Clinical trial results:
Effect of drop-less surgery compared to topical NSAID alone and combination of steroid and NSAID on central macular thickness after cataract surgery, a randomized controlled trial

Summary

EudraCT number	2017-002666-47
Trial protocol	DK
Global end of trial date	18 December 2019

Results information

Result version number	v1 (current)
This version publication date	31 December 2020
First version publication date	31 December 2020

Trial information

Trial identification

Sponsor protocol code	SOAP1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03383328
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dpt. of Ophthalmology, Rigshospitalet-Glostrup
Sponsor organisation address	Valdemar Hansens Vej 1-23, Glostrup, Denmark, 2600
Public contact	Dpt. of Ophthalmology, Ø37, Dpt. of Ophthalmology, Rigshospitalet-Glostrup, 0045 38634770,
Scientific contact	Dpt. of Ophthalmology, Ø37, Dpt. of Ophthalmology, Rigshospitalet-Glostrup, 0045 38634770,

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	15 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2019
Global end of trial reached?	Yes
Global end of trial date	18 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to investigate which anti-inflammatory treatment is best at preventing postoperative inflammation following cataract surgery. We want to compare topical prophylaxis with NSAID eye drops to topical prophylaxis with a combination of NSAID and prednisolone. We also want to compare topical prophylaxis with eye drops to drop-less surgery where the anti-inflammatory drug is administered to the subtenonal space at the conclusion of the surgical procedure. In addition, we want to investigate if topical anti-inflammatory prophylaxis should be initiated preoperatively or postoperatively.

Protection of trial subjects:

To detect complications and quickly initiate treatment participants were closely monitored throughout the study period. At the postoperative visits patients were checked for adverse effects to the anti-inflammatory prophylaxis. The postoperative visits included measuring of best corrected visual acuity and intraocular pressure (IOP) and evaluation of the eye by slit-lamp imaging. The patients were alsoasked for subjective complaints and symptoms related to the treatment.
Postoperative visits were scheduled to detect adverse effects when they were expected to present. I.e. the 3rd-day review would detect excessive postoperative inflammation, early elevations in IOP, complications to application of the steroid depot and complications to surgery that were not detected immediately after surgery. The 3-week review would detect elevated IOP and potential infections or corneal defects following prophylactic treatment. The main purpose of the 3-month review was to detect increased central macular thickness which develops within the first 3 months following surgery. Patients were instructed to contact the investigators immediately if vision got worse, the eye turned red and/or painful or they became sensitive to light, experienced a curtain-like shadow over the visual field, experienced flashes of light or halos around light sources.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 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	Denmark: 470
Worldwide total number of subjects	470
EEA total number of subjects	470

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)	68
From 65 to 84 years	389
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

All participants were recruitet from February 1 2018 to August 15 2019 at Department of Ophthalmology, Rigshospitalet-Glostrup, Denmark.

Pre-assignment

Screening details:

We screened 868 patients who were referred for a preoperative evaluation for cataract surgery at Department of Ophthalmology, Rigshospitalet-Denmark. Of those, 398 were not included; 211 did not want to participate and 187 did not meet criteria for inclusion.

Period 1

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

Blinding implementation details:

Groups were renamed by an independent researcher prior to data analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pred+NSAID-Pre

Arm description:

Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery

Arm type	Active comparator
Investigational medicinal product name	Pred Forte 1%
Investigational medicinal product code	S01BA04
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from three days before cataract surgery until three weeks after cataract surgery.

Investigational medicinal product name	Acular 0.5%
Investigational medicinal product code	S 01 BC 05
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from three days before cataract surgery until three weeks after cataract surgery.

Arm title	Pred+NSAID-Post

Arm description:

Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery

Arm type	Experimental

Investigational medicinal product name	Pred Forte 1%
Investigational medicinal product code	S01BA04
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from the day of cataract surgery until three weeks after cataract surgery.

Investigational medicinal product name	Acular 0.5%
Investigational medicinal product code	S 01 BC 05
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from the day of cataract surgery until three weeks after cataract surgery.

Arm title	NSAID-Pre

Arm description:

Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery

Arm type	Experimental
Investigational medicinal product name	Acular 0.5%
Investigational medicinal product code	S 01 BC 05
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from three days before cataract surgery until three weeks after cataract surgery.

Arm title	NSAID-Post

Arm description:

Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery

Arm type	Experimental
Investigational medicinal product name	Acular 0.5%
Investigational medicinal product code	S 01 BC 05
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop applied to the ocular surface three times per day from the day of cataract surgery until three weeks after cataract surgery.

Arm title	Drop-less

Arm description:

Subtenon depot of 0.5 mL dexamethasone phosphate administered at the conclusion of cataract surgery

Arm type	Experimental
Investigational medicinal product name	Dexamethason Krka phosphate 4 mg/ml solution for injection/infusion
Investigational medicinal product code	H02AB02
Other name	Dexavital
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Ocular use

Dosage and administration details:

Subtenon depot of 0.5 mL dexamethasone phosphate (4 mg/ML) administered at the conclusion of cataract surgery.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to the study design with one group not receiving eye drops, participants and outcome assessors could not be blinded to allocation status. Blinding was achieved by performing data analyses without knowledge of allocation status. This was done by renaming the interventional groups prior to analyzing. Renaming was carried out by a researcher with no relation to the study.

Number of subjects in period 1	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre
Started	94	94	94
Completed	85	92	83
Not completed	9	2	11
Consent withdrawn by subject	3	1	2
Completed last follow-up visit outside timeframe	-	1	3
Lost to follow-up	3	-	2
Criteria for exclusion met after allocation	3	-	4

Number of subjects in period 1	NSAID-Post	Drop-less
Started	94	94
Completed	88	81
Not completed	6	13
Consent withdrawn by subject	2	6
Completed last follow-up visit outside timeframe	-	1
Lost to follow-up	2	1
Criteria for exclusion met after allocation	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	470	470	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age at inclusion			
Units: years			
arithmetic mean	72.1		
standard deviation	± 7.0	-	
Gender categorical Units: Subjects			
Female	290	290	
Male	180	180	
Grading of Nuclear Cataract			
Severity of cataract was determined according to the Age-Related Eye Disease Study (AREDS) system for classification of cataracts			
Units: Subjects			
Nuclear Cataract < 1	2	2	
Nuclear Cataract = 1	13	13	
Nuclear Cataract = 1.5	95	95	
Nuclear Cataract = 2.0	160	160	
Nuclear Cataract = 2.5	124	124	
Nuclear Cataract = 3	72	72	
Nuclear Cataract > 3	4	4	
Not Recorded	0	0	
Cortical Cataract grade			
Severity of cataract was determined according to the Age-Related Eye Disease Study (AREDS) system for classification of cataracts			
Units: Subjects			
Cortical Cataract < 1	230	230	
Cortical Cataract = 1	86	86	
Cortical Cataract = 1.5	51	51	
Cortical Cataract = 2	70	70	

Cortical Cataract = 2.5	19	19	
Cortical Cataract = 3	12	12	
Cortical Cataract > 3	2	2	
Not recorded	0	0	
Posterior Subcapsular Cataract grade			
Severity of cataract was determined according to the Age-Related Eye Disease Study (AREDS) system for classification of cataracts			
Units: Subjects			
PSC < 1	326	326	
PSC = 1	52	52	
PSC = 1.5	26	26	
PSC = 2	25	25	
PSC = 2.5	17	17	
PSC = 3	17	17	
PSC > 3	7	7	
Not recorded	0	0	
Laterality (eye)			
Number of left and right eyes included			
Units: Subjects			
Right eye	246	246	
Left eye	224	224	
Central Macular Thickness			
Measured by optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) using the central 1.0 mm zone of ETDRS (Early Treatment Diabetic Retinopathy Study) grid obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV)			
Units: micrometers			
arithmetic mean	243.2		
standard deviation	± 21.8	-	
Corrected Distance Visual Acuity			
Measured using an ETDRS chart			
Units: logMAR			
arithmetic mean	0.29		
standard deviation	± 0.15	-	
Intraocular Pressure			
Measured using a rebound tonometer (iCare Finland) and controlled by Goldman applanation tonometry intraocular pressure > 25 mm Hg			
Units: mm Hg			
arithmetic mean	14.3		
standard deviation	± 3.9	-	
Anterior Chamber Flare			
Anterior chamber flare was measured on undilated pupils by flare photometer (KOWA FM-600, KOWA Company) using an average of five reliable measurements.			
Units: photons per millisecond			
median	9.7		
inter-quartile range (Q1-Q3)	7.3 to 13.2	-	
Average Retinal Nerve Fiber Layer Thickness			
Retinal Nerve Fiber Layer thickness was measured by peripapillary optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) and obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV)			
Units: micrometers			
arithmetic mean	95.6		
standard deviation	± 12.5	-	

End points

End points reporting groups

Reporting group title	Pred+NSAID-Pre
Reporting group description:	
Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery	
Reporting group title	Pred+NSAID-Post
Reporting group description:	
Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery	
Reporting group title	NSAID-Pre
Reporting group description:	
Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery	
Reporting group title	NSAID-Post
Reporting group description:	
Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery	
Reporting group title	Drop-less
Reporting group description:	
Subtenon depot of 0.5 mL dexamethasone phosphate administered at the conclusion of cataract surgery	

Primary: Central Macular Thickness 3 months postoperative

End point title	Central Macular Thickness 3 months postoperative
End point description:	
Primary outcome was central macular thickness (CMT) at the three-month visit measured by optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) using the central 1.0 mm zone of ETDRS (Early Treatment Diabetic Retinopathy Study) grid obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV)	
End point type	Primary
End point timeframe:	
Three months after cataract surgery	

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91[1]	94	90[2]	92[3]
Units: micrometers				
arithmetic mean (confidence interval 95%)	250.7 (247.6 to 253.7)	250.7 (247.8 to 253.7)	251.3 (248.2 to 254.4)	249.2 (246.2 to 252.3)

Notes:

[1] - 3 participants met criteria for exclusion after allocation.

[2] - 4 participants met criteria for exclusion after allocation.

[3] - 2 participants met criteria for exclusion after allocation.

End point values	Drop-less			

Subject group type	Reporting group			
Number of subjects analysed	89[4]			
Units: micrometers				
arithmetic mean (confidence interval 95%)	255.2 (252.0 to 258.3)			

Notes:

[4] - 5 participants met criteria for exclusion after allocation.

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. Significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125. Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-5.4
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	2.2

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. Significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-5
upper limit	6.2

Variability estimate	Standard error of the mean
Dispersion value	2.2

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. Significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-7
upper limit	4.1
Variability estimate	Standard error of the mean
Dispersion value	2.2

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. Significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-1.1
upper limit	10.1
Variability estimate	Standard error of the mean
Dispersion value	2.2

Secondary: Central macular thickness 3 weeks postoperative

End point title	Central macular thickness 3 weeks postoperative

End point description:

Central macular thickness (CMT) at the three-month visit measured by optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) using the central 1.0 mm zone of ETDRS (Early Treatment Diabetic Retinopathy Study) grid obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV)

End point type	Secondary

End point timeframe:

Three weeks after cataract surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: micrometers				
arithmetic mean (confidence interval 95%)	248.4 (244.8 to 252.1)	251.5 (247.9 to 255.0)	252.2 (248.6 to 255.9)	249.6 (246.1 to 253.2)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: micrometers				
arithmetic mean (confidence interval 95%)	259.7 (255.9 to 263.4)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	8.1
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	8.9
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	16.4
Variability estimate	Standard error of the mean
Dispersion value	2.6

Secondary: Anterior Chamber Flare at 3 days postoperative

End point title	Anterior Chamber Flare at 3 days postoperative

End point description:

Anterior chamber flare was measured on undilated pupils by flare photometer (KOWA FM-600, KOWA Company) using an average of five reliable measurements.

End point type	Secondary

End point timeframe:

Three days after cataract surgery.

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: photons per milisecond				
median (confidence interval 95%)	17.6 (15.7 to 19.7)	18.1 (16.1 to 20.2)	20.6 (18.3 to 23.1)	19.6 (17.5 to 22.0)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: photons per milisecond				
median (confidence interval 95%)	30.4 (27.0 to 34.2)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. This analysis was considered a primary analysis regarding the early postoperative inflammatory respons and significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.73
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-0.25
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[5] - Flare-values were log2-transformed for statistical analyses. Results presented beneath are on log2-scale.

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. This analysis was considered a primary analysis regarding the early postoperative inflammatory respons and significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-0.06
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[6] - Flare-values were log2-transformed for statistical analyses. Results presented beneath are on log2-scale.

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. This analysis was considered a primary analysis regarding the early postoperative inflammatory respons and significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.17
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-0.13
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[7] - Flare-values were log2-transformed for statistical analyses. Results presented beneath are on log2-scale.

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. This

analysis was considered a primary analysis regarding the early postoperative inflammatory respons and significance level was adjusted for multiple testing using Bonferroni correction resulting in a significance level = 0.0125.

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.79
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	0.5
upper limit	1.09
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[8] - Flare-values were log2-transformed for statistical analyses. Results presented beneath are on log2-scale.

