

Table 1: Non-allowed Medications and Washout Periods

Medication	Washout Period
Topical ocular steroids	14 days
Periocular injection of any corticosteroid solution	28 days
Intraocular treatment with a corticosteroid	56 days after implantation
Fluocinolone acetonide drug delivery systems	48 months after implantation
Intravitreal injection	95 days after injection
Systemic treatment with a corticosteroid including oral	14 days
Systemic or parenteral sustained/extended release corticosteroid	180 days
Topical ocular NSAIDs	7 days
Systemic analgesics/pain relievers (e.g. gabapentin, pregabalin, and opioids)	14 days

Systemic acetaminophen, NSAIDs, acetylsalicylic acid, or other anti-inflammatory agents	7 days
BPH medication (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride)	no current or historic use
Immunomodulating or immunosuppressive agents (e.g. cyclosporine, calcineurin inhibitors, antiproliferative agents, mTOR inhibitors, etc.)	56 days
Mast cell stabilizers or anti-histamines (e.g. β2-adrenergic agonists. cromoglicic acid, ketotifen, brompheniramine, cetirizine, diphenhydramine)	7 days

9.2.2 Rescue Medications

- Grade ≥ 2 anterior chamber cells (i.e. ≥ 11cells on the Anterior Chamber Cells grading scale [see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques]) at Visit 5 (Day 8 ± 1) (or after) may be treated with topical ocular steroids and/or topical NSAIDs;
- Severe ocular pain (i.e. 7 to 10 on the Ocular Pain Grading Scale [see Appendix 2: Examination Procedures, Tests, Equipment, and Techniques]) at Visit 4 (Day 4 ± 1) (or after) may be treated with oral acetaminophen.

9.2.3 Special Diet or Activities

There are no special diet or activity restrictions for this study.

9.3 Examination Procedures

Procedures to be performed at each study visit with regard to the study objectives are detailed in Appendix 2: Examination Procedures, Tests, Equipment, and Techniques.

Visit 1 — Screening and Baseline Evaluations (-28 to -1 days 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 (Day -1 to Day -28 [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 (Day -1 to Day -28 [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 — Day 1 (18 to 30 hours 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

Visit 3 — Day 2 (Telephone Call)

- Ocular pain (study eye only)

Visit 4 — Day 4 (± 1 day window)

- 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 — Day 8 (± 1 day window)

- 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 — Day 15 (± 2 day window)

- 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 — Day 22 (± 2 day window)

- 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.

9.4 Schedule of Visits, Measurements and Dosing

9.4.1 Scheduled Visits

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

9.4.2 Unscheduled Visits

In the case of an AE, an unscheduled visit 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.

9.5 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/ Committee for Medicinal Products for Human Use/ICH/135/1995).

9.6 Subject Disposition

9.6.1 Completed Subjects

A completed subject is defined as having completed all 7 visits. Subjects who have discontinued from the study or withdrawn consent/assent will not be considered completed subjects.

9.6.2 Discontinued subjects

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

- AEs
- Protocol violations
- 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.

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 required at the final study visit (Visit 7).

9.7 Study Termination

The study may be stopped at any time by the Investigator (at their respective site), the Sponsor, and/or Ora with appropriate notification.

9.8 Study Duration

Subjects may be screened from Day -28 to Day -1 prior to surgery. The study will involve 7 visits including a follow-up visit at Visit 7 (Day 22). Overall study duration will be 20-52 days, including the screening visit and a follow-up visit.

9.9 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.

10 ADVERSE EVENTS

10.1 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, placebo (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.

10.1.1 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.

10.1.2 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.

10.1.3 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.

10.2 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 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3 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.

10.3.1 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.

10.3.2 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.

10.4 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.

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

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

11 STATISTICAL METHODS

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

11.1 Statistical Hypotheses

The hierarchical statistical hypotheses for evaluating the objectives of the study are as follows:

Primary Endpoint:

> H_{011}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.
>
> H_{111}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).
>
> H_{012}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) = 0.
>
> H_{112}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of anterior chamber cells (score of '0') at Visit 6 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Hierarchical Primary Endpoint:

> H_{021}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.
>
> H_{121}: The difference, between study eyes treated with OCS-01 BID and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 BID – placebo [vehicle]).
>
> H_{022}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) = 0.
>
> H_{122}: The difference, between study eyes treated with OCS-01 QD and study eyes treated with placebo (vehicle), in the proportion of study eyes with absence of pain (score of '0') at Visit 4 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (OCS-01 QD – placebo [vehicle]).

Multiple comparison adjustments for testing OCS-01 BID and OCS-01 QD versus placebo (vehicle) in the absence of anterior chamber cells will not be made (i.e. the testing of H_{011} versus H_{111} and H_{012} versus H_{112} will both be completed at a 2-sided alpha = 0.10). A hierarchical testing strategy will be employed for testing absence of pain; statistical inference will only be made on the absence of pain endpoint if the corresponding OCS-01 dose (BID or QD) demonstrated statistical superiority over placebo (vehicle) in the absence of anterior chamber cells.

11.2 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 (Day 15) (or who discontinue due to lack of efficacy or receive rescue medication prior to Visit 6 [Day 15]) 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.

11.3 Sample Size Determination

With a total of 150 subjects (50 subjects per treatment group: OCS-01 BID, OCS-01 QD, and placebo [vehicle] in the FAS [i.e. 1:1:1 randomization]), the study has 85% power to detect a statistically significant treatment difference between OCS-01 BID and placebo and between OCS-01 QD and placebo for the proportion of subjects with absence of cells on post-operative Visit 6 (Day 15), assuming a 2-sided alpha level of 0.10 and the proportion of subjects with absence of cells is 0.45 (active) and 0.20 (placebo [vehicle]).

Additionally, with this sample size, the study has 83% power to detect a statistically significant treatment difference between OCS-01 (BID or QD) and placebo for the proportion of subjects with absence of ocular pain on post-operative Visit 4 (Day 4), assuming a 2-sided alpha level of 0.10, and the proportion of subjects with absence of ocular pain is 0.50 (active) and 0.25 (placebo [vehicle]).

11.4 Interim Analysis

Interim analyses will not be performed.

11.5 Efficacy Analysis

11.5.1 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 – placebo (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 = 0.10 test unless otherwise stated and corresponding 2-sided 90% and 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.

11.5.2 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 (Day 15) and the absence of pain (i.e. score of '0') at Visit 4 (Day 4).

Primary Efficacy Analysis: The primary efficacy variables, the absence of anterior chamber cells at Visit 6 (Day 15) and the absence of pain at Visit 4 (Day 4), will be summarized using discrete summary statistics, including 2-sided 95% CIs for each treatment group.

For each OCS-01 dose (BID and QD), 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 placebo (vehicle) at Visit 6 (Day 15) 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 placebo (vehicle) at a 2-sided alpha = 0.10 at Visit 6 (Day 15), for either dose of OCS-01 (BID or QD), 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 (Day 4) between the corresponding OCS-01 dose and placebo (vehicle) will be performed using the Pearson chi-squared statistic at a 2-sided alpha=0.10 (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.

11.5.3 Secondary Efficacy Analyses

Secondary Efficacy Measure: The secondary efficacy measures include:

1. Absence of anterior chamber cells at Visits 4, 5, and 7 (Days 4, 8, and 22);
2. Absence of pain at Visits 5, 6, and 7 (Days 8, 15, and 22);
3. Absence of flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22).

4. Absence of both anterior chamber cells and flare at Visits 4, 5, 6, and 7 (Days 4, 8, 15, and 22);
5. Use of rescue medication on or prior to each visit and overall.

Secondary Efficacy Analysis: The secondary efficacy variables, the differences in proportions of: study eyes with absence of anterior chamber cells (Visits 4, ,5 and 7 [Days 4, 8, and 22]), study eyes with absence of pain (Visits 5, 6, and 6 [Days 8, 15, and 22]), study eyes with absence of flare (Visits 4, 5, 6, and 7 [Days 4, 8, 15, and 22]), and study eyes with absence of both anterior chamber cells and anterior chamber flare (Visits 4, 5, 6, and 7 [Days 4, 8, 15, and 22]) will be summarized and analyzed similarly to the primary efficacy summaries and analyses.

