CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

A Phase 3, multicenter, randomized, double-masked clinical trial to assess the efficacy and safety of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo in the treatment of inflammation and pain associated with cataract surgery

CLOSE-2 study

Sponsor Study Code: CLOBOF3-16IA02

[redacted]

Sponsor	Laboratorios Salvat, S.A.
Product/Compound/Device	Clobetasol propionate ophthalmic nanoemulsion 0.05% (SVT-15473)
Phase of the study	3
Author	[redacted]
Company	[redacted]
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Version	Final 2 **Date** 25-MAY-2021

[redacted]

SIGNATURES

Sponsor Study Code: CLOBOF3-16IA02

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Company Laboratorios Salvat, S.A.

Signature: _____ Date/time: _____

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
CSR	Clinical Study Protocol
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model of Repeated Measures
NSAID	Non-Steroidal Anti-Inflammatory Drug
PP	Per Protocol
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
QID	Four times a day (Quater In Die)
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
STEAE	Serious Treatment-Emergent Adverse Event
SUN	Standardization of Uveitis Nomenclature
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CSP) Version 2.0 FINAL Amendment 1 dated February 26, 2020.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on ocular inflammation associated with cataract surgery after one week of treatment.

2.2 Secondary Objectives

Key secondary objective

Efficacy:

- To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on eye pain associated with cataract surgery after one week of treatment.

Other secondary objectives

Efficacy:

- To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on ocular inflammation associated with cataract surgery
- To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on eye pain and on eye discomfort associated with cataract surgery

Safety:

- To evaluate the safety and tolerability of clobetasol propionate ophthalmic nanoemulsion 0.05%

3 ENDPOINTS

3.1 Primary Efficacy Endpoint

- Proportion of patients with anterior chamber cell grade of "0" (absence of cells) compared to placebo at Day 8.

Anterior chamber cell grade will be assessed by the investigator during slit-lamp examination and will be graded on an adapted 6-point scale proposed by the Standardization of Uveitis Nomenclature (SUN) working group (Table 1).

Table 1. Grading scheme for anterior chamber cells

Grade	Cells in field*
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

*Field size is a 1mm by 1 mm slit beam

3.2 Secondary Efficacy Endpoints

Key secondary efficacy endpoint

- Proportion of patients with VAS pain score of "0" (no eye pain) compared to placebo at Day 8.

Eye pain score will be assessed by the patient before any ocular examination and will be scored by ticking on a continuous scale comprised of a 10 cm horizontal line anchored by two verbal descriptions: "no eye pain" (score of 0) and "worst imaginable eye pain" (score of 10).

- Proportion of patients with anterior chamber cell grade of "0" compared to placebo at Day 3, Day 15 and Day 29.

- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber cell grades.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber flare grades.
- Proportion of patients with anterior chamber cell grade of "≤0.5+" and flare grade of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29.
- Proportion of patients with anterior chamber cell grade of "≤1+" compared to placebo at Day 3, Day 8, Day 15 and Day 29.
- Proportion of patients with anterior chamber cell grade of "0" and flare grade of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29.
- Frequency of different signs of ocular inflammation compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different signs of ocular inflammation.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of signs of ocular inflammation.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the visual analog scale (VAS) photophobia score.
- Change from Baseline to Day 8, Day 15 and Day 29 compared to placebo in Snellen best-corrected visual acuity (BCVA) score.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the VAS pain score.
- Proportion of patients with VAS pain of "0" compared to placebo at Day 3, Day 15 and Day 29.
- Change from baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different discomfort grades.
- Proportion of patients with no discomfort ("None") compared to placebo at Day 3, Day 8, Day 15 and Day 29.
- Change over time in the VAS pain score reported in the patients' diaries compared to placebo.

See previous section 3.1 for anterior chamber cell grade and key secondary efficacy endpoint of this section for eye pain VAS score.

- **Anterior chamber cell flare** will be assessed by the investigator during slit-lamp examination and will be graded on a 5-point scale proposed by SUN working group.

Table 2. The SUN working group grading scheme for anterior chamber flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)

4+	Intense (fibrin or plastic aqueous)

- **Signs of ocular inflammation** (chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, keratic precipitates) will be assessed by the investigator during slit-lamp examination. Additionally, the severity of these signs of ocular inflammation will be assessed.

Table 3. Signs of ocular inflammation. Chemosis, bulbar conjunctival injection, ciliary injection, corneal edema and keratic precipitates.

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

Other: The severity of any other sign of ocular inflammation encountered by the investigators (e.g. hypopion, anterior chamber fibrinoid reaction, miosis, papilar or follicular conjunctival reaction, corneal neovascularization) will not be analyzed. They will only be shown in the listings.

- Monocular visual acuity will be completed with the patient's best correction vision in place using the standardized visual acuity measurement **Snellen** Test.

- **The eye discomfort** will be assessed by using the following categorical scale (Table 4)

Table 4. Eye discomfort

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

- The photophobia VAS is a single-item continuous scale comprised of a 10 cm horizontal line anchored by two verbal descriptors, one for each symptom extreme. For photophobia intensity, the scale is anchored by "no photophobia" (score of 0) and "worst imaginable photophobia" (score of 10 cm). The photophobia VAS is completed by the patient:

3.3 Secondary Safety Endpoints

- Number, frequency and severity of adverse events (AEs) up to Day 29.
- Number, frequency and severity of serious AEs (SAEs) up to Day 29.
- Proportion of patients discontinuing the study due to AEs.
- Proportion of patients discontinuing the study due to lack of efficacy.
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in intraocular pressure (IOP).
- Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in physical and eye examination parameters and vital signs.
- Use of concomitant medications up to Day 29

The IOP will be assessed in both eyes using the Goldmann applanation tonometry method (for details see Appendix 3 of CSP) .

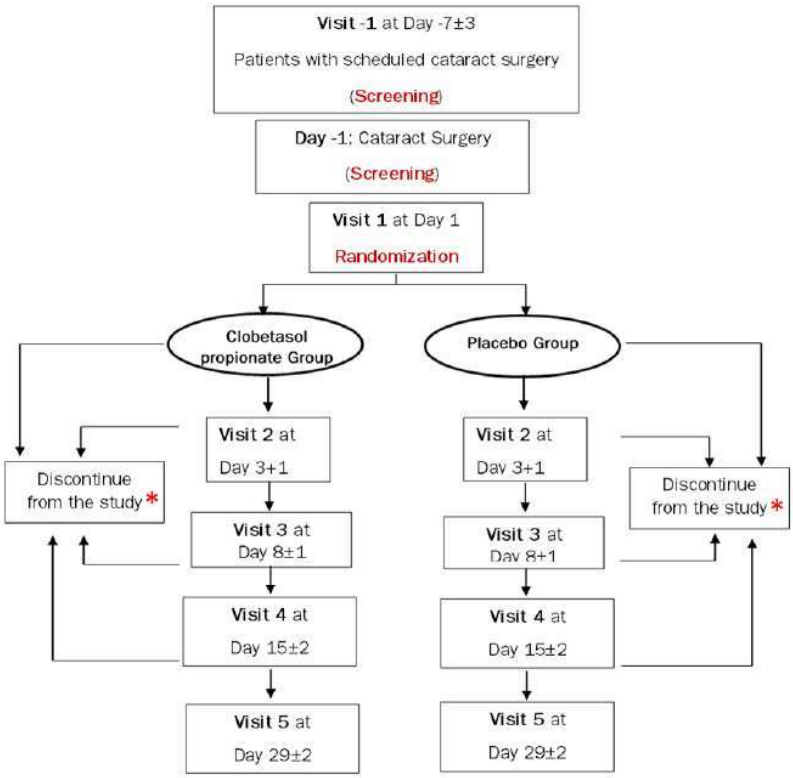
4 OVERALL STUDY DESIGN

4.1 Overview of Study Design

This is a Phase 3, randomised, parallel-group, placebo-controlled, double-masked, multicentre study to assess the efficacy and safety of clobetasol propionate ophthalmic nanoemulsion 0.05% in the treatment of inflammation and pain associated with cataract surgery.

All randomized patients will undergo routine cataract surgery according to the investigator's normal procedures being surgery day considered Day -1 of the study, whereas the day of the randomization/first administration will be considered study Day 1. First administration of the Investigational Medicinal Product (IMP) will take place at the study center, whereas the rest of study medication will be dispensed to patients for self-administration at a dosage of one drop every six hours, four times a day (QID) during 14 days as well as a diary to record the drug instillations.

Figure 1. Diagram of Study Design



* Patients who, for any reason, withdraw from the study treatment will be highly encouraged to continue attending all their remaining study visits to collect the most complete efficacy and safety data.

4.2 Determination of Sample Size

At least 210 patients from approximately 20 sites in the U.S. will participate in this study. Patients will be randomized in a 2:1 ratio to receive either clobetasol propionate ophthalmic nanoemulsion 0.05 % (N=140) or placebo (N=70) for the treatment of inflammation and pain associated with cataract surgery. Dropouts will not be replaced since the expected dropout rate is low (4%).

The sample size calculation is based on a two group $\chi 2$ test with a 0.05 two-sided significance level will have 80% power to detect the difference between a proportion with complete resolution of anterior chamber cells in the active group of 0.22 and the placebo group proportion of 0.07 (odds ratio of 3.747) when the sample size is 202.

5 DATA SETS TO BE ANALYSED

The following analysis sets will be used for the statistical analysis and presentation of data:

- **Full Analysis Set (FAS):** The FAS will be the primary analysis set for the efficacy endpoints and will include all randomized patients. The FAS population will be analyzed according to the planned treatment (rather than treatment actually received).

- **Safety Analysis (SAF) set** The safety set will be the primary analysis set for the safety endpoints and will include all randomized patients who instilled at least one dose of IMP or placebo. The SAF will be analyzed according to the treatment actually received.

- **Per Protocol (PP) Population:** The PP population set will be tested to confirm the robustness of the efficacy analyses and will include all patients in the FAS who have no major protocol deviations (i.e. patients who comply the protocol sufficiently to ensure that the data exhibits the effects of the IMP or placebo when administered as intended). Protocol violations include: violations of entry criteria, lack of compliance and the use of prohibited medication. The PP population will be analyzed according to the treatment actually received.

  Lack of compliance is defined as less than 80% compliance (section 6.3.8).

Efficacy analyses will be based on both the FAS and the PP, but the FAS will be considered the primary analysis population.

Safety analyses will be based on the SAF.

For the efficacy endpoints only visits with IMP and without prohibited/rescue medication will be analyzed for FAS population.

For the efficacy endpoints based in PP population (primary efficacy analysis and key secondary at visit 3) will include all patients in the FAS population who have no major protocol deviations. Without violations of eligibility criteria, lack of compliance at visit 3 (see section 6.3.8 for details) and without the use of rescue/prohibited medication until visit 3.

Only study eye will be analyzed and presented in tables and the non-study eye will only be included in listings.

6 STATISTICAL AND ANALYTICAL PLANS

The planned tables and listings are presented in Section 8.

6.1 Changes in the Planned Analyses

Any changes in the statistical analyses once the SAP has been finalised and the database has been locked should be documented at clinical study report (CSR).

6.2 Blind Review

A Blind Data Review Meeting (BDRM) is planned to occur before treatment unblinding takes place. The main objective of this meeting is to review data and identify protocol deviations in order to assign patients to all the analysis sets. Details of BDRM will be specified in a separate document.

A review of all major and critical protocol deviations and their potential consequences for the analysis will be conducted during the BDRM. Results and actions taken will be summarized in the Pre-Analysis Review document, which will be finalized before treatment unblinding.

A summary table will be provided including the number of patients with critical and major protocol deviations and the number of clinical and major protocol deviations. The protocol deviations will be listed. The number of patients per study population will be provided. Listings for patients excluded from the SAF, FAS and PP set will be provided.

6.3 Hypotheses and Statistical Methods

6.3.1 Definitions

Baseline	(Visit 1 (Day 1, 24 h after the cataract surgery).
Time calculation	Differences between dates to express duration will be calculated as the final date - initial date + 1. To convert these days differences to other units, the following conversion factors will be used: 1 year = 365.25 days and 1 month = 30.4375 days. Ex. Age = (informed consent date – date of birth + 1) / 365.25
Absolute change from Baseline	Absolute change from Baseline at Visit X will be calculated as: Absolute change from Baseline = Visit X - Baseline
Percentage change from Baseline	Percentage change from Baseline at Visit X will be calculated as: Percentage change from Baseline [%] = ((Visit X - Baseline)/Baseline) *100 In case of Baseline = 0 no percentage change from baseline will be calculated.
Signs of ocular inflammation (yes/no)	The presence/absence of the different signs of ocular inflammation: Chemosis, Bulbar conjunctival injection, ciliary injection, corneal edema, keratic precipitates will be defined as: No: grade=0 (absence) Yes: grade=1, 2 or 3 (presence)
Conversion Snellen to LogMar	Step 1. Mar = Snellen Denominator/Snellen Numerator Step 2. LogMar = log (Mar) Example: Snellen 20/40 Mar = 40/20 = 2 LogMar= log(2) = 0.3
Treatment Emergent Adverse Event	Treatment Emergent Adverse Events (TEAEs) are defined as an event that emerges during treatment[1] having been absent pre-treatment or worsens relative to the pre-treatment state: First dose IMP/Pacebo date ≤ start date AE ≤ last dose IMP/Placebo date
Rescue medication	The following prohibited medications will be considered as rescue medication when administered to subjects not responding to IMP or placebo: ▪ Any systemic or local therapy with corticosteroids (other than the study drug) or immunosuppressant (except pre-surgical and/or surgical administration of 1 drop of a topical NSAID or corticosteroid, at the investigator discretion) ▪ Any topical ocular medication (except preservative-free antibiotics for prophylactic purposes and preservative-free artificial tears)

	▪ Any systemic NSAID or opioids drugs (except occasional use of OTC formulations titrated no more than one single dose per week)
Relative day	The relative day of an event that occurs prior to administration of IMP: • Relative day = (Start date)-(Date of administration of IMP). The relative day of an event that occurs on the same day or after administration of IMP: • Relative day = (Start date)-(Date of administration of IMP)+1. Consequently, Day 1 is the same day as the day of administration of IMP, Day -1 is the day before, and Day 2 is the day after.

6.3.2 Summary Statistics

Data will be summarised by means of summary statistics. For continuous data the following summary statistics will be presented: number of observations, mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum. 95% CI of the mean will also be presented for efficacy and safety data. Change from baseline to each post-baseline visit will be also described using descriptive statistics. Categorical data will be presented as counts and percentages.

Summary statistics will be presented by treatment group and visit, as applicable.

Certain presentations (withdrawals, patient exclusion from datasets, baseline and background characteristics and primary efficacy data) may be broken down by study center, if relevant.

All data collected during study follow-up will be displayed and analyzed according to the actual visit data in the eCRF.

6.3.3 Patient/Patient Data Listings

Data collected in the eCRF will generally be listed. eCRF check questions and reminders will not be listed.

Listings will be sorted by study center, patient number, visit (where applicable) and time point (where applicable).

All derived data will be presented in the corresponding data listings.

6.3.4 Demographic and Other Baseline Characteristics

Patient disposition, demographic data and other baseline data will be listed and presented using summary statistics.

Demographic data:

Age, gender, ethnicity, race, weight (pounds), height (inches) and BMI will be summarized by treatment regimen and overall . SAF, FAS and PP population will be used for this presentation.

Relevant Medical History:

Medical history data will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), the latest versionMedical history will be summarized for the SAF by treatment regimen and overall on a per-patient basis (e.g., if a patient reported the same event repeatedly the event will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one Medical History event, and per System Organ Class (SOC) and per Preferred Term (PT) within SOC.

A listing will present all history-related data for the SAF.

Other clinical baseline characteristics:

Urine pregnancy test results and cataract diagnosis date and study eye will be listed for the SAF. Patient disposition will be presented, based on individual study examination dates and end of study status. A listing will be provided (if applicable) for discontinued patients.

6.3.5 Primary Efficacy analysis

The primary efficacy endpoint in this clinical trial is the proportion of patients with anterior chamber cell grade of “0” (absence of cells) compared to placebo at Day 8.

The statistical hypothesis that will be tested for primary efficacy is described as:

- Null Hypothesis (H_0): The difference in proportion of patients with anterior chamber cell grade of “0” at Day 8 between treatment regimes = 0.
- Alternative Hypothesis (H_1): The difference in proportion of patients with anterior chamber cell grade of “0” at Day 8 between treatment regimes ≠ 0.

The aim of the primary analysis of this study is to assess the superiority of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo with respect to the primary efficacy endpoint. The primary analysis will be based on a single study eye for each patient. Each patient’s study eye will be defined as the surgery eye.

A Chi-Square test will be employed to test the proportion of study eyes with complete clearing of anterior chamber cells (count cell = 0) at Visit 3 (Day 8 ± 1 day) without receiving rescue medication as compared between clobetasol propionate ophthalmic nanoemulsion 0.05% dosed QID and placebo dosed QID. The proportion of eyes with absence of cells (anterior chamber cell grade=0) together with its 95% confidence interval (CI) will be presented. Analysis will be conducted both in FAS and PP to test the robustness of the results.

6.3.6 Secondary Efficacy Analyses

6.3.6.1 Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is the proportion of patients with VAS pain score of “0” (no eye pain) compared to placebo at Day 8.

The key secondary analysis will be based on a single study eye for each patient. Each patient's study eye will be defined as the surgery eye.

A Chi-Square test will be performed to test the proportion of study eyes with no pain (VAS = 0) at Visit 3 (Day 8 ± 1 day) without receiving rescue medication as compared between clobetasol propionate ophthalmic nanoemulsion 0.05% dosed QID and placebo dosed QID. The proportion of eyes with no pain together with its 95% confidence interval (CI) will be presented.

Analysis will be conducted both in FAS and PP to test the robustness of the results.

6.3.6.2 Secondary Analysis

The secondary efficacy endpoints are described in Section 3.2. All secondary efficacy endpoints defined in this section will be analysed as exploratory.

For categorical variables, a summary of these endpoints will be presented at each specified timepoint by treatment group and will include the number and percentage of each category with the 95% CI. A chi-square test or Fisher Exact test, as appropiate will be performed to compare proportions between treatments at each timepoint.

For continuous variables: VAS photophia, Snellen best-corrected visual acuity (BCVA) score and VAS pain score, a summary of these endpoints will be presented at each specified timepoint by treatment group. Change from baseline will be derived and presented in the same way.

For variables: Anterior chamber cell grades, anterior chamber flare grades, severity of signs of ocular inflammation and eye discomfort grades categorical and continuous summary statistics will be presented, changes from baseline will also be derived and will be presented as increase, decrease or not change table. In the same way, a table with 2 categories: Improvement and no improvement (increase+no change) will be presented. A chi-square test or Fisher Exact test will be performed to compare proportions between treatments:

Change from baseline to Day 3		
Anterior Chamber Cell Grade	IMP	Placebo
Decrease (Improvement)	n (%)	n (%)
No change	n (%)	n (%)
Increase (Worsening)	n (%)	n (%)
P value chi-square or Fisher	p-value	
Improvement	n (%)	n (%)
No Improvement	n (%)	n (%)
	p-value	

No Improvement = increase + no change

For the variables mentioned above, to see the proportion of patients with different grades, a descriptive table like the following will also be built, no statistical inference will be made:

Grade	IMP			Placebo		
	Baseline	Day X	Change	Baseline	Day X	Change
0	n (%)	n (%)	(%)	n (%)	n (%)	(%)
0.5+	n (%)	n (%)	(%)	n (%)	n (%)	(%)
1+	n (%)	n (%)	(%)	n (%)	n (%)	(%)
2+	n (%)	n (%)	(%)	n (%)	n (%)	(%)
3+	n (%)	n (%)	(%)	n (%)	n (%)	(%)
4+	n (%)	n (%)	(%)	n (%)	n (%)	(%)

Between treatment comparison of the evolution over time will be analysed using a Restricted Maximum Likelihood (REML)-based repeated measures approach (Mixed Model Repeated Measures [MMRM]). The model for analysis will include the change from baseline as a dependent variable, the baseline score as a cavariate, the categorical fixed effects of treatment (IMP, Placebo) and visit and the interaction treatment*visit . An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, alternative covariance structures will be tested. Akaike's information criterion will be used to determine the best fit (smaller AIC).

If it is not possible to apply a MMRM due to the non-normality of the variable, the Mann Whitney Wilcoxon test will be performed.

Secondary efficacy analyses will be performed on the FAS population.

The PP population set will be also tested to confirm the robustness of the secondary analyses.

6.3.7 Sensitivity Analysis

Sensitivity analysis will be carried out for possible intercurrent events such as discontinuation due to AE, lack of efficacy and use of rescue and prohibited medication. New estimands associated to each intercurrent event will be added to the already existing primary estimand accordingly.

6.3.8 Exposure to Treatment

Subjects will record each IMP or placebo administration (e.g., one drop every six hours, during 14 days) on their dispensed diaries.

Compliance is defined as the percentage of actual doses the patient instilled with respect to the number of total doses planned. The planned dose is always one drop of IMP or placebo. Compliance will be summarized categorically (<80%, ≥80% and 100%) by treatment regime. It will be calculated as follows:

Compliance of IMP/Placebo administered %= (num. of doses instilled / num. of planned doses))(ml))*100

Planned doses=56

Compliance at last visit with IMP/Placebo is defined as the percentage of actual doses the patient instilled with respect to the number of total doses planned at the time of the last visit with IMP/Placebo.

Compliance of IMP/Placebo administered % at last visit with IMP/Placebo = (num. of doses instilled / num. of planned doses at last visit with IMP/Placebo))(ml))*100

Planned doses at last visit with IMP/Placebo = (End date IMP/Placebo exposure – First date IMP/Placebo exposure)*4.

Compliance at visit 3 (day 8±1) is defined as the percentage of actual doses the patient instilled with respect to the number of total doses planned at visit 3.

Compliance of IMP/Placebo administered % at visit 3= (num. of doses instilled / num. of planned doses at visit 3))(ml))*100

Planned doses at visit 3=32

In case a scheduled dose was not administered (missed) the missed dose and the reason will be captured in the eCRF as per the patient diary and tabulated by treatment regimen.

All compliance data will be summarized and listed for the SAF.

6.3.9 Concomitant Medications

All concomitant medications/therapies will be classified according to ATC level 3 group text and generic medication name. The medications will be divided into two categories based on start date and end date: Prior Medications and Concomitant Medications: .

- Prior Medications: start date and end date before first day of IMP
- Concomitant Medications:
  - Start date before first day of IMP and end date after or on same day as first day of IMP or no end date, i.e. ongoing after first day of IMP; or
  - Start date after or on same day as first day of IMP

Within concomitant medications, a distinction will be made between rescue medication and prohibited medication.

Incomplete dates will be handled as follows:

- If the start and stop date for a concomitant medication are completely missing, it will be assumed that the medication was started before treatment and classified as Prior Medication.
- If only the start date is missing the medication will be classified as:
  - Prior if end date is before first day of IMP
  - Concomitant if end date is on or after first day of IMP
- If only the end date is missing the medication will be classified as
  - Concomitant if start date is before or on same day as Day 15
- If the year and/or month are available, medication start in relation to the first day of IMP will be evaluated as close as possible (e.g., if only the year when the medication was started is available and ongoing is checked, the medication will be classified as a Concomitant Medication).

- If the medication was started in the same month as the first day of IMP, the medication will be classified as a Concomitant Medication.

Relative day will generally be calculated for all medications except for the ones with an incomplete start date.

Data will be listed for the SAF.Subject´s medications will be presented separately for each timing (i.e. prior, and concomitant medications) in 2 summary tables. In addition, a summary table for rescue and prohibited medication will be presented distinguishing each one in a column .

In the listings will show whether the concomitant medication is rescue medication or prohibited medication.

Rescue medication shall be as reported as such in the eCRD. The following ATC3 codes of concomitant medication will be considered as prohibited medication if they are not classified as rescue medication (all medications will be reviewed and it will be considered whether any medication should be included or excluded in the prohibited classification):

- D07A - Corticosteroids, plain
- D07B - Corticosteroids, combinations with antiseptics
- D07C - Corticosteroids, combinations with antibiotics
- D07X - Corticosteroids, other combinations
- G01B - Combinations of corticosteroids and antiinfectives for gynaecological use
- A01AC - Corticosteroids for local oral treatment
- D01A - Corticosteroids in combination with antifungals
- D10AA - Corticosteroids, combinations for treatment of acne
- C05AA - Antihemorrhoidals with corticosteroids
- S01B – Antiinflammatory agents
- S02B - Corticosteroids
- S02C - Corticosteroids and antiinfectives in combination
- S03B - Corticosteroids
- S03C - Corticosteroids and antiinfectives in combination.
- H02 - Corticosteroids for systemic use.
- L04A - Immunosuppressants
- M01A - Antiinflammatory and antirheumatic product, non-steroids
- N02BE - NSAIDs in combination with paracetamol.
- M01B - Salicylates in combination with corticosteroids.
- M01B - Combinations of antiinflammatory/antirheumatic agents
- N02A - Opioids
- Any ATC3 with ocular route except for S01A, S03A (Antiinfectives) preservative-free for prophylactic purposes and S01X (Other ophthalmologicals) preservative-free.

6.3.10 Adverse Events

AEs data are collected on the 'Adverse Events' eCRF form.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system, the latest version and tabulated by System Organ Class (SOC) and by Preferred Term (PT).

A Treatment-Emergent Adverse Event (TEAE) is defined as an AE observed after starting administration of IMP or placebo (see Section 6.3.1).

TEAEs will be summarized by presenting, for each treatment regimen, the number of events and the number and percentage of patients with:

- Any TEAE
- Any Serious Treatment Emergent Adverse Event (STEAE)
- Any TEAE of Special Interest (TEAESI)
- Any TEAE related to IMP/Placebo
- Any TEAE leading to treatment discontinuation (drug withdrawn)
- Any STEAE related to IMP/Placebo
- Any TEAESI related to IMP/Placebo

The number and percentage of TEAEs by causality and the number and percentage of mild moderate and severe TEAEs will be tabulated by SOC, PT and treatment arm. All tables with TEAEs by SOC and PT stratified by treatment regimen will only be counted by patient once within each PT.

The following tables will be provided with TEAEs by SOC and PT stratified by treatment regimen: TEAEs, TEAEs related to IMP/Placebo, TEAEs leading to discontinuation, STEAEs, STEAEs related to IMP/Placebo, TEAESI and TEAESIs related to IMP/Placebo.

TEAEs, STEAEs and TEAESIs will be tabulated by severity (mild, moderate or severe) and relationship to treatment (No: not related, unlikely related, Yes: possible, probable and certain). If a patient has more than one event with the same PT, the AE will only be counted once and the worst/maximal severity and the worst/strongest relationship will be used.

A listing of all AEs will be presented, whether treatment emergent or not. TEAEs will be flagged in this listing. A separate listing for deaths, STEAEs, AESIs and TEAEs leading to discontinuation will be provided (if any).

The following AEs (SOC, PT) of special interest (AESI) will be evaluated by Investigators at all study visits and time points (as applicable):

- IOP rise over 30 mmHg (SOC- INVESTIGATIONS, PT-INTRAOCULAR PRESSURE INCREASED)
- Pain/discomfort associated with IMP instillation (SOC-EYE DISORDERS, PT-EYE PAIN, OCULAR DISCOMFORT and related with IMP)

SAF will be used for all AE related summaries.

As stated in the study protocol, treatment arms will be compared with respect to safety endpoints descriptively only. No further inferential comparison will be carried out.

6.3.11 Other Safety Assessments

Physical Examination

Full physical examination will consist of assessment of head, eyes, ears, nose throat, mouth, cardiovascular, respiratory, digestive, urogenital, musculoskeletal, nervous/psycological, endocrine/metabolic, hematologic, dermatological, allergies, inmunological and other. The observed values for the physical examination will be recorded in the eCRF by the investigator as “normal” or “abnormal” and if abnormal, assessed as “clinically significant” or “not clinically significant”.

The Investigator will perform full physical examinations at the Screening visit and at the Early Termination visit.

The investigator will perform physical examination following the usual standards of patients’ examination at each study site.

Eye Examination

Pupil function, ocular alignment and motility, visual field by confrontation test, and anterior vitreous will be assessed for normality and clinically significance at the Screening visit and at the Early Termination visits.

Vital Signs

Vital signs will be assessed 15 minutes before any ocular assessment and at least 30±10 minutes before the first study medication administration. For all vital signs parameters (systolic and diastolic blood pressure, heart rate and body temperature) summary statistics will be produced for observed values by visit.

Vital signs data will be listed by patient. All clinically significant abnormal values will be flagged in this listing.

Indirect Ophthalmoscopy

Vitreous humor, central retina, peripheral retina, optic nerve disc and retinal vasculature will be assessed for normality and clinically significance at the Screening, Baseline, Visit 4, Visit 5 and at the Early Termination visit.

Outputs will be based on the SAF.

6.4 Level of Significance, Multiple Comparisons and Multiplicity

All statistical hypotheses will be two-sided and will be performed using a 5% significance level.

No adjustment for multiple comparisons or corrections for multiplicity are foreseen.

6.5 Adjustment for Covariates

Baseline value will be used as a covariate in the MMRM analyses for the continuous secondary efficacy endpoints (see Section 6.3.6).

6.6 Handling of Dropouts and Missing Data

No missing imputation methods are foreseen. As described in the CSP, any missing, unused, or spurious data will be noted in the final Clinical Study Report (CSR) and presented in the data listings.

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following method will be

used, in the event that any date is incomplete after Data Management processing and this date needs to be used for calculation:

- if no field is available: no imputation will be performed,

- if only the year is available: Day “01” and month of “July” will be imputed,

- if the month and year are available: Day “15” will be imputed.

6.7 Multicentre Studies

As stated in the CSP, none of the analyses will be adjusted by study center.

6.8 Examination of Subgroups

NA

6.9 Interim Analysis

No formal Interim Analysis is foreseen for this study.

6.10 Reporting Conventions

P-values ≥0.0001 will be reported to four (4) decimal places; p-values less than 0.0001 will be reported as <0.0001. The mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., standard deviation) will be displayed to two decimal places greater than the original value.

7 REFERENCES

1- ICH E9 Statistical principles for clinical trials (definition Treatment Emergent - An event that emerges during treatment having been absent pre-treatment, or worsens relative)

8 LIST OF OUTPUT

8.1 Tables to be produced for the Clinical Study Report (Section 14 according to ICH E3)

Demographic data and baseline characteristics will be showed stratifying by treatment group (IMP and placebo) and overall.

Efficacy and safety analysis tables will be showed stratifying by treatment group, as well as each timepoint, as applicable.

For continuous variables, summary statistics will be included in the MMRM tables.

14.1 DEMOGRAPHIC DATA

Patient disposition

Table	Title	Pop	Top.Line
14.1.1	Patient disposition: Number of patients in each analysis set and reason for exclusion	ALL	X
14.1.2	Number of patients by visit	ALL	
14.1.3	Reason for finish the study prematurely	ALL	

Demographic and baseline characteristics

Table	Title	Pop	Top.Line
14.1.4	Demographics	SAF	
14.1.5	Urine pregnancy test	SAF	
14.1.6	Cataract diagnosis	SAF	
14.1.7	Relevant Medical History	SAF	

14.2 EFFICACY DATA

Primary efficacy analysis

Table	Title	Pop	Top.Line
14.2.1.1	Percentage of patients with anterior chamber cell grade of “0” compared to placebo at Day 8	FAS	X
14.2.1.2	Percentage of patients with anterior chamber cell grade of “0” compared to placebo at Day 8	PP at Visit 3	

Main Secondary efficacy analysis

Table	Title	Pop	Top.Line
14.2.2.1	Proportion of patients with VAS pain score of "0" (no eye pain) compared to placebo at Day 8.	FAS	X
14.2.2.2	Proportion of patients with VAS pain score of "0" (no eye pain) compared to placebo at Day 8.	PP at visit 3	

Secondary efficacy analysis

Table	Title	Pop	Top.Line
14.2.3.	Proportion of patients with anterior chamber cell grade of "0" compared to placebo at Day 3, Day 15 and Day 29	FAS	X
14.2.4.1	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber cell grades. Improvement and no Improvement table.	FAS	
14.2.4.2	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber cell grades. Descriptive table	FAS	
14.2.5.1	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber flare grades. Improvement and no Improvement table.	FAS	
14.2.5.2	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different anterior chamber flare grades. Descriptive table	FAS	
14.2.6.	Proportion of patients with anterior chamber cell grade of "≤0.5+" and flare grade of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.7.	Proportion of patients with anterior chamber cell grade of "≤1+" compared to placebo at Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.8.	Proportion of patients with anterior chamber cell grade of "0" and flare grade of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.9.1	Frequency of chemosis (yes/no) compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.	FAS	

14.2.9.2	Frequency of bulbar conjunctival injection (yes/no) compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.9.3	Frequency of ciliary injection (yes/no) compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.9.4	Frequency of corneal edema (yes/no) compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.9.5	Frequency of keratic precipitates (yes/no) compared to placebo at Baseline, Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.10.1	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with chemosis (yes/no)	FAS	
14.2.10.2	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with bulbar conjunctival injection (yes/no)	FAS	
14.2.10.3	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with ciliary injection (yes/no)	FAS	
14.2.10.4	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with corneal edema (yes/no)	FAS	
14.2.10.5	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with keratic precipitates (yes/no)	FAS	
14.2.11.1	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of chemosis. Improvement or no Improvement.	FAS	
14.2.11.2	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of chemosis. Descriptive table	FAS	
14.2.11.3	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of bulbar conjunctival injection. Improvement or no Improvement.	FAS	
14.2.11.4	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of bulbar conjunctival injection. Descriptive table	FAS	
14.2.11.5	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of ciliary injection. Improvement or no Improvement	FAS	
14.2.11.6	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of ciliary injection. Descriptive table	FAS	
14.2.11.7	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of corneal edema. Improvement or no Improvement.	FAS	

14.2.11.8	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of corneal edema. Descriptive table	FAS	
14.2.11.9	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of keratic precipitates. Improvement or no Improvement	FAS	
14.2.11.10	Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the severity of keratic precipitates. Descriptive table	FAS	
14.2.12	MMRM. Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the visual analog scale (VAS) photophobia score.	FAS	
14.2.13	MMRM. Change from Baseline to Day 8, Day 15 and Day 29 compared to placebo in Snellen best.corrected visual acuity (BCVA) score.	FAS	
14.2.14	MMRM. Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the VAS pain score.	FAS	X
14.2.15	Proportion of patients with VAS pain of “0” compared to placebo at Day 3, Day 15 and Day 29.	FAS	X
14.2.16.1	Change from baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different discomfort grades. Improvement or no Improvement	FAS	
14.2.16.2	Change from baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the proportion of patients with different discomfort grades. Descritpve table	FAS	
14.2.17.1	Proportion of patients with no discomfort (“None”) compared to placebo at Day 3, Day 8, Day 15 and Day 29.	FAS	
14.2.17.2	Eye discomfort by visit and treatment. Descriptive statistics	FAS	
14.2.18	MMRM. Change over time in the VAS pain score reported in the patients’ diaries compared to placebo.	FAS	X
14.2.19	Percentage of patients with anterior chamber cell grade of “0” compared to placebo at Day 8. Sensitivity Analysis	FAS	

14.3 SAFETY DATA

Adverse events

Table	Title	Pop	Top.Line
14.3.1.1	Summary of Treatment Emergent Adverse Events (TEAEs)	SAF	X
14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	

14.3.1.3	TEAEs by SOC and PT by worst severity	SAF	
14.3.1.4	TEAEs by SOC and PT by worst relationship	SAF	
14.3.1.5	TEAEs related to IMP/Placebo	SAF	
14.3.1.6	TEAEs leading to discontinuation	SAF	
14.3.1.7	Serious TEAEs	SAF	
14.3.1.8	Serious TEAEs related to IMP/Placebo	SAF	
14.3.1.9	TEAEs AESI	SAF	
14.3.1.10	TEAEs AESI related to IMP/Placebo	SAF	
14.3.2	Listings of Deaths Other Serious Adverse Events, and Other Significant Adverse Events	SAF	

14.3.3 [This title is reserved for narratives.]

Other Safety assessments

Table	Title	Pop	Top.Line
14.3.4.1	Absolute and Percentage change from Baseline in Vital Signs by treatment regimen. Descriptive Statistics	SAF	
14.3.4.2	Summary statistics. Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in intraocular pressure (IOP).	SAF	X

Treatment exposure

Table	Title	Pop	Top.Line
14.3.5.1	Compliance with IMP/Placebo % (doses/amount). Descriptive statistics.	SAF	
14.3.5.2	Exposure to IMP/Placebo: Duration of treatment, Number of doses completed/not completed and reasons by treatment regimen. Descriptive statistics	SAF	

Concomitant medications

Table	Title	Pop	Top.Line
14.3.10.1	Summary of Prior Medications and Therapies tabulated by ATC level 3 group and generic medication name	SAF	
14.3.10.2	Summary of All Concomitant Medications (rescue and prohibited medications included) and Therapies tabulated by ATC level 3 group and generic medication name	SAF	

14.3.10.3	Summary of Concomitant Medications (Rescue and prohibited) tabulated by ATC level 3 group and generic medication name	SAF	

8.2 Listings of individual patient data and other information to be produced for the clinical study report (sections 16.1 and 16.2 according to ICH E3)

Listing	Title	Pop	Top.Line
16.1.7	Randomisation scheme	ALL	

Patient disposition

Listing	Title	Pop	Top.Line
16.2.1.1	Patient Disposition	ALL	
16.2.1.2	Screening Failures, Discontinued Subjects, Reason for Discontinuation	ALL	X
16.2.1.3	Visits dates	ALL	
16.2.2.1	Protocol Deviations	ALL	
16.2.3.1	Patients excluded from SAF	ALL	
16.2.3.2	Patients excluded from FAS	ALL	
16.2.3.3	Patients excluded from PP	ALL	

Demographic and baseline characteristics

Listing	Title	Pop	Top.Line
16.2.4.1	Demographic data	SAF	
16.2.4.2	Relevant Medical History	SAF	
16.2.4.4	Urine Pregnancy test	SAF	
16.2.4.5	Cataract diagnosis	SAF	
16.2.4.5	Inclusion Criteria Not Met and Exclusion Criteria Met	SAF	

Compliance

Listing	Title	Pop	Top.Line
16.2.5	Compliance with IMP/Placebo	SAF	

Efficacy data

Listing	Title	Pop	Top.Line
16.2.6.1	Slit Slamp Examination	SAF	
16.2.6.2	BCVA by Snellen chart	SAF	

16.2.6.3	Eye pain (VAS)	SAF	
16.2.6.4	Eye discomfort	SAF	
16.2.6.5	Photophobia	SAF	
16.2.6.6	Indirect ophthalmoscopy	SAF	

Adverse Events

Listing	Title	Pop	Top.Line
16.2.7.1	Adverse Events	SAF	

Other Safety assessments

Listing	Title	Pop	Top.Line
16.2.9	Vital signs	SAF	
16.2.10.1	Physical examination	SAF	
16.2.10.2	Eye examination	SAF	
16.2.10.3	Indirect Ophthalmoscopy	SAF	
16.2.11	IOP measurementsby Goldman Tonometer	SAF	

Concomitant medication

Listing	Title	Pop	Top.Line
16.2.12.1	Prior Medications and Therapies tabulated by ATC level 3 group and WHO preferred name	SAF	
16.2.12.2	All Concomitant Medications and Therapies tabulated by ATC level 3 group and WHO preferred name	SAF	
16.2.12.3	Rescue and prohibited Concomitant Medications tabulated by ATC level 3 group and WHO preferred name	SAF	