2 SYNOPSIS

Study Title	A prospective, multi-center, controlled, double-blind study to evaluate the efficacy and tolerability of a steroid/antibiotic associated treatment following cataract extraction by means of phaco-emulsification.
EudraCT Number	2016-002138-63
Study Code	044-SI
Study Sponsor	S.I.F.I. S.p.A Via Ercole Patti 36, 95025 Lavinaio – Aci S. Antonio (CT) – Italy
Clinical Phase	Phase III trial
Study Design	Prospective, multi-center, controlled, double-blind study
Investigational Product	NETILDEX™ 3mg/ml / 1mg/ml ophthalmic gel
Investigational Product Indication	NETILDEX™ 3mg/ml / 1mg/ml ophthalmic gel is indicated in the treatment of inflammatory conditions of the anterior segment of the eye (post-surgery or not), in the presence or with risk of microbial infection.
Comparator Product	NETILDEX™ 3mg/ml / 1mg/ml eye drops solution
Placebo	XANTERGEL™ ophthalmic gel is a CE-marked class IIa medical device commonly used in the lubrication of the ocular surface. Its composition includes Disodium Hyaluronate and Xanthan Gum.
Active Principles under Investigation	• Netilmicin Sulfate 4.55 mg (3mg/ml) • Dexamethasone Disodium Phosphate 1.32 mg (1mg/ml)
Study Objectives	The primary objective of this study is to demonstrate the efficacy and tolerability of a reduced frequency of administration of NETILDEX ™ 3mg/ml / 1mg/ml ophthalmic gel, administered twice daily (b.i.d.), in comparison with NETILDEX ™ 3mg/ml / 1mg/ml eye drops solution, administered four times a day (q.i.d.), in the prevention of post-surgery ocular inflammation and infection after cataract extraction by means of phaco-emulsification and intra-ocular lens implantation.

Exclusion Criteria	• Patients with medical history of ocular inflammation diseases, Herpes infections, iritis, uveitis or Sjogren's syndrome • Patients who have been treated for external ocular infections within a month before the study enrolment (V1) • Patients with cellularity in the anterior ocular chamber ≥ grade 2 (16-25 cells / field 1x1 mm) • Patients with flare in the anterior ocular chamber ≥ grade 2 (moderate) • Patients with at least one of the following concomitant ocular diseases: ocular infections, uveitis, iritis, iridociclitis, glaucoma, diabetic retinopathy, diabetes, maculopathy, shallow anterior chamber (based on Investigator's judgment) • Patients with PEX Syndrome (Pseudo-exfoliation syndrome) • Patients with poor mydriasis, basing on Investigator's judgment • Patients with intra-ocular pressure > 24 mmHg • Patients who have undergone surgery in the eye involved in the cataract extraction within the 12 months before the study enrolment (V1) • Patients who have received corneal laser treatment in the eye involved in the cataract extraction within the 6 months before the study enrolment (V1) • Patients with known or suspected allergy or hypersensitivity to ophthalmic preservatives, phenylacetic acid derivatives, aminoglycosides, Bromfenac, other NSAIDs, steroids • Patients with traumatic cataract condition • Patients who have been treated or are under treatment with alpha-blocking agents for more than 3 months before the study enrolment (V1) • Patients who have received treatment with anti-histamines, decongestants, anti-inflammatory steroidal or non-steroidal (NSAID) drugs within the 15 days before the study enrolment (V1). Bromfenac, only, will be allowed for 3 days before cataract surgery • Patients who are participating or have participated in other clinical studies within the 30 days before the study enrolment (V1) • Patients receiving any ocular treatment, with the exception of artificial tears • Female Patients who are pregnant or breast-feeding or who wish to become pregnant during the period of the clinical study and for three months later • Female Patients of childbearing age (less than 24 months after the last menstrual cycle) who do not use adequate contraception * • Monocle Patients • Patients with epiretinal membrane as per OCT test at enrolment visit (V1) ** Methods at low risk of contraceptive failure (less than 1% per year) when used consistently, including: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), some intra-uterine devices, abstinence or vasectomized partner. Contraception should be maintained until treatment discontinuation.*

	Visit	Procedures	Day
Study Flow Chart	Visit 3 (V3 – Control 1)	• Visual acuity evaluation • Intra-ocular pressure measurement • Examination with Slit Lamp • Ophthalmoscopy test • Clinical evaluation of signs/symptoms of ocular inflammation (other than flare and cellularity) • Evaluation of global tolerability of Patient (by the Investigator) • Microbial load measurement (for Patients with risk of ocular infections, based on Investigator's judgment) through ocular swab and anti-biogram • Adverse Events / Concomitant Medications	D +1
	Visit 4 (V4 – Control 2)	• Visual acuity evaluation • Intra-ocular pressure measurement • Examination with Slit Lamp • Ophthalmoscopy test • Clinical evaluation of signs/symptoms of ocular inflammation (other than flare and cellularity) • Evaluation of global tolerability of Patient (by the Investigator) • Microbial load measurement (for Patients with risk of ocular infections, based on Investigator's judgment) through ocular swab and anti-biogram • Adverse Events / Concomitant Medications	D +7±1
	Visit 5 (V5 – End of Treatment)	• Visual acuity evaluation • Intra-ocular pressure measurement • Examination with Slit Lamp • Ophthalmoscopy test • Clinical evaluation of signs/symptoms of ocular inflammation (other than flare and cellularity) • Evaluation of global tolerability of Patient (by the Investigator) • Adverse Events / Concomitant Medications	D +15±2

	The study will be monitored by an independent Data Safety Monitoring Board (DSMB). This study may be prematurely terminated by the DSMB, based on pre-defined stopping rules, if in the group of Patients treated with NETILDEX™ 3mg/ml / 1mg/ml ophthalmic gel at least 3 Patients (4.5%) will have inflammation according to examination with Slit Lamp and Bio-microscopy, graded as +3 or more for both cells and flare, at any visit. **Secondary Endpoints:** • Evaluation of antibiotic efficacy within 24 hours after surgery, based on the presence of detected microbial infections (positive ocular swabs and anti-biogram results, if any). The anti-biogram should be performed according to standard procedure at investigational sites, but including at least the test with Netilmicin and Cefuroxime • Measurement of intra-ocular pressure before and after treatment • Evaluation of clinical signs and symptoms of ocular inflammation (other than flare and cellularity) • Evaluation of visual acuity • Evaluation of global tolerability to treatment of Patient (by the Investigator), through a standard questionnaire) • Evaluation of adverse events during the study period
Statistical Analysis	Considering that this study is a two-arm non-inferiority clinical trial, if there is a true difference in favor of the reference treatment of 5%, then 130 Patients are required to be 90% sure that the upper limit of a one-sided 97.5% confidence interval will exclude a difference in favor of the reference group of more than 10%.
Investigational Sites	The study will involve 8 investigational sites.