Clinical trial results:
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.

Summary

EudraCT number	2018-000286-36
Trial protocol	ES IT
Global end of trial date	19 December 2018

Results information

Result version number	v1 (current)
This version publication date	17 October 2020
First version publication date	17 October 2020

Trial information

Trial identification

Sponsor protocol code	LEVODESA_04-2017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	NTC SRL
Sponsor organisation address	Via dei Gracchi, 35, Milano, Italy, 20146
Public contact	Dr. Federico Bertocchi, NTC SRL, 0039 0243850436, federico.bertocchi@ntcpharma.com
Scientific contact	Dr. Federico Bertocchi, NTC SRL, 0039 0243850436, federico.bertocchi@ntcpharma.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	22 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and all applicable laws and regulations.

Background therapy: -

Evidence for comparator:

-

Actual start date of recruitment	03 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 652
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Russian Federation: 140
Worldwide total number of subjects	808
EEA total number of subjects	668

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)	145
From 65 to 84 years	628
85 years and over	35

Subject disposition

Recruitment

Recruitment details:

Study period:
• Date of first enrolment: 03.09.2018
• Date study finalized (LPLV): 19.12.2018
Study centers:
• 42 centers in Italy
• 4 centers in Spain
• 4 centers in Russia
• 1 center in Germany

Pre-assignment

Screening details:

Planned sample size n.800; randomized patients n.808; screened patients n.863

In the section "population of trial subjects", the population of randomized patients (n. 808) has been inserted instead of the population of enrolled patients (n. 863)

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Levofloxacin + Dexamethasone Followed by Dexamethasone

Arm description:

Levofloxacin + dexamethasone ophthalmic solution containing levofloxacin hemihydrate 5.12 mg/ml, corresponding to levofloxacin 5 mg/ml, and dexamethasone sodium phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml (L-DSP), followed by Dexamethasone 1 mg/ml ophthalmic suspension (Maxidex).
Dose and regimen: Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.

Arm type	Experimental
Investigational medicinal product name	Levofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Conjunctival use

Dosage and administration details:

Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Conjunctival use

Dosage and administration details:

Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.

Arm title	Tobramycin + Dexamethasone

Arm description:	
Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex) Dose and regimen: 1 drop - 4 times a day for 14 days	
Arm type	Active comparator
Investigational medicinal product name	Tobramycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Conjunctival use
Dosage and administration details:	
Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex) 1 drop - 4 times a day for 14 days	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Conjunctival use
Dosage and administration details:	
Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex) 1 drop - 4 times a day for 14 days	
Notes:	
[1] - The roles blinded appear inconsistent with a simple blinded trial.	
Justification: This is a randomized, assessor-blinded, parallel-group study	

Number of subjects in period 1	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone
Started	403	405
Received at Least One Treatment	395	393
Completed	388	388
Not completed	15	17
Physician decision	1	2
Consent withdrawn by subject	7	8
Other	-	2
Adverse event	5	3
Lost to follow-up	1	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Levofloxacin + Dexamethasone Followed by Dexamethasone
Reporting group description:	
Levofloxacin + dexamethasone ophthalmic solution containing levofloxacin hemihydrate 5.12 mg/ml, corresponding to levofloxacin 5 mg/ml, and dexamethasone sodium phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml (L-DSP), followed by Dexamethasone 1 mg/ml ophthalmic suspension (Maxidex). Dose and regimen: Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.	
Reporting group title	Tobramycin + Dexamethasone
Reporting group description:	
Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex) Dose and regimen: 1 drop - 4 times a day for 14 days	

Reporting group values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone	Total
Number of subjects	403	405	808
Age categorical 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)	72	73	145
From 65-84 years	312	316	628
85 years and over	19	16	35
Age continuous Units: years			
arithmetic mean	72.20	71.96	
standard deviation	± 8.59	± 8.67	-
Gender categorical Units: Subjects			
Female	234	248	482
Male	169	157	326
Race Units: Subjects			
White	401	403	804
Asian	1	1	2
American Indian or Alaska Native	1	0	1
Native Hawaiian or other Pacific Islander	0	1	1

End points

End points reporting groups

Reporting group title	Levofloxacin + Dexamethasone Followed by Dexamethasone

Reporting group description:

Levofloxacin + dexamethasone ophthalmic solution containing levofloxacin hemihydrate 5.12 mg/ml, corresponding to levofloxacin 5 mg/ml, and dexamethasone sodium phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml (L-DSP), followed by Dexamethasone 1 mg/ml ophthalmic suspension (Maxidex).
Dose and regimen: Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.