Use of rescue medication on or prior to each visit will be summarized by visit and overall using discrete summary statistics.

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

11.6 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.

11.7 Handling of Missing Data

The primary analyses of all efficacy data will use last observation carried forward (LOCF) to impute missing data; data for visits after a subject is discontinued for lack of efficacy or receives

rescue medication will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints. To check robustness of results, sensitivity analyses of the primary efficacy endpoints will include analyses of observed data only, imputing data from subject visits after discontinuation for lack of efficacy or receipt of rescue medication as failures. Tipping point analysis and multiple imputation methods using monotone methodology will also be used to impute missing data as additional sensitivity analyses. PP analyses will use observed data only, with the exception of subjects who have missing data due to discontinuation for lack of efficacy or for subjects who receive rescue medication; for these subjects, missing data after discontinuation or data after receiving rescue medication will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints.

11.8 Demographics and Medical History

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

12 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.

12.1 Protection of Human Subjects

12.1.1 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.

12.1.2 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.

12.1.3 Ethical Conduct of the Study

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

12.2 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.

12.3 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 X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the eCRF serves as the Investigator's record of a subject's study-related data.

12.3.1 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.

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

12.4.1 Labeling/Packaging

Study drug will be packed in single-use vials, with 10 per aluminum pouch and 2 pouches per box. All study drugs will be labeled according to applicable regulatory requirements.

12.4.2 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 (15-25ºC).

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

12.4.3 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.

12.4.4 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.

12.5 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. Data will not be entered for screen failure subjects. 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, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

12.6 Handling of Biological Specimens

Not applicable

12.7 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.

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Appendix 1: Schedule of Visits and Measurements

Study Parameter	Visit 1 (-28 to -1 Day(s) Prior to Surgery)	Visit 2 (Day 1, 18-30 h Post-Surgery)	Treatment Period				Follow-up
			Visit 3 (Day 2, telephone call)	Visit 4 (Day 4 ± 1)	Visit 5 (Day 8 ± 1)	Visit 6 (Day 15 ± 2)	Visit 7 (Day 22 ± 2)
Informed Consent / HIPAA	X						
Demographic Data	X						
Medical and Medication History	X						
Urine pregnancy Test	X						X
Review Inclusion / Exclusion Criteria	X	X					
Medical and Medications Update		X		X	X	X	X
Ocular Pain (Study Eye Only)	X	X	X	X	X	X	X
Pin-hole Visual Acuity	X	X		X	X	X	X
Slit lamp Biomicroscopy	X	X		X	X	X	X
Ocular Inflammation Assessment of the Anterior Chamber Cell and Flare (Study Eye Only)	X	X		X	X	X	X
Intraocular Pressure	X			X	X	X	X
Randomization		X					
Dilated Indirect Ophthalmoscopy	X						X
Dispense Study Medication and Dosing Diary		X					
AE Query		X		X	X	X	X
Exit from Study							X

AE = adverse event; HIPPA =

Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

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 patient viewing distance should be 4 meters. If less than 20 letters are read at 4 meters the patient 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 patient should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The patient should be told that the chart has letters only, no numbers. If the patient 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 patient 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 patient 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 patient 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 patient says he or she cannot read a letter, he or she should be encouraged to guess. If the patient 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:						

Is total number correct at 4 meters 20 letters or more?

□ Yes □ No

- **If Yes, add 30 to total number correct at 4 meters to calculate pin-hole VA**
- **If No, test at 1 meter**

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.

(If ≥ 20 at 4 meters add 30) +_____

Total number correct at 1 meter +_____

Calculated pin-hole VA Score: =_____

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 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
- Iris
- Lens

During Slit Lamp Biomicroscopy: Ocular Inflammation Assessment of the Anterior Chamber Cell and Flare (Study Eye Only)

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, 1x1mm oblique high intensity beam fluorescein dye is to be instilled into the ocular cul-de-sac, or alternatively, fluorescein strips may be used to facilitate this examination.

Anterior Chamber Cells and Flare

The anterior chamber cell count will be recorded as the actual number of cells observed if ≤10 cells are seen (only white blood cells should be counted; red blood cells and pigment cells should not be counted).

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)

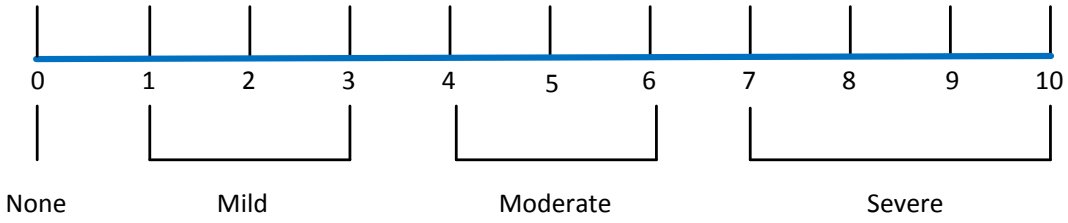
Scale based on (Jabs, Nussenblatt et al. 2005).

Ocular Pain Grading Scale (Study Eye Only)

Ocular pain will be assessed by the patient 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 patient 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 patient will be asked about the eye scheduled for surgery.

The examiner will record the number selected by the patient 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 Goldmann application tonometer affixed to a slit lamp. 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 as indicated in the study flowchart in Appendix 1 after the patient informed consent/authorization, medical history/demographics, urine pregnancy test (if applicable), pin-hole visual acuity, slit lamp biomicroscopy, and tonometry. The examination will not be performed until the patient'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 patient's source document and corresponding electronic case report form.

The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

APPENDIX 3: PROTOCOL AMENDMENT SUMMARY

AMENDMENT 1

BACKGROUND AND RATIONALE FOR AMENDMENT

The purpose of Protocol Amendment 1 is to revise the exclusion/inclusion criteria, revise the naming conventions for the treatment arms and clarify the IP storage condition requirements.

SUMMARY OF CHANGES

In the table below, the protocol text was amended by the following conventions:

- Deletions to the original text are indicated by ~~strike through~~ letters.
- Additions to amended text are indicated by **bold** letters.
- Replacements of wording in the amended text are indicated by ***bold and italicized*** letters.

Section	Reason for Amendment	Protocol Currently Reads	Amended Text
Throughout document	Administrative corrections made throughout document	N/A	N/A
1 SYNOPSIS **Dosage/Dose Regimen/ Instillation/ Application/Use:**	Treatment arm naming conventions revised	[…] Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms: 1. OCS-01 QD – 1 OCS-01 box for AM dosing and 1 placebo (vehicle) box for PM dosing 2. OCS-01 BID – 2 OCS-01 boxes (1 for AM and 1 for PM) 3. Placebo (vehicle) – 2 placebo (vehicle) boxes (1 for AM and 1 for PM). […]	[…] Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms: ***1. OCS-01 QD + Placebo (vehicle) QD*** ***2. OCS-01 BID*** ***3. Placebo (vehicle) BID*** […]
1 SYNOPSIS **Exclusion Criteria**	Revision to inclusion/ exclusion criteria	[…] 5. Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, and other pain medications),	[…] 5. Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, and other pain

		or immunomodulating agents, systemically or in either eye, and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through the duration of the study. Washout periods for medications prior to the day of cataract surgery are as follows: […] […] h. Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): 28 days; […]	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. Washout periods for medications prior to the day of cataract surgery are as follows: [...] [...] h. ***Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): all current or previous use of BPH medications excludes participation in this study.*** […]
1 SYNOPSIS **Exclusion Criteria**	Revision to inclusion/ exclusion criteria	[…] 8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). Subjects taking IOP-lowering medication must be on ≤ 2 IOP-lowering medications. Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]). […]	[…] 8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). ***Subjects taking IOP-lowering medication must not be on more than 1 IOP-lowering medication.*** Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]). […]
1 SYNOPSIS **Exclusion Criteria**	Revision to inclusion/ exclusion criteria	13. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in the study eye;	13. ***Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in either the fellow eye or the study eye;***

6 STUDY POPULATION 6.4 Exclusion Criteria	Revision to inclusion/ exclusion criteria	[…] 5. Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, and other pain medications), or immunomodulating agents, systemically or in either eye, and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through the duration of the study. Washout periods for medications prior to the day of cataract surgery are as follows: […] […] h. Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): 28 days; […]	[…] 5. ***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 history of use of medications for benign prostatic hyperplasia (BPH) from the washout period through the duration of the study.*** Washout periods for medications prior to the day of cataract surgery are as follows: […] […] ***h. Medications for BPH (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride): all current or previous use of BPH medications excludes participation in this study.*** […]
6 STUDY POPULATION 6.4 Exclusion Criteria	Revision to inclusion/ exclusion criteria	[…] 8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). Subjects taking IOP-lowering medication must be on ≤ 2 IOP-lowering medications. Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]). […]	[…] 8. Have an IOP ≤ 5 mmHg or ≥ 22 mmHg in either eye at Visit 1 (Day -1 to Day -28 [prior to surgery]). ***Subjects taking IOP-lowering medication must not be on more than 1 IOP-lowering medication.*** Prostaglandin analogs are not allowed within 4 weeks of Visit 2 (Day 1 [18 to 30 hours post-surgery]). […]

6 STUDY POPULATION 6.4 Exclusion Criteria	Revision to inclusion/ exclusion criteria	[…] 13. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in the study eye; […]	[…] 13. ***Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, or rubeosis iritis) in either the fellow eye or the study eye;*** […]
8 STUDY MATERIALS 8.1.2 Instructions for Use and Administration	Treatment arm naming conventions revised	[…] Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms: • OCS-01 QD – 1 OCS-01 box for AM dosing and 1 placebo (vehicle) box for PM dosing • OCS-01 BID – 2 OCS-01 boxes (1 for AM and 1 for PM) • Placebo (vehicle) – 2 placebo (vehicle) boxes (1 for AM and 1 for PM) […] […] For Visit 1, 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). […]	[…] Each subject will receive a master kit containing an AM dosing box and a PM dosing box. Each dosing box will contain 2 aluminum pouches with 10 single-use vials each. The master kit's contents will be as follows for subjects randomized to each of the respective treatment arms: • ***OCS-01 QD + Placebo (vehicle) QD*** • ***OCS-01 BID*** • ***Placebo (vehicle) BID*** […] […] ***For Visit 2, 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).*** […]
9 STUDY METHODS AND PROCEDURES 9.1.5 Methods for	Clarification regarding use of randomization number instead of subject number	[…] Each subject who qualifies for entry will be assigned a subject number and corresponding treatment according to the	[…] ***Each subject who qualifies for entry will be assigned a randomization number and corresponding treatment according to the***

<table>
<tr>
<td>Assignment to Treatment Groups:</td>
<td></td>
<td>randomization code. Study drug will be randomly assigned using a 1:1:1 assignment ratio, stratified by site, via an interactive response system. […]</td>
<td>randomization code. Study drug will be randomly assigned using a 1:1:1 assignment ratio, stratified by site, via an interactive response system. […]</td>
</tr>
<tr>
<td>9 STUDY METHODS AND PROCEDURES

9.2.1 Prohibited Medications/ Treatments</td>
<td>Revision to inclusion/ exclusion criteria</td>
<td>• […] Anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, and other pain medications), or immunomodulating agents, systemically or in either eye, and/or the use of medications for BPH, from the washout period through the duration of the study; […]

[…] Table 2: Non-allowed Medications and Washout Periods
<table>
<tr><th>Medication</th><th>Washout Period</th></tr>
<tr><td>Topical ocular steroids</td><td>14 days</td></tr>
<tr><td>Periocular injection of any corticosteroid solution</td><td>28 days</td></tr>
<tr><td>Intraocular treatment with a corticosteroid</td><td>56 days after implantation</td></tr>
<tr><td>Fluocinolone acetonide drug delivery systems</td><td>48 months after implantation</td></tr>
<tr><td>Intravitreal injection</td><td>95 days after injection</td></tr>
<tr><td>Systemic treatment with a corticosteroid including oral</td><td>14 days</td></tr>
<tr><td>Systemic or parenteral sustained/extende</td><td>180 days</td></tr>
</table>
</td>
<td>• […] 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; […]

