



Clinical trial results:

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.

Summary

EudraCT number	2016-002138-63
Trial protocol	IT
Global end of trial date	31 March 2020

Results information

Result version number	v1
This version publication date	20 August 2020
First version publication date	20 August 2020
Summary attachment (see zip file)	SAP (044SI_Statistical Report_20190729.pdf) SYNOPSIS 044/SI (Synopsis 044-SI.pdf)

Trial information

Trial identification

Sponsor protocol code	044-SI
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SIFI SpA
Sponsor organisation address	Via Ercole Patti, 36, Lavinaio (CT), Italy, 95025
Public contact	Clinical Development, S.I.F.I. S.p.A., +39 +39-0957922238, claudine.civiale@sifigroup.com
Scientific contact	Clinical Development, S.I.F.I. S.p.A., +39 0957922238, claudine.civiale@sifigroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to show that the administration of a reduced dose of NETILDEX™ gel 2 times a day starting on the day of cataract extraction by means of phaco-emulsification and administered until 14 days after surgery is sufficient to obtain a non-inferior efficacy of the NETILDEX™ eye drops solution administered 4 times a day for the same period.

Protection of trial subjects:

The study was monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB could recommend stopping the study for futility, if at least 3 patients (4.5%) in the same Group have grade +3 or more for both cells and flare at the examination with slit lamp and bio-microscopy, at any time during the study.

Background therapy:

Cataract is an ophthalmic disease that usually affects the elderly population. Cataract surgery with phaco-emulsification is now the most frequently performed intraocular surgical procedure in the developed world. However, differences in surgical technique impact the severity of surgical trauma and post-operative recovery. The amount of post-operative ocular pain and inflammation plays a significant role in the Patient's perception of the surgical success.

Several ophthalmic products have been studied in the management of post-surgery ocular inflammation and pain following cataract surgery. Corticosteroids are considered the gold standard for the treatment of ocular inflammation, and their most commonly used route of administration is the topical instillation as eye drops formulation.

After topical administration of Dexamethasone, the concentration in the anterior chamber increases and declines within hours, necessitating frequent daily instillations of eye drops for several weeks. This might be associated with compliance issues, particularly in elderly Patients or in individuals with disabilities. A pharmaceutical formulation allowing for a less frequent administration could therefore be an attractive alternative.

Evidence for comparator:

NETILDEX™ eye drops solution, containing Netilmicin Sulfate 4.55 mg (3mg/ml) and Dexamethasone Disodium Phosphate 1.32 mg (1mg/ml), is already available for Patients.

A new ophthalmic gel, preservative-free formulation has been developed. This new formulation has been tested in pre-clinical animal studies and in a clinical trial. The new formulation contains Xanthan gum, a high molecular mass polysaccharide approved by the FDA in 1969 for food products. It is used in the product as viscosity enhancer and to give to the product pseudo-plastic characteristics and prolonged ocular retention time.

Actual start date of recruitment	09 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 155
Worldwide total number of subjects	173
EEA total number of subjects	173

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28
From 65 to 84 years	134
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The enrollement at the investigational sites was stopped at the achievement of 173 randomized patients versus the target of 180 randomized patients. The rational of this decision is due to the fact that the number of statistically evaluable patients were already reached (160 ITT population patients versus the 130 requested in the protocol).

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Pre-assignment

Screening details:

Male and female Patients, aged > 40 years, undergoing cataract extraction by means of phaco-emulsification and intra-ocular lens implantation according to inclusion criteria and after to be thoroughly informed about all aspects of the study, including scheduled study visits and activities, and to have signed the informed consent form.

Period 1

Period 1 title	overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

All daily study products will be manufactured in indistinguishable single dose plastic vials, labeled in accordance with hour of administration. In accordance with the double-blind design of the study, daily treatment for patients randomized to group A (NETILDEX™ ophthalmic gel), will be of 2 doses of active treatment and 2 doses of indistinguishable placebo. For blinding purposes, Group B (NETILDEX™ eye drops solution) medications labels will consist in an aluminum envelope for each dose of the

Arms

Are arms mutually exclusive?	Yes
Arm title	Netildex Ophthalmic gel

Arm description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Arm type	Experimental
Investigational medicinal product name	NETILDEX™ ophthalmic gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution in single-dose container
Routes of administration	Ophthalmic use

Dosage and administration details:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Arm title	NETILDEX™ eye drops solution
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Arm description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Arm type	Active comparator
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Investigational medicinal product name	NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution in single-dose container
Routes of administration	Ophthalmic use

Dosage and administration details:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Number of subjects in period 1^[1]	Netildex Ophthalmic gel	NETILDEX™ eye drops solution
Started	85	83
Completed	80	81
Not completed	5	2
Consent withdrawn by subject	4	1
Adverse event, non-fatal	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Five patients were randomized but had not received any study treatments (3 to NETILDEX™ Ophthalmic Gel, 2 to NETILDEX™ Eye Drops); Thus the number of patients reported in the baseline period is not 173 but 168.

Baseline characteristics

Reporting groups

Reporting group title	Netildex Ophthalmic gel
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Reporting group title	NETILDEX™ eye drops solution
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Reporting group values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution	Total
Number of subjects	85	83	168
Age categorical			
1. Male or female Patients 2. Patients aged ≥ 40 years old 3. Patients undergoing cataract extraction surgery through phaco-emulsification and intra-ocular lens implantation 4. Patients with grade 2 or 3 according to LOCS III system for grading age-related cataract			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	15	31
From 65-84 years	65	62	127
85 years and over	4	6	10
Age continuous			
1. Male or female Patients 2. Patients aged ≥ 40 years old 3. Patients undergoing cataract extraction surgery through phaco-emulsification and intra-ocular lens implantation 4. Patients with grade 2 or 3 according to LOCS III system for grading age-related cataract			
Units: years			
arithmetic mean	72.2	73.2	
standard deviation	± 8.8	± 8.3	-
Gender categorical			
Units: Subjects			
Female	48	57	105
Male	37	26	63

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population is defined as all patients who received 7 days of study treatment and had the SLIT lamp examination at baseline visit3 (day 1) and endpoint visit 4 (day 7)

Subject analysis set title	The Safety Analysis Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis population is defined as all patients registered, who received at least one dose of study treatment

Subject analysis set title	The Per-Protocol (PP) populations
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol Population is defined as all subjects of the ITT population who completed regularly the study with no major violations of the eligibility criteria or during study conduction

Reporting group values	ITT population	The Safety Analysis Population	The Per-Protocol (PP) populations
Number of subjects	160	168	158
Age categorical			
1.Male or female Patients 2.Patients aged ≥ 40 years old 3.Patients undergoing cataract extraction surgery through phaco-emulsification and intra-ocular lens implantation 4.Patients with grade 2 or 3 according to LOCS III system for grading age-related cataract			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	29	31	27
From 65-84 years	121	127	121
85 years and over	10	10	10
Age continuous			
1.Male or female Patients 2.Patients aged ≥ 40 years old 3.Patients undergoing cataract extraction surgery through phaco-emulsification and intra-ocular lens implantation 4.Patients with grade 2 or 3 according to LOCS III system for grading age-related cataract			
Units: years			
arithmetic mean	72.8	72.7	73
standard deviation	± 8.3	± 8.6	± 7.8
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Netildex Ophthalmic gel
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Reporting group title	NETILDEX™ eye drops solution
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Subject analysis set title	ITT population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT Population is defined as all patients who received 7 days of study treatment and had the SLIT lamp examination at baseline visit3 (day 1) and endpoint visit 4 (day 7)

Subject analysis set title	The Safety Analysis Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety analysis population is defined as all patients registered, who received at least one dose of study treatment

Subject analysis set title	The Per-Protocol (PP) populations
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per-Protocol Population is defined as all subjects of the ITT population who completed regularly the study with no major violations of the eligibility criteria or during study conduction

Primary: Measurement of Inflammation Conditions in the Anterior Ocular Chamber After Cataract Extraction Through Slit Lamp and Bio-microscopy

End point title	Measurement of Inflammation Conditions in the Anterior Ocular Chamber After Cataract Extraction Through Slit Lamp and Bio-microscopy
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End point description:

the primary efficacy variable is the measurement of inflammation (cellularity and flare) at endpoint (V4), in the anterior ocular chamber, after cataract extraction, examined with slit lamp and bio-microscopy.

Based on these two measurements, a Patient is defined as:

Full responder: if both cellularity and flare are of degree zero Partial responder: if at least one of the two measurements (cellularity and flare) is of degree zero The difference of Full responders after 7 days from surgery has been analysed for non-inferiority of NETILDEX™ Ophthalmic Gel using a non-inferiority margin of -0.10 and a Confidence Interval of 97.5%.

No responder: if both cellularity and flare are greater than zero

End point type	Primary
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End point timeframe:

Throughout study completion, approximately 9 weeks.

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80 ^[1]	80 ^[2]		
Units: participants				
Full responder	72	76		
Partial responder	8	4		
No responder	0	0		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Measurement of Inflammation
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Statistical analysis description:

The primary analysis compares the ITT population (Full responder) of NETILDEX™ Ophthalmic Gel (n=80 patients) and NETILDEX™ Eye Drops (n=80 patients).

The difference of Full responders after 7 days from surgery has been analysed for non-inferiority of NETILDEX™ Ophthalmic Gel using a non-inferiority margin of -0.10 and a Confidence Interval of 97.5%. The primary analysis compares the ITT population of NETILDEX™ Ophthalmic Gel (n=80 patients) and NETILDEX™ Eye Drops (n=80 patients).

Comparison groups	Netildex Ophthalmic gel v NETILDEX™ eye drops solution
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	< 0.025 ^[4]
Method	Confidence Interval
Parameter estimate	Discrete (counting) variable
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.58
upper limit	0.158

Notes:

[3] - The efficacy parameter utilized has been the combination of two clinical parameters, Flare and Cellularity

The non inferiority test results indicate that the GEL Group is noninferior to the DROP Group since the lower limit of the 97.5% Confidence Interval is Greater than the noninferiority limit of -0.10.

[4] - The hypotheses for noninferiority has been stated in terms of the difference in the proportions $D = p_{\text{test}} - p_{\text{ctrl}}$ where test is Netildex gel and ctrl is Netildex drops solution.

The null and alternative hypotheses are the following:

$H_0: D = p_{\text{test}}$

Secondary: Microbial load measurement

End point title	Microbial load measurement
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End point description:

Microbial load measurement (for Patients with risk of ocular infections, based on Investigator's judgment) through ocular swab, evaluating the antibiotic efficacy 24 hours after surgery, based on the number of detected microbial infections (presence of positive 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.

End point type	Secondary
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End point timeframe:

Throughout study completion, approximately 9 weeks.

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 ^[5]	83 ^[6]		
Units: participants	0	0		

Notes:

[5] - Safety Population

[6] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of a Potential Variation in the Intra-ocular Pressure Related to the Use of the Gel Formulation Compared to the Eye-drops Formulation, Through Its Measurement Before and After Treatment.

End point title	Assessment of a Potential Variation in the Intra-ocular Pressure Related to the Use of the Gel Formulation Compared to the Eye-drops Formulation, Through Its Measurement Before and After Treatment.
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End point description:

IOP was measured in both eyes at Visit 1 (Screening examination), Visit 3 (Day 1), Visit 4 (Day 7±1), Visit 5 (Day 15±2) and Visit 6 (Day 60±3) by using a Goldman applanation tonometer (average of two measurements), recording of the time of measurement. All IOP measurements on the same patient will be performed by the same physician with the same tonometer.

Intra-ocular pressure data (change from visit 1) has been tabulated with central and dispersion variables before and after treatment.

End point type	Secondary
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End point timeframe:

Throughout study completion, approximately 9 weeks.

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 ^[7]	83 ^[8]		
Units: change in IOP				
arithmetic mean (standard deviation)				
Day 1 after surgery	0.7 (± 2.5)	0.2 (± 2.2)		
Day 7 after surgery	-0.3 (± 1.9)	-0.6 (± 2.1)		
Day 15 after surgery	-0.6 (± 2.1)	-0.5 (± 2.2)		
Follow up Day 60 after surgery	-0.9 (± 1.9)	-0.7 (± 2.1)		

Notes:

[7] - Safety population

[8] - Safety Population

Statistical analyses

Statistical analysis title	Intra-ocular pressure (change from visit 1)
Statistical analysis description: Evaluation of intra-ocular pressure (change from Visit 1): tabulated with central and dispersion variables before and after treatment along with one-sided 97.5% confidence interval of the difference.	
Comparison groups	Netildex Ophthalmic gel v NETILDEX™ eye drops solution
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.4758 ^[10]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.2238
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.3944
upper limit	0.819
Variability estimate	Standard deviation
Dispersion value	0.3131

Notes:

[9] - Student's t test for independent samples

[10] - The p-value of the difference between The two groups is 0.4758, so we do not reject the null hypothesis

TIPO DI VARIABLE ESTIMATE: CONTINUE VARIABLE

Secondary: Evaluation of Clinical Signs and Symptoms of Ocular Inflammation

End point title	Evaluation of Clinical Signs and Symptoms of Ocular Inflammation
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End point description:

Evaluation of ocular inflammation signs/symptoms during the study (other than flare and cellularity) - Total score

- Scoring System for Conjunctival hyperemia. 0 none
 - 1.mild (some vessel injected)
 - 2.moderate (diffuse injection, individual vessels discernible)
 - 3.severe (intense injection, individual vessels not easily discernible)

- Scoring System for Corneal edema and Lid edema. 0 none
 - 1.mild
 - 2.moderate
 - 3.severe

- Scoring System for Ocular discomfort (pain, photophobia, tearing). 0 none
 - 1.mild (present but not distressing)
 - 2.moderate (distressing but not interfering with daily life)
 - 3.severe (very distressing and interfering with daily life)

Evaluation of ocular inflammation signs/symptoms during the study - Total score Safety sample - change from Day 1 It is reported below the number of patients with none discomfort

End point type	Secondary
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End point timeframe:

Throughout study completion, approximately 9 weeks.

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 ^[11]	83 ^[12]		
Units: Total score				
arithmetic mean (standard deviation)				
Visit 3	0.7 (± 1)	0.7 (± 1.3)		
Visit 4	0.2 (± 0.5)	0.1 (± 0.4)		
Visit 5	0.1 (± 0.4)	0.1 (± 0.4)		

Notes:

[11] - Safety Population

Visit V3: 83 patients analysed

Visit 4 82 patients analysed

Visit 5: 81 patient

[12] - Safety Population

Visit 3: 83 patient analysed

Visit 4 and Visit 5: 82 patients analysed

Statistical analyses

Statistical analysis title	Evaluation of Clinical Signs and Symptoms of Ocula
Comparison groups	Netildex Ophthalmic gel v NETILDEX™ eye drops solution
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other ^[13]
P-value	= 0.9392 ^[14]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.0122
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.2734
upper limit	0.2978
Variability estimate	Standard deviation
Dispersion value	0.9261

Notes:

[13] - It has been verified the non significative difference between both groups

[14] - The p-value of the difference between the two groups is 0.9329 so we do not reject the null hypothesis

Tipo di variable estimate: continue variable

Secondary: Evaluation of Visual Acuity Through Standard Measurement Systems.

End point title	Evaluation of Visual Acuity Through Standard Measurement Systems.
End point description:	
Visual acuity with correction (best corrected visual acuity) was measured in the operated eye at Screening, Visit 3 (Day 1), Visit 4 (Day 7±1), Visit 5 (Day 15±2) and Visit 6 (Day 60±3). No relevant difference along the study and between treatment groups are present	
End point type	Secondary
End point timeframe:	
Throughout study completion, approximately 9 weeks.	

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: units on a scale				
arithmetic mean (standard deviation)				
before surgery	0.5 (± 0.2)	0.5 (± 0.2)		
Day 1 after surgery	0.6 (± 0.4)	0.6 (± 0.4)		
Day 7 after surgery	0.7 (± 0.4)	0.7 (± 0.5)		
Day 15 after surgery	0.7 (± 0.4)	0.7 (± 0.4)		

Statistical analyses

Statistical analysis title	Evaluation of Visual Acuity
Statistical analysis description:	
Visual acuity with correction (best corrected visual acuity) was measured in both eyes at Visit 1 (Screening examination), and in the operated eye only at Visit 3 (Day 1), Visit 4 (Day 7±1), Visit 5 (Day 15±2) and Visit 6 (Day 60±3). Dilated ophthalmoscopy was performed in the affected eye only at Screening examination (Visit 1/up to Day 0) and at Visit 3 (Day 1), Visit 4 (Day 7±1), Visit 5 (Day 15±2) and Visit 6 (Day 60±3).	
Comparison groups	NETILDEX™ eye drops solution v Netildex Ophthalmic gel
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3823 ^[15]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.0131
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.0761
upper limit	0.05
Variability estimate	Standard deviation
Dispersion value	0.201

Notes:

[15] - The p-value of the difference between the two groups is 0.6823, so we do not reject the null hypothesis

Secondary: Evaluation of the Global Tolerability of NETILDEX™ Ophthalmic Gel in Treated Patients (by the Investigator), Through a Standard Questionnaire.

End point title	Evaluation of the Global Tolerability of NETILDEX™ Ophthalmic Gel in Treated Patients (by the Investigator), Through a Standard Questionnaire.
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End point description:

This outcome was assessed by interviewing the patients about their symptoms (such as burning, stinging and itching) experienced at at Visit 3 (Day 1), Visit 4 (Day 7±1) and Visit 5 (Day 15±2). These symptoms were individually assessed by using a 0 to 3 categorical rating scale.

Changes in Burning, stinging and itching compared to Day 1 Burning/stinging/blurred vision scores: (0) none; (1) mild (present but not distressing); (2) moderate (distressing but not interfering with daily life); (3) severe (very distressing and interfering with daily life)

End point type	Secondary
End point timeframe:	
Within 2 weeks after cataract surgery.Global subjective tolerability score at day 15 after surgery day.	

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 ^[16]	83 ^[17]		
Units: participants				
None	79	80		
Mild	0	1		
Moderate	1	0		
Severe	0	0		
Missing Data	5	2		

Notes:

[16] - Safety population

[17] - Safety Population

Statistical analyses

Statistical analysis title	Evaluation of the Global Tolerability
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Statistical analysis description:

The global subjective tolerability was assessed at Visit 3 (Day 1), Visit 4 (Day 7±1) and Visit 5 (Day 15±2) interviewing the subject on his/her global sensation and asking to rate using a 0 to 3 categorical scale, as follow:

Score	Evaluation
Score	Evaluation
0	none
1	mild (present but not distressing)
2	moderate (distressing but not interfering with daily life)
3	severe (very distressing and interfering with daily life)

Comparison groups	Netildex Ophthalmic gel v NETILDEX™ eye drops solution
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 1 ^[19]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)

Notes:

[18] - Comparison between groups of the frequency distributions for the categories decreased/unchanged

Fisher's Exact test for the presence of cells with values <5

Categorical variable

parameter estimate.....: Odds Ratio NOT ESTIMABLE

CI (sides, lower and upper limits): NOT ESTIMABLE

variability estimate.....: NOT ESTIMABLE

dispersion value.....: NOT ESTIMABLE

[19] - The p-value of the difference between the two groups is 1.0000, so we do not reject the null hypothesis

Tipo di parameter estimate: Comparison between groups of the frequency distributions for the categories decreased/unchanged

Secondary: Evaluation of the Safety of NETILDEX™ Ophthalmic Gel Through the Collection and Evaluation of Adverse Events.

End point title	Evaluation of the Safety of NETILDEX™ Ophthalmic Gel Through the Collection and Evaluation of Adverse Events.
End point description:	Ten patients out of 168 experienced at least one AE: on NETILDEX™ Eye Drops. All adverse events were assessed by the investigators as mild or moderate and properly documented in source documents and eCRF. All AE were already known and all patients apart one completed the study.
End point type	Secondary
End point timeframe:	Throughout study completion, approximately 9 weeks.

End point values	Netildex Ophthalmic gel	NETILDEX™ eye drops solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 ^[20]	83 ^[21]		
Units: participants	4	6		

Notes:

[20] - Safety Population

[21] - Safety Population

Statistical analyses

Statistical analysis title	Evaluation of the Adverse Events
Statistical analysis description:	Safety evaluation will include assessments of frequency and severity of adverse events, clinically-significant laboratory abnormalities and physical examination findings. Comparison between groups of the frequency distributions for the categories presence/absence AE
Comparison groups	Netildex Ophthalmic gel v NETILDEX™ eye drops solution
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other ^[22]
P-value	= 0.5325 ^[23]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.5779
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.4287
upper limit	5.8075

Notes:

[22] - Fisher's Exact test for the presence of cells with values <5

[23] - The p-value of the difference between the two groups is 0.5325, so we do not reject the null hypothesis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall Trial and 2 months follow-up after day of surgery

Adverse event reporting additional description:

MedDRA (10.0)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	NETILDEX™ Ophthalmic Gel
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Bromfenac 0.9 mg/ml 1 drop twice daily (b.i.d.) for 3 days before cataract surgery.

NETILDEX™ ophthalmic gel: 1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) ophthalmic gel immediately after the surgery then 1 drop twice daily (b.i.d.) from Day 1 until Day 14 after surgery + 1 drop of XANTERGEL™ ophthalmic gel twice daily (b.i.d.) from Day 1 until Day 14 after surgery.

Bromfenac 0.9 mg/ml 1 drop twice daily (b.i.d.) for 3 days before cataract surgery.

Reporting group title	NETILDEX™ Eye Drops Solution
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Reporting group description:

1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Bromfenac 0.9 mg/ml 1 drop twice daily (b.i.d.) for 3 days before cataract surgery.

NETILDEX™ eye drops solution: 1 drop of NETILDEX™ (Netilmicin Sulfate 3mg/ml / Dexamethasone Disodium Phosphate 1mg/ml) eye drops solution immediately after the surgery then 1 drop four times a day (q.i.d.) from Day 1 until Day 14 after surgery.

Bromfenac 0.9 mg/ml 1 drop twice daily (b.i.d.) for 3 days before cataract surgery

Serious adverse events	NETILDEX™ Ophthalmic Gel	NETILDEX™ Eye Drops Solution	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	2 / 83 (2.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Vascular occlusion	Additional description: Vascular occlusion not related to drug treatment		

subjects affected / exposed	0 / 85 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macula edema			
subjects affected / exposed	0 / 85 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4.76 %

Non-serious adverse events	NETILDEX™ Ophthalmic Gel	NETILDEX™ Eye Drops Solution	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 85 (4.71%)	4 / 83 (4.82%)	
Injury, poisoning and procedural complications			
Fibrin deposition on lens postoperative			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Investigations			
subjects affected / exposed	2 / 85 (2.35%)	0 / 83 (0.00%)	
occurrences (all)	3	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 85 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Eye disorders			
Eye disorders			
subjects affected / exposed	1 / 85 (1.18%)	3 / 83 (3.61%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
dyspepsia , nausea			
subjects affected / exposed	2 / 85 (2.35%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			

Hordelum			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2017	Protocol version 2.0 (16 February 2017) has been implemented according to the requests raised by the German Competent Authority (BfArM) on the 27th December 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported