CLINICAL STUDY PROTOCOL

Protocol Title:	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
Acronym/Protocol Number:	CLOSE-1/ CLOBOF3-16IA01
Investigational Product:	Clobetasol propionate ophthalmic nanoemulsion 0.05% (SVT-15473)
Global Coordinating Principal Investigator:	[redacted]
Sponsor:	Laboratorios Salvat, S.A. Gall 30-36 08950 - Esplugues de Llobregat - Barcelona - Spain
Version Nº:	Final 2.0 (Amendment 1)
Date:	26 February 2020

Previous versions:

Version	Date
v. Final 1.0	06 November 2019

SPONSOR'S SIGNATURE PAGE

Sponsor:	Laboratorios Salvat, S.A.
Clinical Protocol Number:	CLOBOF3-16IA01
Investigational product:	Clobetasol propionate ophthalmic nanoemulsion 0.05% (SVT-15473)
Protocol Title:	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

This study will be conducted according to the protocol and in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization, the Declaration of Helsinki, and applicable regulatory requirements

Approved by:

_____ _____

Enrique Jiménez, MD
Medical Director
Laboratorios Salvat, S.A.

Date

_____ _____

Susana Román
Clinical Trial Manager
Laboratorios Salvat, S.A.

Date

INVESTIGATOR'S SIGNATURE PAGE

Sponsor:	Laboratorios Salvat, S.A.
Clinical Protocol Number:	CLOBOF3-16IA01
Investigational product:	Clobetasol propionate ophthalmic nanoemulsion 0.05% (SVT-15473)
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All documentation that has been supplied to me by Laboratorios Salvat, S.A. (the Sponsor) and/or the Sponsor's designee concerning this study, and that has not been previously published, will be kept in the strictest confidence. This documentation includes, but is not limited to, the study protocol, the Investigator's Brochure, and Electronic Case Report Form (eCRF).

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor or their designee and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and do agree to abide by all the conditions and instructions contained in this protocol.

_____ _____

Signature (Principal Investigator) Date

_____

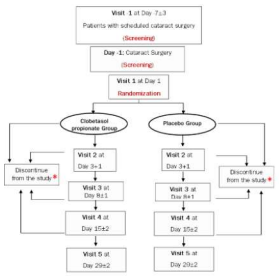
Printed Name

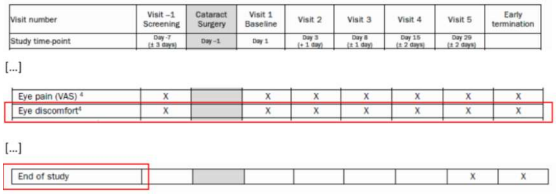
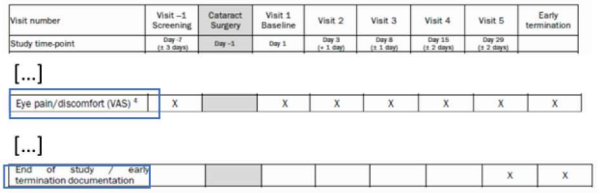
PROTOCOL SUMMARY OF CHANGES			
Page no.	Changes in Protocol Amendment 1 [26 February 2020] (New information is marked in red)	Page no.	Protocol V1.0 [06 November 2019] (Removed/updated information is marked in blue)
24/108	Key Secondary Objective: Efficacy To assess the effect of clobetasol propionate 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 eye pain and on eye discomfort associated with cataract surgery	4/90	Secondary Objectives: Efficacy […] - To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on eye pain/discomfort associated with cataract surgery
28/108	Exclusion Criteria: 20) Presence of IOP ≥24 mmHg in the study eye at Visit 1	8/90	Exclusion Criteria: 20) Presence of IOP ≥24 mmHg at Visit 1

28/108	**Study Evaluations:** **Visit-1** (Screening; Day –7 ± 3 days): **[…]** - Eye pain evaluation (VAS) - Eye discomfort evaluation […] **Visit 1** (Baseline; Day 1, 24h after the surgery): […] - Eye pain evaluation (VAS) - Eye discomfort evaluation **[…]** **Visit 2** (Day 3 + 1 day): - Eye pain evaluation (VAS) - Eye discomfort evaluation **[…]** **Visit 3** (Day 8 ± 1 day): - Eye pain evaluation (VAS) - Eye discomfort evaluation **[…]** **Visit 4** (Day 15 ± 2 day): - Eye pain evaluation (VAS) - Eye discomfort evaluation **[…]** **Visit 5** (Day 29 ± 2 day): - Eye pain evaluation (VAS) - Eye discomfort evaluation **[…]**	8/90	**Study Evaluations:** **Visit-1** (Screening; Day –7 ± 3 days): **[…]** - Eye pain/discomfort evaluation (VAS) […] **Visit 1** (Baseline; Day 1, 24h after the surgery): […] - Eye pain/discomfort evaluation (VAS) **[…]** **Visit 2** (Day 3 + 1 day): - Eye pain/discomfort evaluation (VAS) **[…]** **Visit 3** (Day 8 ± 1 day): - Eye pain/discomfort evaluation (VAS) **[…]** **Visit 4** (Day 15 ± 2 day): - Eye pain/discomfort evaluation (VAS) **[…]** **Visit 5** (Day 29 ± 2 day): - Eye pain/discomfort evaluation (VAS) **[…]**

32/108	**Key secondary endpoint:** • Proportion of patients with VAS pain of "0" (no eye pain) compared to placebo at Day 8 **Secondary endpoints:** Efficacy […] • 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	12/90	**Secondary endpoints:** Efficacy […] • Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the VAS pain/discomfort score • Proportion of patients with VAS pain/discomfort of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29 • Change over time in the VAS pain/discomfort score reported in the patients' diaries compared to placebo

34/108	Key Secondary Analysis: The aim of the key secondary analysis of this study is to assess the superiority of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo with respect to the key secondary endpoint in the FAS. 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. The test will be the proportion of study eyes with no pain (VAS pain = 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 using the chi square statistic. The PP population set will be also tested to confirm the robustness of the key secondary analysis.	n/a	There is no previous information about *Key Secondary Analysis* in protocol version final 1.0 06 November 2019.
49/108	Secondary Objectives a) 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. b) Other secondary objectives Efficacy […] - To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on eye pain and on eye discomfort associated with cataract surgery.	30/90	Secondary Objectives Efficacy […] - To assess the effect of clobetasol propionate ophthalmic nanoemulsion 0.05% on eye pain/discomfort associated with cataract surgery. […]

50/108	4.1 Overview If a patient wants to discontinue from the study, he/she will be treated according to the clinical practice. Patients who discontinue the study treatment, will be requested to continue attending their remaining study visits. If the patient does not accept, and wants to discontinue from the study, they will be encouraged to at least attend the Early Termination Visit (Section 4.3.2.8) as soon as possible.	31/90	4.1 Overview If a patient wants to discontinue from the study, he/she will be treated according to the clinical practice. Patients who discontinue the treatment will complete the assessments planned for Early Termination Visit (Section 4.3.2.8) as soon as possible.
51/108	**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.	32/90	**Figure 2 Diagram of Study Design** 

52/108	Table 1 Schedule of Observations  […] 4.VAS scales and discomfort should be assessed prior to any physical evaluation […]	33/90	Table 1 Schedule of Observations  […] 4. VAS scales should be assessed prior to any physical evaluation […]

From 54 to 58/108	4.3.2.1 Visit –1 (Screening visit at Day –7 ± 3 days) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […] 4.3.2.2 Visit 1 (Baseline visit at Day 1, 24 h after the cataract surgery) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […] After IMP administration: - Distribution of patient diary: o Throughout the study, patients or caregivers should record on it: doses and schedule of IMP administration, eye pain VAS scores and cataract surgery-associated symptoms. […] 4.3.2.3 Visit 2 (Day 3 + 1 day) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […]	From 35 to 40/90	4.3.2.1 Visit –1 (Screening visit at Day –7 ± 3 days) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […] 4.3.2.2 Visit 1 (Baseline visit at Day 1, 24 h after the cataract surgery) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […] After IMP administration: - Distribution of patient diary: o Throughout the study, patients or caregivers should record on it: doses and schedule of IMP administration, eye pain/discomfort and photophobia VAS scores and cataract surgery-associated symptoms. […] 4.3.2.3 Visit 2 (Day 3 + 1 day) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation 4.3.2.4 Visit 3 (Day 8 ± 1 day) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […]

	4.3.2.4 Visit 3 (Day 8 ± 1 day) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […] 4.3.2.5 Visit 4 (Day 15 ± 2 days) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […] 4.3.2.6 Visit 5 (Day 29 ± 2 days) […] - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation […] 4.3.2.8 Early Termination Visit At any time, the investigator will make every attempt to ensure that an Early Termination Visit will be held, in the case of patient discontinuing the study (see Section 5.3). At the Early Termination Visit, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes): - Eye pain (VAS) – to be assessed prior to any physical evaluation - Eye discomfort – to be assessed prior to any physical evaluation		4.3.2.5 Visit 4 (Day 15 ± 2 days) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […] 4.3.2.6 Visit 5 (Day 29 ± 2 days) […] - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […] 4.3.2.8 Early Termination Visit (anytime during the 14 days Treatment period) In case of early treatment discontinuation or withdrawal of the study during the 14-days treatment period (Section 5.3), every attempt will be made to ensure an Early Termination Visit will be held. At Early Termination Visit, the following activities and assessments will be performed (NOTE: All ocular assessments must be performed in both eyes): - Eye pain/discomfort (VAS) – to be assessed prior to any physical evaluation […]

	[…]		
61/108	5.2 Exclusion Criteria 20) Presence of IOP ≥24 mmHg in the study eye at Visit 1	42/90	5.2 Exclusion Criteria 20) Presence of IOP ≥24 mmHg at Visit 1

61/108	5.3 Withdrawal, Premature Discontinuation of Study Medication, and Replacement of Patients Patients are free to discontinue their participation in the study at any time. Additionally, patients may be withdrawn from study at any time, if deemed necessary by the investigator (after discussion with the Medical Monitor). Withdrawal from the study will not affect or prejudice the patients' further care or treatment. Potential reasons for withdrawal of patients from this study are: · The decision of a patient to withdraw informed consent · Patient is lost to follow-up (Section 5.3.1) Potential reasons for premature discontinuation of study medication include, but are not limited to: · Occurrence of a treatment-emergent AE (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the patient if he/she continues to receive study medication. The investigator must follow the patient until the AE resolves or satisfactorily stabilizes · Administration of a rescue medication. Any patient placed on rescue therapy will discontinue the use of the IMP (see Sections 6.7.1 and 6.7.2) · Patient's failure to comply with protocol requirements or study related procedures · In case of pregnancy. The investigator will continue the follow-up of the patient until the end of the pregnancy · Any surgery (different from the actual routine cataract surgery on the study eye) in the study or contralateral eye In any case of premature discontinuation of study medication, the investigator must make extensive efforts to ensure that the patient will attend all his/her remaining study visits until study completion	43/90	5.3 Withdrawal, Premature Discontinuation of Study Medication, and Replacement of Patients Patients are free to discontinue their participation in the study at any time. Withdrawal from the study will not affect or prejudice the patients' further care or treatment. Additionally, patients may be withdrawn from study at any time, if deemed necessary by the investigator. Potential reasons for withdrawal of patients from this study are: · The decision of a patient to withdraw informed consent · Investigator withdrawal of the patient (after discussion with Medical Monitor) · Occurrence of a treatment-emergent AE (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the patient if he/she continues to receive study medication. The investigator must follow the patient until the AE resolves or satisfactorily stabilizes · Patient is lost to follow-up (Section 5.3.1) · Administration of a rescue medication. Any patient placed on rescue therapy will discontinue use of the IMP and continue his/her study participation through Visit 5 (Sections 6.7 and 6.7.2) · Patient's failure to comply with protocol requirements or study related procedures · Pregnancy · Any surgery (different from the actual routine cataract surgery on the study eye) in the study or contralateral eye […]

	(at Visit 5), aiming to collect the most complete efficacy and safety data. […]		
68/108	6.7.2 Rescue Medication Any patients not responding adequately to the IMP may be rescued and placed on alternate therapy (Section 6.7) at the investigator's discretion at any time. The choice of rescue medication is at the investigator's discretion. Any patient placed on rescue therapy will discontinue the use of the IMP and the investigator must made extensive efforts to ensure that the patient will attend all his/her remaining study visits, until study completion, aiming to collect the most complete efficacy and safety data. Additionally, patients will be asked to phone the study center at any time to speak to a member of the medical personnel should they experience any worsening of ocular conditions or other AEs. […]	51/90	6.7.2 Rescue Medication Any patients not responding adequately to the IMP may be rescued and placed on alternate therapy (Section 6.7) at the investigator's discretion at any time. The choice of rescue medication is at the investigator's discretion. Any patient placed on rescue therapy will discontinue use of the IMP and continue his/her study participation through Visit 5. Patients will be asked to phone the study center at any time to speak to a member of the medical personnel should they experience any worsening of ocular conditions or other AEs. […]

69/108	7.1 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 silt-lamp examination and will be graded on an adapted 6-point scale proposed by the Standardization of Uveitis Nomenclature (SUN) working group (23) (Table 2) Table 2 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 †Feld size is a 1 mm by 1 mm slit beam	52/90	7.1 Primary Efficacy Endpoint Proportion of patients with anterior chamber cell grade of "0" (absence of cells) compared to placebo at Day 8. 7.2 Primary efficacy assessment Anterior chamber cell grade will be assessed by the investigator during silt-lamp examination and will be graded on a 6-point scale proposed by the Standardization of Uveitis Nomenclature (SUN) working group (23) (Table 2) Table 2 The SUN working group grading scheme for anterior chamber cells **Grade** / **Cells in field†** 0 / <1 0.5+ / 1-5 1+ / 6-15 2+ / 16-25 3+ / 26-50 4+ / >50 †Feld size is a 1 mm by 1 mm slit beam

69/108	7.2 Key Secondary Efficacy Endpoint Proportion of patients with VAS pain 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 (100 mm) horizontal line anchored by two verbal descriptions: "no eye pain" (score of 0) and "worst imaginable eye pain" (score of 10).  	n/a	There is no previous information about *Key Secondary Efficacy Endpoint* in the protocol version final 1.0 06 November 2019.

71/108	7.3 Other Secondary Efficacy Endpoints Other secondary efficacy endpoints will be: […] · 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	53/90	7.3 Secondary Efficacy Endpoints The secondary efficacy endpoints will be: […] · Change from Baseline to Day 3, Day 8, Day 15 and Day 29 compared to placebo in the VAS pain/discomfort score · Proportion of patients with VAS pain/discomfort of "0" compared to placebo at Day 3, Day 8, Day 15 and Day 29 · Change over time in the VAS pain/discomfort score reported in the patients' diaries compared to placebo

71/111	7.3.1 Secondary efficacy assessments […] ·The eye pain VAS is a single-item continuous scale comprised of a 10 cm (100 mm) horizontal line anchored by two verbal descriptors, one for each symptom extreme. For eye pain intensity, the scale is anchored by "no eye pain" (VAS score of 0) and "worst imaginable eye pain" (score of 100 mm) The eye pain VAS is completed by the patient. Details and instructions for use of eye pain VAS can be found in Appendix 4 ·The eye discomfort will be assessed by using the categorical scale which can be found in Appendix 5 ·The photophobia VAS is a single-item continuous scale comprised of a 10 cm (100 mm) 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 100 mm) The photophobia VAS is completed by the patient. Details and instructions for use of photophobia VAS can be found in Appendix 6	54/90	7.3.1 Secondary efficacy assessments […] ·The eye pain/discomfort VAS is a single-item continuous scale comprised of a 10 cm (100 mm) horizontal/vertical line anchored by two verbal descriptors, one for each symptom extreme. For eye pain/discomfort intensity, the scale is anchored by "no eye pain/discomfort" (score of 0) and "worst imaginable eye pain/discomfort" (score of 100 mm) The eye pain/discomfort VAS is completed by the patient. Details and instructions for use of eye pain/discomfort VAS can be found in Appendix 4 ·The photophobia VAS is a single-item continuous scale comprised of a 10 cm (100 mm) horizontal/vertical 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 100 mm) The photophobia VAS is completed by the patient. Details and instructions for use of photophobia VAS can be found in Appendix 5
72/108	7.5.2 Medical History A detailed medical history of relevant conditions and procedures will be obtained by the investigator or qualified designee at the Screening visit (Visit –1) and recorded as required in the Medical History section of the eCRF. […]	55/90	7.5.2 Medical History A detailed medical history of relevant conditions and procedures will be obtained by the investigator or qualified designee at the Baseline visit (Visit –1) and recorded as required in the Medical History section of the eCRF. […]

75/108	8.2 Appropriateness of Measurements Standardized methods for measurements of efficacy and safety variables will be used. The investigator assessment instruments and Patient-Reported Outcomes (eye pain and photophobia VAS and discomfort categorical scale) are accepted standards for clinical evaluation.	57/90	8.2 Appropriateness of Measurements Standardized methods for measurements of efficacy and safety variables will be used. The investigator assessment instruments and Patient-Reported Outcomes (eye pain/discomfort and photophobia VAS) are accepted standards for clinical evaluation.
80/108	8.3.8 SAE Reporting Contact Details All SAEs should be faxed or sent by e-mail to [redacted] within 24 hours of the investigator becoming aware of the event(s). If the SAE Report Form Clinical Trials is faxed, the "Fax cover sheet, SAE report" should be used. [redacted] Fax: [redacted] E-mail: [redacted]	63/90	8.3.8 SAE Reporting Contact Details All SAEs should be faxed or sent by e-mail to [redacted] within 24 hours of the investigator becoming aware of the event(s). If the SAE Report Form Clinical Trials is faxed, the "Fax cover sheet, SAE report" should be used. [redacted] Fax: [redacted] Phone: [redacted] E-mail: [redacted]
85/108	9.1.10 Primary Analysis […] The PP population set will be also tested to confirm the robustness of the primary analysis. The primary estimand (efficacy estimand) will be defined as the effect of the randomized treatments in all subjects meeting selection criteria assuming continuation of randomized treatments for the duration of the study regardless of actual compliance.	67/90	9.1.10 Primary Analysis […] The PP population set will be also tested to confirm the robustness of the primary analysis.

85/108	9.1.11 Key Secondary Analysis The aim of the key secondary analysis of this study is to assess the superiority of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo with respect to the key secondary endpoint in the FAS. 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. The test will be the proportion of study eyes with no pain (pain = 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 using the chi square statistic. The PP population set will be also tested to confirm the robustness of the key secondary analysis.	n/a	There is no previous information about *Key Secondary Analysis* in the protocol version final 1.0 06 November 2019.
86/108	9.1.14 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 / prohibited medication. New estimands associated to each intercurrent event will be added to the already existing primary estimand accordingly.	n/a	There is no previous information about *Key Secondary Analysis* in the protocol version final 1.0 06 November 2019.

<table>
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<td>102/108</td>
<td>13.2 Appendix 2
Slit Lamp Examination
[…]
- Anterior Chamber Cells
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<tr><td>0</td><td>0</td></tr>
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<tr><td>1+</td><td>6-15</td></tr>
<tr><td>2+</td><td>16-25</td></tr>
<tr><td>3+</td><td>26-50</td></tr>
<tr><td>4+</td><td>>50</td></tr>
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[…]</td>
<td>85/90</td>
<td>13.2 Appendix 2
Slit Lamp Examination
[…]
- Anterior Chamber Cells
<table>
<tr><th>Grade</th><th>Cells in field</th></tr>
<tr><td>0</td><td><1</td></tr>
<tr><td>0.5+</td><td>1-5</td></tr>
<tr><td>1+</td><td>6-15</td></tr>
<tr><td>2+</td><td>16-25</td></tr>
<tr><td>3+</td><td>26-50</td></tr>
<tr><td>4+</td><td>>50</td></tr>
</table>
[…]</td>
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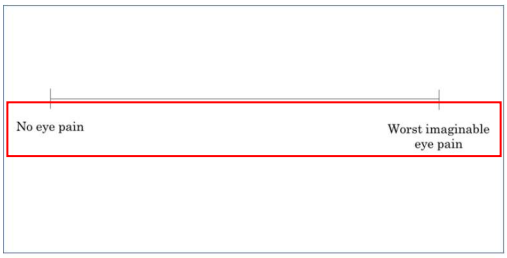
106/108	13.4 Appendix 4 Eye Pain- Visual Analogue Scale (VAS) Please assess the eye pain by ticking the scale, which describes eye pain the best.  	89/90	13.4 Appendix 4 Eye Pain/Discomfort - Visual Analogue Scale (VAS) Please assess the eye pain/discomfort by ticking the scale, which describes eye pain/discomfort the best. 
107/108	13.5 Appendix 5 Discomfort Assessment Please assess the severity of the eye discomfort by using the following scale. **Grade** / **Description** 0 None 1 Mild 2 Moderate 3 Severe	n/a	There is no previous information about *Discomfort Assessment* in the protocol version final 1.0 06 November 2019.

108/108	13.6 Appendix 6 Photophobia - Visual Analogue Scale (VAS) […]		There is no *Appendix 6* in protocol version 1.0 06 Nov 2019.

PROTOCOL SYNOPSIS

Sponsor:	Laboratorios Salvat, S.A
Title:	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-1 Study
Short title:	Clobetasol propionate ophthalmic nanoemulsion 0.05% for the treatment of inflammation and pain associated with cataract surgery
Acronym	CLOSE-1
Study Number:	CLOBOF3-16IA01
Study Phase:	Phase 3
Study Centers:	Up to 20 centers in the US.
Study Period	The anticipated first patient in (FPI) is 1Q 2020 and the planned last patient last visit (LPLV) is 4Q 2020
Objectives:	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 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%
Study Design:	This is a phase 3, randomized, parallel-group, double-masked, placebo-controlled, multicenter study. This study will compare the efficacy and safety of clobetasol propionate ophthalmic nanoemulsion 0.05% to placebo (vehicle), when administering

	one drop four times a day (QID) during 14 days after routine unilateral cataract surgery. Overall, 210 patients are planned to be randomized into the study. They will be screened across 20 centers in the US. Patients who experience postoperative inflammation on the first day following routine cataract surgery and who meet all other eligibility criteria will be randomized to one of two study groups 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. Patients will undergo routine cataract surgery according to the investigator's normal procedures. The day of the cataract surgery will be considered Day –1 of the study, whereas the day of the randomization and the first administration of the investigational medicinal product (IMP) will be considered Day 1 of the study. Six (6) study visits are planned: Visit –1 (Screening; Day –7 ± 3 days), Visit 1 (Baseline; Day 1, 24h after the surgery), Visit 2 (Day 3 + 1 day), Visit 3 (Day 8 ± 1 day), Visit 4 (Day 15 ± 2 days), and Visit 5 (Day 29 ± 2 days). An attempt should be made to schedule patients at approximately the same time during the day at each study visit. The investigator will administer the first dose of IMP on Day 1 at the study center. Study medication will be then dispensed to patients for self-administration during the study at a dosage of one drop QID during 14 days. Patients will be provided with diaries to record their daily dosing. Doses should be administered approximately 6 hours apart. In addition, patients will be asked to make note of any missed doses and the reason for the missed dosage. The intent is to capture missed doses, per se, rather than a shifted dosing schedule.
Study medication, Dosage, and Route of Administration:	**Test product:** Clobetasol propionate ophthalmic nanoemulsion 0.05% is an oil-in-water (o/w) nanoemulsion containing the active ingredient clobetasol propionate at a concentration of 0.05% weight per weight (w/w). Clobetasol propionate ophthalmic nanoemulsion 0.05% is a clear solution or slightly yellowish nanoemulsion at a concentration of 0.05%. **Reference product (placebo):** Placebo (vehicle) is identical in appearance and composition to clobetasol propionate ophthalmic nanoemulsion 0.05% but without the active substance.
Patient Population:	Patients of 18 years of age and older. At least 210 patients will be randomized (140 to clobetasol arm, 70 to placebo arm, in a 2:1 randomization ratio) in order to have 202 evaluable patients (4% lost to follow-up rate expected).

Rational for the Study:	Cataract surgery is one of the most common surgical procedures performed worldwide. In fact, in 2017, 3.8 million cataracts procedures were performed in the US. Despite of surgical advances, pain and inflammation after ophthalmic surgery continues to be a burden on both patients and physicians. The treatment of postoperative pain is essential for hospitalized patients, but it is even more important for patients who are treated on an outpatient basis. Thus, appropriate counseling and pain management should be provided to improve quality of life. Clobetasol propionate ophthalmic nanoemulsion 0.05% will be administered as a topical ophthalmic nanoemulsion. Patients are expected to self-administer one drop of either clobetasol propionate ophthalmic nanoemulsion 0.05% or placebo control QID. Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. This study will examine effect and tolerability for 14 days of clobetasol propionate ophthalmic nanoemulsion 0.05% dosed QID. This study is being conducted to support an application for approval to market clobetasol propionate ophthalmic nanoemulsion 0.05% in the US for the indication of inflammation and pain after ocular surgery. The reference (comparator) product in this study, the vehicle, is expected to provide a lower efficacy rate when compared to clobetasol 0.05%.
Eligibility Criteria:	**Inclusion Criteria:** 1) Male or female, age 18 years or older on day of consent 2) Patients with routine unilateral cataract surgery on the day prior to study randomization 3) Patients with at least 5 cells in anterior chamber on the first day after surgery (at Visit 1) 4) Willing and able to understand and provide written informed consent form (ICF) (at Visit –1) 5) Women who satisfy one of the following: a) Are of child-bearing potential who are not pregnant or lactating and who are either abstinent or sexually active on an acceptable method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, like hormonal contraception (oral pills, implantable device, or skin patch), intrauterine device, bilateral tubal occlusion, or double barrier) for at least 4 weeks prior to Visit 1 and throughout the study (i.e., until Day 29), OR Are post-menopausal (have had no menstrual cycle for at least one year prior to Visit –1) or have undergone a sterilization procedure (bilateral tubal ligation, hysterectomy, hysterectomy with unilateral

	or bilateral oophorectomy or bilateral oophorectomy) at least 6 months prior to Visit –1 **Exclusion Criteria:** 1) Systemic administration of any corticosteroid or immunosuppressant drugs in the previous 2 weeks prior to the first instillation of the IMP 2) Periocular injection in the study eye of any corticosteroid solution within 4 weeks prior to the first instillation of the IMP, or of any corticosteroid depot within 2 months prior to the first instillation of the IMP (Ozurdex® [dexamethasone]: within prior 6 months; Iluvien® [fluocinolone]: within prior 36 months) 3) Instillation of any topical ocular corticosteroid, non-steroidal antiinflammatory drug (NSAID), mast cells stabilizers, antihistamines or decongestants within 2 weeks prior to the first instillation of the IMP, except pre-surgical and/or surgical administration of 1 drop of a topical NSAID or corticosteroid, at the investigator discretion 4) Prescription of any topical ocular medication, except preservative-free antibiotics for prophylactic purposes 5) Any history of glaucoma or ocular hypertension in the study eye 6) History or presence of endogenous uveitis 7) Any current corneal abrasion or ulceration 8) Any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease 9) Known hypersensitivity or contraindication to the study drug or any of its components 10) History of steroid-related IOP increase 11) Previous surgery in the last 4 weeks prior to the Screening visit (Visit –1) or new surgery scheduled to be performed before the end of the study period on the contralateral eye 12) Presence of ocular hemorrhage which interferes with the evaluation of post-surgery inflammation 13) Presence of intraoperative complications during the cataract surgical procedure that may increase post-operative inflammation; this includes, in particular, patients with ocular hemorrhage, floppy iris syndrome, increased IOP (≥24 mmHg), posterior capsule rupture and injections of gas into the vitreous body 14) Increased cumulative dissipated energy value during phacoemulsification (increased energy used for phacoemulsification exert additional stress on iris and other anterior chamber structures and may generate excessive inflammation) 15) Presence of zonular dialysis (rupture of zonular fibers that attach lens to the ciliar body which may lead to partial luxation of the lens / lens capsule and is a serious complication of cataract surgery)

	16) Presence of Fuchs´ endothelial dystrophy (loss of endothelial cells that may result in chronic corneal edema after cataract surgery especially if high energy was used during phacoemulsfication) 17) Presence of cornea guttata 18) Pupil dilation lower than 4.5 mm 19) Presence of lower lacrimal duct obstruction and/or history of infectious dacryocystitis 20) Presence of IOP ≥24 mmHg in the study eye at Visit 1 21) Participation in any study of an investigational topical or systemic new drug or device within 30 days prior to the Screening visit (Visit –1), or at any time during the study 22) Prior participation in the study described in this protocol, unless patient was not randomized 23) In the opinion of the investigator or Study Coordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eye drops 24) Disease, condition (including monocular patients), or disorder that in the judgement of investigator could confound study assessments or limit compliance to study protocol
Study Evaluations:	Visit –1 (Screening; Day –7 ± 3 days) - ICF signature - Inclusion/exclusion criteria assessment - Demographic data - Relevant medical history - Prior medications - Urine pregnancy test (only for females of childbearing potential) - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS) - Physical and eye examination - Slit-lamp examination: ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates

	- IOP - BCVA measured by Snellen chart - Indirect ophthalmoscopy - Adverse events assessment Visit 1 (Baseline; Day 1, 24h after the surgery) - Inclusion/exclusion criteria assessment - Relevant medical history - Urine pregnancy test (only for females of childbearing potential) - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS) - Vital signs examination - Slit-lamp examination: ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates - IOP - BCVA measured by Snellen chart - Indirect ophthalmoscopy - Prior medications - Randomization of the patient - Dispensation of IMP and administration of the first dose - Distribution of the patient diary - Concomitant medications - Adverse events assessment Visit 2 (Day 3 + 1 day) - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS)

	- Vital signs examination - Slit-lamp examination ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates - IOP - Review of patient diary - Adverse event assessment Visit 3 (Day 8 ± 1 day) - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS) - Vital signs examination - Slit-lamp examination ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates - IOP - BCVA measured by Snellen chart - Review of patient diary - Adverse events assessment - Concomitant medications Visit 4 (Day 15 ± 2 days) and - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS)

	- Vital signs examination - Slit-lamp examination ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates - IOP - BCVA measured by Snellen chart - Indirect ophthalmoscopy - Review and return of the patient diary - Return of the remaining study medication - Adverse events assessment - Concomitant medications Visit 5 (Day 29 ± 2 days) - Eye pain evaluation (VAS) - Eye discomfort evaluation - Photophobia evaluation (VAS) - Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment - Slit-lamp examination ✓ Anterior chamber cell ✓ Anterior chamber flare ✓ Chemosis ✓ Bulbar conjunctival injection ✓ Ciliary injection ✓ Corneal edema ✓ Keratic precipitates - IOP - BCVA measured by Snellen chart - Indirect ophthalmoscopy - Adverse events assessment

	- Concomitant medications
Efficacy Assessments:	**Primary endpoint:** • Proportion of patients with anterior chamber cell grade of "0" (absence of cells) compared to placebo at Day 8 **Key secondary endpoint:** • Proportion of patients with VAS pain score of "0" (no eye pain) compared to placebo at Day 8 **Secondary endpoints:** **Efficacy** • 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 score 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
Safety Assessments:	<u>Safety</u> • Number, frequency and severity of adverse events (AEs) up to Day 29 • Number, frequency and severity of Serious AE (SAE) 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.
Study Medication Compliance:	Compliance will be assessed by comparing study product accountability records with the dosing information recorded daily by the patients in the patient diaries. The center will document this comparison along with verification of the numbers of used and unused study product single-dose vials. The numbers of missed doses as assessed at each clinic visit should be documented in the eCRF as per the patient diary. Patients' diaries will be reviewed by the study staff at each study visit during the treatment period.
Statistical Methods:	*Data sets to be analyzed* Analysis will include the following populations: - 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. - Safety Population: The safety set will be the primary analysis set for the safety endpoints and will include all randomized patients who took at least one dose of IMP. The safety set 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 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. 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 safety set. *Summary statistics* In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, confidence intervals, standard deviation, minimum, Q1, median, Q3 and maximum value. Change from baseline to each post-baseline visit will be also described using descriptive statistics. Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit. Individual patient data will be listed for all enrolled patients. Listings will be sorted by center and patient number and labelled by randomized treatment group. *Missing data* Data not collected after rescue therapy has been initiated will not be considered missing since the primary measure is a responder measure where rescue is considered treatment failure. Patients with missing data for the analysis of the primary endpoint will be assigned the status of treatment failure. *Primary analysis* 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 endpoint in the FAS. 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. The test will be 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 using the chi square statistic. The PP population set will be also tested to confirm the robustness of the primary analysis. *Key Secondary Analysis* The aim of the key secondary analysis of this study is to assess the superiority of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo with respect to the key secondary endpoint in the FAS. 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.

	The test will be the proportion of study eyes with no pain (VAS pain = 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 using the chi square statistic. The PP population set will be also tested to confirm the robustness of the key secondary analysis. *Secondary analysis* For continuous variables, a summary of these endpoints will be prepared at each specified timepoint and will include an estimate of the mean change from baseline for each treatment group and of the adjusted treatment difference and 95% confidence interval. The between-treatment comparison will employ a mixed model of repeated measures (MMRM) with treatment as fixed factor and baseline as a covariate. For categorical variables, a summary of these endpoints will be prepared at each specified timepoint and will include the number and percentage of each category. A chi-square test will be performed. Confidence intervals on the difference between pairwise comparisons of treatments with the placebo group will be computed. These analyses will not be adjusted for study center. 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. *Safety analysis* The analyses of safety and tolerability outcomes will be performed on the safety population. Safety outcomes include AEs, vital signs, physical and eye examination and will be analyzed overall and by treatment arm. More detailed description of the statistical methods will be provided in the statistical analysis plan.

Table of Contents

Figures in Text

Tables in Text

List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
CA	Competent Authority
CFR	Code of Federal Regulations
C_{max}	Maximum serum concentration
eCRF	Electronic Case Report Form
EDTA	EthyleneDiamineTetraacetic Acid
ERG	Electroretinography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INN	International Nonproprietary Name
IOP	Intraocular Pressure
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDPE	Low-density polyethylene
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model of Repeated Measures
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-The-Counter
o/w	oil-in-water
PD	Pharmacodynamics

PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
QID	Four times a day (*Quater In Die*)
QSR	Quality System Regulations
RA	Regulatory Authorities
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
STEAE	Serious Treatment-Emergent Adverse Event
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
US	United States of America
VAS	Visual Analog Scale
w/w	weight per weight

1. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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2. INTRODUCTION

2.1 Background

Global estimates suggest that 94 million people are visually impaired because of cataracts, and of these, 20 million are blind (1). Because the incidence of cataracts increases with age, an increase in the elderly population will lead to a significant increase in cataract prevalence. Cataracts currently affect approximately 26 million Americans (2), and approximately 25% of people in the United States of America (US) aged 65 to 69 years have cataracts, a proportion increasing to more than 68% of those aged over 80 years (3).

Cataract surgery is one of the most common surgical procedures performed worldwide. In fact, in 2017, 3.8 million cataracts procedures were performed in the US. The range of different types of procedures in ophthalmic surgery is broad, and the profile and characteristics of patients are widely varied (healthy young children, elderly patients and patients with multiple concomitant diseases and even neonates). The phacoemulsification technique was introduced in the treatment of cataract in 1967 and gained acceptance in the early 1990s when safety and efficacy improved. The efficacy of the phacoemulsification technique and the increase in life expectancy are the reasons for the increasing number of procedures performed.

Despite of surgical advances, pain and inflammation after ophthalmic surgery continues to be a burden on both patients and physicians (4). Postoperative inflammation is manifested principally as bulbar and ciliary hyperemia, corneal edema and aqueous cells and flare. The treatment of postoperative pain is essential for hospitalized patients, but it is even more important for patients who are treated on an outpatient basis (5).

Although cataract extraction is common, little is known about postoperative recovery and pain after phacoemulsification with intraocular lens implantation. However, knowledge of the postoperative complaints associated with ophthalmic surgery is necessary because these complaints may delay recovery and may significantly influence quality of life after the procedure (6).

The postoperative pain after this procedure was studied and found that 55% of patients had no pain or discomfort postoperatively, 32% reported slight discomfort, 8% of patients experienced mild pain and only 5% suffered moderate to severe pain (5,7).

Pain after ophthalmic surgery may be considered a sign of a possible complication. Severe pain is assumed to be a sign of postoperative inflammation or infection, making it a concern for both patient and physician. However, a surgery without perioperative complications may also be associated with significant postoperative pain during the early recovery. Thus, appropriate counseling and pain management should be provided to improve quality of life (6).

Also, uncontrolled inflammation may lead to serious side effects, such as posterior synechia, uveitis, cystoid macular edema or secondary glaucoma. Management of inflammation is thus a mainstay in modern cataract surgery (8). Despite surgical advances, post-cataract surgery inflammation is still a common cause of patient discomfort, delayed recovery and reduced visual outcome (9).

2.1.1 *Current management of inflammation and pain associated with cataract surgery*

Currently, two classes of drug therapies are considered the standard treatment for both the prophylaxis and treatment of post-cataract ocular inflammation in all patient groups: corticosteroids and Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Many studies have been published over the years examining the efficacy and safety of these preparations, administered

either alone or in combination, yet so far no clear guidelines or consensus has been reached on best practice for the management of post-cataract surgery inflammation (10).

Corticosteroids are traditionally used for short-term control of ocular inflammation and are a mainstay of treatment regimens following cataract surgery. Compared with NSAIDs, corticosteroids have a wider range of activity in relieving inflammation. Ophthalmic corticosteroids have a very well-known effect in ocular tissues such as reduction of the cellular immune response, reduction of inflammatory vascular permeability, stabilization of the blood-aqueous barrier, limitation of fibrinoid exudation, inhibition of fibroblast transdifferentiation, inhibition of epithelial proliferation, inhibition of inflammatory corneal neovascularization, retardation of wound healing, elevation of intraocular pressure and induction of cataracts (11). Corticosteroids act to reduce inflammation at multiple points in the inflammatory cascade, including both the cyclo-oxygenase pathway and the lipoxygenase pathway through inhibition of phospholipase A2, producing a reduction in both prostaglandins and leukotrienes (9).

The administration of current corticosteroids, however, have limitations and are prone to side effects (8). Treatments acting locally and with little or no systemic action are therefore of interest. Effective, safe, and locally acting anti-inflammatory treatments of long-lasting duration administered by immediately post-surgery could benefit both the patients and the health system.

Currently, corticosteroids such as loteprednol (Lotemax® and Inveltys®), dexamethasone (Dextenza® and Dexycu®), difluprednate (Durezol®) and rimexolone (Vexol®) are commercialized for ocular inflammation and pain following ophthalmic surgery (12–17). Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations which could be due to the ease of administration and patient compliance (18,19). All these treatments are delivered as eye drops or are at least topically administered except for one of the formulations of dexamethasone, which is provided as an intracanalicular insert that is reabsorbable and does not require removal (12–17).

2.1.2 *Investigational Medicinal Product (IMP)*

The active ingredient of this investigational new drug (IND) clobetasol propionate ophthalmic nanoemulsion 0.05%, is clobetasol propionate (International Nonproprietary Name [INN]: clobetasol propionate micronized).

Clobetasol propionate is a synthetic fluorinated corticosteroid of the glucocorticoid class approved in the US for the treatment of other inflammatory topical processes since December 27, 1985 (Temovate® Cream) showing a positive benefit-risk profile as its efficacy is widely demonstrated with a good safety profile. Over the years, clobetasol propionate formulations have extended, being now available under various formulations, including cream, ointment, gel, solution, lotion, foam and shampoo, for short-term treatment of various skin conditions. The compound is an analog of prednisolone and has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Clobetasol propionate ophthalmic nanoemulsion 0.05% is being developed in Spain as a nanoemulsion for ocular administration for the proposed indication: treatment of inflammation and pain associated with ocular surgery. Currently, it has not been approved for commercial distribution in any country.

Clobetasol propionate is structurally similar to other corticosteroids, such as difluprednate, which is approved in the US (Durezol®) for the same indication as proposed for the nanoemulsion formulation of clobetasol propionate. Clobetasol propionate ophthalmic nanoemulsion 0.05% would constitute an alternative treatment for the proposed indication.

2.1.3 *Summary of Non-Clinical Findings*

Clobetasol propionate has a well-known anti-inflammatory, anti-pruritic, and vasoconstrictive activity and has been widely used in humans as topical anti-inflammatory drug for many years. Thus, there is extensive non-clinical documentation on chemical and pharmaceutical properties, pharmacology, pharmacokinetics, and toxicology of clobetasol propionate covering various routes of administration, including ocular administration.

Additionally, its safety and efficacy are based on US Food and Drug Administration (FDA)'s findings of safety for previously approved clobetasol propionate drug products and supported by literature publications. The listed reference drugs are:

- Temovate® (clobetasol propionate emollient cream 0.05%)
- Temovate® (clobetasol propionate ointment 0.05%)
- Clobex® Lotion (clobetasol propionate lotion 0.05%)
- Clobex® Spray (clobetasol propionate spray 0.05%)

In addition to the public information about clobetasol propionate safety profile by topical route of administration, the Sponsor has conducted its own non-clinical studies to assess the IND efficacy and safety profile. The following non-clinical studies have been conducted:

- Study BB08-17: Efficacy in a rabbit model of post-surgery inflammation (Paracentesis)
- Study BB07-17: Efficacy in an acute endotoxin-induced uveitis model in rabbit
- Study BB09-17: Systemic exposure in rabbit after ophthalmic administration
- Study BB10-17: Ocular tissue distribution after ophthalmic administration in pigmented and non-pigmented rabbits
- Study 17C369Q1G124/ 18C369Q1G150: Evaluation of the safety and distribution after ophthalmic topical administration into Dutch belted rabbits

The whole detail and results of these non-clinical studies can be found in the Investigator Brochure.

The pivotal non-clinical studies have been performed following a complete evaluation of different parameters like among others clinical signs, hematology, clinical chemistry parameters, gross pathology, organ weights, histopathology, toxico-kinetics and ocular distribution, clinical ophthalmic examinations, intraocular pressure measurements and electroretinography, being an exhaustive evaluation of the safety profile of the new IND.

<u>Non-clinical pharmacology</u>

The proposed clinical posology for this phase 3 study is one drop (0.03 mL) of the IND into the affected eye four times a day (QID) for a 14-day treatment period. The Sponsor has performed two pharmacodynamics (PD) studies that confirmed the suitability of the proposed dose by ocular administration (Study BB08-17 and study BB07-17). The IND exhibited anti-inflammatory efficacy significantly decreasing prostaglandin E2 (PGE2) levels in aqueous humor in a well-established post-surgery *in vivo* inflammation rabbit model and in an acute endotoxin-induced uveitis rabbit model.

<u>Safety Pharmacology</u>

The safety pharmacology of the IND relies on the data obtained in 1975 by Irie et al (20). The studies conducted consisted of an assessment of the neurological, cardiovascular, pulmonary, renal and gastrointestinal effects where clobetasol propionate was administered via intraperitoneal, intravenous and subcutaneous routes.

Pharmacokinetics (PK)

Pharmacokinetics evaluation of the IND is based on three non-clinical studies (study BB09-17, study BB10-17 and study 17C369Q1G124/18C369Q1G150) and is further completed by data of two studies that assessed the PK of clobetasol propionate ointment in animal models following subcutaneous and percutaneous administration of Temovate® Cream (21), and three animal model studies assessing the dermal toxicity of clobetasol propionate spray (Clobex® Spray) (22).

Clobetasol propionate showed poor systemic absorption in all the ophthalmic administration studies, with systemic exposure in rabbits below the limit of quantification (1 ng/mL) after single instillation, being still low even after 28 days of QID topical ophthalmic dosing in Dutch belted rabbits (Cmax values were mostly below 10 ng/mL). After ophthalmic administration, clobetasol propionate exhibited a high bioavailability in cornea and aqueous humor but the concentrations of the product were negligible in the other analyzed ocular tissues. No differences in product concentrations and ocular distribution were observed between the assessed rabbit strains.

The excretion of topically ophthalmic administered IND is expected to follow the same pattern that subcutaneous and dermal administration, whereby most of the administered dose is excreted in feces.

Toxicity

Clobetasol propionate has been widely used as a dermal corticosteroid for several years to treat various skin disorders. Therefore, there is a well-known reported toxicity data in different animal models that have endorsed the topical use of this drug substance in humans.

The complete formulation of the IND contains excipients, which are mostly used for ophthalmic administration according to the FDA inactive ingredients database and at similar concentrations.

Study 17C369Q1G124/18C369Q1G150 undertook a complete evaluation to confirm the ocular toxicity in order to ensure the safety profile of the IND analyzing from general morphological ocular observations up to specific tissue functionality. Ocular discharge was seen in multiple animals throughout the dosing period. Nevertheless, histopathological analysis of the eyes, including bulbar conjunctiva and cornea, did not reveal any associated inflammation or other pathology of the epithelium, proving that ocular discharge was not considered adverse. Intraocular pressure (IOP) remained in the normal physiological range throughout the study and did not differ substantially between control and treatment groups. Electroretinography (ERG) analysis indicating normal function of the inner and outer retina and no clear pattern of changes in amplitude vs. implicit time was found. Furthermore, histopathological analysis of the eyes found no pathological changes in the retina and therefore no correlation with the minimal ERG changes observed.

The evaluation of the ocular tolerance and safety profile was completed with the 28-day toxicity study (study 17C369Q1G124/18C369Q1G150) where animals received a bilateral dose of one drop (0.03 mL, equivalent to 0.015 mg of clobetasol)/eye QID during 28 days' treatment, with a maximum exposure of 0.12 mg clobetasol/day (3.36 mg of clobetasol propionate over

a period of 28 days). The treatment duration of the proposed phase 3 clinical trial is 14 days and the duration of the pivotal repeated dose toxicity study is 28 days.

This study showed that the IND exhibited no ocular toxicity and only expected corticosteroid-related systemic changes with repeated topical ophthalmic administration. The no-observed-adverse-effect level (NOAEL) for ocular toxicity in this study was 0.132 mg/eye, which is above the planned maximum dose of the proposed phase 3 study (0.066 mg/eye/day, for a total of 0.924 mg/eye over 14 days). Thus, the duration of the repeated-dose toxicity assessment is considered sufficient to support the phase 3 clinical trial.

Human equivalent dosing

In order to evaluate the rabbit/human systemic dose safety margins, the comparison of Human Equivalent Dose (HED) in rabbits (one drop of IND QID to both eyes) to the various total daily doses in adults and children (one drop of IND QID to one or both eyes) was performed based on relevant body weight and conversion factors to estimate exposure (FDA Guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005).

Systemic HED in the rabbit study was 17 - or 8.4- times higher compared to dosing in one or both eyes of adults, respectively and 8.2 -or 4.1- times higher compared to dosing in one or both eyes of children, respectively.

Considering the above margin safety calculations and taking into account that the phase 3 trial will use the same clinical concentration (0.05%) for a shorter treatment period (14 days vs. 28 days for the pivotal non-clinical study), and that systemic exposure by ocular route will be lower, thus leading to safer profiles if compared to other studied administration routes (oral, intraperitoneal, intravenous and subcutaneous), the Sponsor considers the non-clinical data sufficient to support a human phase 3 study.

2.1.4 *Summary of Clinical Findings*

No clinical trials have yet been performed with the IND in the proposed indications, although the active substance (clobetasol propionate) is approved and commonly used as a topical agent for skin disorders, and therefore, there is considerable exposure of the general population to this agent.

The summary of findings from non-clinical studies that potentially have clinical significance can be found in Section 2.1.3 and in the Investigator Brochure.

2.2 Rationale for the Study

Cataract surgery is one of the most common surgical procedures performed worldwide. In fact, in 2017, 3.8 million cataracts procedures were performed in the US.

Despite of surgical advances, pain and inflammation after ophthalmic surgery continues to be a burden on both patients and physicians. The treatment of postoperative pain is essential for hospitalized patients, but it is even more important for patients who are treated on an outpatient basis.

Also, pain after ophthalmic surgery may be considered a sign of a possible complication. Severe pain is assumed to be a sign of postoperative inflammation or infection, making it a concern for both patient and physician. However, a surgery without perioperative complications may also be associated with significant postoperative pain during the early

recovery. Thus, appropriate counseling and pain management should be provided to improve quality of life.

Clobetasol propionate ophthalmic nanoemulsion 0.05% will be administered as a topical ophthalmic nanoemulsion.

Patients are expected to self-administer one drop of either clobetasol propionate ophthalmic nanoemulsion 0.05% or placebo control QID.

Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. This study will examine effect and tolerability for 14 days of clobetasol propionate ophthalmic nanoemulsion 0.05% dosed QID.

This study is being conducted to support an application for approval to market clobetasol propionate ophthalmic nanoemulsion 0.05% in the US for the indication of inflammation and pain after ocular surgery. The reference (comparator) product in this study, the vehicle, is expected to provide a lower efficacy rate when compared to clobetasol 5%.

2.3 Risk-Benefit Assessment

Benefits

Clobetasol is a synthetic fluorinated corticosteroid. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Older corticosteroids have been used since the 1950's, while new molecules were more recently developed and have been proven effective in controlled clinical trials.

Ophthalmic corticosteroids have a very well-known effect by decreasing the number and function of inflammatory cells, vascular permeability, and by inhibiting chemical mediators of inflammation, thus it could be considered that corticosteroids have a class effect for their indications in post-surgical inflammation.

Particularly, clobetasol propionate has been approved for the treatment of other inflammatory topical processes for over 30 years (Temovate® Cream) showing a positive benefit-risk profile as its efficacy is widely demonstrated with a good safety profile. Moreover, the use of corticosteroids for short-term treatment of local inflammation, usually in the anterior segment of the eye (including inflammation post-surgery) is widely supported in the literature.

Risks

It is known that exogenous corticosteroids can cause hypertension and other cardiovascular adverse effects including a hypercoagulability state and dyslipidemia. However, these adverse effects are linked to long-term systemic exposure to corticosteroids.

Ocular administration of clobetasol propionate and other corticosteroids have been linked to rare ocular adverse events (AEs) such as IOP elevation, cataracts, ocular hypertension, glaucoma or inhibition of wound healing. The limited exposure planned for this study (one drop QID/14 days) aims to prevent these rare AEs.

Benefit-Risk Assessment

Topical corticosteroids are safer than systemic glucocorticoids due to the lower systemic exposure. Furthermore, ocular administration results in even lower systemic exposure, below

limits of quantitation in different studies. In relation to systemic exposure, the local administration of ocular corticosteroids enables the use of smaller doses for equivalent or greater local corticosteroid concentration, more target-specific drug application, and reduced risk of systemic AEs. Non-clinical studies showed that clobetasol propionate ophthalmic nanoemulsion 0.05% exhibited no ocular toxicity and only expected corticosteroid-related systemic changes with repeated topical ophthalmic administration. Furthermore, the clinical dose and systemic exposure are expected to be lower in humans than in the animal model used (please consult the investigator Brochure for further information).

Systemic absorption is not expected after ocular administration of clobetasol propionate ophthalmic nanoemulsion 0.05%, thus lowering the risks of systemic adverse reactions (AR) usually seen with clobetasol propionate or other corticosteroids, while acting locally to reduce ocular inflammation and pain.

In summary, considering that:

- The safety profile of corticosteroids, including topical clobetasol propionate, is very well known;
- Corticosteroids have been used by ophthalmologists over the past 50 years;
- Ophthalmologic administration of corticosteroids for the treatment of inflammation and pain associated with cataract surgery shows a positive benefit-risk profile;
- Systemic exposure of corticosteroids after ophthalmic administration is minimal, and is expected to be even lower with clobetasol propionate ophthalmic nanoemulsion 0.05%;
- Results from preclinical studies with clobetasol propionate ophthalmic nanoemulsion 0.05% showed no ocular toxicity and systemic levels under the limit of quantification,

The Sponsor believes that the data presented above support the conduct of the proposed phase 3 clinical trials of clobetasol propionate ophthalmic nanoemulsion 0.05% for the treatment of inflammation and pain associated with cataract surgery.

3. OBJECTIVES

3.1 Primary Objective

Efficacy

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

3.2 Secondary Objectives

a) 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.

b) 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%.

4. OVERALL DESIGN AND PLAN OF THE STUDY

4.1 Overview

This is a phase 3, randomized, parallel-group, double-masked, placebo-controlled, multicenter study.

This study will compare the efficacy and safety of clobetasol propionate ophthalmic nanoemulsion 0.05% to placebo (vehicle), when administering one drop QID during 14 days after routine unilateral cataract surgery.

Approximately a 15% of screening failures is expected. Overall, 210 patients are planned to be randomized into the study. They will be screened across 20 centers in the US. Patients who experience postoperative inflammation on the first day following routine cataract surgery and who meet all other eligibility criteria will be randomized to one of two study groups 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.

Patients will undergo routine cataract surgery according to the investigator's normal procedures.

The day of the cataract surgery will be considered Day –1 of the study, whereas the day of the randomization and the first administration of the IMP will be considered Day 1 of the study.

Six study visits are planned: Visit –1 (Screening; Day –7 ± 3 days), Visit 1 (Baseline; Day 1, 24h after the surgery), Visit 2 (Day 3 + 1 day), Visit 3 (Day 8 ± 1 day), Visit 4 (Day 15 ± 2 days), and Visit 5 (Day 29 ± 2 days) (Table 1). An attempt should be made to schedule patients at approximately the same time during the day at each study visit.

If a patient wants to discontinue from the study, he/she will be treated according to the clinical practice. Patients who discontinue the study treatment will be requested to continue attending their remaining study visits. If the patient does not accept and wants to discontinue from the study, they will be encouraged to at least attend the Early Termination Visit (Section 4.3.2.8) as soon as possible.

An informed consent form (ICF) must be obtained from each patient prior to the commencement of any study procedure. All patients must be given ample time to review the ICF and to ask any question related to the study prior to their participation. All participant patients will be provided with a copy of the signed ICF.

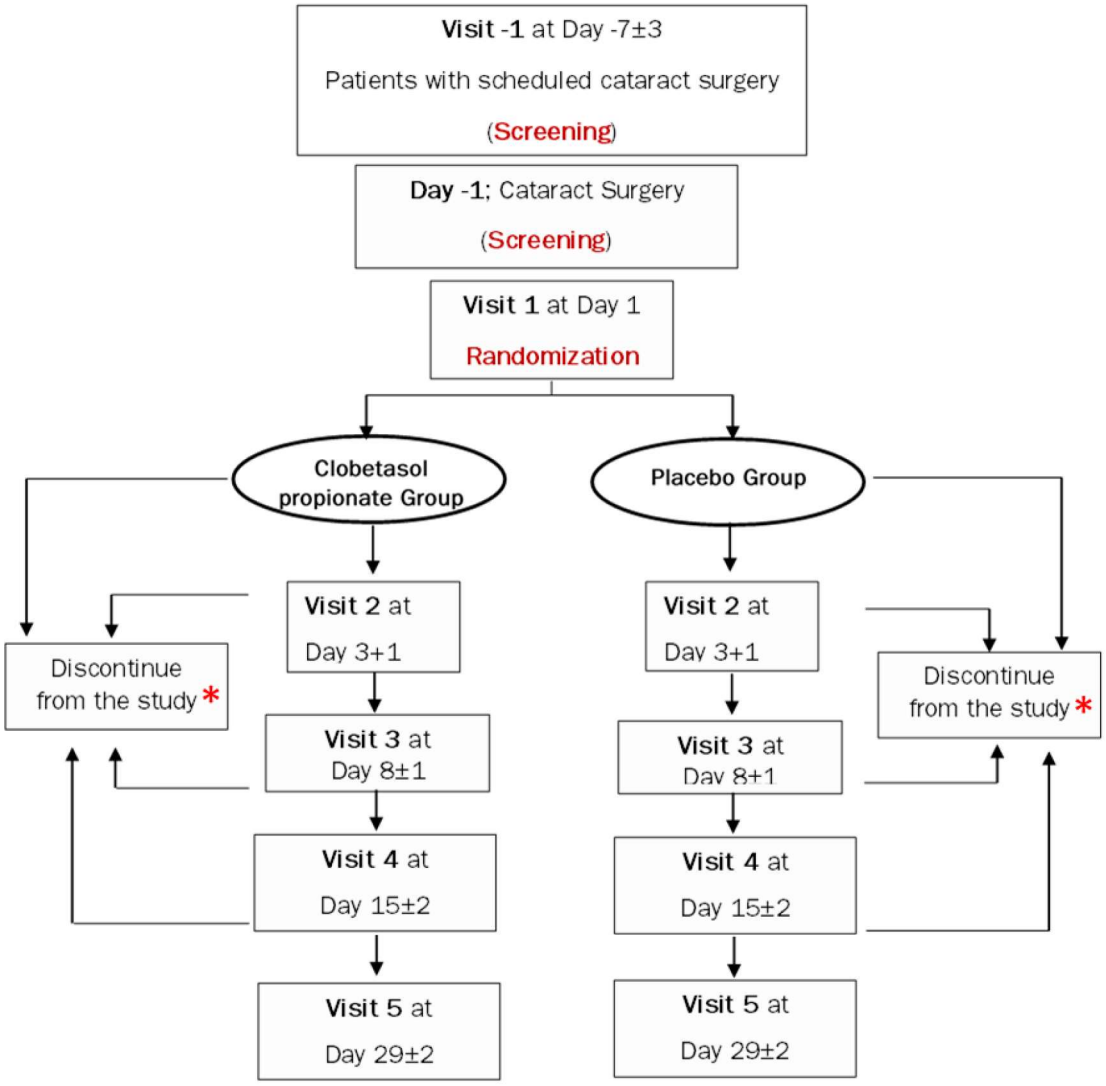
The investigator will administer the first dose of IMP on Day 1 at the study center. Study medication will be then dispensed to patients for self-administration during the study at a dosage of one drop QID during 14 days.

Patients will be provided with diaries to record their daily dosing. Doses should be administered approximately 6 hours apart. In addition, patients will be asked to make note of any missed doses and the reason for the missed dosage. The intent is to capture missed doses, *per se*, rather than a shifted dosing schedule.

As this is a double-masked study, all patients, investigators, sub-investigators, and center personnel involved in measuring, monitoring and obtaining data in the study will be masked to patient treatment assignment. The study medication will be packaged in a masked fashion and will be administered and dispensed by the investigator according to patients' randomization numbers. In addition, all Sponsor's and vendors' personnel involved in the on-site monitoring and direct management of the data and study centers will remain masked to individual patient data.

Protocol waivers of exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Table 1, are essential and required for study conduct.

Figure 3 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 Justification for Study Design

This is a randomized, parallel group, double-masked, placebo-controlled, multicenter study, efficacy, safety and tolerability phase 3 study. Full details on study design are presented in Section 4.1.

Clobetasol propionate is marketed in the US for short-term topical use since 1985 (Temovate® Cream) and under many different proprietary names (Clobevate®, Cormax®, Embeline®, Olux®, Clobex®, etc...) over the years, showing a positive benefit-risk profile with a good long-term safety profile. There is extensive non-clinical documentation on chemical and pharmaceutical properties, pharmacology, PK, and toxicology of clobetasol propionate covering various routes of administration, including ocular administration.

Additionally, the Sponsor has conducted its own non-clinical studies to assess the Clobetasol propionate ophthalmic nanoemulsion 0.05% efficacy and safety profile (Section 2.1.3) and considers this non-clinical data sufficient to support a human phase 3 study.

The study is double-masked, and placebo controlled to ensure unbiased data collection and to account for the placebo effect.

4.3 Study Conduct

4.3.1 *Schedule of Observations*

A schedule of observations and assessments to be performed during the study is provided in Table 1.

Table 1 Schedule of Observations

Visit number	Visit –1 Screening	Cataract Surgery	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Early termination
Study time-point	**Day -7 (± 3 days)**	**Day –1**	**Day 1**	**Day 3 (+ 1 day)**	**Day 8 (± 1 day)**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	
Eligibility criteria	X		X					
Dated and signed Informed consent for study participation [1]	X							
Demographic data	X							
Relevant medical history [2]	X		X					
Prior medications [3]	X		X					
Urine pregnancy test	X		X					
Eye pain (VAS) [4]	X		X	X	X	X	X	X
Eye discomfort [4]	X		X	X	X	X	X	X
Photophobia (VAS) [4]	X		X	X	X	X	X	X
Vital signs examination [5]			X	X	X	X	X	X
Physical and eye examination	X							X
Slit-lamp examination	X		X	X	X	X	X	X
Intraocular pressure	X		X	X	X	X	X	X
Best-corrected visual acuity - Snellen	X		X		X	X	X	X
Indirect ophthalmoscopy	X		X			X	X	X
Randomization			X					
Dispensation of IMP			X					
Administration of first IMP dose			X					
Distribution of patient diary			X					
Review of patient diary				X	X	X		X[6]
Return of patient diary						X		X[6]

Return of remaining IMP						X		X[6]
Adverse events [7]	X		X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X
End of study							X	X

Abbreviations: IMP, investigational medicinal product; VAS, visual analog scale.

All ocular assessments must be performed in both eyes.

1. Informed consent must be signed and dated prior to any study-related procedure and before any data is recorded in the case report form
2. Relevant medical history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures). Relevant medical history at Visit 1 (Day 1) will cover the time from the Visit –1 (Screening).
3. Medications taken 2 months prior to Visit -1 (prior 36 months for ocular implants and/or intravitreal injections)
4. VAS scales and discomfort should be assessed prior to any physical evaluation
5. Vital signs assessments to be completed 15 min before any ocular assessment. Additionally, baseline Vital signs on Visit 1 to be completed at least 30 ± 10 min before IMP administration.
6. If occurred within the 14 days planned for the treatment period.
7. Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as adverse events.

4.3.2 *Observations by Visit*

The study assessments described in the sections below are presented in detail in Section 7.2 (Primary Efficacy Assessments), Section 7.5.1 (Demographic and Baseline Data) and Section 8 (Assessments of Safety). Recording and reporting of AEs are described in detail in Section 8.3.

The day of the cataract surgery will be considered Day –1 of the study, whereas the day of the randomization and the first administration of the IMP will be considered Day 1 of the study.

The order of the assessments/activities within a visit will be performed depending on the center/investigator's preference, with the exception of:

- Written informed consent at Visit –1 (Screening visit) should be obtained before any study specific procedure.
- Assessment of inclusion/exclusion criteria at Visit 1 (Baseline) before any other study assessment/activity.
- VAS scales should be assessed prior to any physical evaluation throughout the study.
- Vital signs should be obtained at least 15 min before any ocular assessment throughout the study. Additionally, at Visit 1 vital signs should be obtained at least 30 ± 10 min before IMP administration. Vital signs should be obtained for a patient in the same manner throughout the study, for instance obtained from the same arm.
- Assessments/activities at Visit 1 that should be performed before the IMP administration.

The timing of all study events is shown in Table 1.

An attempt should be made to schedule patients at approximately the same time during the day at each study visit.

Detailed information on study assessments is provided in Sections 7 and 8.

4.3.2.1 Visit –1 (Screening visit at Day –7 ± 3 days)

This visit will be coincident (whenever possible) with the standard of care pre-surgery scheduled visit.

Before participating in the study, patients will be informed both verbally and in writing about the purpose of the study, its procedures and any risks or discomforts involved with participation.

A signed ICF must be obtained from each participant before any study-related procedure can take place. Only patients who fulfil all eligibility criteria (Section 5) will be enrolled in the study.

At Visit –1, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- ICF signature
- Inclusion/exclusion criteria assessment
- Demographic data
- Relevant medical history
- Prior (2 months; 36 months for ocular implants and/or intravitreal injections) medications
- Urine pregnancy test – only for females of childbearing potential
- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Physical and eye examination
- Slit-lamp examination
    - ✓ Anterior chamber cell
    - ✓ Anterior chamber flare
    - ✓ Chemosis
    - ✓ Bulbar conjunctival injection
    - ✓ Ciliary injection
    - ✓ Corneal edema
    - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart
- Indirect ophthalmoscopy
- Adverse events assessment

4.3.2.2 Visit 1 (Baseline visit at Day 1, 24 h after the cataract surgery)

At Visit 1, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

Prior to IMP administration:

- Inclusion/exclusion criteria assessment
- Relevant medical history
- Urine pregnancy test – only for females of childbearing potential
- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment; also to be completed at least 30 ± 10 min before IMP administration
- Slit-lamp examination
    - ✓ Anterior chamber cell
    - ✓ Anterior chamber flare
    - ✓ Chemosis
    - ✓ Bulbar conjunctival injection
    - ✓ Ciliary injection
    - ✓ Corneal edema
    - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart
- Indirect ophthalmoscopy
- Prior medications
- Randomization of the patient
- Dispensation of IMP and administration of the first dose

After IMP administration:

- Distribution of patient diary:
    - Throughout the study, patients or caregivers should record on it: doses and schedule of IMP administration, eye pain VAS scores and cataract surgery-associated symptoms.
- Concomitant medications
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs. Additionally, the routine cataract surgery at Day –1 will not be reported as an AE.)

4.3.2.3 Visit 2 (Day 3 + 1 day)

At Visit 2, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment
- Slit-lamp examination
    - ✓ Anterior chamber cell
    - ✓ Anterior chamber flare
    - ✓ Chemosis
    - ✓ Bulbar conjunctival injection
    - ✓ Ciliary injection
    - ✓ Corneal edema
    - ✓ Keratic precipitates
- IOP
- Review of patient diary
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs)
- Concomitant medications

4.3.2.4 Visit 3 (Day 8 ± 1 day)

At Visit 3, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment
- Slit-lamp examination
    - ✓ Anterior chamber cell
    - ✓ Anterior chamber flare
    - ✓ Chemosis
    - ✓ Bulbar conjunctival injection
    - ✓ Ciliary injection
    - ✓ Corneal edema
    - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart

- Review of patient diary
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs)
- Concomitant medications

4.3.2.5 Visit 4 (Day 15 ± 2 days)

At Visit 4, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment
- Slit-lamp examination
  - ✓ Anterior chamber cell
  - ✓ Anterior chamber flare
  - ✓ Chemosis
  - ✓ Bulbar conjunctival injection
  - ✓ Ciliary injection
  - ✓ Corneal edema
  - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart
- Indirect ophthalmoscopy
- Review and return of the patient diary
- Return of the remaining study medication
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs)
- Concomitant medications

4.3.2.6 Visit 5 (Day 29 ± 2 days)

At Visit 5, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation

- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment
- Slit-lamp examination
  - ✓ Anterior chamber cell
  - ✓ Anterior chamber flare
  - ✓ Chemosis
  - ✓ Bulbar conjunctival injection
  - ✓ Ciliary injection
  - ✓ Corneal edema
  - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart
- Indirect ophthalmoscopy
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs)
- Concomitant medications

4.3.2.7 Unscheduled Visit

If an unscheduled visit is necessary to follow an intercurrent event, any untoward findings related to that event should be captured as AEs and/or as concomitant therapies on source documents and relevant sections of the electronic case report form (eCRF). If the event meets the requirement for an SAE, please record on the SAE section of the eCRF and follow all SAE-related procedures (see Section 8.3.5).

4.3.2.8 Early Termination Visit

At any time, the investigator will make every attempt to ensure that an Early Termination Visit will be held in the case of a patient discontinuing the study (see Section 5.3).

At the Early Termination Visit, the following activities and assessments will be performed (**NOTE**: All ocular assessments must be performed in both eyes):

- Eye pain (VAS) – to be assessed prior to any physical evaluation
- Eye discomfort – to be assessed prior to any physical evaluation
- Photophobia (VAS) – to be assessed prior to any physical evaluation
- Vital signs examination (temperature, blood pressure and pulse) – to be completed 15 min before any ocular assessment
- Physical and eye examination
- Slit-lamp examination
  - ✓ Anterior chamber cell
  - ✓ Anterior chamber flare

  - ✓ Chemosis
  - ✓ Bulbar conjunctival injection
  - ✓ Ciliary injection
  - ✓ Corneal edema
  - ✓ Keratic precipitates
- IOP
- BCVA measured by Snellen chart
- Indirect ophthalmoscopy
- Review and return of the patient diary
- Return of the remaining study medication
- AE assessment (**NOTE**: Expected changes or the presence of inflammation or pain resulting from routine cataract surgery will not be captured as AEs)
- Concomitant medications

4.3.3 *Study Period*

The anticipated first patient in (FPI) is 1Q 2020 and the planned last patient last visit (LPLV) is 4Q 2020.

4.3.4 *Study Termination*

The end of study is defined as the date of the LPLV.

5. STUDY POPULATION

5.1 Inclusion Criteria

Patients will be eligible for study participation if they meet all of the following criteria:

1) Male or female, age 18 years or older on day of consent
2) Patients with routine unilateral cataract surgery on the day prior to study randomization
3) Patients with at least 5 cells in anterior chamber on the first day after surgery (at Visit 1)
4) Willing and able to understand and provide written ICF (at Visit –1)
5) Women who satisfy one of the following:
   a) Are of child-bearing potential who are not pregnant or lactating and who are either abstinent or sexually active on an acceptable method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, like hormonal contraception (oral pills, implantable device, or skin patch), intrauterine device, bilateral tubal occlusion, or double barrier) for at least 4 weeks prior to Visit 1 and throughout the study (i.e., until Day 29),

      OR

   b) Are post-menopausal (have had no menstrual cycle for at least one year prior to Visit –1) or have undergone a sterilization procedure (bilateral tubal ligation, hysterectomy, hysterectomy with unilateral or bilateral oophorectomy or bilateral oophorectomy) at least 6 months prior to Visit –1

5.2 Exclusion Criteria

The patients meeting any of the following criteria will not be permitted to enter the study:

1) Systemic administration of any corticosteroid or immunosuppressant drugs in the previous 2 weeks prior to the first instillation of the IMP
2) Periocular injection in the study eye of any corticosteroid solution within 4 weeks prior to the first instillation of the IMP, or of any corticosteroid depot within 2 months prior to the first instillation of the IMP (Ozurdex® [dexamethasone]: within prior 6 months; Iluvien® [fluocinolone]: within prior 36 months).
3) Instillation of any topical ocular corticosteroid, NSAID, mast cells stabilizers, antihistamines or decongestants within 2 weeks prior to the first instillation of the IMP, except pre-surgical and/or surgical administration of 1 drop of a topical NSAID or corticosteroid, at the investigator discretion
4) Prescription of any topical ocular medication, except preservative-free antibiotics for prophylactic purposes
5) Any history of glaucoma or ocular hypertension in the study eye
6) History or presence of endogenous uveitis
7) Any current corneal abrasion or ulceration
8) Any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease
9) Known hypersensitivity or contraindication to the study drug or any of its components
10) History of steroid-related IOP increase

11) Previous surgery in the last 4 weeks prior to the Screening visit (Visit –1) or new surgery scheduled to be performed before the end of the study period on the contralateral eye

12) Presence of ocular hemorrhage which interferes with the evaluation of post-surgery inflammation

13) Presence of intraoperative complications during the cataract surgical procedure that may increase post-operative inflammation; this includes, in particular, patients with ocular hemorrhage, floppy iris syndrome, increased IOP (≥24 mmHg), posterior capsule rupture and injections of gas into the vitreous body

14) Increased cumulative dissipated energy value during phacoemulsification (increased energy used for phacoemulsification exert additional stress on iris and other anterior chamber structures and may generate excessive inflammation)

15) Presence of zonular dialysis (rupture of zonular fibers that attach lens to the ciliar body which may lead to partial luxation of the lens / lens capsule and is a serious complication of cataract surgery)

16) Presence of Fuchs´ endothelial dystrophy (loss of endothelial cells that may result in chronic corneal edema after cataract surgery especially if high energy was used during phacoemulsfication)

17) Presence of *cornea guttata*

18) Pupil dilation lower than 4.5 mm

19) Presence of lower lacrimal duct obstruction and/or history of infectious dacryocystitis

20) Presence of IOP ≥24 mmHg in the study eye at Visit 1

21) Participation in any study of an investigational topical or systemic new drug or device within 30 days prior to the Screening visit (Visit –1), or at any time during the study

22) Prior participation in the study described in this protocol, unless patient was not randomized

23) In the opinion of the investigator or study coordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eye drops

24) Disease, condition (including monocular patients), or disorder that in the judgement of Investigator could confound study assessments or limit compliance to study protocol

5.2.1 *Restrictions*

Patients will be permitted to continue all their current ocular treatments, including the use of artificial tears, eyelid massage, or warm compresses, if they commit to using the same brand/regimen throughout the study.

None of the ocular treatments, whether over the counter (OTC) or prescription or study medication, should be used within 5 minutes of another ocular treatment during the study. Study medication should not be used within 30 minutes prior to any study visit.

5.3 Withdrawal, Premature Discontinuation of Study Medication, and Replacement of Patients

Patients are free to discontinue their participation in the study at any time. Additionally, patients may be withdrawn from study at any time, if deemed necessary by the investigator

(after discussion with the Medical Monitor). Withdrawal from the study will not affect or prejudice the patients' further care or treatment.

Potential reasons for withdrawal of patients from this study are:

- The decision of a patient to withdraw informed consent
- Patient is lost to follow-up (Section 5.3.1)
- Potential reasons for premature discontinuation of study medication include, but are not limited to: Occurrence of a treatment-emergent AE (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the patient if he/she continues to receive study medication. The investigator must follow the patient until the AE resolves or satisfactorily stabilizes
- Administration of a rescue medication. Any patient placed on rescue therapy will discontinue the use of the IMP (see Sections 6.7.1 and 6.7.2)
- Patient's failure to comply with protocol requirements or study related procedures
- In case of pregnancy. The investigator will continue the follow-up of the patient until the end of the pregnancy
- Any surgery (different from the actual routine cataract surgery on the study eye) in the study or contralateral eye

In any case of premature discontinuation of study medication, the investigator must make extensive efforts to ensure that the patient will attend all his/her remaining study visits until study completion (at Visit 5), aiming to collect the most complete efficacy and safety data.

The reason and date the patient is withdrawn from the study will be documented in the eCRF (e.g. lost to follow-up, consent withdrawn, AEs, etc.).

If a patient is withdrawn from the study, the investigator should attempt to complete all discharge procedures (including the Early Termination Visit; Section 4.3.2.8). All AE s should be followed up according to Section 8.3.6.

If a patient is withdrawn from the study, or withdraw his/her consent, all data collected until the time of withdrawal will be used in the analyses, unless this is prohibited by local regulations.

Patients who drop out from the study will not be replaced.

5.3.1 *Lost to Follow-up*

A patient will be considered lost to follow-up if he/she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a patient fails to return to the center for a required study visit:

- The center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.3.2 *Premature Termination of the Study*

The investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The Institutional Review Board (IRB) and Regulatory Authorities (RA) should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study, or potential study patients
- A decision on the part of the Sponsor to suspend or discontinue development of clobetasol propionate ophthalmic nanoemulsion 0.05%
- The Sponsor decides to discontinue the study

If the RA obtains information that raises doubts about the safety or scientific validity of the clinical study, the RA can suspend or prohibit the study.

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients.

5.4 Planned Sample Size

The study will be conducted in approximately 20 centers in the US. Approximately a 15% of screening failures is expected. At least 210 patients will be randomized (140 to clobetasol arm, 70 to placebo arm, in a 2:1 randomization ratio) in order to have 202 evaluable patients (4% lost to follow-up rate expected).

A rationale of the calculation of sample size is provided in Section 9.1.1.

Patient selection will be based on the inclusion and exclusion criteria. Patients who meet each of the inclusion criteria at the Screening Visit and/or Baseline Visit (as applicable) and none of the exclusion criteria at the Screening Visit and/or Baseline Visit (as applicable) are eligible to be randomized in this study. A patient could be re-screened only after the Sponsor's approval.

5.5 Patient Identification and Randomization

Patients will be randomized at Visit 1, (24 h after cataract surgery) after eligibility criteria re-valuation. Randomization will be conducted through an Interactive Web Response System (IWRS) include blocking. The IWRS will assign a patient number, which will be used to identify the patient during screening and, if applicable, throughout the duration of the study. Patients who do not meet the eligibility criteria will be registered as screen failures through the IWRS.

6. STUDY MEDICATION

6.1 Identity

Investigational Medication

Generic name	Clobetasol propionate ophthalmic nanoemulsion 0.05 %
Trade name	Not applicable
Dosage form	Ophthalmic nanoemulsion, sterile
Manufacturer	SALVAT
Description	Ophthalmic nanoemulsion in single-dose low-density polyethylene (LDPE) translucent vials containing 0.17 mL deliverable volume

Reference Medication

Generic name	Vehicle
Trade name	Not applicable
Dosage form	Ophthalmic nanoemulsion, sterile
Manufacturer	SALVAT
Description	Ophthalmic nanoemulsion in single-dose low-density polyethylene (LDPE) translucent vials containing 0.17 mL deliverable volume

Clobetasol propionate ophthalmic nanoemulsion 0.05% is an oil-in-water (o/w) nanoemulsion containing the active ingredient clobetasol propionate at a concentration of 0.05% weight per weight (w/w). The compendial name as per the European Pharmacopoeia is clobetasol propionate.

Clobetasol propionate ophthalmic nanoemulsion 0.05% is a clear solution or slightly yellowish nanoemulsion at a concentration of 0.05%.

Placebo (vehicle) is identical in appearance and composition to clobetasol propionate ophthalmic nanoemulsion 0.05% but without the active substance.

Inactive ingredients in the IMPs are polysorbate 80, medium chain triglycerides, benzalkonium chloride, ethylenediaminetetraacetic acid (EDTA), povidone, tris(hydroxymethyl)aminomethane hydrochloride, tris(hydroxymethyl)aminomethane, glycerin and water for injection.

6.2 Administration

Study medication will be supplied in single-dose vials containing 0.20 mL (approximately 0.17 mL deliverable volume) per vial. A medication kit contains 6 pouches with 2 strips of 5 vials in each pouch, for a total of 60 vials and a plastic bag labelled with the kit number.

The first dose of the IMP should be administered by the investigator or a designated study team member at Visit 1. After that, the investigator or a designated study team member will remove 4 vials from the opened pouch. He or she will place the removed vials (used one and unused ones) in a bag provided with the kit and store them at the study site in a secure location for traceability. The remaining 5 vials will be returned to the medication kit, for dispensation to the patient. Finally, the patient will receive a kit with 55 vials for their self-administration in the study eye QID for 14 consecutive days.

6.2.1 *Method of Assigning Patients to Treatment Groups*

A total of 210 patients will be randomized 2:1 to the following 2 arms:

1. Clobetasol propionate ophthalmic nanoemulsion 0.05%: 140 patients
2. Placebo: 70 patients

Patients will be randomized into one of two arms, based on a computer-generated 2:1 ratio randomization schedule. A randomization number will be assigned to each patient in addition to the patient ID number.

The disclosure of the randomization schedule will be done when finishing the evaluation of the corresponding arm or in case it is needed to provide convenient medical care to any patient due to AEs.

6.2.2 *Dose and Treatment Regimens in the Study*

The IMP will be administered as ophthalmic treatment.

The proposed clinical posology is one drop (0.03 mL) of IMP into the affected eye QID for a 14-day treatment period. Doses should be administered approximately 6 hours apart.

This posology is selected based on pre-clinical data of clobetasol propionate ophthalmic micronized. Systemic HED in the rabbit study was 17-times higher compared to dosing in one eye of adults.

Accordingly, the suggested dose for this study is aligned with current efficacy and safety-proved doses of clobetasol.

If a patient's medication is lost by breakage or spillage, the investigator will retrieve the replacement medications and communicate to Sponsor. The reason why the replacement medication has been used should be documented on the eCRF “Comments Form”.

6.3 Packaging, Labeling, and Storage

All IMP used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP), guidelines for Quality System Regulations (QSR), and applicable regulations.

The IMP is manufactured by Crystal Pharma S.A.U., in compliance with the current USP correspondent monograph. The excipients used are commonly used in this kind of pharmaceutical preparations of ophthalmic nanoemulsions.

The primary packaging is a low-density polyethylene (LDPE) single-dose vial with a volume of approximately 0.20 mL (approximately 0.17 mL deliverable volume). As clobetasol propionate is known to be light-sensitive and the immediate container (vial) is semi-permeable, the vials will be contained in an aluminium foil overwrap pouch and a carton box for protection. Each

pack contains two strips of 5 single-use vials wrapped in a protective heat-sealed foil pouch. Each vial contains approximately 0.10 mg of clobetasol propionate. The dose is one drop (approximately 0.03 mL) that corresponds to 0.015 mg of clobetasol propionate.

The bulk product is prepared by dissolving the drug substance in the organic phase followed by addition of the aqueous phase until the nanoemulsion is formed. The other excipients are added in the preparation vessel and then transferred to holding tanks. The holding tanks are connected to the filling suite for blow-fill-seal process and packaging. The LDPE resin is extruded and molded, the bulk solution is aseptically filled, and the vial is completely sealed in one continuous automated process. The vials will be subsequently placed into an aluminum foil overwrap pouch and heat-sealed to protect the product.

Specifications have been established for the drug product and are controlled by the correspondent analytical methods developed specifically for clobetasol propionate ophthalmic nanoemulsion 0.05%.

Except for the change in manufacturing center, the supportive batches will be fully representative of the clinical trial batches. The clinical trial batches that will be manufactured at Laboratorios Salvat, S.A. will also be placed on stability and will be monitored at least over the duration of the study.

The containers will be relabeled as investigational drug.

To maintain the double-masking, the investigational product and placebo will be provided in packaging that will be identical in appearance and labeling. A label with “CLOBOF3-16IA01 Investigational Drug Product”, or similar language, will be affixed to each pouch containing eye dropper vials and will include the appropriate instructions for storage.

Drug labels will comply with the legal requirements and will be printed in the language of each clinical center. All study drugs will be provided with labels indicating that the product is for investigational purpose only. The labels will include a code that ensures the masking, the protocol number, the storage conditions and all the details required by the applicable regulations.

The IMP will be stored in a secure area with limited access. The IMP should not be freeze. Other storage conditions will be observed as per the labelling instructions of the IMP.

6.4 Masking and Breaking the Mask

Clobetasol propionate ophthalmic nanoemulsion 0.05% and placebo will be identical in appearance and will be self-administered by the patients with identical schedules (QID for 14 days) in order to guarantee the double-masking conditions. The sample labels had no information that would allow identification of the treatment administered.

The masking system will be done by a website platform. All patients and treatments will be codified in the mentioned platform.

The investigator, Sponsor, patient and monitor involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the treatment being administered in case of clobetasol and placebo arms. The double-masking of the clobetasol and placebo arms will be maintained throughout the conduct of the study. Only once all study data has been verified and the database locked, individual patients will be unmasked.

The study randomization should only be broken for valid medical or safety reasons, for example, a SAE where it is necessary for the investigator to know which treatment the participant is receiving to ensure the appropriate SAE treatment. In the event of an emergency, the investigator will have to decide on the necessity of unmasking the patient’s treatment

assignment. The investigator will report about this event to the Sponsor as soon as possible. If unmasking occurs, the investigator must record the reason for unmasking, as well as the date and time of the event. Corresponding information will be recorded on the eCRF and will be documented in a note to file which will be filed in the Trial Master File.

6.5 Drug Accountability

The Sponsor has the responsibility of providing the IMP for free and perfectly identified and prepared in agreement with GMP's procedure.

The medication of the clinical trial only can be sent to the investigation center after having obtained all the applicable approvals (e.g. IRBs).

The IMP supplier [redacted] will send the samples of medication to the Pharmacy Service of the study center together with the pertinent documentation (fundamentally, the analytical memory of the samples).

The Pharmacy Service is responsible of receiving the samples of medication, to verify and/or to assure that they follow the in-force legislation of labelling, to preserve them correctly and to send them to the study center after verifying that all the approvals have been obtained and the contracts have been signed.

The investigator, or the responsible investigator with delegated function, must assure the correct reception in the study center of the medication for the clinical trial (inventory of samples and review of the labelling) as well as his correct storage according to the specific procedure of conservation. The reception and storage of the medication in the study center will be documented properly according the guidelines established in the corresponding SOP.

The IMPs must be tracked using two logs:

- A center-specific log to track the complete inventory (that is, what is shipped between the center and the Sponsor)
- A patient-specific log to track what is dispensed to and returned by the patient. The investigator and the pharmacist, if applicable, must agree not to dispense any IMP to any person, except patients enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the IMPs. This log must be available for inspection at any time.

Patients will be instructed to return all single-dose vials, both used and unused, to the center at Visit 4 or at Early Termination Visit (if applicable), for which compliance will be assessed by the investigator or designee, utilizing the patient diary.

6.6 Compliance

Compliance will be assessed by comparing study product accountability records with the dosing information recorded daily by the patients in the patient diaries. The center will document this comparison along with verification of the numbers of used and unused study product single-dose vials. The numbers of missed doses as assessed at each clinic visit should be documented in the eCRF as per the patient diary.

Patients' diaries will be reviewed by the study staff at each study visit during the treatment period.

6.7 Prior and Concomitant Medications

All medications (including OTC, vitamins, and antacids) taken 2 months prior to Screening visit (Visit –1) (36 months prior for ocular implants and/or intravitreal injections) and throughout the study duration, must be recorded on the eCRF. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an AE will be recorded for each medication.

Patients will be asked to phone the study center at any time to speak to a member of the medical personnel should they require any concomitant medication.

Medication, which is considered necessary for the patient safety and well-being, may be given at the discretion of the investigator. However, concomitant medication administered during the study may lead to withdrawal of the patient from the IMP (Section 6.7.1).

6.7.1 *Prohibited Concomitant Medications*

The use of the following medications is not permitted during the study:

- 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)

The aforementioned medications will be considered as rescue medications when administered in patients not responding to the IMP (Section 6.7.2).

6.7.2 *Rescue Medication*

Any patients not responding adequately to the IMP may be rescued and placed on alternate therapy (Section 6.7) at the investigator's discretion at any time.

The choice of rescue medication is at the investigator's discretion. Any patient placed on rescue therapy will discontinue the use of the IMP and the investigator must made extensive efforts to ensure that the patient will attend all his/her remaining study visits until study completion, aiming to collect the most complete efficacy and safety data.

Additionally, patients will be asked to phone the study center at any time to speak to a member of the medical personnel should they experience any worsening of ocular conditions or other AEs.

Rescued patients will be considered treatment failures, but the need for rescue therapy will not be considered an AE.

6.8 Medical Care of Patients after the End of the Study

Clobetasol propionate ophthalmic nanoemulsion 0.05% is an IMP under development and will consequently not be available for treatment of the patients after study completion.

After their participation in the study, patients will continue treatment in accordance with the study center's clinical practice guidelines and standard of care.

7. ASSESSMENTS OF EFFICACY

The timings of the assessments are described in Section 4.3.1 and Table 1.

7.1 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 silt-lamp examination and will be graded on an adapted 6-point scale proposed by the Standardization of Uveitis Nomenclature (SUN) working group (23) (Table 2)

Table 2 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

†Feld size is a 1 mm by 1 mm slit beam

7.2 Key Secondary Efficacy Endpoint

Proportion of patients with VAS pain 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 (100 mm) horizontal line anchored by two verbal descriptions: "no eye pain" (score of 0) and "worst imaginable eye pain" (score of 10).

7.3 Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be:

- 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

7.3.1 *Secondary efficacy assessments*

See previous Section 7.1 for anterior chamber cell grade.

- 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 the SUN working group (23) (Table 3)

Table 3 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 (see Appendix 2)
- The IOP will be assessed in both eyes using the Goldmann applanation tonometry method (see Appendix 3)
- Monocular visual acuity will be completed with the patient's best correction vision in place using standard of care Snellen chart
- The eye pain VAS is a single-item continuous scale comprised of a 10 cm (100 mm) horizontal line anchored by two verbal descriptors, one for each symptom extreme. For eye pain intensity, the scale is anchored by "no eye pain" (VAS score of 0) and "worst imaginable eye pain" (score of 100 mm)

  The eye pain VAS is completed by the patient. Details and instructions for use of eye pain VAS can be found in Appendix 4

- The eye discomfort will be assessed by using the categorical scale which can be found in Appendix 5
- The photophobia VAS is a single-item continuous scale comprised of a 10 cm (100 mm) 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 100 mm)

  The photophobia VAS is completed by the patient. Details and instructions for use of photophobia VAS can be found in Appendix 6

7.4 Secondary Safety Endpoints

The secondary safety endpoints will be:

- Number, frequency and severity of AEs up to Day 29
- Number, frequency and severity of Serious AE (SAE) 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 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

7.5 Demographic and Other Baseline Characteristics

7.5.1 *Demographic and Baseline Data*

The following demographic and baseline data will be collected at the Screening Visit (Visit –1):

- Year of birth
- Sex
- Race
- Weight and height. Body mass index (BMI) will be calculated from these

7.5.2 *Medical History*

A detailed medical history of relevant conditions and procedures will be obtained by the investigator or qualified designee at the Screening visit (Visit –1) and recorded as required in the Medical History section of the eCRF.

Relevant medical history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures). Additionally, present status of visual function (including patient´s self-assessment of visual status, visual needs, any recent or current visual symptoms, and the use of eyeglasses or contact lens), ocular symptoms (e.g., eyelid swelling, diplopia, redness, photophobia) and past ocular history (e.g. prior eye disease, injuries, surgery and other treatments and medications) will be collected. Relevant medical history at Visit 1 (Day 1) will cover the time from the Visit –1 (Screening). For following visits, any medical events

of significance that occurred after the signing of informed consent will be recorded on the corresponding AEs section of the eCRF, except the routine cataract surgery at Day –1.

The medical history classification will be based in the Medical Dictionary for Regulatory Activities (MedDRA) (latest version available) and system organ class (SOC) and preferred term (PT) will be also provided.

7.5.3 *Prior and Concomitant Medication*

Prior medications taken within 2 months prior to the Screening visit (Visit –1) (36 months prior for ocular implants and/or intravitreal injections) will be recorded at the Screening Visit (Visit –1), including OTC products.

Concomitant medications (including OTC products) and its duration will be recorded in the concomitant medication log/section of the eCRF throughout the study.

Prior medication is defined as medication received prior to first IMP intake. Any medication received at least once after the first IMP intake will be considered as concomitant medication. This means, a medication might be assigned to both, prior and concomitant medication. If no unambiguous assignment to prior and concomitant medication is possible due to incomplete or missing dates, the medication will be assigned to both, prior and concomitant medication.

8. ASSESSMENTS OF SAFETY

AEs will be recorded during the whole study period. For further information of definitions and reporting of AEs and SAEs, see Section 8.3 below.

8.1 Specification of Safety Parameters

8.1.1 *Physical and Eye Examinations*

Physical examination at the Visit -1 should be done following the usual standards of patients' examination at each study site.

Any pathological finding will be registered in the eCRF.

A pathological physical examination finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE, or if it causes the patients to discontinue the study. If a pathological physical examination finding is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated physical examination finding should be considered additional information.

In addition to the physical examination described above, an extended eye examination will be performed at Visit -1, including but not limited to:

- Visual fields by confrontation
- Pupillary function (e.g., size and response to light, relative afferent pupillary defect)
- Ocular alignment and motility (e.g., cover/uncover test, alternate cover test, version and duction assessment)
- Fundus examination: mid and posterior vitreous, retina (including posterior pole and periphery), vasculature, and optic nerve

8.1.2 *Ophthalmoscopy*

An indirect ophthalmoscopy will be performed using distance or non-contact slit-lamp lenses.

Ophthalmoscopy findings will be recorded and assessed as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

8.1.3 *Vital Signs*

The following vital signs will be monitored as safety variables:

- Diastolic and systolic bloody pressure (mmHg)
- Heart rate (beats per minute)
- Axillary body temperature (°C)

Measurements of heart rate, axillary body temperature and systolic and diastolic blood pressure will be carried out after at least 5 minutes resting in the supine position and systolic and diastolic blood pressure measured always on the same arm.

Baseline Vital signs on Visit 1 to be completed at least 30 ± 10 min before IMP administration. All other vital signs assessments to be completed before any ocular assessment.

The observed values will be recorded and assessed as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

An asymptomatic abnormal vital sign finding must only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE, or if it causes the patient to discontinue the study. If an abnormal vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign result should be considered additional information.

8.1.4 *Pregnancy Test*

Standard urine pregnancy test will be performed in female patients of childbearing potential both at Visit –1 (Screening) and Visit 1 (Baseline).

8.2 Appropriateness of Measurements

Standardized methods for measurements of efficacy and safety variables will be used. The investigator assessment instruments and Patient-Reported Outcomes (eye pain and photophobia VAS and discomfort categorical scale) are accepted standards for clinical evaluation.

8.3 Adverse Events

Safety parameters will be monitored by the investigator and any impairment will be treated appropriately by the corresponding physician and recorded in the eCRF.

The safety assessment will be performed following ICH - GCP Guidelines and according to the applicable US Code of Federal Regulations (CFR).

8.3.1 *Definitions*

8.3.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Medical disorders present at the time of the first administration of IMP are only considered AEs if they significantly worsen after this time. All baseline conditions should be recorded as part of the Medical History.

8.3.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ARs. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

8.3.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSARs are AEs that are believed to be related to an IMP and are both unexpected (i.e. the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are patient to expedited reporting to the applicable RA and will be unmasked with regard to treatment identity for the purpose of regulatory reporting.

8.3.1.4 Serious Adverse Event (SAE)

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization (any hospitalization except observational admissions of less than 24 hours)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is another medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

Life-threatening in the definition of a SAE or serious AR refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual patient
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE

8.3.2 *Timing*

Adverse events will be recorded from the time of informed consent completion, throughout the study, and at early termination. Adverse events that were on-going when the patient completed the study will continue to be followed until resolution or until the investigator decides that the AE is stable; AEs will be coded using the MedDRA dictionary.

8.3.3 *Recording Adverse Events*

Volunteered, observed, and elicited AEs will be recorded. This includes AEs the patient reports spontaneously, those the investigator observes, and those the elicited in response to questions from the study staff. Patients will be asked open-ended questions, such as "How have you been feeling since your last visit?", at each study visit.

All AEs that occur during the study must be recorded in the AE section of the eCRF. All AEs eCRF entries should contain a brief description of the event, date and time of onset, duration, intensity, treatment required, relationship to study medication, action taken with regard to study medication, outcome, and whether the event is classified as serious.

8.3.4 *Assessment of Adverse Events*

Each AE and SAE will be assessed by the investigator with regard to the following categories:

8.3.4.1 Severity

Severity describes the intensity of an event. The severity of each AE must be assessed by the investigator and recorded on the eCRF as mild, moderate or severe according to the following definitions:

Mild: The AE does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance.

Moderate: The AE produces some impairment of function or it interferes with usual activities but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe: The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

If an AE changes in severity, the worst severity should be reported.

8.3.4.2 Relationship to Study Medication

Causality will be assessed according to the WHO Causality Assessment:

Related to IMP

Certain: Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Re-challenge satisfactory, if necessary.

Probable/Likely: Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Re-challenge not required.

Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.

Unlikely: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.

All AEs judged as having a reasonable suspected causal relationship to the IMP (i.e. possibly, probably, certain) will be considered as related to IMP. Any AE that is considered to be related to the IMP is described as an AR.

8.3.5 *Reporting Serious Adverse Events*

The investigator is responsible for ensuring that all SAEs occurring from the time of signing of ICF until 30 days following the final dose of the study drug must be reported to the Sponsor through [redacted] immediately, but in any event no later than 24 hours of any center personnel becoming aware of the event. Initial reports should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify patients by unique code numbers assigned in the study. The patients' names, personal identification numbers, and/or addresses must not be included neither in the attached documentation (when appropriate) and will never be provided to the Sponsor. The following information is **mandatory** for the initial report:

- Patient study ID
- Study treatment (masked, if applicable)
- Start date (time, if relevant) of the study treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the investigator should supply the Sponsor with any additional requested information (e.g. autopsy reports and terminal medical reports).

8.3.6 *Follow-Up of Adverse Events*

Any AE that is ongoing when the patient is withdrawn from the study should be followed up until the AE is resolved or the investigator decides that the AE is stable and needs no further follow-up. The date when the investigator considers one of these outcomes to have occurred for the last ongoing AE for a patient will be considered the last visit for this patient, and the outcome should be recorded in the eCRF.

8.3.7 *Reporting Safety Information*

All study patients will be carefully monitored for the occurrence of AEs during the study period from the signing of informed consent to the completion of the last follow-up visit. The investigator will collect AEs with a non-leading question such as "have you experienced any new health problems or worsening of existing conditions" as well as reporting events directly observed by the investigator or spontaneously volunteered by patients.

A clinical laboratory abnormality should be documented as an AE if meet the following conditions: the test finding is accompanied by clinical symptoms AND/OR the abnormality suggests a disease and/or organ toxicity AND/OR the abnormality is of a degree that requires

additional diagnostic evaluation(s) or medical/surgical intervention AND/OR the abnormality is considered clinically significant by the clinician.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the patient, or reported in answer to an open question by the investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding study drug
- Opinion on causality
- Seriousness (as defined in Section 8.3.1 for definition of SAE, SAR and Suspected Unexpected Serious Adverse Reaction)
- Outcome

8.3.7.1 Abnormal Vital Signs

Reporting of abnormalities as vital signs findings and AEs should be avoided.

An asymptomatic abnormal vital sign finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE or if it causes the patient to discontinue the study.

If an abnormal vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign result should be considered additional information.

8.3.8 *SAE Reporting Contact Details*

All SAEs should be faxed or sent by e-mail to [redacted] within 24 hours of the investigator becoming aware of the event(s). If the SAE Report Form Clinical Trials is faxed, the "Fax cover sheet, SAE report" should be used.

[redacted]

Fax: [redacted]

E-mail: [redacted]

Any unexpected fatal or life-threatening suspected AR will be reported to regulatory authorities, IRBs, and investigators in accordance with US legislation.

[redacted] will be responsible for the preparation of CIOMS notification forms as part of its pharmacovigilance services. [redacted] will send completed CIOMS forms to [redacted] for electronic submission to the FDA. [redacted] will make submissions to FDA within 1 day of receipt from [redacted]

[redacted]

Address: [redacted]

Phone: [redacted]

E-mail: [redacted]

[redacted]

Address: [redacted]

Phone: [redacted]

E-mail: [redacted]

8.3.9 *Adverse Events of Special Interest*

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
- Pain/discomfort associated with IMP instillation

An AESI may or may not be serious. Nevertheless, the investigator is responsible for ensuring that all AESIs are reported to the Sponsor immediately, but in any event no later than 24 hours of any site staff becoming aware of the event. Further instructions on how to report AESIs will be provided separately.

8.3.10 *Precautions/Overdose*

The risk of overdosing in general in this study is considered to be very low. The planned maximum exposure will be approximately 0.066 mg/day of clobetasol propionate (approximately 0.924 mg of clobetasol propionate over a period of 14 days). The total amount of clobetasol propionate administered in the toxicological pre-clinical study (at the highest dose) was 4 times above the clinical trial dose, exhibiting no ocular toxicity. Systemic HED in pre-clinical study was 17-times higher compared to dosing in one eye of adults.

An expected AR that could represent a severe condition is the induction of IOP rise (and associated ocular pain and redness). In case of IOP >30mmHg, the investigator discretion is advised, using preferred standard of care at the study site. The use of specific ocular hypotensor eye drops (like beta blockers / alpha agonists / carbonic anhydrase inhibitors) is recommended.

Nevertheless, unintentional administration of any dose that deviates from the scheduled regimen will be documented and reported by center personnel.

8.3.11 *Pregnancy*

Female patients will be instructed to notify the investigator immediately if they become pregnant from the signing of informed consent until 30 days following the final dose of study drug. Male patients will be instructed to notify the investigator immediately if their partner becomes pregnant. Pregnant patients will be withdrawn from further study treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the study.

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the investigator should report

pregnancies according to the procedures and timelines described for reporting of SAEs (Section 8.2.5). The pregnancy report form should be used instead of the SAE form.

The pregnant patient or pregnant partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

8.3.12 *Protocol Deviations Due to an Emergency or Adverse Event*

In the case of an emergency or AE, departures from the protocol may be necessary. Such protocol deviations will be determined as allowable on a case-by-case basis. The investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency. The Medical Monitor and the investigator will confer to decide whether the patient should continue to receive study medication. All protocol deviations and the reasons for such deviations must be noted in the eCRF.

9. STATISTICAL METHODS

9.1 General Statistical Methods

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, confidence intervals, standard deviation, minimum, Q1, median, Q3 and maximum value. Change from baseline to each post-baseline visit will be also described using descriptive statistics. Categorical data will be presented as counts and percentages.

The data will be presented for each treatment group by visit.

Individual patient data will be listed for all enrolled patients. Listings will be sorted by center and patient number and labelled by randomized treatment group.

Before unmasking the study data, a separate statistical analysis plan (SAP), which will provide the technical details of the statistical analysis outlined below, will be prepared and approved.

For statistical analyses, the following definitions will be applied:

- Baseline: Baseline is defined as Visit 1 (Day 1, 24 h after the cataract surgery).
- Randomized treatment group: The treatment that was assigned at the time of randomization.

The assessments performed at Visit 1 (Day 1) will be considered the baseline values.

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

Unless otherwise stated, all statistical tests will be conducted using two-sided alpha = 0.05.

9.1.1 *Sample Size*

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. Considering a 4% lost to follow-up rate a final sample size of 210 patients will be required (140 clobetasol, 70 placebo, in a 2:1 randomization ratio).

9.1.2 *Interim Analyses*

An interim analysis is not planned for this study.

9.1.3 *Missing, Unused, and Spurious Data*

Any missing, unused, or spurious data will be noted in the final clinical study report (CSR) and presented in the data listings.

9.1.4 *Analysis Populations*

Analysis will include the following populations:

- **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.

- **Safety Population**: The safety set will be the primary analysis set for the safety endpoints and will include all randomized patients who took at least one dose of IMP. The safety set 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 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.

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 safety set.

9.1.5 *Patient Disposition*

The numbers of patients in each treatment group who completed the study and who terminated early will be tabulated. For patients who terminated early, primary and secondary reasons for termination will be tabulated. Patients who were excluded from each of the study populations defined in Section 9.1.4, and their reasons for exclusion, will be listed.

9.1.6 *Demographics and Baseline Characteristics*

Patient disposition, demographic and other baseline data will be summarized by randomized treatment group. Both the FAS and PP will be used for this presentation.

Frequency tables for medical history will present the percentage of patients per SOC and PT.

9.1.7 *Protocol Deviations*

Protocol deviations are defined as violations from the procedures outlined in the protocol. **Major** protocol deviations are protocol violations likely to affect the study results and leading to the exclusion of the patient from the MPP.

Once the database has been completed and considered as “clean”, a data masked review will be conducted before the database lock in order to identify all major protocol violations and assign patients into each of the analysis sets as defined in Section 9.1.4.

Patients with protocol deviations will be presented in the data listings. Protocol violations will be tabulated by treatment group and violation.

The protocol deviations are considered critical (or very serious) and major (or severe), according to the following definitions:

- **Critical or very serious:** Deviations affecting / they have adversely affected the rights, safety or welfare of patients and / or the quality and integrity of data
- **Major or serious:** Deviations that may affect / have adversely affected the rights, safety or welfare of patients and / or the quality and integrity of data.

The Sponsor or designee will report the protocol deviations to the Health Authorities according to local rules and regulations.

9.1.8 *Compliance with Study Medication*

Duration of treatment and treatment compliance will be presented for the FAS population by randomized treatment group using summary statistics.

9.1.9 *Concomitant Medications*

Prior and concomitant treatment will be coded according to WHO Drug Dictionary.

Concomitant medication and concomitant therapy will be summarized for the FAS population by randomized treatment group as percentage of patients being treated with each type of medication/therapy classified according to Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 3 (pharmacological subgroup).

Prior treatment will be summarized the same way as concomitant treatment.

9.1.10 *Primary Analysis*

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 endpoint in the FAS.

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.

The test will be 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 using the chi square statistic.

The PP population set will be also tested to confirm the robustness of the primary analysis.

The primary estimand (efficacy estimand) will be defined as the effect of the randomized treatments in all subjects meeting selection criteria assuming continuation of randomized treatments for the duration of the study regardless of actual compliance.

9.1.11 *Key Secondary Analysis*

The aim of the key secondary analysis of this study is to assess the superiority of clobetasol propionate ophthalmic nanoemulsion 0.05% compared to placebo with respect to the key secondary endpoint in the FAS.

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.

The test will be the proportion of study eyes with no pain (pain = 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 using the chi square statistic.

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

9.1.12 *Secondary Analysis*

For continuous variables, a summary of these endpoints will be prepared at each specified timepoint and will include an estimate of the mean change from baseline for each treatment group and of the adjusted treatment difference and 95% confidence interval. The between-

treatment comparison will employ a mixed model of repeated measures (MMRM) with treatment as fixed factor and baseline as a covariate.

For categorical variables, a summary of these endpoints will be prepared at each specified timepoint and will include the number and percentage of each category. A chi-square test will be performed. Confidence intervals on the difference between pairwise comparisons of treatments with the placebo group will be computed. These analyses will not be adjusted for study center.

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.

9.1.13 *Safety Analyses*

The total number of patients with at least one AE and the total number of AEs will be presented. The number of patients and the number of AEs overall and in each by randomized treatment group will be tabulated by SOC and by PT. AEs will also be tabulated versus worst severity and worst relationship to treatment. In this table, patients with AEs will be identified by their patient number.

The number of patients with TEAEs and the number of TEAEs overall and in each sub-set will be tabulated by SOC and PT. Frequency tables for the overall population and by each sub-set will also be presented for TEAEs related to study drug, TEAEs leading to study drug discontinuation, TEAEs of special interest, serious TEAEs (STEAEs), and STEAEs related to study medication. Additional summary tables will be provided for TEAEs with worst severity by SOC and PT per patient and TEAEs with worst relationship by SOC and PT per patient.

Listings of patients with STEAEs, deaths and STEAEs leading to discontinuation and individual narrative summaries for these cases will be provided. In the listings, patients with TEAEs will be identified by their patient number.

9.1.13.1 Other Safety Assessments

- Physical and Eye Examination

Physical and eye examination data will be summarized for the safety population by each by randomized treatment group.

- Vital Signs

Vital signs will be summarized by treatment group, together with changes from baseline.

Shift tables will show the number of patients who changed from normal/abnormal at Baseline to normal/abnormal at each time of assessment.

9.1.14*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 / prohibited medication. New estimands associated to each intercurrent event will be added to the already existing primary estimand accordingly.

9.2 Changes in Statistical Methods

Any deviation(s) from the original statistical analysis plan (as described in the study protocol or in the SAP) will be described and justified in a protocol amendment and/or in a revised SAP and/or in the final report, as appropriate.

If, after the study has begun, but prior to any unmasking, changes are made to primary hypothesis, or the statistical methods related to this hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

10. DATA HANDLING AND RECORD KEEPING

10.1 Data Quality Assurance

Audits or inspections, including source data verification, may be performed by representatives of [redacted] the Sponsor, a Competent Authority (CA) and/or an IRB.

10.2 Access to Source Data and Documentation

The investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate RA, and the IRB, if required.

10.3 Record Retention

The investigator/institution should maintain essential documents (as defined in ICH E6 GCP) as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval.

It is the responsibility of the Sponsor to inform the investigator/institution in writing as to when the documents no longer need to be retained.

10.4 Protocol Deviations

The classification of protocol deviations in major or minor deviations will be mutually agreed between the Sponsor and [redacted] at the start of the study.

A major protocol deviation occurs when the patient, investigator, or Sponsor fails to adhere to significant protocol requirements affecting selection criteria, administration of study treatment and administration of prohibited medication.

Failure to comply with GCP guidelines will also result in a major protocol deviation. The Sponsor will determine if a major protocol deviation will result in withdrawal of a patient.

Deviations to the study protocol will be documented in a Protocol Deviation Log.

The Sponsor or delegate is responsible for immediately reporting major deviations according to applicable regulations, as well as deviations from the study protocol that substantially affect the integrity or the safety of the patients or the scientific validity of the study, to the CA.

Protocol deviations will be reviewed during a meeting before database lock in order to allocate the patients into the different analysis sets.

10.5 Case Report Forms and Source Documentation

It is the responsibility of the investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the patient is in a clinical study
- The identity of the study e.g. study code

- Patient screening number and/or patient number
- That informed consents for the patient and/or their legal representatives were obtained and the date
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Patient health service identification number

The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRF. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Sections of eCRF will be monitored on a regular basis.

10.6 Data Management

Data management and handling of data will be conducted by Bioclever 2005 SLU according to the study specific Data Management Plan with ICH guidelines and Bioclever 2005 SI SOPs.

A 21 CFR Part 11-complaint eCRF system will be used to capture data from the study. Data entry will be performed by the study center personnel. Validation and data queries will be handled by the Bioclever 2005 SLU Data Management Team. The data will be subjected to validation according to Bioclever 2005 SLU SOPs in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the center by the study center personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

10.7 Monitoring

The monitor will visit the study center on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants (patients and/or their legal representatives)

- AEs have been reported as required
- Data are being accurately recorded in the eCRF
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The investigator and the center are receiving sufficient information and support throughout the study

Moreover, during monitoring visits the data recorded in the eCRF, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the patient in the study i.e. source data verification.

11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice

The study will be conducted in compliance with the protocol, US CFR applicable to clinical studies (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312), ICH GCP and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

11.2 Informed Consent

In obtaining and documenting informed consent, the investigator must comply with 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and should adhere to ICH GCP.

All patients will receive written and verbal information regarding the study at a prior interview. This information will emphasize that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

It is the personal responsibility of the investigator to obtain written informed consent from the patient and/or his/her legal representative (if applicable). No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the patient and/or his/her legal representative.

Prior to obtaining written informed consent, the investigator or a designee must explain to potential patients and/or their legal representatives, the aims, methods, and potential hazards of the study and any discomfort it may entail.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients and/or their legal representatives. Prior to enrolling a patient in the study, an Informed Consent Form must be signed and dated by the patient and/or his or her legal representative and the investigator on the same day. The patients and/or their legal representatives will receive a copy of the written information (Patient Information Sheet) as well as a copy of the signed Informed Consent Form.

If parts of the informed consent process (such as giving information) may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the center delegation log.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in a clinical study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

The data will be processed in accordance with the specifications outlined by the federal or state law to ensure that requirements regarding personal data protection are met (e.g. Health Insurance Portability and Accountability Act rules). If an external organization will process data on behalf of the Sponsor, a contractual procedure will be signed between the Sponsor and the external organization to ensure compliance with the above-mentioned legislation.

11.3 Approval of Study Protocol

This protocol, proposed ICF and other information provided to patients, and all appropriate amendments will be submitted to the applicable IRB for review and approval. This study will be conducted only after approval of the protocol has been granted by the appropriate IRB and a copy of the approval has been received by the Sponsor.

The investigator must not screen any patients before receiving written approval from the IRB.

The name and occupation of the chairman and members of the IRB will be supplied to the Sponsor. The investigator will provide required progress reports and report all SAEs to the IRB as required by the IRB.

11.4 Amending the Protocol

The investigators must read the protocol thoroughly and must follow the instructions. Waivers for enrollment should be avoided, and the Sponsor does not plan to provide any waivers. Any amendment to the protocol containing major modifications will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

11.5 Confidentiality and Data Protection

Patient data will be protected by ensuring that no captured data contain patient names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that patient initials, demographics (including birthdate), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form, and listings containing information that could be used to identify an individual patient will not be included in any public disclosures of the study.

11.6 Liability and Insurance

The Sponsor must provide insurance or must indemnify (legal and financial coverage) the investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence or non-compliance with the protocol.

11.7 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

11.8 Publication Policy

After completion of the study, a CSR will be prepared according to the ICH Guideline for Structure and Content of CSR (ICH E3) by the Sponsor designee in close collaboration with the investigator and the Sponsor.

All publications and presentations must be based upon the CSR.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential

information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this study. If an investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

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13. APPENDICES

13.1 Appendix 1

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best

proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must

be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo,

or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

13.2 Appendix 2

Slit Lamp Examination

The examination will be performed at every Visit with the slit lamp using a beam of 1.0 mm height and 1.0 mm width with the beam at maximum luminance and using the high powered lens if using Haag-Streit model slit lamp. If alternate model used, center to assure a 1.0 mm by 1.0 mm window with high magnification is achieved.

This procedure will be the same for all patients observed at the investigator's center.

- Anterior Chamber Cells

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

- 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)

- Chemosis

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

- Bulbar conjunctival injection

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

- Ciliary injection

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

- Corneal edema

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

- Keratic precipitates

Grade	Description
0	None
1	Mild

2	Moderate
3	Severe

- Other: 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). Their severity will not be registered.

13.3 Appendix 3

Intraocular Pressure

Calibration of Tonometer

The Goldmann tonometer shall be used for IOP measurements. The tonometer must be calibrated before first use and calibration will be checked by the investigator prior to measuring IOP for each patient, with the weight system at 0, 2, and 6 grams as supplied by the manufacturer. When the calibration steps provide readings within ± 0.5 mmHg of the target value for each weight, the tonometer is considered adequately calibrated. The investigator must maintain written documentation (e.g., unit model or serial number, calibration date, name/initial of person performing calibration, indication of pass or fail) of the calibration of each tonometer throughout the study period.

IOP Measurement

IOP will be taken as follows:

1. Anaesthetize the selected eye of the patient.
2. Stain with sodium fluorescein.

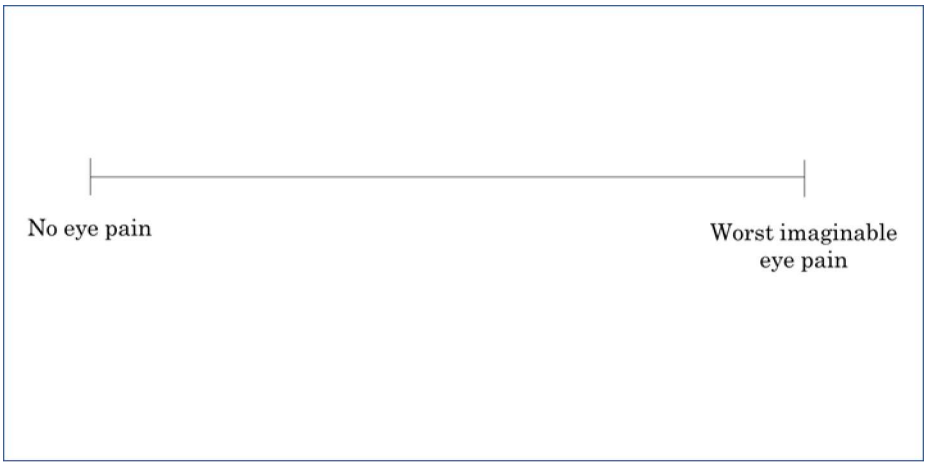
   NOTE – step may be combined by using an anesthetic to which sodium fluorescein has already been added.
3. Set the tonometer drum to a force corresponding to an IOP of 10 mmHg. Wherever possible, do not touch the eyelid with the fingers to open the palpebral aperture. If the palpebral aperture is not wide enough to allow the tonometer cone to make contact, instruct the patient to open their eyes wider.
4. Direct the patient to view a distance fixation point.

   NOTE – If distance fixation cannot be maintained and ***near fixation is used, this fact should be recorded****.*
5. Measure the IOP for the mean of the ocular pulse and remove the tonometer from the eye.
6. Repeat steps if the measurement was not valid due to the following reasons:
   - The patient felt a sensation
   - The eyelid was touched
   - The fluorescein ring was too broad or too small
   - Any other circumstances suggesting that the measurement may have been inaccurate
7. If there is any evidence that the anesthetic is no longer fully effective, then re-administer anesthetic.
8. Record the IOP, as the mean of 3 valid measures. Measure and record means for both eyes.

13.4 Appendix 4

Eye Pain - Visual Analogue Scale (VAS)

Please assess the eye pain by ticking the scale, which describes eye pain the best.



13.5 Appendix 5

Discomfort Assessment

Please assess the severity of the eye discomfort by using the following scale.

Grade	Description
0	None
1	Mild
2	Moderate
3	Severe

13.6 Appendix 6

Photophobia - Visual Analogue Scale (VAS)

Please assess the photophobia by ticking the scale, which describes photophobia the best.