Secondary: Intraocular Pressure - 3 days postoperative

End point title	Intraocular Pressure - 3 days postoperative

End point description:

Intraocular pressure measured 3 days after surgery using a rebound tonometer (Icare, Finland)

End point type	Secondary

End point timeframe:

Three days after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: mm Hg				
arithmetic mean (confidence interval 95%)	13.6 (12.9 to 14.2)	13.4 (12.8 to 14.0)	11.5 (10.9 to 12.1)	11.0 (10.4 to 11.6)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: mm Hg				
arithmetic mean (confidence interval 95%)	10.3 (9.7 to 11.0)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-1.2
Variability estimate	Standard error of the mean
Dispersion value	0.43

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.43

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	-2.4
Variability estimate	Standard error of the mean
Dispersion value	0.44

Secondary: Intraocular Pressure - 3 weeks postoperative

End point title	Intraocular Pressure - 3 weeks postoperative

End point description:

Intraocular pressure (IOP) was measured using a rebound tonometer (Icare, Finland)

End point type	Secondary
End point timeframe:	
Three weeks after surgery	

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: mm Hg				
arithmetic mean (confidence interval 95%)	12.1 (11.6 to 12.6)	12.4 (11.9 to 12.9)	11.0 (10.5 to 11.5)	10.6 (10.1 to 11.2)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: mm Hg				
arithmetic mean (confidence interval 95%)	11.1 (10.6 to 11.6)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.8
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.35

Secondary: Intraocular Pressure - 3 months postoperative	
End point title	Intraocular Pressure - 3 months postoperative

End point description:

Intraocular pressure (IOP) was measured using a rebound tonometer (Icare, Finland).

End point type	Secondary

End point timeframe:

Three months after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: mm Hg				
arithmetic mean (confidence interval 95%)	11.0 (10.5 to 11.5)	11.2 (10.7 to 11.7)	10.7 (10.2 to 11.2)	10.7 (10.2 to 11.2)

End point values	Drop-less			

Subject group type	Reporting group			
Number of subjects analysed	88			
Units: mm Hg				
arithmetic mean (confidence interval 95%)	10.8 (10.3 to 11.4)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.34

Secondary: Number of cells in anterior chamber - 3 days postoperative

End point title	Number of cells in anterior chamber - 3 days postoperative

End point description:

Number of cells in the anterior chamber was coundted in a 1 mm by 1 mm light beam during slit-lamp examination.

End point type	Secondary

End point timeframe:

Three days after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	94	90	92
Units: cells				
arithmetic mean (confidence interval 95%)	3.4 (3.0 to 3.9)	3.8 (3.3 to 4.4)	4.1 (3.3 to 5.0)	4.0 (3.4 to 4.5)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: cells				
arithmetic mean (confidence interval 95%)	5.5 (4.5 to 6.7)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre) using Welchs' two-sample t-test. P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Welchs' two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.35

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre) using Welchs' two-sample t-test. P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Welchs' two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre) using Welchs' two-sample t-test. P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Post

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Welchs' two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.35

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre) using Welchs' two-sample t-test. P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Welchs' two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.58

Secondary: Corrected Distance Visual Acuity - 3 days postoperative

End point title	Corrected Distance Visual Acuity - 3 days postoperative

End point description:

Corrected Distance Visual Acuity was measured using en ETDRS chart.

End point type	Secondary

End point timeframe:

Three days after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	93	90	92
Units: logMAR				
arithmetic mean (confidence interval 95%)	0.10 (0.07 to 0.13)	0.10 (0.06 to 0.13)	0.07 (0.03 to 0.10)	0.10 (0.06 to 0.13)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: logMAR				
arithmetic mean (confidence interval 95%)	0.11 (0.07 to 0.14)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructure covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Corrected Distance Visual Acuity - 3 weeks postoperative

End point title	Corrected Distance Visual Acuity - 3 weeks postoperative
End point description:	
Visual acuity was measured using an ETDRS chart.	
End point type	Secondary
End point timeframe:	
Three weeks after cataract surgery	

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	93	90	92
Units: logMAR				
arithmetic mean (confidence interval 95%)	0.02 (-0.01 to 0.05)	0.03 (0.00 to 0.06)	0.02 (-0.02 to 0.04)	0.01 (-0.01 to 0.04)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: logMAR				
arithmetic mean (confidence interval 95%)	0.05 (0.02 to 0.08)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values

were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Corrected Distance Visual Acuity - 3 months postoperative

End point title	Corrected Distance Visual Acuity - 3 months postoperative

End point description:

Measured using an ETDRS chart.

End point type	Secondary

End point timeframe:

Three months after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	93	90	92
Units: logMAR				
arithmetic mean (confidence interval 95%)	-0.01 (-0.04 to 0.01)	0.00 (-0.03 to 0.02)	0.00 (-0.03 to 0.02)	-0.01 (-0.04 to 0.01)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: logMAR				
arithmetic mean (confidence interval 95%)	0.01 (-0.02 to 0.03)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.01

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.01

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.01

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Subjective Tolerance of Treatment - 3 days postoperative

End point title	Subjective Tolerance of Treatment - 3 days postoperative

End point description:

Participants were asked if they felt "No discomfort or mild discomfort" or "Moderate or severe discomfort".

End point type	Secondary

End point timeframe:

Three days after surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	87	90
Units: participants				
number (not applicable)				
No or mild discomfort	81	87	82	87
Moderate or severe discomfort	7	6	5	3

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: participants				
number (not applicable)				

No or mild discomfort	72			
Moderate or severe discomfort	11			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made between the control group (Pred+NSAID-Pre) and the comparison groups. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Fisher exact

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Fisher exact

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Fisher exact

Secondary: Subjective Tolerance of Treatment - 3 weeks postoperative

End point title	Subjective Tolerance of Treatment - 3 weeks postoperative

End point description:

Participants were asked if they felt "No discomfort or mild discomfort" or "Moderate or severe discomfort".

End point type	Secondary

End point timeframe:

Three weeks after cataract surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	93	88	90
Units: Participants				
number (not applicable)				
No or mild discomfort	86	92	85	86
Moderate or severe discomfort	1	1	3	4

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Participants				
number (not applicable)				
No or mild discomfort	79			
Moderate or severe discomfort	4			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple

testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Fisher exact

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Fisher exact

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Pairwise comparisons were made with control (Pred+NSAID-Pre). P-values were adjusted for multiple testing with the False Discovery Rate method. An adjusted p-value < 0.05 was considered statistically significant.

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Fisher exact

Secondary: Average Retinal Nerve Fiber Layer Thickness - 3 weeks postoperative	
End point title	Average Retinal Nerve Fiber Layer Thickness - 3 weeks postoperative

End point description:

Retinal Nerve Fiber Layer thickness was measured by peripapillary optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) and obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV)

End point type	Secondary

End point timeframe:

Three weeks after cataract surgery

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	92	88	91
Units: micrometers				
arithmetic mean (confidence interval 95%)	99.4 (97.8 to 101.1)	98.5 (96.9 to 100.0)	98.0 (96.4 to 99.6)	97.6 (96.0 to 99.2)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: micrometers				
arithmetic mean (confidence interval 95%)	102.8 (101.1 to 104.4)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	1.1

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	1.1

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	5.6
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Average Retinal Nerve Fiber Layer Thickness - 3 months postoperative

End point title	Average Retinal Nerve Fiber Layer Thickness - 3 months postoperative

End point description:

Retinal Nerve Fiber Layer thickness was measured by peripapillary optical coherence tomography (OCT, DRI OCT Triton, Topcon Europe Medical BV) and obtained from the in-build software (IMAGEnet 6, Topcon Europe Medical BV).

End point type	Secondary

End point timeframe:

Three months after cataract surgery.

End point values	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre	NSAID-Post
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	92	88	91
Units: micrometers				
arithmetic mean (confidence interval 95%)	99.8 (98.1 to 101.4)	99.3 (97.7 to 101.0)	97.7 (96.0 to 99.4)	98.0 (96.4 to 99.7)

End point values	Drop-less			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: micrometers				
arithmetic mean (confidence interval 95%)	98.6 (96.9 to 100.3)			

Statistical analyses

Statistical analysis title	Pred+NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Pred+NSAID-Post
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	NSAID-Pre vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Pre
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	NSAID-Post vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v NSAID-Post
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	Dropless vs. Pred+NSAID-Pre

Statistical analysis description:

Constrained linear mixed model with an unstructured covariance pattern and inherent baseline adjustment. The model implicitly handled missing values by maximum likelihood estimation. P-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. An adjusted p-value < 0.05 was considered statistically significant.
Pairwise comparisons were made with control (Pred+NSAID-Pre).

Comparison groups	Pred+NSAID-Pre v Drop-less

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	1.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed for each participant from inclusion until completion of/termination from study.

Adverse event reporting additional description:

Patients were asked for symptoms and adverse events at each postoperative visit and patient journals were investigated for records of adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	Not applicable
Dictionary version	0

Reporting groups

Reporting group title	Pred+NSAID-Pre

Reporting group description:

Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery

Reporting group title	Pred+NSAID-Post

Reporting group description:

Combination of prednisolone- and ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery

Reporting group title	NSAID-Pre

Reporting group description:

Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation three days before surgery

Reporting group title	NSAID-Post

Reporting group description:

Monotherapy with ketorolac eye drops three times per day until three weeks after surgery with initiation on the day of surgery

Reporting group title	Drop-less

Reporting group description:

Subtenon depot of 0.5 mL dexamethasone phosphate administered at the conclusion of cataract surgery

Serious adverse events	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 89 (1.12%)	3 / 93 (3.23%)	1 / 91 (1.10%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma stage IV	Additional description: Hospitalized due to abdominal pain. Examinations showed ascites and disseminated pancreatic cancer. Died in relation to exploratory laparatomy. Had not received any investigational medicine.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Orthostatic hypotension	Additional description: Tendency to fall. Previous cerebral apoplexia. Hospitalized due to social circumstances. Found to have orthostatic hypotension.		
subjects affected / exposed	1 / 89 (1.12%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Syncope	Additional description: Hospitalized due to low bloodpressure and syncope/fainting. Known to have ischemic heart disease and ICD-pacemaker. Had not been given any study medication.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation	Additional description: Hospitalized due to paroxystic atrial fibrilation. Had not received any study medication.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest	Additional description: Witnessed cardiac arrest, defibrillated twice and return of spontaneous circulation after 5 minutes. Hospitalized and treated with percutan cardiac intervention (PCI). Alive and well.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction	Additional description: Hospitalized due to sudden loss of balance and control of the left arm. Had not received any study medication.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery occlusion	Additional description: Sudden debut of aphasia and hemiparesis. Examinations showed occlusion of two cerebral arteries.		
subjects affected / exposed	1 / 89 (1.12%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amaurosis fugax	Additional description: Sudden pain and distorted vision/loss of vision on the right eye for 5-10 minutes, no symptoms afterwards. Hospitalized for further examinations.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment	Additional description: Surgically treated for retinal detachment following cataract surgery.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer	Additional description: Patient with known liver cirrhosis hospitalized due to suspected bleeding esophagal varices. Endoscopic examination showed a non-bleeding esophagal varice and two fibrin covered gastric ulcera.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erysipelas	Additional description: Hospitalized for antibiotic treatment of erysipelas. Had not received any study medication.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric perforation	Additional description: Was hospitalized due to acute abdominal pain, nausia and vomiting. Was found to have a ureteric perforation and was surgically treated.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis	Additional description: Hospitalized for antibiotic treatment		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Hospitalized due to severe pain and cramps in upper and lower extremities.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Syncope	Additional description: Syncope due to dehydration after physical work in the sun. Was hospitalized and rehydrated.		

subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	NSAID-Post	Drop-less	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 91 (3.30%)	5 / 87 (5.75%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma stage IV	Additional description: Hospitalized due to abdominal pain. Examinations showed ascites and disseminated pancreatic cancer. Died in relation to exploratory laparatomy. Had not received any investigational medicine.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Orthostatic hypotension	Additional description: Tendency to fall. Previous cerebral apoplexia. Hospitalized due to social circumstances. Found to have orthostatic hypotension.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Syncope	Additional description: Hospitalized due to low bloodpressure and syncope/fainting. Known to have ischemic heart disease and ICD-pacemaker. Had not been given any study medication.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Hospitalized due to paroxystic atrial fibrilation. Had not received any study medication.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Witnessed cardiac arrest, defibrillated twice and return of spontaneous circulation after 5 minutes. Hospitalized and treated with percutan cardiac intervention (PCI). Alive and well.		
subjects affected / exposed	1 / 91 (1.10%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral infarction	Additional description: Hospitalized due to sudden loss of balance and control of the left arm. Had not received any study medication.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery occlusion	Additional description: Sudden debut of aphasia and hemiparesis. Examinations showed occlusion of two cerebral arteries.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amaurosis fugax	Additional description: Sudden pain and distorted vision/loss of vision on the right eye for 5-10 minutes, no symptoms afterwards. Hospitalized for further examinations.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment	Additional description: Surgically treated for retinal detachment following cataract surgery.		
subjects affected / exposed	1 / 91 (1.10%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer	Additional description: Patient with known liver cirrhosis hospitalized due to suspected bleeding esophagal varices. Endoscopic examination showed a non-bleeding esophagal varice and two fibrin covered gastric ulcera.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erysipelas	Additional description: Hospitalized for antibiotic treatment of erysipelas. Had not received any study medication.		
subjects affected / exposed	1 / 91 (1.10%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureteric perforation	Additional description: Was hospitalized due to acute abdominal pain, nausia and vomiting. Was found to have a ureteric perforation and was surgically treated.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis	Additional description: Hospitalized for antibiotic treatment		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Hospitalized due to severe pain and cramps in upper and lower extremities.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Syncope	Additional description: Syncope due to dehydration after physical work in the sun. Was hospitalized and rehydrated.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pred+NSAID-Pre	Pred+NSAID-Post	NSAID-Pre
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 89 (25.84%)	36 / 93 (38.71%)	30 / 91 (32.97%)
Surgical and medical procedures			
Burning sensation	Additional description: Burning sensation/pain when subtenon depot was applied		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Pain	Additional description: Pain/soreness during cataract surgery		
subjects affected / exposed	0 / 89 (0.00%)	2 / 93 (2.15%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Intraocular lens repositioning			
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Lens dislocation	Additional description: Retained lens fragments in the anterior chamber after cataract surgery and need for surgical removal.		
subjects affected / exposed	1 / 89 (1.12%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Posterior capsule rupture	Additional description: Rupture of the posterior capsule during phacoemulsification.		

subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	2 / 91 (2.20%)
occurrences (all)	23	36	31
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 89 (1.12%)	0 / 93 (0.00%)	2 / 91 (2.20%)
occurrences (all)	23	36	31
Nausea			
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	1 / 91 (1.10%)
occurrences (all)	23	36	31
General disorders and administration site conditions			
Malaise	Additional description: Malaise immediately after cataract surgery.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Eye disorders			
Pain	Additional description: Pain or soreness in the eye during the postoperative period		
subjects affected / exposed	2 / 89 (2.25%)	0 / 93 (0.00%)	1 / 91 (1.10%)
occurrences (all)	23	36	31
Inflammation	Additional description: Insufficiently controlled intraocular reaction / inflammation in the anterior chamber.		
subjects affected / exposed	2 / 89 (2.25%)	5 / 93 (5.38%)	5 / 91 (5.49%)
occurrences (all)	23	36	31
Dry eye	Additional description: Dry eye symptoms that needed additional lubricating treatment.		
subjects affected / exposed	7 / 89 (7.87%)	18 / 93 (19.35%)	13 / 91 (14.29%)
occurrences (all)	23	36	31
Macular cyst	Additional description: One or more cysts present on macular optical coherence tomography (OCT).		
subjects affected / exposed	2 / 89 (2.25%)	3 / 93 (3.23%)	4 / 91 (4.40%)
occurrences (all)	23	36	31
Blepharitis	Additional description: Blepharitis was noted as an adverse event if it was found at a postoperative visit and the patient was not previously treated for blepharitis.		
subjects affected / exposed	1 / 89 (1.12%)	2 / 93 (2.15%)	3 / 91 (3.30%)
occurrences (all)	23	36	31
Corneal abrasion			
subjects affected / exposed	3 / 89 (3.37%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Intraocular pressure increased	Additional description: Elevated intraocular pressure > 25 mm Hg immediately after cataract surgery.		

subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Corneal oedema	Additional description: Significant corneal oedema after cataract surgery.		
subjects affected / exposed	4 / 89 (4.49%)	3 / 93 (3.23%)	1 / 91 (1.10%)
occurrences (all)	23	36	31
Skin and subcutaneous tissue disorders			
Skin irritation	Additional description: Itching in palms and feet.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Skin reaction	Additional description: Edema and / or redness of the skin surrounding the eye		
subjects affected / exposed	2 / 89 (2.25%)	0 / 93 (0.00%)	1 / 91 (1.10%)
occurrences (all)	23	36	31
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: Fracture of an extremity during participation in the study.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Pain	Additional description: Muscular pain in extremities or lower back.		
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	1 / 91 (1.10%)
occurrences (all)	23	36	31
Infections and infestations			
Viral infection	Additional description: Common cold		
subjects affected / exposed	0 / 89 (0.00%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Gastroenteritis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 93 (0.00%)	0 / 91 (0.00%)
occurrences (all)	23	36	31
Cystitis			
subjects affected / exposed	1 / 89 (1.12%)	1 / 93 (1.08%)	0 / 91 (0.00%)
occurrences (all)	23	36	31

Non-serious adverse events	NSAID-Post	Drop-less	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 91 (34.07%)	68 / 87 (78.16%)	
Surgical and medical procedures			
Burning sensation	Additional description: Burning sensation/pain when subtenon depot was applied		
subjects affected / exposed	0 / 91 (0.00%)	13 / 87 (14.94%)	
occurrences (all)	30	68	

Pain	Additional description: Pain/soreness during cataract surgery		
subjects affected / exposed	0 / 91 (0.00%)	2 / 87 (2.30%)	
occurrences (all)	30	68	
Intraocular lens repositioning			
subjects affected / exposed	1 / 91 (1.10%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Lens dislocation	Additional description: Retained lens fragments in the anterior chamber after cataract surgery and need for surgical removal.		
subjects affected / exposed	0 / 91 (0.00%)	3 / 87 (3.45%)	
occurrences (all)	30	68	
Posterior capsule rupture	Additional description: Rupture of the posterior capsule during phacoemulsification.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences (all)	30	68	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 91 (2.20%)	4 / 87 (4.60%)	
occurrences (all)	30	68	
Nausea			
subjects affected / exposed	1 / 91 (1.10%)	2 / 87 (2.30%)	
occurrences (all)	30	68	
General disorders and administration site conditions			
Malaise	Additional description: Malaise immediately after cataract surgery.		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Eye disorders			
Pain	Additional description: Pain or soreness in the eye during the postoperative period		
subjects affected / exposed	0 / 91 (0.00%)	13 / 87 (14.94%)	
occurrences (all)	30	68	
Inflammation	Additional description: Insufficiently controlled intraocular reaction / inflammation in the anterior chamber.		
subjects affected / exposed	4 / 91 (4.40%)	40 / 87 (45.98%)	
occurrences (all)	30	68	
Dry eye	Additional description: Dry eye symptoms that needed additional lubricating treatment.		
subjects affected / exposed	14 / 91 (15.38%)	23 / 87 (26.44%)	
occurrences (all)	30	68	
Macular cyst	Additional description: One or more cysts present on macular optical coherence tomography (OCT).		

subjects affected / exposed	0 / 91 (0.00%)	11 / 87 (12.64%)	
occurrences (all)	30	68	
Blepharitis	Additional description: Blepharitis was noted as an adverse event if it was found at a postoperative visit and the patient was not previously treated for blepharitis.		
subjects affected / exposed	2 / 91 (2.20%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Corneal abrasion			
subjects affected / exposed	4 / 91 (4.40%)	3 / 87 (3.45%)	
occurrences (all)	30	68	
Intraocular pressure increased	Additional description: Elevated intraocular pressure > 25 mm Hg immediately after cataract surgery.		
subjects affected / exposed	1 / 91 (1.10%)	0 / 87 (0.00%)	
occurrences (all)	30	68	
Corneal oedema	Additional description: Significant corneal oedema after cataract surgery.		
subjects affected / exposed	2 / 91 (2.20%)	4 / 87 (4.60%)	
occurrences (all)	30	68	
Skin and subcutaneous tissue disorders			
Skin irritation	Additional description: Itching in palms and feet.		
subjects affected / exposed	0 / 91 (0.00%)	0 / 87 (0.00%)	
occurrences (all)	30	68	
Skin reaction	Additional description: Edema and / or redness of the skin surrounding the eye		
subjects affected / exposed	1 / 91 (1.10%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: Fracture of an extremity during participation in the study.		
subjects affected / exposed	0 / 91 (0.00%)	2 / 87 (2.30%)	
occurrences (all)	30	68	
Pain	Additional description: Muscular pain in extremities or lower back.		
subjects affected / exposed	2 / 91 (2.20%)	2 / 87 (2.30%)	
occurrences (all)	30	68	
Infections and infestations			
Viral infection	Additional description: Common cold		
subjects affected / exposed	0 / 91 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Gastroenteritis			
subjects affected / exposed	1 / 91 (1.10%)	1 / 87 (1.15%)	
occurrences (all)	30	68	
Cystitis			

subjects affected / exposed occurrences (all)	1 / 91 (1.10%) 30	0 / 87 (0.00%) 68	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33086290