[…] Table 3: Non-allowed Medications and Washout Periods
<table>
<tr><th>Medication</th><th>Washout Period</th></tr>
<tr><td>Topical ocular steroids</td><td>14 days</td></tr>
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<tr><td>Systemic treatment with</td><td>14 days</td></tr>
</table>
</td>
</tr>
</table>

		d release corticosteroid		a corticosteroid including oral	
		Topical ocular NSAIDs	7 days	Systemic or parenteral sustained/extended release corticosteroid	180 days
		Systemic analgesics/pain relievers (e.g. gabapentin, pregabalin, and opioids)	14 days	Topical ocular NSAIDs	7 days
		Systemic acetaminophen, NSAIDs, acetylsalicylic acid, or other anti-inflammatory agents	7 days	Systemic analgesics/pain relievers (e.g. gabapentin, pregabalin, and opioids)	14 days
		BPH medication (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride)	28 days	Systemic acetaminophen, NSAIDs, acetylsalicylic acid, or other anti-inflammatory agents	7 days
		Immunomodulating or immunosuppressive agents (e.g. cyclosporine, calcineurin inhibitors, antiproliferative agents, mTOR inhibitors, etc.)	56 days	BPH medication (e.g. alpha adrenergic blocking agents including tamsulosin, silodosin, alfuzosin, and finasteride)	***no current or historic use***
		Mast cell stabilizers or anti-histamines (e.g. β2-adrenergic agonists. cromoglicic acid, ketotifen, brompheniramine, cetirizine, diphenhydramine)	7 days	Immunomodulating or immunosuppressive agents (e.g. cyclosporine, calcineurin inhibitors, antiproliferative agents, mTOR inhibitors, etc.)	56 days
				Mast cell stabilizers or anti-histamines (e.g. β2-adrenergic agonists. cromoglicic acid, ketotifen, brompheniramine, cetirizine, diphenhydrami	7 days

			ne)
12.4 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug 12.4.2 Storage of Study Drug	Clarification on the IP storage condition requirements	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. […] […] Once dispensed to subjects, study drug should be stored at room temperature.	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. […] […] ***Once dispensed to subjects, study drug should be stored at ambient temperature.***

Appendix 4: Ora Approvals

Protocol Title:	A Randomized, Double-masked, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Two Doses of OCS-01 compared to Vehicle in the Treatment Inflammation and Pain Following Cataract Surgery
Protocol Number:	DX216
Protocol Date:	08Aug2019

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol.

DocuSigned by Dr. David Hollander

Signed: Dr. David Hollander | I approve this document 8/9/2019 9:27:42 AM PDT Date: 8/9/2019

GA23C6929D2A42D79ACABD19D58AD442

Name: David Hollander, M.D., M.B.A.
Title: Chief Medical Officer
Company: Ora, Inc.

DocuSigned by Aron Shapiro

Signed: | I approve this document 8/9/2019 9:02:23 AM PDT Date: 8/9/2019

Name: Aron Shapiro
Title: Sr. Vice President, Retina and OD&O
Company: Ora, Inc.

DocuSigned by Dale USNER

Signed: Dale USNER | I approve this document Date: 8/9/2019

41F8B523Z3EC424CA740A308E0A4DB77

Name: Dale Usner, Ph.D.
Title: Biostatistician
Company: SDC

DocuSigned by Robert Rapoza

Signed: Robert Rapoza | I approve this document 8/9/2019 9:41:56 AM PDT Date: 8/9/2019

Name: Robert Rapoza
Title: Director, Clinical Operations
Company: Ora, Inc.

DocuSigned by Amy Baggeroer

Signed: Amy Baggeroer | I approve this document 8/9/2019 8:57:10 AM PDT Date: 8/9/2019

Name: Amy Baggeroer
Title: Clinical Project Manager, OD&O
Company: Ora, Inc.

DocuSigned by Michelle Olsen

Signed: Michelle Olsen | I approve this document Date: 8/9/2019

Name: Michelle Olsen, Ph.D.
Title: Regulatory Writer
Company: Ora, Inc.

Appendix 5: Investigator's Signature

Protocol Title: A Randomized, Double-masked, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Two Doses of OCS-01 compared to Vehicle in the Treatment Inflammation and Pain Following Cataract Surgery
Protocol Number: DX216
Protocol Date: 08Aug2019

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 the Sponsor and its agents 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: