



CLINICAL TRIAL PROTOCOL

An international, multicenter, randomized, blinded-assessor, parallel-group clinical study comparing eye drops of combined LEvofloxAcin + DEXamethasone for 7 days followed by dexamethasone alone for an additional 7 days vs. tobramycin + dexamethasone for 14 days for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults – LEADER 7

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AMENDMENT 1

The main purpose of this amendment is to address concerns raised during review of the study protocol by regulatory authorities (BfArM) regarding inclusion/exclusion criteria and the conditions requiring temporary interruption or permanent discontinuation of study treatments. The following changes to the protocol have been made in light of these requests:

- Inclusion criterion 3 was modified to clarify that the study will enroll patients scheduled for cataract surgery (not yet performed) (*Section 5.1*). The criterion has been split into two, one indicating the inclusion of patients scheduled for surgery (not yet performed), and the other stating that only patients who completed surgery without complications will be randomized.
- Exclusion criterion 9, which previously referred to contraindications to ocular treatment with levofloxacin, tobramycin or dexamethasone in general terms, now indicates all the specific contraindications to study treatments as stated in their respective Summary of Product Characteristics (SPC) or Investigator's Brochure (IB) (*Section 5.2*). Since the warnings and precautions related to study treatments apply to situations that may arise following screening, a sub-section has been added to the treatment section of the protocol listing all the warnings and precautions as per SPC or IB (*Section 6.6*). Specific situations requiring study treatment discontinuation according to SPC or IB have been added to *Section 7.1*.
- Exclusion Criterion 11 now states that participation in previous clinical studies is possible if at least 5 half-lives of the IMP used in the previous studies have passed between the end of treatment in the previous study and the start of treatment in this clinical study.
- The amendment now states that temporary interruption of study treatment and dose modifications are not foreseen in the protocol (*Section 7.1*). Additional information has also been added indicating the conditions for permanent discontinuation.

The amended protocol also clarifies that testing of visual acuity is to be performed according to local practice. Minimum visual acuity of the contralateral eye required for study entry (Exclusion criteria 8) has consequently been converted and is now stated using various standards (*Section 5.2*).

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable laws and regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or Competent Authority, except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC before the changes are implemented. All changes to the consent form will be IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Number	LevoDesa_04-2017
EudraCT Number	2018-000286-36
Title	An international, multicenter, randomized, blinded-assessor, parallel-group clinical study comparing eye drops of combined LEvofloxAcin + DExamethasone foR 7 days followed by dexamethasone alone for an additional 7 days vs. tobramycin + dexamethasone for 14 days for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults – LEADER 7.
Phase	III
Sponsor	NTC S.r.l.
International Chairman	Prof. Francesco Bandello, Full Professor of Ophthalmology, Director of Clinica Oculistica of the Università Vita-Salute, Istituto Scientifico San Raffaele, Milan.
Investigational sites	The study will be conducted at approximately 80 centers located in Italy, Germany, Spain and Russia.
Rationale	<p>In clinical practice, topical treatment following cataract surgery is frequently administered using a combination between an antibiotic and a corticosteroid to promote patient adherence to therapy and to obtain both prevention of infection and treatment of post-surgical inflammation. The combination of tobramycin and dexamethasone is among the most widely used combinations, but treatment usually lasts for two or more weeks, sometimes tapering posology over several weeks afterwards. This therapeutic strategy may however be inappropriate in terms of preventing the development of bacterial resistance, which is favored by prolonged treatment and the use of sub-therapeutic doses. For this reason, antibiotic treatment should not be prolonged beyond the time necessary for the healing of surgically induced epithelial lesions, and therefore should not last more than a week.</p> <p>Based on these considerations, a product associating a broad-spectrum antibiotic with a highly effective corticosteroid that can be used for a short period of time (one week) would be of considerable interest.</p> <p>The combination of levofloxacin 0.5% and dexamethasone 0.1% tested in this study is the first combination of a steroid and a quinolone under development and represents a major step forward in this direction.</p> <p>The purpose of this study is to evaluate the efficacy of a combination of levofloxacin and dexamethasone by demonstrating that its use for a limited time of one week, followed by treatment with dexamethasone alone, is not inferior to longer treatment with tobramycin + dexamethasone in</p>

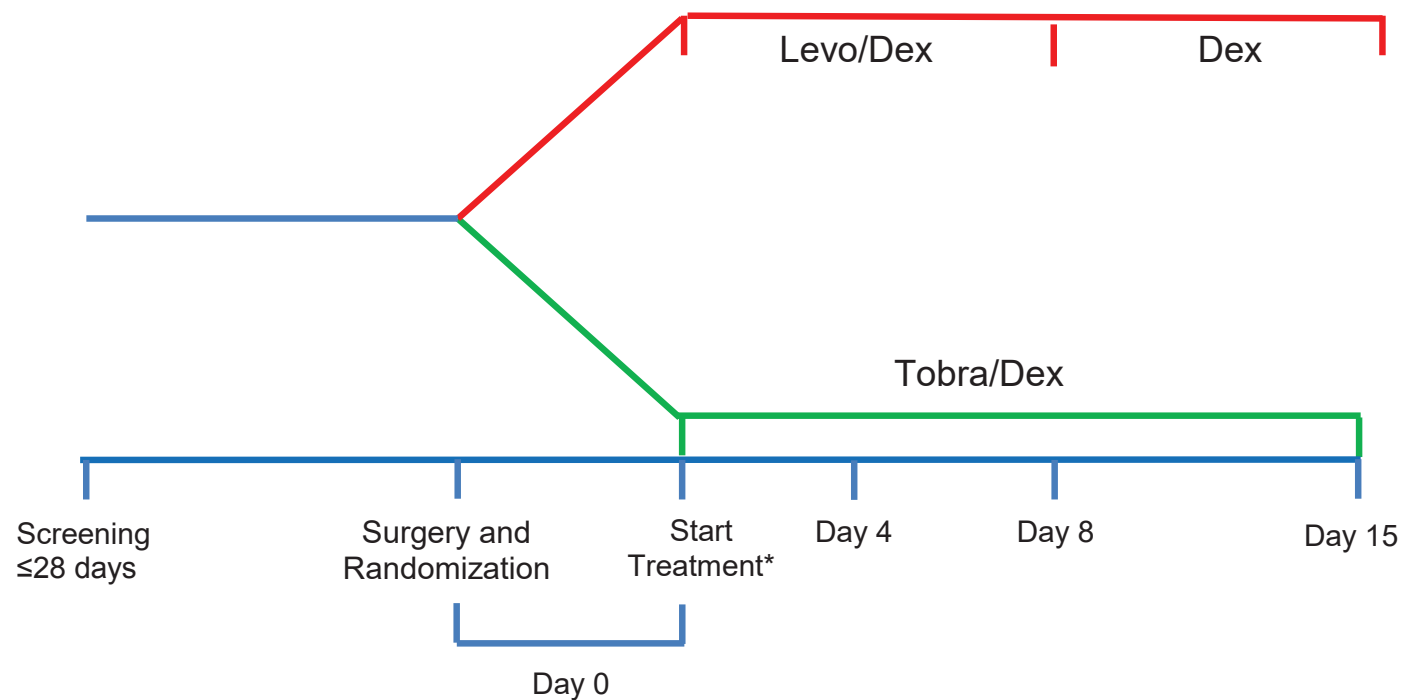
	preventing and treating ocular inflammation and in preventing post-operative infection while limiting the emergence of antibiotic resistance.
Objectives	<p>Efficacy: to demonstrate the non-inferiority of combined levofloxacin + dexamethasone eye drops for 7 days followed by dexamethasone eye drops alone for an additional 7 days vs. standard treatment tobramycin + dexamethasone eye drops for 14 days in the prevention and treatment of postoperative ocular inflammation and prevention of infection.</p> <p>Safety and tolerability:</p> <ul style="list-style-type: none"> • To evaluate the safety of combined levofloxacin + dexamethasone eye drops. • To evaluate the tolerability of combined levofloxacin + dexamethasone eye drops. <p>Compliance: to evaluate compliance with prescribed treatment.</p>
Endpoints	<p>Primary efficacy The proportion of patients without signs of anterior ocular chamber inflammation (sum of cells and flare score = 0) after 14 days of treatment.</p> <p>Secondary efficacy</p> <ul style="list-style-type: none"> • Incidence of endophthalmitis • Proportion of patients without signs of anterior ocular chamber inflammation after 3 and 7 days of treatment • Conjunctival hyperemia after 3, 7 and 14 days of treatment • Total Ocular Symptoms Score (TOSS) after 3, 7 and 14 days of treatment • Ocular pain/discomfort after 3, 7 and 14 days of treatment • Use of rescue therapy during treatment <p>Safety</p> <ul style="list-style-type: none"> • Intraocular pressure (IOP) • Visual acuity • Adverse events <p>Tolerability</p> <ul style="list-style-type: none"> • Global evaluation • Burning, stinging, blurred vision <p>Compliance</p> <ul style="list-style-type: none"> • Assessment of patient diary
Type of study	This is an international, multicenter, randomized, blinded-assessor, parallel-group clinical study. The Investigators in charge of evaluating study parameters will be blinded to treatment assignment. A separate investigational staff will be unblinded and responsible for assigning and dispensing/return study products.
Study Population	The study will enroll 800 adult male and female patients undergoing cataract surgery.
Inclusion criteria	Inclusion criteria prior to surgery

	<ol style="list-style-type: none"> 1. Signed written informed consent must be obtained before any assessment is performed 2. Male or female, age ≥ 40 years 3. Scheduled senile or presenile cataract surgery (not yet performed). 4. Willing to interrupt the use of contact lenses for the entire duration of the study 5. Able and willing to follow study procedures 6. For females of childbearing potential, the use of highly effective contraception and agreement to use such a method during study participation <p>Inclusion criteria following surgery</p> <ol style="list-style-type: none"> 7. Surgery completed without complications
<p>Exclusion criteria</p>	<ol style="list-style-type: none"> 1. Ocular conditions that at the discretion of the Investigator may interfere with the efficacy and/or safety evaluations (e.g. ocular herpes, blepharitis, conjunctivitis, uveitis, keratitis, diabetic retinopathy, retinal vein occlusions, retinal vasculitis, retinal angiomatous proliferation, pseudoexfoliation syndrome, intraoperative floppy iris syndrome, etc.) 2. Patients undergoing bilateral cataract surgery 3. Patients under treatment with prostaglandin analogues or intravitreal injections of anti-VEGF (vascular endothelial growth factor) drugs 4. Systemic diseases that may interfere with the results of the study (e.g. rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, systemic lupus erythematosus, scleroderma with major ocular involvement, etc.) 5. Any condition that could interfere with correct instillation of eye drops 6. Ocular surgery in the study eye (including laser surgery) in the 3 months before screening 7. Monocular patients 8. Visual Acuity (VA) $< 20/80$ of the contralateral eye measured as ETDRS or Snellen 20 feet, equal to 0.25 in decimal 9. Contraindication to ocular treatment with Tobradex[®], Maxidex[®] or levofloxacin/dexamethasone as follows: <ul style="list-style-type: none"> • Herpes simplex keratitis, vaccinia, varicella and other viral diseases of the cornea and conjunctiva • Fungal and mycobacterial diseases of ocular structures or untreated parasitic eye infections • Uncontrolled intraocular hypertension • Uncontrolled glaucoma <p>Tobradex[®] is contraindicated also in case of untreated purulent infections of the eye, whereas Maxidex[®] is contraindicated in acute, untreated bacterial infections.</p> 10. Hypersensitivity to the products or their excipients 11. Participation in other clinical studies if at least 5 half-lives of the IMP used in the previous studies have not passed between the end of treatment in the previous study and the start of treatment in this clinical study.

	12. Pregnancy or breastfeeding
Study drugs	<p>Test arm: levofloxacin + dexamethasone ophthalmic solution containing levofloxacin hemihydrate 5.12 mg/ml, corresponding to 5 mg/ml levofloxacin + dexamethasone 21-phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml for 7 days, 1 drop - 4 times a day, followed by dexamethasone ophthalmic suspension 1.0 mg/ml (Maxidex®) for an additional 7 days, 1 drop - 4 times a day.</p> <p>Control arm: tobramycin + dexamethasone ophthalmic suspension containing tobramycin 3 mg/ml + dexamethasone 1 mg/ml (Tobradex®) for 14 days, 1 drop - 4 times a day.</p>
Study procedures	<p>Patients scheduled for cataract surgery who have provided written informed consent will undergo screening procedures to verify eligibility. Immediately following phacoemulsification performed by an experienced surgeon, patients who complete surgery without complications will be assigned to one of the following two treatment groups in a 1:1 ratio according to a randomization list stratified by center:</p> <ul style="list-style-type: none"> ❖ Study arm: levofloxacin + dexamethasone eye drops for 7 days followed by dexamethasone eye drops (Maxidex®) for another 7 days. ❖ Control arm: tobramycin + dexamethasone eye drops (Tobradex®) for 14 days. <p>Treatment will begin either immediately after randomization according to local routine clinical practice (in those patients who are not bandaged after surgery), or immediately after removal of dressing of operated eye. Doses administered on the same day as surgery will be considered additional to the full protocol dosage regimen (4 instillations per day for 14 days). Patients will be given a diary on which to record times of instillation. Diaries will be collected to evaluate compliance with treatment. After surgery, patients will undergo visits on Day 4, Day 8 and Day 15 (end of study) to evaluate efficacy, safety and tolerability.</p>
Sample size	<p>The study plans to enroll 800 patients: 400 patients will be assigned to the test treatment and 400 to standard treatment.</p> <p>A sample size of 362 patients in each group is required to assess the non-inferiority of the test treatment vs. the standard therapy (i.e. lower limit of the 95% Confidence Interval of the difference in proportions, $\pi_T - \pi_S > -0.10$) with 80% power and by applying a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level, assuming that the expected difference in proportions is 0 and the proportion in the standard group is 0.64.</p> <p>The total sample size (362 + 362 = 724) is adjusted to 800 patients considering an expected dropout rate of about 10% using Freedman's formula: $n' = 100 * n / 100 - x$, where x is the expected dropout rate.</p>
Statistics	<p>Primary endpoint: The proportion of patients without signs of anterior chamber inflammation (sum of cells and flare score = 0) after 14 days of treatment will be calculated to evaluate the non-inferiority of the test treatment vs. the standard therapy. Non-inferiority will be assessed by computing the two-tailed 95% confidence interval (CI) of the difference</p>

	<p>between the two proportions $\pi_T - \pi_S$. Non-inferiority is met if the 95% CI does not cross the predefined non-inferiority margin $\Delta = -0.10$ and lies entirely to the right of the margin (i.e. non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the difference is > -0.10).</p> <p>If the 95% CI of the difference lies completely to the right of 0, the test treatment can be considered more effective than the standard treatment at a 5% significance level.</p> <p>Secondary endpoints: Descriptive statistics and two-sided 95% CIs of the difference between treatments will be computed for the secondary endpoints.</p>
Duration of the study	<p>Estimated date of the first visit of the first patient (FPFV): Q3, 2018</p> <p>Estimated date of the first visit of the last patient (LPFV): Q1, 2019</p> <p>Estimated date of the last visit of the last patient (LPLV): Q1, 2019</p>
Participant Duration	The study, for each patient, will last 14 days following cataract surgery.
Version and Date	V 2.0 – 12 July 2018

1.2 STUDY DESIGN



Levo/Dex=levofloxacin/dexamethasone

Dex=dexamethasone

Tobra/Dex=tobramycin/dexamethasone

* Treatment begins either immediately after randomization in patients not bandaged after surgery, or immediately after removal of eye dressing

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Visit 1 Screening ^a -28 days max	Visit 2 Surgery	Visit 3 Day 4	Visit 4 Day 8	Visit 5 Day 15 (EOS)
Signed written informed consent	X				
Demography	X				
Medical history	X				
Inclusion/exclusion criteria	X	X			
Concomitant medications	X	X	X	X	X
Urine pregnancy test ^b		X			
Surgery		X			
Randomization ^c		X			
Dispensation of treatment and diary		X		X ^f	
Slit lamp examination ^d	X		X	X	X
TOSS			X	X	X
Diagnosis of endophthalmitis			X	X	X
Ocular pain and discomfort			X	X	X
Use of rescue therapy			X	X	X
Intraocular pressure	X		X	X	X
Visual acuity (as per local practice)	X				X
Local tolerability ^e			X	X	X
Adverse events	X	X	X	X	X
Return of treatment				X	X
Return of diary/compliance			X	X	X

TOSS = Total Ocular Symptoms Score; EOS = End of Study

Additional visits may be scheduled in case of patient need.

^a Screening to be performed not more than 28 days prior to surgery

^b A urine pregnancy test (dipstick) is required for women of childbearing potential.

^c Patients who complete surgery without complications will be randomized immediately after surgery.

^d Slit lamp examination of anterior chamber: cells score and aqueous flare (Tyndall effect) score; assessment of conjunctival hyperemia.

^e Global evaluation on a 4-point scale. Burning, stinging, blurred vision on a 4-point scale.

^f Second period of treatment will start after drug dispensation at Day 8

2 INTRODUCTION

2.1 STUDY RATIONALE

In clinical practice, topical treatment following cataract surgery is frequently administered using a combination between an antibiotic and a corticosteroid to promote patient adherence to therapy and to obtain both the prevention of infection and the treatment of post-surgical inflammation. The combination of tobramycin and dexamethasone is among the most widely used combinations, but treatment usually lasts for two or more weeks, sometimes tapering posology over several weeks. This therapeutic strategy may however be inappropriate in terms of preventing the development of bacterial resistance, which is favored by prolonged treatment and the use of sub-therapeutic doses. For this reason, antibiotic treatment should not be prolonged beyond the time necessary for the healing of surgically induced epithelial lesions, and therefore should not last more than a week.

Based on these considerations, a product associating a broad-spectrum antibiotic with a highly effective corticosteroid that can be used for a short period of time (one week) would be of considerable interest.

The combination of levofloxacin and dexamethasone tested in this study is the first combination of a quinolone and a steroid under development and represents a major step forward in this direction. Levofloxacin 0.5% + dexamethasone 0.1% ophthalmic solution is an antibiotic/anti-inflammatory combination indicated for the treatment of inflammatory ocular conditions, where bacterial ocular infection or a risk of bacterial ocular infection exists. The active components of this combination are currently available in marketed ophthalmic products.

The purpose of this study is to evaluate the efficacy of a combination between levofloxacin and dexamethasone by demonstrating that the short-term use of this combination for a limited time of one week, followed by treatment with dexamethasone alone, is not inferior to longer treatment with tobramycin + dexamethasone in reducing the incidence of post-operative inflammation/infections while limiting emergence of antibiotic resistance.

2.2 BACKGROUND

Cataract is an ocular condition that causes vision impairment due to changes in opacity of the ocular lens. Cataract is an age-related condition, but smoking, ocular trauma, exposure to ultraviolet light, diabetes and drug-induced metabolic changes in the lens are risk factors for lens opacification causing cataract.¹

The only cure for cataract is a surgical procedure: the opaque lens is removed and replaced with an artificial intraocular lens.^{2,3} Nowadays, the surgical procedure of choice is phacoemulsification with intraocular lens implantation.⁴ The technique, initially developed in 1967, is based on high-energy ultrasound to emulsify the cataractous lens nucleus, with the fragments being subsequently aspirated with an ultrasound probe. The corneal incision required for this technique is much

smaller (3 mm or less) than the limbal incision (usually an 11-mm incision between cornea and sclera) used in the past to remove the entire lens.²

As the surgical procedure has become less invasive, patients usually no longer require in-patient hospital care after surgery, with recovery usually uneventful and pain-free. Cataract surgery may however cause corneal trauma, ocular inflammation and ocular dryness, which can result in ocular irritation during the recovery period.⁵⁻⁷ These conditions may cause different types of ocular discomfort such as pain, burning, stinging, foreign body sensation, itchiness and glare in the operated eye. The incidence of ocular irritation symptoms experienced during the first postoperative hours may be as high as 98%.⁸

Conjunctival hyperemia, anterior chamber cells and flare, and cystoid macular edema are some possible signs of inflammation after cataract surgery.⁹ The severity of the inflammation varies from patient to patient. In many cases, inflammation is self-limiting, but drug therapy is used to shorten resolution time and alleviate ocular discomfort.¹⁰

Steroidal agents and non-steroidal anti-inflammatory drugs (NSAIDs) are used to prevent and treat postoperative inflammation occurring after surgery. Corticosteroids inhibit the lipoxigenase pathway leading to the leukotriene production and thus reduce tissue swelling and prevent edema.^{9,11} They have been used for decades to prevent ocular inflammation and many ophthalmic surgeons prefer a 1 to 6-week period of topical corticosteroids after cataract surgery.

According to the practice pattern studies published by the ASCRS (American Society of Cataract and Refractive Surgery 2012, practice pattern study), Canadian Ophthalmological Society study 2012¹² and European Society of Cataract and Refractive Surgeons (ESCRS), there are variations in postoperative drug therapy provided to individual patients and among different countries. In Europe, dexamethasone was the most commonly used steroidal anti-inflammatory drug and was chosen as the preferred drug by 71% of ophthalmological surgeons.¹³

Endophthalmitis is a rare yet severe condition that occurs in 0.03–0.3% of patients undergoing cataract surgery.^{14,15} Endophthalmitis is a vision-threatening complication of cataract surgery. Swollen eyelids, ocular pain, conjunctival hyperemia, decreased visual acuity, anterior chamber cells and an opaque vitreous are signs of endophthalmitis. This condition usually appears during the first days after surgery, and in 80% of cases endophthalmitis will have developed during the first 6 weeks after surgery.^{15,16}

Topically applied antibiotics are routinely used for the prophylaxis of postoperative bacterial ocular infections such as endophthalmitis. Intraocular, usually intracameral, or subconjunctival, antibiotics are used during surgery, and both pre- and postoperative topical applications are also provided.¹⁴

To increase the efficacy of this approach, a broad antibacterial spectrum antibiotic should be chosen. A prospective observational study was conducted to determine the antibiotic susceptibility patterns of conjunctival bacterial flora isolated preoperatively from patients undergoing anterior

segment surgery. Conjunctival cultures were obtained from 120 eyes on the day of surgery before povidone-iodine or antibiotic application. Bacterial isolates were identified and tested for antibiotic susceptibility. Of these 120 eyes, 21 (18%) showed no bacterial growth. Of the 143 bacterial strains isolated from the remaining 99 eyes, 112 (78%) were coagulase-negative staphylococci (CNS). Among the CNS, greater than 90% were susceptible to cefotaxime, levofloxacin, imipenem, meropenem, vancomycin, and each of the aminoglycosides except neomycin. Between 70% and 90% of the CNS were susceptible to ceftazidime, neomycin, ciprofloxacin, ofloxacin, norfloxacin, and chloramphenicol. Less than 70% of the isolated CNS were sensitive to the penicillin analogues, erythromycin, and tetracycline.¹⁷

Based on the previously mentioned results, quinolones clearly represent a rational approach to the prevention of ocular infections after cataract surgery. Indeed, among available antibiotics for ophthalmic use, quinolones are characterized by a broad spectrum that includes both the Gram-positive and Gram-negative bacteria that are most frequently responsible for ocular bacterial infections.

Levofloxacin belongs to the class of quinolones. The mechanism of action of levofloxacin and other fluoroquinolone consists in the inhibition of bacterial topoisomerase IV and DNA gyrase, enzymes required for DNA replication, transcription, repair and recombination.^{18,19}

The spectrum of activity against ocular pathogens includes aerobic Gram-positive microorganisms (*S. aureus* MSSA, *S. pyogenes*, *S. pneumoniae*, viridans group streptococci), aerobic Gram-negative bacteria (*E. coli*, *H. influenzae*, *P. aeruginosa* commonly isolates) and other organisms (e.g. *Chlamydia trachomatis*). Caution should be taken for Methicillin-resistant Staphylococcus Aureus (MRSA), *S. epidermidis* and *P. aeruginosa* hospital isolates, due to possible acquired resistance¹⁹. Literature data confirm that resistance is not common for levofloxacin, which is active against several fluoroquinolone or other antibiotic-resistant strains, but cross-resistance with other fluoroquinolones cannot be ruled out.¹⁹

A prospective, randomized, controlled trial compared the efficacy of topical levofloxacin in combination with povidone iodine irrigation vs. povidone iodine alone in reducing conjunctival bacteria. The authors concluded that the study showed an enhancing effect of using topical levofloxacin in combination with povidone irrigation in reducing conjunctival bacteria in patients undergoing intraocular surgery.²⁰

Results from a retrospective, 10-year review of all cases with culture-proven endophthalmitis at a single institute revealed that susceptibility of the most common organisms to levofloxacin was 58.5% for gram-positive organisms and 100% for gram-negatives. No single antibiotic provided coverage for all the microbes isolated.²¹

A prospective observational study of consecutive cases of patients registered from April 2006 to March 2007 to have a routine conjunctival culture was carried out before cataract operation. This study documents the resistance of conjunctival bacteria of patients undergoing cataract surgery to the most common antibiotics. The authors concluded that none of the antibiotics tested, including

cefuroxime and levofloxacin, was active against all isolated conjunctival bacteria. Based on the resistance patterns and other prophylactic effects, two phases of local prophylaxis were suggested: first, eliminating Staphylococci and respiratory bacteria with rifampicin or chloramphenicol preoperatively; second, giving levofloxacin from 1 h before surgery until 6 days afterwards to eradicate the small quantity of Enterococci and Gram-negative rods since the visual outcome of the post-surgical endophthalmitis cases caused by these bacteria was the most serious.^{22,23}

When comparing the efficacy of quinolones in bacterial conjunctivitis, levofloxacin (third generation) eye drops showed significantly greater microbial eradication rates than ofloxacin²⁴ (second generation), and very similar efficacy when compared to gatifloxacin²⁵ and moxifloxacin (fourth generation)²⁶.

In most cases, postoperative care after cataract surgery consists of topical anti-inflammatory and antibacterial drug therapy. The combined administration of corticosteroids and antibiotics guarantees a powerful anti-inflammatory effect, and contemporarily a preventive/therapeutic action against infections related either to the intensity of the inflammatory process or to the immunosuppressive effect of the steroid. Combined administration also favors the proper administration of the two agents, reduces the possibility of inaccurate dosage and improves patient compliance with medication.

However, use of such a combination should also be in line with the modern approach to antimicrobial therapy aimed at avoiding the increase of bacterial resistance caused by inappropriate use of the antibiotic.²⁷ ESCRS guidelines emphasize the importance of rational use especially when a broad-spectrum antibiotic is used.²⁸

Among the most widely used combination is the one between tobramycin and dexamethasone, whose administration usually lasts for two or more weeks, sometimes tapering posology over several weeks. Tapering is however inappropriate in terms of preventing the development of bacterial resistance, which is favored by prolonged treatment and the use of sub-therapeutic doses.

For this reason, antibiotic treatment should not be prolonged beyond the time necessary for the healing of surgically induced epithelial lesions, and therefore should not last more than a week.²⁹

The confirmation that non-rational therapeutic practice remains widespread comes from a recent study on the adherence of some Italian ophthalmology centers to the recommendations of the ESCRS Guidelines. This study has shown that topical postoperative treatment is used in 100% of the centers and that in more than half of them treatment is continued for two or more weeks. In most cases, the antibiotic is administered using corticosteroid combinations, and in one third of the cases dosage is tapered over a few weeks. The study divided the participating centers according to the incidence of endophthalmitis in two groups (one with incidence < 0.13 per thousand, the other with incidence > 0.13 per thousand) and observed that in the group with lower incidence of infections, centers that prescribe topical post-operative antibiotic for one week and do not taper posology are prevalent.³⁰

Based on these considerations, there is a clear interest in having a combination between a broad-spectrum antibiotic and a highly effective corticosteroid to be used for a short period, followed by treatment with corticosteroid alone. The combination of levofloxacin and dexamethasone tested in this study is the first combination of a quinolone and a steroid under development and represents a major step forward in the management of these patients. The therapeutic strategy tested in this trial, with the combination of levofloxacin and dexamethasone to be used for just one week followed by another week of treatment with dexamethasone alone, is ideal in providing the same anti-inflammatory activity as compared to standard therapy while doing away with the tapering routinely adopted at present. This approach is in line with more recent guidelines issued by scientific societies and health organizations in terms of preventing antibiotic resistance.^{31, 32}

The combination of levofloxacin 5 mg/ml and dexamethasone 1 mg/ml is a new fixed dose combination of an antibiotic, levofloxacin 5 mg/ml, and a corticosteroid, dexamethasone sodium phosphate, corresponding to dexamethasone 1 mg/ml.

The concentration of dexamethasone (1 mg/ml) is well established in ophthalmic solutions both as sole active ingredient and in combination with an antibiotic (e.g. tobramycin) to prevent ocular inflammation following cataract surgery. The penetration of this agent from 0.1% solutions in the aqueous humor is adequate to exert its potent anti-inflammatory activity at the site of action.³³ The dexamethasone 21-phosphate salt is freely soluble in water, allowing its use in water solution. The solution does not require shaking before application and guarantees homogeneity of content of the active ingredient at each application.

Dexamethasone is considered the gold standard in the management of postoperative ocular inflammation and constitutes the reference treatment of controlled studies on new drugs or treatments in development.

The pharmacokinetics of both levofloxacin and dexamethasone confirm that after application to the eye in the form of eye drop solution, both active drugs reach high concentrations in the aqueous humor, with a peak of aqueous levels between 90 and 150 minutes, and detectable concentrations after 12 hours from dosing.³³⁻³⁸ Conversely, the concentrations in plasma are negligible, guaranteeing a lack of systemic effects at least during the short course treatment in this study. The best dosage schedule indicated in literature on the pharmacokinetics of both ingredients is every 6 hours.^{24, 39}

The purpose of this study is to demonstrate that the use of a combination of levofloxacin and dexamethasone for a limited time of one week, followed by treatment with corticosteroid alone, is not inferior in preventing or reducing post-operative inflammation and preventing post-operative infections as compared to a two-week treatment with a combination of tobramycin and dexamethasone, while being in line with the most recent guidelines issued by scientific societies and health organizations in terms of preventing antibiotic resistance.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

In toxicity studies, the only toxicity data reported for dexamethasone were those related to an exaggerated pharmacological activity including a negative feedback on the pituitary-adrenal axis. Systemic effects are however not expected or are negligible when the drug is topically administered as eye drops and for a limited period. Nevertheless, its potential effect on fetal development and on newborns suggests it be used very carefully in pregnant women and to discard the milk during lactation.^{40,41}

Possible adverse effects of topical ocular corticosteroid therapy include an increase of intraocular pressure (IOP), inhibition of corneal wound healing and increased likelihood of infection and serious complications, but systemic adverse effects are rare.^{9,10}

Levofloxacin is not toxic on reproduction and does not have mutagenic or carcinogenic potential. It is not irritating after eye instillation, but it is phototoxic at very high doses and photosensitization cannot be excluded.^{19,42} Patients should therefore not be exposed to direct sunlight during treatment with eye drops containing levofloxacin.

In clinical studies involving over 1600 patients, no serious ophthalmic or systemic adverse reactions were reported for the combination of tobramycin + dexamethasone (Tobradex[®]), comparator drug for this study. The most frequently reported adverse reactions were eye pain, increased intraocular pressure, eye irritation (burning upon instillation) and eye pruritus occurring in less than 1% of patients.⁴³

2.3.2 KNOWN POTENTIAL BENEFITS

The efficacy of dexamethasone as an anti-inflammatory agent and of levofloxacin as antibiotic in ophthalmology is well established. Combining the two agents would favor their proper administration, reduce the possibility of inaccurate dosage and improve patient compliance.

The combination would also allow the implementation of a shorter antibiotic treatment period as compared to other marketed products and thus prevent the emergence of antibiotic resistance.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In light of the considerations stated above, the potential benefits of this study surely appear to outweigh the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Efficacy		
To demonstrate the non-inferiority of combined levofloxacin + dexamethasone eye drops for 7 days followed by dexamethasone eye drops alone for an additional 7 days vs. standard treatment tobramycin + dexamethasone eye drops for 14 days in the prevention and treatment of postoperative ocular inflammation and prevention of infection.	<p>Primary endpoint The proportion of patients without signs of anterior chamber inflammation (sum of cells and flare score = 0) after 14 days of treatment</p> <p>Secondary endpoints</p> <ul style="list-style-type: none"> • Incidence of endophthalmitis • Proportion of patients without signs of anterior ocular chamber inflammation after 3 and 7 days of treatment • Conjunctival hyperemia after 3, 7 and 14 days of treatment • Total Ocular Symptoms Score (TOSS) after 3, 7 and 14 days of treatment • Ocular pain/discomfort after 3, 7 and 14 days of treatment • Use of rescue therapy during treatment 	The endpoints are considered suitable for evaluating ocular inflammation and infection following cataract surgery.
Safety and tolerability		
To evaluate the safety of combined levofloxacin – dexamethasone eye drops.	<ul style="list-style-type: none"> • Intraocular pressure (IOP) • Visual acuity • Adverse events 	The safety endpoints are considered standard for the indication and for the drugs under study.
To evaluate the tolerability of combined levofloxacin – dexamethasone eye drops.	<ul style="list-style-type: none"> • Global evaluation • Burning, stinging, blurred vision 	The endpoints are considered suitable for evaluating the tolerability of an ophthalmic product.
Compliance		
To evaluate compliance with prescribed treatment.	<ul style="list-style-type: none"> • Assessment of patient diary 	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an international, multicenter, phase III, randomized, blinded-assessor, parallel-group clinical study to evaluate the non-inferiority of the test treatment vs. standard treatment. The Investigator in charge of evaluating study parameters will be blinded to treatment assignment. A separate investigational staff will be unblinded and responsible for assigning and dispensing/return study products.

Patients scheduled for cataract surgery who have provided written informed consent will undergo screening procedures. Immediately following phacoemulsification performed by an experienced surgeon, patients who complete surgery without complications will be assigned to one of the following two treatment groups in a 1:1 ratio according to a randomization done by IWRS stratified by center:

❖ Test arm

- Levofloxacin + dexamethasone eye drops for 7 days, followed by dexamethasone eye drops (Maxidex[®]) for an additional 7 days.

❖ Control arm

- Tobramycin + dexamethasone eye drops (Tobradex[®]) for 14 days.

Treatment will begin immediately or after removal of dressing of the operated eye. Doses administered on the same day as surgery will be considered additional to the full protocol dosage regimen (4 instillations per day for 14 days).

Patients will be given a diary on which to record times of instillation. Diaries will be collected to evaluate compliance with treatment.

After surgery, patients will undergo visits on Day 4, Day 8 and Day 15 (end of study) to evaluate efficacy, safety and tolerability.

The study will be conducted at approximately 80 centers located in Italy, Germany, Spain and Russia and will enroll 800 patients.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The combination of tobramycin and dexamethasone has been chosen as control treatment since it is the most commonly used fixed combination in ophthalmology in both Europe and the U.S. As the primary efficacy endpoint of the study is related to the prevention and resolution of ocular inflammation, and given that the anti-inflammatory component of the test and control

combinations is the same (dexamethasone 1 mg/ml), a non-inferiority design was deemed appropriate for this study. In fact, the study aims to demonstrate that levofloxacin 5 mg/ml + dexamethasone 1 mg/ml eye drops is at least as effective as the control treatment in terms of anti-inflammatory effect, while offering significant advantages such as the possibility of administering a proven, effective, broad-spectrum antibiotic for a shorter treatment period, thereby reducing the risk of developing antibiotic resistance.

A blinded-assessor design was chosen because particularly suitable for studies involving the topical administration of the drug to be tested when a double-blinded design is not feasible. Furthermore, compared to the double-dummy methodology, the blinded-assessor design has the advantage of not having to administer both active drug and placebo, which can cause dilution of the active test drug or control and an increase of clearance from the site of action.

4.3 JUSTIFICATION FOR DOSE

The concentration of dexamethasone (1 mg/ml) and dose (1 drop, 4 times a day) in both the test and standard combinations is well established in ophthalmic solutions, both as sole active ingredient or in combination with an antibiotic. Levofloxacin is also well established as sole active ingredient of ophthalmic solutions at a concentration of 5 mg/ml and at a dose of 1 drop, 4 times a day.

Tobradex[®] will be administered as per label.

4.4 END OF STUDY DEFINITION

A participant is considered as having completed the study if he or she has completed all phases of the study including the last visit as indicated in the Schedule of Activities (SoA), [Section 1.3](#).

The end of the study is defined as completion of the last visit as shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, a subject must meet all the following criteria:

5.1.1 INCLUSION CRITERIA PRIOR TO SURGERY

1. Signed written informed consent must be obtained before any assessment is performed
2. Male or female, age ≥ 40 years
3. Scheduled senile or presenile cataract surgery (not yet performed).
4. Willing to interrupt the use of contact lenses for the entire duration of the study

5. Able and willing to follow study procedures
6. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or must agree to use an effective method of contraception, which include an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicide.

5.1.2 INCLUSION CRITERIA FOLLOWING SURGERY

7. Surgery completed without complications

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Ocular conditions that at the discretion of the Investigator may interfere with the efficacy and/or safety evaluations (e.g. ocular herpes, blepharitis, conjunctivitis, uveitis, keratitis, diabetic retinopathy, retinal vein occlusions, retinal vasculitis, retinal angiomatous proliferation, pseudoexfoliation syndrome, intraoperative floppy iris syndrome, etc.)
2. Patients undergoing bilateral cataract surgery
3. Patients under treatment with prostaglandin analogues or intravitreal injections of anti-VEGF (vascular endothelial growth factor) drugs
4. Systemic diseases that may interfere with the results of the study (e.g. rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, systemic lupus erythematosus, scleroderma with major ocular involvement, etc.)
5. Any condition that could interfere with correct instillation of eye drops
6. Ocular surgery in the study eye (including laser surgery) in the 3 months before screening
7. Monocular patients
8. Visual Acuity (VA) < 20/80 of the contralateral eye measured as ETDRS or Snellen 20 feet, equal to 0.25 in decimal
9. Contraindications to ocular treatment with Tobradex[®], Maxidex[®] or levofloxacin/dexamethasone as follows:
 - Herpes simplex keratitis, vaccinia, varicella and other viral diseases of the cornea and conjunctiva
 - Fungal and mycobacterial diseases of ocular structures or untreated parasitic eye infections
 - Uncontrolled intraocular hypertension
 - Uncontrolled glaucomaTobradex[®] is contraindicated also in case of untreated purulent infection of the eye, whereas Maxidex[®] is contraindicated in acute, untreated bacterial infections.
10. Hypersensitivity to the study product or its excipients

11. Participation in other clinical studies if at least 5 half-lives of the IMP used in the previous studies have not passed between the end of treatment in the previous study and the start of treatment in this clinical study.
12. Pregnancy or breastfeeding

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention. A minimal set of data about screen failure patients is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will enroll subjects already scheduled for cataract surgery and no other recruitment strategies are required.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study drugs for the two treatment arms are as follow:

- Test arm: levofloxacin + dexamethasone ophthalmic solution followed by dexamethasone ophthalmic suspension (Maxidex[®])
- Control arm: tobramycin + dexamethasone ophthalmic suspension (Tobradex[®])

6.1.2 DOSING AND ADMINISTRATION

❖ Test arm

- Levofloxacin + dexamethasone eye drops for 7 days, 1 drop - 4 times a day (hours 8.00, 13.00, 18.00 and 23.00 ± 30 minutes), followed by dexamethasone eye drops alone (Maxidex[®]) for an additional 7 days, 1 drop - 4 times a day (hours 8.00, 13.00, 18.00 and 23.00 ± 30 minutes).

❖ Control arm

- Tobramycin + dexamethasone eye drops (Tobradex[®]) for 14 days, 1 drop - 4 times a day (hours 8.00, 13.00, 18.00 and 23.00 ± 30 minutes).

In both arms, patients will start treatment according to local routine clinical practice, i.e. either immediately after randomization in those patients who are not bandaged after surgery, or soon after removal of dressing of operated eye. Doses administered on the same day as surgery will be considered additional to the full protocol dosage regimen (4 instillations per day for 14 days).

6.1.2.1 MISSED DOSES

If one dose of study treatments is missed, the patient should get in touch with the unblinded site staff and get advice on how to continue treatment. If this is not possible, the following approach should be implemented: if time to next dose is more than 2.5 hours, medication should be taken as soon as possible. If time to next dose is less than 2.5 hours, the patient should wait until it is time to apply the next dose.

Missing more than one dose per day or more than three doses per week will be considered a major deviation from the protocol.

The patient must be instructed to indicate the doses not applied and the reason in the diary accurately.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study drugs will be provided by the Sponsor. Upon arrival of investigational products at the site, the pharmacist and/or unblinded staff should check them for any damage and verify their proper identity, quantity, integrity of seals and report any deviations. Upon receipt, all study treatments must be stored according to the label instructions in a secured location. Unblinded site staff designated by the Principal Investigator, will maintain accurate records of the product's delivery to the study site, the inventory at the site, the use by each subject (compliance will be verified through patient diaries) and the return to the Sponsor or alternative disposition of unused products. Monitoring of drug inventory will be performed by the field monitor during the study conduct and a copy of the reconciliation log will be provided by the investigators at the completion of the study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Test arm

- Levofloxacin 5 mg/ml – dexamethasone 1 mg/ml eye drops

Composition in active ingredients: levofloxacin hemihydrate 5.12 mg/ml, corresponding to 5 mg/ml, and dexamethasone 21-phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml.

The Investigational Medicinal Product (IMP) is a sterile ophthalmic, clear, greenish-yellow isotonic solution with a pH of 7.2. The finished product is packaged in a 5 ml light-resistant LDPE bottle with ophthalmic dropper and PP screw cap.

- Dexamethasone 1 mg/ml eye drops suspension (Maxidex[®])

Control arm

- Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex[®]).

Each treatment kit contains two boxes. Each box contains one bottle of eye drops. Kit boxes assigned to patients in the levofloxacin + dexamethasone arm will contain one packaged bottle of levofloxacin + dexamethasone eye drops and one packaged bottle of dexamethasone eye drops (Maxidex[®]), whereas kits assigned to patients in the tobramycin + dexamethasone arm will contain two packaged bottles of tobramycin + dexamethasone eye drops (Tobradex[®]). Patients will be given one packaged bottle of eye drops upon randomization following surgery and the other one at the visit on day 8 of the study.

Medication labels will comply with legal requirements and will be printed in the local language.

6.2.3 PRODUCT STORAGE AND STABILITY

All study drugs (Tobradex[®], Maxidex[®] and Levofloxacin 5 mg/ml – dexamethasone 1 mg/ml eye drops) are to be stored at room temperature not higher than 25° C, not frozen and not refrigerated.

6.2.4 PREPARATION

Study treatments are ready for use and do not require preparation.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a randomized, blinded-assessor study. Patients will be assigned to one of the two following treatment groups in 1:1 ratio according to a randomization list stratified by center:

- Test arm: levofloxacin + dexamethasone ophthalmic solution for 7 days followed by dexamethasone ophthalmic suspension (Maxidex[®]) alone for an additional 7 days
- Control arm: tobramycin 3 mg/ml + dexamethasone 1 mg/ml (Tobradex[®]) ophthalmic suspension for 14 days

The randomization numbers will be generated using procedures that ensure that treatment assignment is unbiased. A patient randomization list will be produced using a validated system that automates the assignment of randomization numbers.

Patients who fulfill all inclusion criteria and none of the exclusion criteria will be randomized following surgery via an Interactive Web Response System (IWRS) that will assign the patient a

randomization number linked to a treatment arm. Unblinded staff is to use the IWRS to obtain the study treatment to be given to the patient.

The physician in charge of assessing study parameters will be blinded to treatment assignment (blinded assessor). The blinded assessor will not have access to the randomization page of the eCRF. A separate investigational staff will be unblinded and responsible for assigning and dispensing/return study products. Study treatment will be dispensed upon randomization and on Day 8.

6.4 STUDY INTERVENTION COMPLIANCE

Compliance will be evaluated through the patient diary, in which the subject is to record all treatment administrations.

6.5 CONCOMITANT THERAPY

Medications to be reported in the electronic Case Report Form (eCRF) are concomitant prescription medications, over-the-counter medications and supplements. The use of concomitant medications is to be recorded at each visit.

6.5.1 PROHIBITED CONCOMITANT THERAPY

The following treatments are not permitted:

- Topical antibiotics
- Systemic antibiotics for prophylactic purposes
- Topical or systemic steroids

6.5.2 RESCUE THERAPY

Rescue therapy is defined as the introduction or dose modification of any local or systemic non-randomized medication required to manage the emergence or worsening of ocular inflammation and or infection.

The name and dosage regimen of the rescue medication as well as the date and time of administration must be recorded in the eCRF.

6.6 WARNINGS AND PRECAUTIONS RELATED TO STUDY TREATMENTS

The warnings and precautions related to the use Tobradex[®], Maxidex[®] and levofloxacin/dexamethasone as stated in their respective SPCs/IB are listed in the tables below:

Tobradex®
Both topical corticosteroids and NSAIDs may slow corneal healing. Caution is therefore advised when using topical dexamethasone and topical NSAIDs concomitantly.
Prolonged use of topical ophthalmic corticosteroids (i.e. longer than the maximum duration used in clinical trials [24 days]) may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and reduced visual acuity and visual fields defects. It is advisable that intraocular pressure be checked frequently. The risk of corticosteroid-induced raised intraocular pressure is increased in predisposed patients (e.g. diabetes).
Corticosteroids can reduce resistance to bacterial, viral, fungal, or parasitic infections and promote their development and mask clinical signs of an infection.
Sensitivity to topically administered aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such as erythema, itching, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops during use of this medicine, treatment should be discontinued. Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.
Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when used concomitantly.
Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients. In these cases, treatment should be progressively discontinued
Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued.
Prolonged use of antibiotics may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.
In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
Benzalkonium chloride used as a preservative may cause irritation of the eye.

Maxidex®
Both topical corticosteroids and NSAIDs may slow corneal healing. Caution is therefore advised when using topical dexamethasone and topical NSAIDs concomitantly.
Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and reduced visual acuity and visual fields defects. It is advisable that intraocular pressure be checked frequently. The risk of corticosteroid-induced raised intraocular pressure is increased in predisposed patients (e.g. diabetes).
Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral and fungal infections and mask the clinical signs of infections. In such cases antibiotic therapy is

Maxidex®
mandatory. Fungal infection should be suspected in patients with persistent corneal ulceration and corticosteroids therapy should be discontinued if fungal infection occurs.
In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
Benzalkonium chloride used as a preservative may cause irritation of the eye.

Levofloxacin/dexamethasone
Both topical corticosteroids and NSAIDs may slow corneal healing. Caution is therefore advised when using topical dexamethasone and topical NSAIDs concomitantly.
Systemic fluoroquinolones have been associated with hypersensitivity reactions, even following a single dose. If an allergic reaction does occur, discontinue the medication.
As levofloxacin is phototoxic at very high doses and photosensitization may not be excluded, patients should not be exposed to direct sunlight during treatment.
Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If worsening of infection occurs, or if a clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy.
Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity, visual field defects and posterior sub-capsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure and lens should be checked routinely and frequently. The risk of corticosteroid-induced raised intraocular pressure is increased in predisposed patients (e.g. diabetes).
Fungal infection should be suspected in patients with persistent corneal ulceration and corticosteroids therapy should be discontinued if fungal infection occurs.
In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
Topical corticosteroids should not be used for longer than one week except under ophthalmic supervision, with regular checks of intraocular pressure.
Benzalkonium chloride used as preservative may cause irritation of the eye.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Treatment may be discontinued permanently, regardless of treatment arm, if any adverse event, medical condition or situation warrants discontinuation of treatment. The following situations call for permanent discontinuation of study treatments as per SPC/IB:

Tobradex®
Hypersensitivity to Tobradex®.
Cushing's syndrome and/or adrenal suppression.
Fungal infections.

Maxidex®
Fungal infections.

Levofloxacin/dexamethasone
Allergic reactions.
Worsening of infection or lack of clinical improvement.
Fungal infections.

Discontinuation from treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated in the study protocol. If a clinically significant finding is identified after enrollment, the investigator will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Patients discontinuing treatment will be asked to undergo the assessments planned for the End of Study (EOS) Visit (see the SoA in [Section 1.3](#)).

Temporary treatment interruptions and dose modifications are not foreseen in the protocol. See [Section 6.1.2.1](#) for information concerning the management of missed doses.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not complete the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF ASSESSMENTS

The following visits will be performed as listed in the SoA. Additional visits will be made available to patients in case of need.

Visit 1: Screening (to be performed not more than 28 days prior to surgery)

Upon signing the informed consent form each patient is uniquely identified by a patient ID number which is composed of the site number and a sequential number assigned automatically by the eCRF. Once assigned to a patient, the patient ID number will not be reused.

At screening, after obtaining signed written informed consent, inclusion/exclusion criteria will be checked and the following assessments will be performed/data collected:

- Demographics
- Medical history
- Use of concomitant medications

- Slit lamp examination
- Intraocular pressure
- Visual acuity
- Adverse events

Visit 2 - Day of surgery

Prior to surgery, inclusion/exclusion criteria will be rechecked, and the following assessments will be performed/data collected:

- Use of concomitant medications, including prophylactic pre-operative medications to be stopped before surgery
- Adverse events occurred after previous visit.

Women of childbearing potential will be required to undergo a urine pregnancy test (dipstick).

Patients who completed surgery without complications will be randomized to one of the two treatment arms and will be provided with study drug needed until visit at day 8 (first period of treatment) and a diary on which to record times of instillations.

Visit 3 - Visit on day 4 after 3 full days of treatment

On Day 4, patients should return their diaries to evaluate compliance. The following assessments will be performed/data collected on Day 4:

- Concomitant medications
- Slit lamp examination
- Evaluation of any ocular infections
- Total Ocular Symptom Score (TOSS)
- Ocular pain/discomfort
- Use of rescue therapy
- Intraocular pressure
- Local tolerability (global evaluation/burning, stinging, blurred vision)
- Adverse events occurred after previous visit

Visit 4 - Visit on day 8 after 7 full days of treatment

On Day 8, patients should return unused medication and completed diary to evaluate compliance and will receive a new supply of medication needed until end of study and a new diary. The second period of treatment will start after the new supply.

The following assessments will be performed/data collected on Day 8:

- Concomitant medications

- Slit lamp examination
- Evaluation of any ocular infections
- TOSS
- Ocular pain/discomfort
- Use of rescue therapy
- Intraocular pressure
- Local tolerability (global evaluation/burning, stinging, blurred vision)
- Adverse events occurred after previous visit

Visit 5 - Visit on day 15 after 14 full days of treatment (end of study)

On Day 15, patients should return unused medication and completed diary to evaluate compliance. The following assessments will be performed/data collected on Day 15:

- Concomitant medications
- Slit lamp examination
- Evaluation of any ocular infections
- TOSS
- Ocular pain/discomfort
- Use of rescue therapy
- Intraocular pressure
- Visual acuity
- Local tolerability (global evaluation/burning, stinging, blurred vision)
- Adverse events occurred after previous visit

END OF STUDY

After the end of study visit performed at day 15, patients will be managed according to standard routine practice applied by each center.

8.2 EFFICACY ASSESSMENTS

- **Slit lamp examination**

A slit lamp examination will be performed at Visit 1 (screening) and on Day 4 (Visit 3), Day 8 (Visit 4), and Day 15 (Visit 5) to evaluate cells in the anterior chamber and aqueous flare as follows:

Cells in anterior chamber: results are to be provided as a score: 0 = no cells; 1 = 1–5 cells; 2 = 6–15 cells; 3 = 16–30 cells; 4 = >30 cells.⁴⁸

Aqueous flare (Tyndall effect): results are to be provided as a score: 0 = absent; 1 = trace barely detectable; 2 = mild intensity (iris and lens details clear); 3 = moderate intensity (iris and lens details not clear); 4 = strong intensity (iris and lens details not visible and fibrin in the anterior chamber).⁴⁴

Conjunctival hyperemia will be evaluated and results provided as a score as follows: 0 = absence of inflammation, 1 = mild inflammation (some vessels injected), 2 = moderate inflammation (diffuse injection of vessels, but individual vessels are still discernable) 3 = severe inflammation (intense injection of vessels, individual vessels not easily discernable).⁴⁵

- **Endophthalmitis**

All cases of endophthalmitis occurring following cataract surgery are to be reported at all visits.

- **Total Ocular Symptom Score (TOSS)**

The TOSS is a patient-reported evaluation of 3 ocular symptoms: itching/burning, hyperemia of conjunctiva and tearing. Each symptom is given a score: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The TOSS will be evaluated on Days 4, 8, and 15.⁴⁶ See Appendix 1.

- **Ocular pain/discomfort**

Overall ocular pain and discomfort will be evaluated by the subject at Days 4, 8 and 15 on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

- **Use of rescue therapy**

All rescue therapy used following cataract surgery is to be reported at all visits (see [Section 6.5.2](#)).

8.3 SAFETY, TOLLERABILITY AND OTHER ASSESSMENTS

Safety will be monitored by evaluating all adverse events, especially increases in intraocular pressure (IOP) (measured at each visit following surgery) and drop in visual acuity assessed as per local clinical practice (measured on Day 15).

Local tolerability will be evaluated at all visits following surgery as follows:

- Global evaluation on a 4-point scale: 0 = no intolerability, 1 = mild intolerability, 2 = moderate intolerability, 3 = maximum intolerability.
- Burning, stinging, blurred vision on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Compliance will be evaluated on Day 4, Day 8 and Day 15 by means of a patient diary in which the instillations are to be recorded.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event can be defined as any untoward medical occurrence associated with the use of an intervention in humans after providing written informed consent for participation in the study until the end of study visit, whether considered intervention-related or not.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. Investigators are to judge the causal relationship of the event with the study intervention as "suspected", "unsuspected" or "unknown".

8.4.3.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with onset dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the previous visit. Events will be followed for outcome information until resolution or stabilization.

8.4.5 ADVERSE EVENT REPORTING

All identified non-serious AEs (related and unrelated) must be recorded and described on the eCRF.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

Every Serious Adverse Event (SAE), regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness.

Any SAE experienced after this 30-day period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes,

complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Information about all SAEs will be recorded on the eCRF. In case of technical difficulties, SAE notification can be carried out by contacting the Contract Research Organization (CRO) OPIS in charge of Pharmacovigilance via email at all_phv@opis.it or by fax using the following number: Fax: +39 0362 633622.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study Sponsor and should be provided as soon as possible. The study Sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than seven calendar days after the Sponsor's initial receipt of the information.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC and as per national regulatory requirements in participating countries.

8.4.7 REPORTING EVENTS TO PARTICIPANTS

Should an event occur that changes the overall benefit/risk ratio of the study, the Sponsor shall evaluate if a risk minimization measure is needed. Should this measure require a substantial amendment to the protocol, the informed consent and patient information will be revised and submitted to the patient for written consent.

8.4.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4.9 REPORTING OF PREGNANCY

The investigator shall report all pregnancy exposure occurring in a female patient or in a male patient's partner within 24 hours to the Sponsor using the Pregnancy Reporting Form of the eCRF. In case of technical difficulties, pregnancy notification can be carried out by contacting the Contract Research Organization (CRO) OPIS in charge of Pharmacovigilance via email at all_phv@opis.it or by fax using the following number: Fax: +39 0362 633622. The investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of the trial is to demonstrate the non-inferiority of combined levofloxacin + dexamethasone for 7 days followed by dexamethasone alone for an additional 7 days vs. standard treatment tobramycin + dexamethasone for 14 days in the prevention and treatment of postoperative ocular inflammation and prevention of infection.

The primary endpoint is the proportion of patients without signs of anterior chamber inflammation (sum of cells and flare score = 0) after 14 days of treatment. The following non-inferiority hypotheses will be tested:

$$H_0 : \pi_T - \pi_S \leq -\Delta$$

$$H_1 : \pi_T - \pi_S > -\Delta$$

Where π_T and π_S are the proportions of patients without signs of anterior chamber inflammation in the test and standard treatments, respectively, and the non-inferiority margin is $\Delta = 10\%$.

Secondary endpoints:

- Incidence of endophthalmitis
- Proportion of patients without signs of anterior ocular chamber inflammation after 3 and 7 days of treatment
- Conjunctival hyperemia after 3, 7 and 14 days of treatment
- Total Ocular Symptoms Score (TOSS) after 3, 7 and 14 days of treatment
- Ocular pain/discomfort after 3, 7 and 14 days of treatment
- Use of rescue therapy during treatment

No formal statistical hypotheses will be tested for the secondary endpoints.

9.2 SAMPLE SIZE DETERMINATION

The study plans to enroll 800 patients: 400 patients will be assigned to the test treatment and 400 to standard treatment.

A sample size of 362 patients in each group is required to assess the non-inferiority of the test treatment vs. the standard therapy (i.e. lower limit of the 95% Confident Interval of the difference in proportions, $\pi_T - \pi_S > -0.10$) with 80% power and by applying a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level, assuming that the expected difference in proportions is 0 and the proportion in the standard group is 0.64.⁴⁷

The total sample size ($362 + 362 = 724$) is adjusted to 800 patients considering an expected dropout rate of about 10% using Freedman's formula⁴⁸: $n' = 100 * n / 100 - x$, where x is the expected dropout rate.

9.3 POPULATIONS FOR ANALYSES

The following populations have been defined for analysis:

- Safety set: all randomized patients who take at least one dose of study treatments.
- Full Analysis Set (FAS): all randomized patients who take at least one dose of study treatment. According to the Intention to Treat (ITT) principle, patients who discontinue the study treatment are considered as failures. Appropriate methods for the replacement of missing values will be detailed in the statistical analysis plan.
- Per protocol (PP) set: All randomized patients who do not have significant protocol violations that regard inclusion/exclusion criteria or that can condition efficacy evaluations, including the use of rescue medication.

The efficacy analyses will be performed on the FAS, having those on the PP population as supportive. The safety and tolerability analyses will be performed on the Safety population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous data will be summarized with standard descriptive statistics (i.e. the mean, standard deviation, minimum, median and maximum, 95% confidence limits). Categorical data will be summarized by frequencies and percentages.

No statistical test will be performed for between-group differences in demographic and baseline features (medical history and efficacy data).

Medical history and adverse events will be described according to System Organ Classes (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by treatment group.

Previous/concomitant medications will be presented by treatment group using the World Health Organization Drug Dictionary (WHO-DD).

All analysis will be performed using SAS version 9.4 or later.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The proportion of patients without signs of anterior chamber inflammation (sum of cells and flare score = 0) after 14 days of treatment will be calculated to evaluate the non-inferiority of the test

treatment vs. the standard therapy. Non-inferiority will be assessed by computing the two-tailed 95% confidence interval (CI) of the difference between the two proportions $\pi_T - \pi_S$. Non-inferiority is met if the 95% CI does not cross the predefined non-inferiority margin $\Delta = -0.10$ and lies entirely to the right of the margin (i.e. non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the difference is > -0.10).

If the 95% CI of the difference lies completely to the right of 0, the test treatment can be considered more effective than the standard treatment at a 5% significance level.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Descriptive statistics and two-sided 95% CIs of the difference between treatments will be computed for the following secondary endpoints:

- Incidence of endophthalmitis
- Proportion of patients without signs of anterior chamber inflammation (sum of cells and flare score = 0) after 3 and 7 days of treatment
- Proportion of patients with conjunctival hyperemia score equal to 0 after 3, 7 and 14 days of treatment
- Proportion of patients with TOSS score equal to 0 after 3, 7 e 14 days of treatment
- Proportion of patients with ocular pain/discomfort score equal to 0 after 3, 7 and 14 days of treatment
- Proportion of patients using rescue therapy during treatment

9.4.4 SAFETY ANALYSES

Adverse Events

All safety analyses will be performed on the Safety set. No missing data handling approach will be applied.

The incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded throughout the study will be presented overall and by treatment group. According to the onset date of the event, AEs will be defined as follows:

- Treatment-emergent AE: event with an onset date after treatment initiation
- Non-treatment-emergent AE: event with an onset date between informed consent and treatment initiation

Non-treatment-emergent AEs will be listed only.

Treatment-emergent AEs will be summarized by MedDRA dictionary system organ class and preferred term. A summary of treatment-emergent AEs by system organ class, preferred term and

severity will be also provided. All related treatment-emergent AEs, treatment-emergent SAEs, treatment-emergent AEs with an outcome of death, treatment-emergent AEs leading to treatment discontinuation will be summarized by MedDRA dictionary system organ class and preferred term and will also be listed.

All deaths will be listed together with all their details.

Intraocular pressure

The number of patients with a significant increase (> 6 mmHg) in intraocular pressure will be recorded and summarized descriptively. The comparison between test treatment and standard treatment in the incidence of significant increase of IOP will be made by means of 95% CI of the difference between treatments.

Visual acuity

The number of patients with a decrease in visual acuity measured as per local clinical practice will be recorded and summarized descriptively. The comparison between test treatment and standard treatment in the drop of visual acuity will be made by means of 95% CI of the difference between treatments.

9.4.5 TOLERABILITY ANALYSES

Local tolerability will be analyzed descriptively. Two-sided 95% CI will also be provided.

9.4.6 ANALYSIS OF COMPLIANCE

For each treatment, compliance will be evaluated through an evaluation of the number of instillations recorded in the patient diary.

9.4.7 BASELINE DESCRIPTIVE STATISTICS

Medical history and demographic features will be summarized descriptively. No statistical test will be performed for between-group differences in demographic and baseline features.

9.4.8 PLANNED INTERIM ANALYSES

No interim analysis is planned.

9.4.9 SUB-GROUP ANALYSES

No sub-group analyses are planned.

9.4.10 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Patient listings will be provided.

9.4.11 EXPLORATORY ANALYSES

No exploratory analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by the IRB/IEC and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants,

investigator, Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the IRB/IEC, Regulatory Authorities and Sponsor, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IEC and regulatory authorities.

10.1.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples (urine for pregnancy test) in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Contract Research Organization (CRO) (OPIS s.r.l.) working on behalf of the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Only the study center will be able to link the study ID number to the

patient's identity. The study data entry and study management systems used by clinical sites and by OPIS research staff will be secured and password protected.

10.1.5 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable, no biological samples will be stored for future use during this study.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific Monitoring Plan (MP). No information in source documents about the identity of the patients/subjects will be disclosed.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Following written Standard Operating Procedures, monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related facilities, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities.

Independent audits may be conducted by the Sponsor to ensure compliance with the protocol and GCP, and that monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture system until they are trained.

Web-based software will be used and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring user ID and password and may read, modify, and update only the information entered at his or her site and according to their profile. Each page reports site code and subject code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The investigator will certify that the data entered in the eCRF are complete and accurate.

After database lock, the investigator will receive a CD-ROM of subject data for archiving at the investigational site.

Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. The occurrence of any protocol deviations will also be checked.

If clarifications are needed, the Data Manager will raise queries through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using MedDRA.

The database will be locked after all the above actions have been completed and the database has been declared complete and accurate.

10.1.9 STUDY RECORDS RETENTION

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than twenty-five (25) years from the completion of the study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with the national laws.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP). The noncompliance may be on the part of either the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations. All deviations must be addressed in study source documents.

10.1.11 INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy covering this clinical trial. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC and/or regulatory authorities.

10.1.12 PUBLICATION AND DATA SHARING POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

This study will ensure that the public has access to the published results of the research.

Enrolment of patients in the study will be competitive. Therefore, pending confirmation from the journal accepting the manuscript, the main publication reporting the results of the study will include as main authors the names of the Chairman of the study, National Coordinators and Principal Investigators of the five centers enrolling the most patients. Names of Principal Investigators of all other sites will be mentioned in the full list of participating centers added to the text of the publication.

As this is a multicenter study, the first publication must be related to data collected from all patients enrolled and analyzed under the Sponsor's responsibility. The investigator shall not publish or communicate data collected in only one center or part of the centers before publication of the complete results of the study, unless prior written authorization from the Sponsor has been provided.

Any publication and/or communication project regarding the study and/or its results, whether obtained during the study or after the study end, shall be submitted to the Sponsor at least 30 days for a publication and 15 days for an abstract before the planned date of communication and/or submission for a publication. The Sponsor shall make comments on the project within 15 days of receipt of the project for a publication and within 7 days for an abstract. The investigator who submitted the project shall take the Sponsor's comments into due consideration. Nevertheless, should the investigator who submitted the project decide not to modify the project according to the Sponsor's comments, he/she shall provide the Sponsor with the grounds for his/her decision in writing.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or subjects, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

10.1.13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ASCRS	American Society of Cataract Refractive Surgery
CI	Confidence Interval
CNS	Coagulase-Negative Staphylococci
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
eCRF	electronic Case Report Forms
VEGF	Vascular Endothelial Growth Factor
EOS	End of Study
ESCRS	European Society of Cataract and Refractive Surgeons
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MP	Monitoring Plan
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin-Resistant Staphylococcus Aureus
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOSS	Total Ocular Symptoms Score
VA	Visual Acuity
WHO-DD	World Health Organization Drug Dictionary

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12 APPENDICES

APPENDIX 1: TOTAL OCULAR SYMPTOMS SCORE (TOSS)

TOSS Questionnaire

Please answer the following questions by marking the box that best represents your answer:

Have you experienced any of the following, and if so with what intensity?	None	Mild	Moderate	Severe
1. Itching/burning?				
2. Redness?				
3. Tearing (eyes watering)?				

TOSS Questionnaire Scoring

Total Ocular Symptom Score

1. Add up scores for the three symptoms.

None = 0

Mild = 1

Moderate = 2

Severe = 3