Reporting group title	Tobramycin + Dexamethasone

Reporting group description:

Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex)
Dose and regimen: 1 drop - 4 times a day for 14 days

Primary: Proportion of Participants Without Signs of Anterior Chamber Inflammation

End point title	Proportion of Participants Without Signs of Anterior Chamber Inflammation

End point description:

The proportion of participants without signs of anterior chamber inflammation (sum of cells and flare score = 0). The following non-inferiority hypotheses has been tested: H0 : πT − πS ≤ - Δ; H1 : πT − πS > - Δ. Where πT and πS are the proportion of participants without signs of anterior chamber inflammation in the test and standard treatments, respectively, and the non-inferiority margin is Δ = 10%.

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Primary

End point timeframe:

Day 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Number of participants without signs	376	373		
Number of participants with signs	19	20		

Statistical analyses

Statistical analysis title	Non-inferiority test

Statistical analysis description:

Difference between proportions of patients without signs of anterior chamber inflammation (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	0.0028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0275
upper limit	0.0331

Secondary: Incidence of endophthalmitis

End point title	Incidence of endophthalmitis

End point description:

The incidence of endophthalmitis was assessed and reported. Diagnosis of endophthalmitis is based on clinical evaluation of signs and symptoms (such as swollen eyelids, ocular pain, conjunctival hyperemia, decreased visual acuity, opaque vitreous) through slit lamp examination, and microbiological tests on conjunctival or corneal swabs.

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set).

This outcome was not analyzed by applying the Last Observation Carried Forward (LOCF) method to impute missing values if at least one post-baseline value was available.

End point type	Secondary

End point timeframe:

Day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Visit 3 - Day 4: patients evaluable at the Visit	393	393		
Visit 3 - Day 4: no diagnosis of endophthalmitis	393	393		
Visit 4 - Day 8: patients evaluable at the Visit	391	393		
Visit 4 - Day 8: no diagnosis of endophthalmitis	391	393		
Visit 5 – Day 15: patients evaluable at the Visit	389	391		

Visit 5 – Day 15: no diagnosis of endophthalmitis	389	391		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Without Signs of Anterior Ocular Chamber Inflammation

End point title	Proportion of Participants Without Signs of Anterior Ocular Chamber Inflammation

End point description:

Proportion of participants without signs of anterior chamber inflammation (sum of cells and flare score = 0).

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

Day 4 and 8

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Visit 3 - Day 4: N. of participants without signs	289	302		
Visit 3 - Day 4: N. of participants with signs	106	91		
Visit 4 - Day 8: N. of participants without signs	338	341		
Visit 4 - Day 8: N. of participants with signs	57	52		

Statistical analyses

Statistical analysis title	Superiority Test (Visit 3 – Day 4)

Statistical analysis description:

Difference between proportions of patients without signs of anterior chamber inflammation (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Tobramycin + Dexamethasone v Levofloxacin + Dexamethasone Followed by Dexamethasone

Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.0368
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0972
upper limit	0.0236

Statistical analysis title	Superiority Test (Visit 4 – Day 8)

Statistical analysis description:

Difference between proportions of patients without signs of anterior chamber inflammation (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0602
upper limit	0.0362

Secondary: Proportion of patients with presence/absence of conjunctival hyperemia

End point title	Proportion of patients with presence/absence of conjunctival hyperemia

End point description:

Conjunctival hyperemia was evaluated with slit lamp 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).

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

Day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Visit 3 - Day 4: Score=0	337	323		
Visit 3 - Day 4: Score>0	58	70		
Visit 4 - Day 8: Score=0	348	358		
Visit 4 - Day 8: Score>0	47	35		
Visit 5 - Day 15: Score=0	371	375		
Visit 5 - Day 15: Score>0	24	18		

Statistical analyses

Statistical analysis title	Superiority Test (Visit 3 – Day 4)
Statistical analysis description: Difference between proportions of patients without conjunctival hyperemia (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.0313
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0202
upper limit	0.0828

Statistical analysis title	Superiority Test (Visit 4 – Day 8)
Statistical analysis description: Difference between proportions of patients without conjunctival hyperemia (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.0299

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0725
upper limit	0.0126

Statistical analysis title	Superiority Test (Visit 5 – Day 15)
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0463
upper limit	0.0164

Secondary: Total ocular symptoms score (TOSS)

End point title	Total ocular symptoms score (TOSS)

End point description:

The TOSS is a patient-reported evaluation in the TOSS Questionnaire of 3 ocular symptoms: itching/burning, hyperemia of conjunctiva and tearing. A score was given in the presence of symptoms: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

Day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: score on a scale				
arithmetic mean (standard deviation)				
Visit 3 - Day 4	0.29 (± 0.63)	0.37 (± 0.73)		
Visit 4 - Day 8	0.28 (± 0.67)	0.26 (± 0.62)		
Visit 5 - Day 15	0.17 (± 0.49)	0.17 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular Pain/Discomfort: 4-point Scale

End point title	Ocular Pain/Discomfort: 4-point Scale

End point description:

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

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

Day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Day 4: Presence/absence of ocular pain: Score=0	360	361		
Day 4: Presence/absence of ocular pain: Score>0	35	32		
Day 8: Presence/absence of ocular pain: Score=0	366	366		
Day 8: Presence/absence of ocular pain: Score>0	29	27		
Day 15: Presence/absence of ocular pain: Score=0	377	373		
Day 15: Presence/absence of ocular pain: Score>0	18	20		

Statistical analyses

Statistical analysis title	Superiority Test (Visit 3 – Day 4)

Statistical analysis description:

Difference between proportions of patients with an ocular pain and discomfort score of zero (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone

Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.0072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0461
upper limit	0.0318

Statistical analysis title	Superiority Test (Visit 4 – Day 8)
Statistical analysis description:	
Difference between proportions of patients with an ocular pain and discomfort score of zero (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-0.0047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0406
upper limit	0.0312

Statistical analysis title	Superiority Test (Visit 5 – Day 15)
Statistical analysis description:	
Difference between proportions of patients with an ocular pain and discomfort score of zero (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.0053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0246
upper limit	0.0352

Secondary: Use of Rescue Therapy

End point title	Use of Rescue Therapy

End point description:

All rescue therapy used following cataract surgery is to be reported at all visits.

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

During all the treatment until day 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Patients with rescue therapy	3	1		
Patients with no rescue therapy	392	392		

Statistical analyses

Statistical analysis title	Superiority Test

Statistical analysis description:

Difference between proportions of patients with any rescue therapy (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.0051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0049
upper limit	0.015

Secondary: Intraocular Pressure (IOP)

End point title	Intraocular Pressure (IOP)

End point description:

IOP is measured using a tonometer. IOP is measured as mmHg; normal intraocular pressures average between 12-22 mm Hg.

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Secondary

End point timeframe:

At day 0 (screening) and at day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 1 - Screening	15.16 (± 2.48)	15.12 (± 2.41)		
Visit 3 - Day 4	14.26 (± 2.73)	14.49 (± 2.81)		
Visit 4 - Day 8	14.29 (± 2.51)	14.45 (± 3.03)		
Visit 5 - Day 15	14.45 (± 2.65)	14.37 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Visual Acuity

End point title	Visual Acuity

End point description:

Visual acuity was assessed as per local clinical practice, i.e. with the Snellen (feet) or the ETDRS (meter) chart. Visual acuity was then analysed using decimal unit. Decimal score is the decimal expression of the Snellen (feet) or the ETDRS (meter) charts in which the numerator indicates the distance from the chart and the denominator indicates the size of the smallest line that can be read. Decimal values were provided directly from the investigator or computed as a result of the Snellen or ETDRS fraction. Generally decimal values from 0.01 to 0.10 indicate severe vision loss; decimal values from 0.125 to 0.25 indicate moderate vision loss; decimal values from 0.32 to 0.63 indicate mild vision loss; decimal values from 0.8 to 1.6 indicate normal vision. Lower decimal values correspond to a reduced visual acuity and worst outcomes, while higher decimal values indicate an improved visual acuity and better outcomes.

The analysis population is represented by all randomized patients

End point type	Other pre-specified

End point timeframe:

At day 0 (screening) and at day 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: decimal score				
arithmetic mean (standard deviation)				
Visit 1 - Screening	0.41 (± 0.23)	0.41 (± 0.26)		
Visit 5 - Day 15	0.88 (± 0.19)	0.89 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Adverse Events

End point title	Adverse Events

End point description:

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

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Other pre-specified

End point timeframe:

From baseline to the end of the treatment, corresponding to 15 days and 30 days (for SAEs) after the last day of study participation.

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
Patients with TEAEs	56	51		
Patients with serious TEAEs	4	2		
Patients with TEAEs suspected to be study related	26	26		
Patients with TEAEs leading to discontinuation	4	3		
Patients with fatal TEAEs	1	0		
Patients with severe TEAEs	3	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Global Evaluation of Local Tolerability

End point title	Global Evaluation of Local Tolerability

End point description:

Global evaluation was evaluated on a 4-point scale: 0 = no intolerability, 1 = mild intolerability, 2 = moderate
intolerability, 3 = maximum intolerability

The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)

End point type	Other pre-specified

End point timeframe:

Day 4, 8, 15

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: score on a scale				
arithmetic mean (standard deviation)				
Visit 3 - Day 4	0.03 (± 0.21)	0.01 (± 0.09)		
Visit 4 - Day 8	0.01 (± 0.11)	0.03 (± 0.19)		
Visit 5 - Day 15	0.02 (± 0.15)	0.02 (± 0.13)		

Statistical analyses

Statistical analysis title	Superiority Test - Global evaluation - Visit 3

Statistical analysis description:

Difference between mean value of global evaluation
(Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0178
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.0406

Statistical analysis title	Superiority Test - Global evaluation - Visit 4
Statistical analysis description: Difference between mean value of global evaluation (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.0127
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0343
upper limit	0.009

Statistical analysis title	Superiority Test - Global evaluation - Visit 5
Statistical analysis description: Difference between mean value of global evaluation (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0199
upper limit	0.0201

Other pre-specified: Burning, Stinging, Blurred Vision	
End point title	Burning, Stinging, Blurred Vision
End point description: Burning, stinging, blurred vision were evaluated on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)	
End point type	Other pre-specified
End point timeframe: Day 4, 8, 15	

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: score on a scale				
arithmetic mean (standard deviation)				
Burning: visit 3 - day 4	0.08 (± 0.27)	0.09 (± 0.29)		
Burning: visit 4 - day 8	0.06 (± 0.24)	0.11 (± 0.35)		
Burning: visit 5 - day 15	0.07 (± 0.29)	0.07 (± 0.27)		
Stinging: visit 3 - day 4	0.05 (± 0.23)	0.04 (± 0.20)		
Stinging: visit 4 - day 8	0.07 (± 0.29)	0.07 (± 0.26)		
Stinging: visit 5 - day 15	0.06 (± 0.26)	0.04 (± 0.20)		
Blurred vision: visit 3 - day 4	0.06 (± 0.27)	0.05 (± 0.23)		
Blurred vision: visit 4 - day 8	0.06 (± 0.25)	0.04 (± 0.22)		
Blurred vision: visit 5 - day 15	0.03 (± 0.20)	0.01 (± 0.11)		

Statistical analyses

Statistical analysis title	Superiority Test - Burning - Visit 3
Statistical analysis description:	
Difference between mean value of burning (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.0153
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0541
upper limit	0.0236

Statistical analysis title	Superiority Test - Burning - Visit 4
Statistical analysis description:	
Difference between mean value of burning (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone

Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.0582
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1003
upper limit	-0.0161

Statistical analysis title	Superiority Test - Burning - Visit 5
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0364
upper limit	0.0422

Statistical analysis title	Superiority Test - Stinging - Visit 3
Statistical analysis description:	
Difference between mean value of stinging (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0076
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0229
upper limit	0.0382

Statistical analysis title	Superiority Test - Stinging - Visit 4
Statistical analysis description:	
Difference between mean value of stinging	

(Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.0387

Statistical analysis title	Superiority Test - Stinging - Visit 5

Statistical analysis description:

Difference between mean value of stinging
(Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0141
upper limit	0.0505

Statistical analysis title	Superiority Test - Blurred vision - Visit 3

Statistical analysis description:

Difference between mean value of blurred vision
(Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)

Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0153
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.0505

Statistical analysis title	Superiority Test - Blurred vision - Visit 4
Statistical analysis description: Difference between mean value of blurred vision (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0181
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0148
upper limit	0.051

Statistical analysis title	Superiority Test - Blurred vision - Visit 5
Statistical analysis description: Difference between mean value of blurred vision (Levofloxacin+Dexamethasone vs. Tobramycin+Dexamethasone)	
Comparison groups	Levofloxacin + Dexamethasone Followed by Dexamethasone v Tobramycin + Dexamethasone
Number of subjects included in analysis	788
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.0181
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0048
upper limit	0.041

Other pre-specified: Assessment of Patient Diary (Compliance)	
End point title	Assessment of Patient Diary (Compliance)
End point description: Treatment compliance is derived from the number of instillations each day during the study treatment exposure The analysis population is represented by all randomized patients who received at least one dose of study treatment (Full Analysis Set)	
End point type	Other pre-specified
End point timeframe: Day 15	

End point values	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	393		
Units: Count of Participants				
No missed dose	332	332		
1 missed dose per day or 3 missed doses per week	59	57		
> 1 missed dose per day or > 3 missed doses per we	4	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to the end of the treatment, corresponding to 15 days and 30 days (for SAEs) after the last day of study participation.

Adverse event reporting additional description:

It is not possible to attribute Adverse Events to Dexamethasone alone following treatment with Levofloxacin + Dexamethasone

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Levofloxacin + Dexamethasone Followed by Dexamethasone

Reporting group description:

Levofloxacin + dexamethasone ophthalmic solution containing levofloxacin hemihydrate 5.12 mg/ml, corresponding to levofloxacin 5 mg/ml, and dexamethasone sodium phosphate 1.32 mg/ml, corresponding to dexamethasone 1 mg/ml (L-DSP), followed by Dexamethasone 1 mg/ml ophthalmic suspension (Maxidex)
Dose and regimen: Levofloxacin + dexamethasone sodium phosphate eye drops for 7 days, 1 x 30 µl drop - 4 times a day, followed by dexamethasone eye drops (Maxidex) for an additional 7 days, 1 drop - 4 times a day.

Reporting group title	Tobramycin + Dexamethasone

Reporting group description:

Tobramycin 3 mg/ml + dexamethasone 1 mg/ml eye drops suspension (Tobradex)
Dose and regimen: 1 drop - 4 times a day for 14 days

Serious adverse events	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 395 (1.01%)	2 / 393 (0.51%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 395 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial Infarction			

subjects affected / exposed	1 / 395 (0.25%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Retinal Detachment			
subjects affected / exposed	1 / 395 (0.25%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Levofloxacin + Dexamethasone Followed by Dexamethasone	Tobramycin + Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 395 (13.16%)	49 / 393 (12.47%)	
General disorders and administration site conditions			
Disorders not specified	Additional description: Tables for SOC and PT have not been required for non-serious adverse events but have been carried out for all adverse events (serious and non serious adverse events togheter) and only for serious events.		
subjects affected / exposed	52 / 395 (13.16%)	49 / 393 (12.47%)	
occurrences (all)	52	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported