# STATISTICAL ANALYSIS PLAN

## A Randomized, Double-masked, Vehicle-controlled Study Evaluating the Efficacy and Safety of OCS-01 eyedrops compared to Vehicle in the Treatment of Inflammation and Pain Following Cataract Surgery

Sponsor: Oculis Operations Sàrl
EPFL Innovation Park
Building D
1015 Lausanne, Switzerland

Protocol Number: DX218

Author: [redacted]

Date: 13JUL2023

Version: 1.0

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**List of Abbreviations**

| Abbreviation | Definition |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| CI | Confidence Interval |
| CS | Clinically Significant |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| FAS | Full Analysis Set |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IOP | Intraocular Pressure |
| logMAR | Logarithm of the Minimum Angle of Resolution |
| IRT | Interactive Response Technology |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| mmHg | Millimeters of Mercury |
| NCS | Not Clinically Significant |
| NSAID | Non-steroidal Anti-inflammatory Drug |
| PDF | Portable Document Format |
| PP | Per Protocol |
| PT | Preferred Term |
| QD | *Quaque die* (Once per Day) |
| RTF | Rich Text Format |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDC | Statistics & Data Corporation |
| SDTM | Study Data Tabulation Model |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| TE-SAE | Treatment-Emergent Serious Adverse Event |
| VA | Visual Acuity |
| WHODrug | World Health Organization Drug Dictionary |

## 1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol DX218, Version 1.0 dated 10MAY2022.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

## 2. Study Objectives

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

### 2.1 Primary Efficacy Measures

The primary efficacy measures are the following, listed in hierarchical order:

- Absence of anterior chamber cells (i.e., score of “0”) at Visit 6 (
- Absence of pain (i.e., score of “0”) at Visit 4

### 2.3 Safety Measures

The primary safety measures include the following:

- Change from baseline in pin-hole visual acuity (VA) (without any other correction) as measured on the ETDRS chart
- Change from baseline of intraocular pressure (IOP)
- Change in endothelial cell density assessed at Visit 8

- Adverse event (AE) rates

Additional safety measures described in the protocol include:

- Slit lamp biomicroscopy parameters;
- Dilated indirect ophthalmoscopy parameters;
- Endothelial cell parameters, including density, %hexagonal, and %CV.

[redacted]

[redacted]

## 3. Study Design and Procedures

### 3.1 General Study Design

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

Subjects will be randomized 1:1 to receive OCS-01 or placebo (vehicle) QD. Subjects will dose 1 drop in the study eye QD for 14 days, beginning 1 day post-surgery in the operated eye. The study will last 91-125 days, including screening and a follow-up visit at Visit 8 (Day 90) for endothelial cell density assessment.

Study visits will be followed by the expected study day corresponding to the visit in parentheses in all tables and listings to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit:

**Table 1.** Study Visit Windows

| Scheduled Visit | Planned Study Day | Visit Window |
|---|---|---|
| Visit 1 | Screening/Baseline Evaluations | -28 to -1 days prior to surgery |
| Visit 2 | Day 1 | 18 to 30 hours post-surgery |
| Visit 3 | Day 2 | ± 0 days |
| Visit 4 | Day 4 | ± 1 day |
| Visit 5 | Day 8 | ± 1 day |
| Visit 6 | Day 15 | ± 2 days |

| Scheduled Visit | Planned Study Day | Visit Window |
|---|---|---|
| Visit 7 | Day 22 | ± 2 days |
| Visit 8 | Day 90 | ± 7 days |

### 3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Table 2.

**Table 2.** Schedule of Visits and Assessments

| Study Parameter | Visit 1 ( -28 to -1 Day(s) Prior to Surgery) | Visit 2 (Day 1, 18-30hrs 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) | Visit 8 (Day 90 + 7) |
| Informed Consent / HIPAA | X | | | | | | | |
| Demographic Data | X | | | | | | | |
| Medical and Medication History | X | | | | | | | |
| Urine pregnancy Test | X | | | | | | X | |
| Review Inclusion / ExclusionCriteria | 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 ofthe 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 andDosing Diary | | X | | | | | | |
| AE Query | | X | | X | X | X | X | X |
| Endothelial Cell Density | X | | | | | | | X |
| Exit from Study | | | | | | | | X |

AE = Adverse Event; HIPAA = Health Insurance Portability and Accountability Act
Study eye only: Ocular Inflammation Assessment ofthe Anterior Chamber Cell and Flare; Ocular Pain

## 4. Study Treatments

Study eyes will be treated with either OCS-01 (dexamethasone Ophthalmic Suspension, 1.5% (15 mg/mL) QD or placebo (vehicle) QD ophthalmic suspension during the treatment period of the study.

### 4.1 Method of Assigning Subjects to Treatment Groups

At Visit 2 [redacted] each subject who signed an informed consent form at Visit 1 [redacted] 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). No subjects should be rescreened except in special circumstances in which sites should obtain approval to re-screen. 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. Subjects will be randomly assigned to either OCS-01 QD or placebo (vehicle) QD using a 1:1 assignment ratio, stratified by site, via an interactive response system.

Randomization numbers will be assigned in sequential order at each site beginning with 1001 and will follow the two digit site number (e.g., randomized subject 1005 at Site 99 will have Randomization Number 99-1005). Sequentially numbered study drug kits will be provided to each investigational site, in accordance with the site-specific randomized study drug kit list, which consists of sequential 4-digit kit ID numbers. The interactive response system (IRT) will be utilized to assign the randomized subject the lowest 4-digit study drug kit number available at their investigative site associated with randomized treatment, in a masked manner to the site study team. If a randomized subject is discontinued from the study for any reason, their randomization number and randomized study drug kit number will not be reassigned.

The subject number will be used to identify subjects in all datasets and listings for this study.

### 4.2 Masking and Unmasking

An independent, unmasked biostatistician who is not otherwise involved in the trial will generate the complete randomized study drug kit list. The subject, Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

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 the protocol. More details about the emergency unmasking process can be found in the IRT Plan as a separate document.

[redacted]

## 6. Data Preparation

### 6.1 Input Data

Study data from source documents will be entered into the electronic Case Report Forms (eCRF) supplied by Statistics & Data Corporation (SDC) using the electronic data capture (EDC) system iMedNet™ v1.221.2 or higher. Additional details about the EDC system can be found in the Data Management Plan as a separate document.

In addition, the following study data which is not captured directly within the iMedNet system but is obtained from external vendors will also be included for analysis. These data sources are described in detail in data transfer agreements developed between data management and the respective external laboratory or reading center:

- Endothelial cell density

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate and all prerequisites for database lock have been met, including availability of all external data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been classified (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

Any changes to the database after data have been locked or after unmasking can only be made with the approval of the Sponsor in consultation with SDC and per SDC standard operating procedures (SOPs). Adjustments to or repeats of analyses will be conducted as appropriate and in consultation with Sponsor.

### 6.2 Output Data

Data from iMedNet and external data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM version 1.7 model and will be implemented using the SDTM Implementation Guide version 3.3 and the most recent version of SDTM Controlled Terminology at the time of programming start. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21 version 4.02. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

## 7. Analysis Populations

### 7.1 Full Analysis Set

The full analysis set (FAS) will consist of all randomized subjects, analyzing subjects under the treatment to which they were randomized.

### 7.2 Per Protocol

The per protocol (PP) population is a subset of the FAS and includes subjects who remain in the study through Visit 6 [redacted]) with no major protocol violations that would affect the assessment of the primary efficacy endpoints of the study, analyzing subjects under the treatment received. Major protocol violations will be identified prior to unmasking treatment.

### 7.3 Safety

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.

## 8. General Statistical Considerations

### 8.1 Unit of Analysis

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.

### 8.2 Missing or Inconclusive Data Handling

Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.

- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

The strategy for handling intercurrent events from Section 2.5 will be utilized for imputing missing data during the primary analyses of the primary efficacy variables.

### 8.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study medication. Change from baseline will be calculated as, Follow-up Visit – Baseline Visit.

### 8.4 Data Analysis Conventions

All data analyses will be performed by SDC after the study is completed and the database has been locked and released for unmasking, as described in Section 6.2. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values.

Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment groups and placebo (vehicle) will be calculated as active minus placebo (vehicle) and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Unless otherwise specified, tabular summaries will be presented by treatment group and, where appropriate, visit. Listings will be based on all randomized subjects, unless specified otherwise, and sorted by subject number, visit, and parameter as applicable.

[redacted]

## 9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers of subjects who were screened, screen failures, and randomized, by treatment group and overall for all screened subjects. The numbers and percentages of subjects who were included in the FAS, Per-Protocol, and Safety analysis populations as well as who completed the study and discontinued from the study will be presented by treatment group and overall for all randomized subjects. Subjects who are not discontinued from the study will be considered study completers. The reasons for discontinuation will be summarized by treatment group and overall for all discontinued subjects. Percentages will be calculated using discontinued subjects as the denominator. The reasons for study discontinuation that will be summarized include: adverse event (AE), lost to follow-up, protocol violation, study terminated by sponsor, withdrawal by subject, lack of efficacy, and other. The number and percentage of subjects with any deviation, major deviation, and minor deviation will be summarized by treatment group and overall for all randomized subjects.

The reasons for screen failure (i.e., subject did not meet eligibility criteria) will be displayed with the percentages calculated using total number of screen failures as the denominator.

Details of the study randomization, including study site, randomization date, randomized treatment, and actual treatment, will be provided within a subject listing.

A subject listing for subject disposition will include study completion or discontinuation date, study completion status, and the primary reason for study discontinuation (if applicable).

For protocol deviations, a subject listing will be provided that includes the date of the deviation, visit at which the deviation occurred, the deviation category, the deviation description, if the deviation was related to COVID-19, and the classification of whether the deviation was judged to be major or minor in a masked review prior to database lock.

A subject listing of inclusion/exclusion criteria will include whether if all eligibility criteria were met, the specific eligibility criterion which was not met (if applicable), and the visit at which the eligibility criterion was not met (if applicable).

A subject listing of analysis population inclusion will include whether criteria were met for inclusion in the FAS, Per-Protocol population, and Safety population.

## 10. Demographic and Pretreatment Variables

### 10.1 Demographic Variables

The demographic variables collected in this study include age, gender, ethnicity, race, and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Iris color will be summarized at the eye level. Demographic variables will be summarized for the FAS.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years.

The number and percentage of subjects will be presented, overall and by treatment, for age category, gender, ethnicity, race, iris color, and study site.

A subject listing that includes all demographic variables will be provided.

## 11. Medical History and Concomitant Medications

### 11.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

Ocular medical history will be summarized using discrete summary statistics and presented by treatment group and overall separately for study eyes and fellow eyes by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. Non-ocular medical history will be similarly summarized at the subject level. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs will be sorted in alphabetical order, and PTs within an SOC will be sorted in order of descending frequency across all subjects.

Listings of medical history will be generated separately for ocular and non-ocular data.

### 11.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global B3 01Mar2022 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next highest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Prior medications are defined as those medications with an end date before the date of initiation of study drug administration. Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Concomitant medications will be summarized using the FAS. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per

ATC text. At each level of subject summarization, a subject will be counted once if they report one or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes and preferred names within an ATC class will be sorted in alphabetical order.

All medications utilized for lowering IOP or for rescue will be noted in the subject listing of prior and concomitant medications. IOP-lowering medications and rescue medications are each a subset of medications where the investigator has indicated on the eCRF that the medication was used to lower IOP or rescue. Rescue medications and criteria are described in Section 4.3.

The number and percentage of subjects initiating IOP-lowering medications will be presented by treatment group for each post-baseline visit as well as across all post-baseline visits for the Safety population.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular data. A separate listing will be generated for IOP-lowering medications.

### 11.3 IOP-Lowering Procedures

All IOP-lowering procedures will be coded using MedDRA Version 25.0 and presented in a subject listing.

## 12. Dosing Compliance and Treatment Exposure

### 12.1 Dosing Compliance

Details of individual administrations of study medication done at home by subjects are not captured within the clinical database, therefore dosing compliance will not be summarized.

### 12.2 Treatment Exposure

The number and percent of subjects receiving at least one dose of study medication (i.e., Safety population) will be summarized as part of subject disposition.

Although not captured directly on the eCRF, additional variables related to study drug administration will also be derived for summarization:

- Study drug interruption (yes/no), where interruptions will be identified via presence of a TEAE where action taken with study drug was marked as “drug interrupted” or a protocol deviation indicating study drug was interrupted.
- Premature discontinuation of study drug (yes/no), where discontinuations will be identified via presence of a TEAE where action taken with study drug was marked as “drug withdrawn” or a protocol deviation indicating study drug was prematurely discontinued. Subjects who discontinue the study prior to Visit 6 ([redacted]) will also be reviewed to verify if study drug was prematurely discontinued or not.
- Study drug completion, defined as those subjects where premature discontinuation of study drug is not equal to “yes”.

A masked data review will be conducted prior to database lock and unmasking to identify any other cases of study drug interruption or premature discontinuation of study drug which are known to have occurred,

but are not identified through the criteria above. The classifications from this final review will be used for analysis.

The number and percentage of subjects with study drug interruption, premature discontinuation of study drug, and study drug completion will be presented by treatment group.

Subject data listings will be generated to present details of study drug assignment, study drug replacement, as well as first instillation of study medication performed in-clinic on Visit 2 [redacted] Details about study drug accountability will also be listed.

## 13. Efficacy Analyses

### 13.1 Primary Analysis

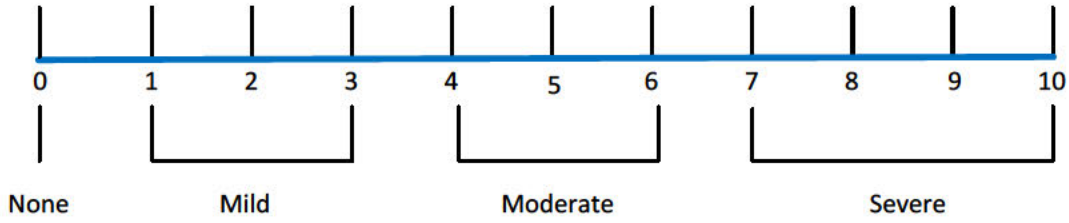
The primary efficacy variables are the following:

- Absence of anterior chamber cells, defined as a score of "0," at Visit 6 ([redacted]
- Absence of pain, defined as a score of "0," at Visit 4 ([redacted]

The anterior chamber cell score for study eyes will be recorded as well as the anterior chamber cell count if the actual number of cells observed is 10 cells or fewer (only white blood cells should be counted; red blood cells and pigment cells should not be counted). The assessment of anterior chamber cells will be performed prior to any other procedure that requires dilation of the pupil, such as dilated indirect ophthalmoscopy, to avoid cells from being introduced into the anterior chamber. The 5-unit grading scale for anterior chamber cells is from 0 to 4 where 0 = 0 cells, 1 = 1 to 10 cells, 2 = 11 to 25 cells, 3 = 26 to 50 cells, and 4 = >50 cells. Anterior chamber cell status will be classified as "Absent" for a grade of '0' or "Present" for a grade of 1 to 4.

Ocular pain in study eyes will be assessed by the subject utilizing a pain rating number scale graded from 0 to 10. Subjects will assess the level of pain they are experiencing in the study eye at the time of the assessment. The examiner will ask the subject the following question in reference to the below figure and will record the number selected by the subject on the appropriate eCRF:

*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.*




Ocular pain status will be classified as "Absent" for a grade of '0' or "Present" for a grade of 1 to 10.

For the primary and sensitivity analyses of absence of anterior chamber cells and absence of ocular pain, discrete summary statistics and two-sided 95% asymptotic normal CIs will be presented by treatment group for each primary efficacy variable. The difference in treatment group absence rates (OCS-01 minus placebo [vehicle]) will also be provided for each primary efficacy variable. Anterior chamber cells, including cell counts, and ocular pain scores from the FAS will be presented by visit in subject listings.

[redacted]

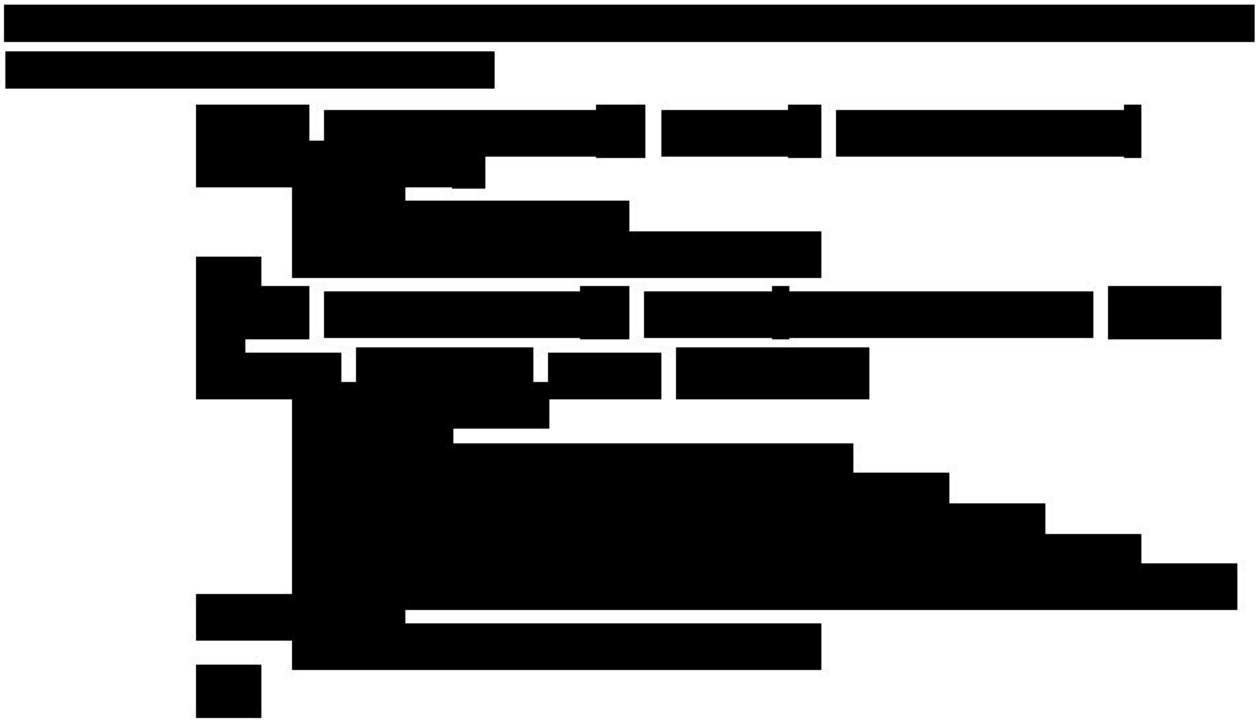
Sections 13.1.1 to 13.1.5 describe the sensitivity analyses for the handling of intercurrent events to be performed for the primary efficacy variables.

### 13.1.1 SENSITIVITY ANALYSIS I

The handling of intercurrent events will be updated as follows:

- Receipt of rescue medication: observed data for visits after receipt of rescue medication will be singly imputed as failure [hypothetical strategy].
- Missing data for any reason: missing data will be multiply imputed from the placebo (vehicle) treatment arm assuming missingness not at random [hypothetical strategy].

[redacted]



[redacted]

### 13.1.2 SENSITIVITY ANALYSIS II

The intercurrent event will be updated as follows:

- Receipt of rescue medication: observed data for visits after receipt of rescue medication will be singly imputed as failure [hypothetical strategy].
- Missing data for any reason: missing data will be multiply imputed using randomized treatment-based MCMC methodology [hypothetical strategy].

[redacted]

[redacted]

#### 13.1.3 SENSITIVITY ANALYSIS III

The primary efficacy analysis will be performed using the PP population with observed data only. Treatment comparisons will be made using Pearson's chi-squared test. If any of the expected cell counts are less than five, an exact 95% CI for the difference in proportions and Fisher's exact test will be used instead.

#### 13.1.4 SENSITIVITY ANALYSIS IV

The primary efficacy analysis will be performed using the FAS with observed data only. Treatment comparisons will be made using Pearson's chi-squared test. If any of the expected cell counts are less than five, an exact 95% CI for the difference in proportions and Fisher's exact test will be used instead.

#### 13.1.5 SENSITIVITY ANALYSIS V

The handling of intercurrent events will be updated as follows:

- Receipt of rescue medication: observed data for visits after receipt of rescue medication will be singly imputed as failure [hypothetical strategy].
- Missing data for any reason: missing data will be singly imputed as failure [hypothetical strategy].

Treatment comparisons will be made using Pearson's chi-squared test. If any of the expected cell counts are less than five, an exact 95% CI for the difference in proportions and Fisher's exact test will be used instead.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

## 14. Safety Analyses

All safety analyses will be conducted using the Safety population.

### 14.1 Adverse Events

An Adverse Event (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. All AEs will be coded using MedDRA Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated.

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 them 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.

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.

Only suspected TEAEs are considered treatment-related TEAEs.

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.

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
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

TEAEs with a missing relationship to study drug will be counted as suspected treatment-related TEAEs for all summaries of suspected treatment-related TEAEs. All summaries of expected and unexpected TEAEs will include only suspected treatment-related TEAEs. TEAEs with missing severities will be counted as severe for all summaries by maximum severity.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one TEAE by treatment group. This summary will also include breakdowns of TEAEs further categorized as treatment-emergent serious adverse events (TE-SAEs), suspected treatment-related TEAEs, expected TEAEs, unexpected TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to death, and TEAEs by maximum severity. Separate summaries will be created for all events, ocular events in study eyes, ocular events in fellow eyes, and non-ocular events.

TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT for the following categories of TEAEs:

- Ocular TEAEs by SOC and PT
- Non-Ocular TEAEs by SOC and PT
- Ocular TE-SAEs by SOC and PT
- Non-Ocular TE-SAEs by SOC and PT
- Suspected Treatment-related Ocular TEAEs by SOC and PT
- Suspected Treatment-related Non-Ocular TEAEs by SOC and PT
- Expected Ocular TEAEs by SOC and PT

- Expected Non-Ocular TEAEs by SOC and PT
- Unexpected Ocular TEAEs by SOC and PT
- Unexpected Non-Ocular TEAEs by SOC and PT
- Ocular TEAEs by SOC, PT, and Maximum Severity
- Non-Ocular TEAEs by SOC, PT, and Maximum Severity

Ocular TEAEs will be summarized at the subject level for study and fellow eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. To count the number of subjects with any TEAEs by maximum severity, if a subject has multiple TEAEs coded to the same SOC or PT within an SOC, the subject will be counted once under the maximum severity for that SOC or PT. In the summary, SOCs will be listed in ascending alphabetical order,. and PTs within each SOC will be listed in order of descending frequency for the OCS-01 treatment group.

All AEs will be presented in a subject listing. In addition, all SAEs and AEs leading to study drug discontinuation will be presented in separate listings.

### 14.2 Pin-Hole Visual Acuity

Pin-hole visual acuity (VA) is assessed at each visit using an Early Treatment Diabetic Retinography Study (ETDRS) chart. Pin-hole VA testing will be done with a pin-hole occluder at a viewing distance of 4 meters at the beginning of each study visit (i.e., prior to slit lamp examination). If less than 20 letters are read at 4 meters the subject will perform the assessment again at a viewing distance of 1 meter. If at least 20 letters are read correctly at 4 meters, pin-hole VA is computed as 30 plus the number of letters correct at 4 meters. If less than 20 letters are read correctly at 4 meters, pin-hole VA is computed as the number of letters correct at 4 meters plus the number of letters correct at 1 meter.

For presentations in tables and listings, pin-hole VA will be converted from number of letters correct to a logarithm of the minimum angle of resolution (logMAR) score using the following formula:

logMAR VA = 1.70 – 0.02*(Number of letters correct)

Summaries of pin-hole VA will be based on study eyes.

Pin-hole VA actual values at Visits 1, 2, 4, 5, 6, and 7 ([redacted] and change from baseline at Visits 4, 5, 6, and 7 ([redacted]) will be summarized by visit and treatment group using continuous summary statistics.

Worsening of pin-hole visual acuity by at least 2 lines (10 letters) from the ETDRS scale from the previous visit at Visits 4, 5, 6, and 7 ([redacted]) will be summarized by visit and treatment group using discrete summary statistics.

A subject listing of pinhole visual acuity by visit will be presented.

### 14.3 Intraocular Pressure (IOP)

Intraocular pressure (IOP) in mmHg will be measured using a Goldmann application tonometer. Both eyes will be tested, with the right eye preceding the left eye. Two IOP measurements will initially be collected per eye. If the two IOP measurements differ by 2 mmHg or less, the mean of the two IOP measurements will be calculated and recorded as the final IOP measurement. If the two IOP measurements differ by more than 2 mmHg, a third (consecutive) IOP measurement will be collected and the median IOP measurement will be recorded as the final IOP measurement. For a given subject for a given eye, the dataset will have either the mean or median of the IOP measurements, but not both. The available measure will be used as the analysis value for IOP listings, summaries, and analyses.

Summaries of IOP will be based on study eyes.

IOP actual values at Visits 1, 4, 5, 6, and 7 ( ) and change from baseline at Visits 4, 5, 6, and 7 ( ) will be summarized by visit and treatment group using continuous summary statistics.

Eyes with IOP of 30 mmHg or more at Visits 1, 4, 5, 6, and 7 ( ) as well as eyes with an increase from baseline in IOP of 10 mmHg or more at Visits 4, 5, 6, and 7 (D ) will be summarized by visit and treatment group using discrete summary statistics.

A subject listing of IOP by visit will be presented.

### 14.4 Endothelial Cell Parameters

Endothelial cell density will be assessed by specular microscopy. The image of the corneal endothelium will be obtained when the instrument captures the light reflected from the optical interface between the corneal endothelium and the aqueous humor. Multiple microphotographs will be performed for each eye, after which the device will perform an automatic analysis of the selected area and calculate the average number of cells per 1 $mm^2$. The microscope will then provide a histogram determining the endothelial cell population size and specify the minimum, maximum, and average cell size of the selected area. The pleomorphism of endothelial cells will also be evaluated, indicating the percentage of hexagonality.

Summaries of endothelial cell parameters will be based on study eyes.

Endothelial cell parameters (density, %hexagonal, and %CV) actual values at Visits 1 and 8 ( and change from baseline at Visit 8 will be summarized by visit and treatment group using continuous summary statistics. The p-values from two-sample t-tests comparing changes from baseline in endothelial cell density parameters between treatment groups will also be presented.

A subject listing of endothelial cell parameters by visit will be presented.

### 14.5 Dilated Indirect Ophthalmoscopy

A dilated indirect ophthalmoscopic examination of the vitreous, retina, macula, choroid, optic nerve, and lens will be performed at Visits 1 and 7 ([redacted]). The results for each region will be graded as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS).

Summaries of dilated ophthalmoscopy parameters will be based on study eyes.

The results for each region at Visits 1 and 7 ([redacted]) will be summarized by visit and treatment group using discrete summary statistics. Percentages will be based on the number of subjects in each treatment group with responses.

Shifts from baseline at Visit 7 ([redacted] for the dilated ophthalmoscopy parameters will be summarized by treatment group using discrete summary statistics. Percentages will be based on the number of subjects in each treatment group with responses at both Visits 1 and 7 ([redacted]

A subject listing of the dilated ophthalmoscopy parameters will also be produced.

### 14.6 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the eyelid, conjunctiva, cornea, anterior chamber, iris, and lens will be performed at each visit. The results will be graded as normal, abnormal NCS, or abnormal CS.

Summaries of slit-lamp biomicroscopy parameters will be based on study eyes.

The results for each region at Visits 1, 4, 5, 6, and 7 ([redacted]) will be summarized by visit and treatment group using discrete summary statistics. Percentages will be based on the number of subjects in each treatment group with responses.

Shifts from baseline at Visits 4, 5, 6, and 7 ([redacted]) for the dilated ophthalmoscopy parameters will be summarized by visit and treatment group using discrete summary statistics. Percentages for each visit will be based on the number of subjects in each treatment group with responses at both Visit 1 and the respective visit.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

### 14.7 Clinical Laboratory Data

Results from the urine pregnancy test at Visits 1 and 7 [redacted]) will be provided in a subject listing.

## 15. Interim Analyses

Interim analyses will not be performed for this study.

## 16. Changes from Protocol-Stated Analyses

The SAP includes the following changes from the protocol-stated analyses:

1. After discussion with the sponsor, the definition of the Per Protocol population in the SAP has omitted the parenthetical "(or who discontinue due to adverse event or lack of efficacy or receive rescue medication prior to Visit 6 [Day 15])" which is present in the Per Protocol population definition from the protocol version 1.0.

## 17. References


1. *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 05 February 1998.
2. *ICH Harmonised Tripartite Guideline: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials E9(R1)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 20 November 2019.
3. *ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 30 November 1995.


## 18. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

## 19. Tables

Tables that will be included in the topline delivery are shown in boldface font.

| Table Number | Title | Population |
|---|---|---|
| **Table 14.1.1.1** | **Subject Disposition** | |
| Table 14.1.1.2 | Reasons for Screen Failures | Screen Failed Subjects |
| **Table 14.1.2** | **Demographics** | **Full Analysis Set** |
| Table 14.1.3.1 | Ocular Medical History | Safety Population |
| Table 14.1.3.2 | Non-Ocular Medical History | Safety Population |
| Table 14.1.4.1 | Ocular Concomitant Medications | Full Analysis Set |
| Table 14.1.4.2 | Non-Ocular Concomitant Medications | Full Analysis Set |
| Table 14.1.4.3 | Post-Baseline IOP-Lowering Medications by Visit | Safety Population |
| **Table 14.2.1.1.1** | **Absence of Anterior Chamber Cells at Visit 6 (Day 15) in Study Eyes - Primary Analysis** | **Full Analysis Set** |
| Table 14.2.1.1.2 | Absence of Anterior Chamber Cells at Visit 6 (Day 15) - Sensitivity Analysis I | Full Analysis Set |
| Table 14.2.1.1.3 | Absence of Anterior Chamber Cells at Visit 6 (Day 15) - Sensitivity Analysis II | Full Analysis Set |

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|---|---|---|
| **Table 14.2.1.1.4** | **Absence of Anterior Chamber Cells at Visit 6 (Day 15) - Sensitivity Analysis III** | **Per Protocol Population** |
| Table 14.2.1.1.5 | Absence of Anterior Chamber Cells at Visit 6 (Day 15) - Sensitivity Analysis IV | Full Analysis Set |
| Table 14.2.1.1.6 | Absence of Anterior Chamber Cells at Visit 6 (Day 15) - Sensitivity Analysis V | Full Analysis Set |
| **Table 14.2.1.2.1** | **Absence of Ocular Pain at Visit 4 (Day 4) - Primary Analysis** | **Full Analysis Set** |
| Table 14.2.1.2.2 | Absence of Ocular Pain at Visit 4 (Day 4) - Sensitivity Analysis I | Full Analysis Set |
| Table 14.2.1.2.3 | Absence of Ocular Pain at Visit 4 (Day 4) - Sensitivity Analysis II | Full Analysis Set |
| **Table 14.2.1.2.4** | **Absence of Ocular Pain at Visit 4 (Day 4) - Sensitivity Analysis III** | **Per Protocol Population** |
| Table 14.2.1.2.5 | Absence of Ocular Pain at Visit 4 (Day 4) - Sensitivity Analysis IV | Full Analysis Set |
| Table 14.2.1.2.6 | Absence of Ocular Pain at Visit 4 (Day 4) - Sensitivity Analysis V | Full Analysis Set |
| [redacted] | [redacted] | [redacted] |
| **Table 14.3.1.1** | **Overall Summary of Treatment-Emergent Adverse Events** | **Safety Population** |
| **Table 14.3.1.2.1** | **Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term** | **Safety Population** |
| Table 14.3.1.2.2 | Non-Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.3.1 | Ocular TE-SAEs by System Organ Class and Preferred Term | Safety Population |

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|---|---|---|
| Table 14.3.1.3.2 | Non-Ocular TE-SAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.4.1 | Suspected Treatment-Related Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.4.2 | Suspected Treatment-Related Non-Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.5.1 | Expected Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.5.2 | Expected Non-Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.6.1 | Unexpected Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.6.2 | Unexpected Non-Ocular TEAEs by System Organ Class and Preferred Term | Safety Population |
| Table 14.3.1.7.1 | Ocular TEAEs by System Organ Class, Preferred Term, and Maximum Severity | Safety Population |
| Table 14.3.1.7.2 | Non-Ocular TEAEs by System Organ Class, Preferred Term and Maximum Severity | Safety Population |
| Table 14.3.2 | Pin-Hole Visual Acuity (logMAR) in Study Eyes by Visit | Safety Population |
| **Table 14.3.3** | **Intraocular Pressure in Study Eyes by Visit** | **Safety Population** |
| **Table 14.3.4** | **Endothelial Cell Density in Study Eyes by Visit** | **Safety Population** |
| Table 14.3.5 | Dilated Indirect Ophthalmoscopy in Study Eyes by Visit | Safety Population |
| Table 14.3.6 | Slit Lamp Biomicroscopy in Study Eyes by Visit | Safety Population |
| Table 14.3.7 | Treatment Exposure | Safety Population |

**20. Listings**

| Listing Number | Title | Population |
|---|---|---|
| Listing 16.1.7 | Randomization Schedule | All Randomized Subjects |
| Listing 16.2.1.1 | Subject Disposition | All Randomized Subjects |
| Listing 16.2.2.1 | Protocol Deviations | All Randomized Subjects |
| Listing 16.2.2.2 | Inclusion/Exclusion Criteria Violations | All Enrolled Subjects |
| Listing 16.2.3 | Population Inclusion | All Enrolled Subjects |
| Listing 16.2.4.1 | Demographics | All Randomized Subjects |
| Listing 16.2.4.2.1 | Ocular Medical History | All Randomized Subjects |
| Listing 16.2.4.2.2 | Non-Ocular Medical History | All Randomized Subjects |
| Listing 16.2.4.3.1 | Prior and Concomitant Ocular Medications | All Randomized Subjects |
| Listing 16.2.4.3.2 | Prior and Concomitant Non-Ocular Medications | All Randomized Subjects |

| | | |
|---|---|---|
| Listing 16.2.4.3.3 | Prior and Concomitant IOP Lowering Medications | All Randomized Subjects |
| Listing 16.2.4.4 | IOP Lowering Procedures | All Randomized Subjects |
| Listing 16.2.4.5 | Cataract Surgery | All Randomized Subjects |
| Listing 16.2.5.1 | Study Drug Administration | All Randomized Subjects |
| Listing 16.2.5.2 | Study Drug Accountability | All Randomized Subjects |
| Listing 16.2.6.1 | Anterior Chamber Cells and Flare | All Randomized Subjects |
| Listing 16.2.6.2 | Ocular Pain | All Randomized Subjects |
| Listing 16.2.7.1 | Adverse Events | All Randomized Subjects |
| Listing 16.2.7.2 | Serious Adverse Events | All Randomized Subjects |
| Listing 16.2.7.3 | Adverse Events Leading to Study Drug Discontinuation | All Randomized Subjects |
| Listing 16.2.8 | Urine Pregnancy Test - Subjects of Childbearing Potential | Subjects of Childbearing Potential |
| Listing 16.2.9.1 | Pin-Hole Visual Acuity | All Randomized Subjects |
| Listing 16.2.9.2 | Intraocular Pressure | All Randomized Subjects |
| Listing 16.2.9.3 | Endothelial Cell Density | All Randomized Subjects |
| Listing 16.2.9.4 | Dilated Indirect Ophthalmoscopy | All Randomized Subjects |
| Listing 16.2.9.5 | Slit Lamp Biomicroscopy | All Randomized Subjects |